

MedStudy

17TH EDITION | 2021-2022

Internal Medicine Core

HANNAHAN

BOOK

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Welcome to the 19th Edition of MedStudy's *Internal Medicine Core*!

This 19th edition represents the knowledge, expertise, and labor of love of superb physician educators from Internal Medicine residencies and teaching hospitals across the U.S. This edition has been extensively rewritten to ensure that the information is tightly focused on what you need to know, reflects the current standards of care, and references the most recent practice guidelines.

Think of your *Internal Medicine Core* as a series of well-crafted lectures given by the best teachers you've ever had—those teachers who had a knack for connecting with you and for clearly explaining obtuse concepts. These lectures are casual, yet concise, and focused on the medical knowledge needed for a strong Internal Medicine practice and to easily pass the boards. This Core is foundational and is used as the source for all of MedStudy's Q&As, Flashcards, Audio Pearls, Live Courses, and Video Board Review.

But casual, concise, and focused content is not enough—there's still a lot of material! How can you determine what, out of all this content, is the most important to know; what you're most likely to be tested on? And how in the world do you get it into your long-term memory?

First: How do you identify what's most important?

Our writers and editors know what you need to know, they teach it every day. They've identified the must-know, most-asked information from each main topic and highlighted it in yellow. The Preview | Review questions at the beginning of each main topic are based on the most board-relevant info from this highlighted material.

Second: How do you get this must-know information into your long-term memory?

We'll show you! We call it the MedStudy Method. You can read about this method in the *StudyWise* guide that came with your Core. Hint: The Preview | Review questions are key! Be sure to read this carefully and thoroughly before you jump into the Core. This may be the most important little book you can read at this moment. It will unsettle you by de-bunking 6 learning myths that may be holding you back—and will reveal the 2 secrets to long-term learning.

When I started MedStudy in 1990, I set out to cut through the clutter and make learning the essentials of medicine as easy as possible. This is still my focus and that of every one of MedStudy's 50+ employees and 200+ physician contributors. We are truly honored to be a part of your medical education, and we hope our efforts will allow you to have a more balanced life, more confidence in your practice, and a lot more fun. Welcome to the community of over 100,000 MedStudy physicians who strive for excellence in patient care.

Study Strong,



Robert A. "Tony" Hannaman, MD
MedStudy's Founder and Editor in Chief



Core Features Bring the Reading to Life

While you're reading these pages, it's meant to feel like you're sitting in a live lecture from your favorite professor.

Preview | Review Questions

Preview, study, and review the highest-yield material. See highlighted text for the answers

PREVIEW | REVIEW

- What are the urine serum Na⁺, and serum with SIADH?

Highlighted text

Must-know content—including answers to Preview | Review questions—is highlighted in yellow

primary thyroid abnormalities of thyroidism. If the TSH hypothyroidism. If the for hyperthyroidism is 1

Bold text

This text denotes important lists and defined terms

pattern of iodine diffuse, focal, or m
RAIU: The patient iodine; and then roid determine by the gl

Burgundy text

Just as a great teacher emphasizes certain words to get your attention, we use burgundy text to do the same

up by the gland normal) for vario
RAIU is increased
• Graves disease
TSH-secreting

These patient status. High AD, which lowers se, inappropriately h also high. Remember adrenal insuff similarly to SIADH. Treat SIADH. See No

Hospitalist sidebar

Text of particular interest to hospitalists is flagged with a gray vertical line

Table 1-1: Overview

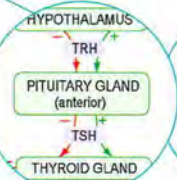
TSH	FT ₄	
Low	Normal	Print
High	High	Sub

Tables & charts

Synthesize the most relevant and related information

Medical images & figures

Visualize concepts with medical images—including diagnostic scans and x-rays, photos, ECGs, and exquisitely drawn figures



The Truth About Learning Medicine

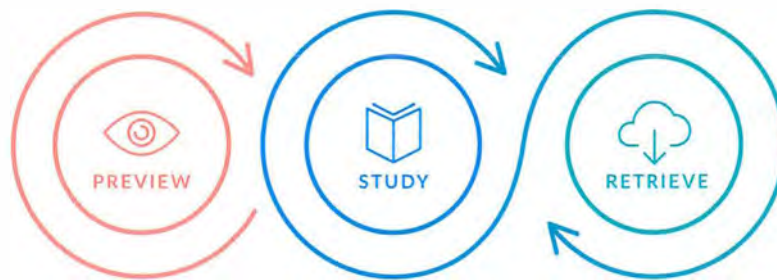
For 30 years, we've been creating innovative study materials that make learning medicine easier. A few years ago, MedStudy's Founder and Editor-in-Chief, Robert A. "Tony" Hannaman, MD started a quest to determine the best way to transfer all this required medical knowledge into long-term memory so it would be durable and easily accessible. He dove into the latest brain science on how memories are made and the best evidence-based learning techniques. He discovered that many of our assumptions and much of what we're taught about learning is simply wrong!

After much study, consultation with experts, pondering, writing, and rewriting, he sculpted what he'd learned into a new study method that we call the MedStudy Method. This is a prescription for the most effective way to truly *learn* medicine. The accompanying *StudyWise* guide is a fun, must-read presentation of the MedStudy Method and the science behind it.

Every MedStudy product—from this Core, to our Q&A bank, to the Flashcards, to the Video Board Review—has been hand-crafted to match best practices from the MedStudy Method. And the result is something unprecedented and powerful. By following the Method, you'll learn, retain, and easily recall all the medical information you need, whether you're seeing patients or taking boards.

The MedStudy Method helps you get off that proverbial hamster wheel of cramming, testing, forgetting... repeat.

We included *StudyWise* with your Core—it's a quick read, but it's a game-changer. The following is a sneak peek into the 3-phased approach to studying.



PREVIEW

The day before you dig into the study material, recall everything you can about it using the Preview | Review questions as prompts.



STUDY

Read through your material carefully, seeking understanding. Don't memorize!



RETRIEVE

Again, using the Preview | Review questions as prompts, practice recall of the same study material over progressively longer intervals. This moves your study material into easily accessible long-term memory!



REFRESH

Go back through the study material only as needed to refresh your understanding.

19th Edition *Internal Medicine Core*

CME START DATE:
December 1, 2020

CME EXPIRATION DATE:
December 1, 2023

Eligible for a maximum 150 CME Credits and 150 ABIM MOC Credits

CME ACCREDITATION

MedStudy is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

MedStudy designates this enduring material for a maximum of 150 AMA PRA Category 1 Credits™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

This credit may be submitted to the American Osteopathic Association (AOA) for Category 2 Credit. All other health care professionals completing this continuing education activity will be issued a certificate of participation.

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Successful completion of this CME activity, which includes participation in the evaluation component, enables the participant to earn 150 Medical Knowledge MOC points in the American Board of Internal Medicine's (ABIM) Maintenance of Certification (MOC) program. Participants will earn MOC points equivalent to the amount of CME credits claimed for the activity. It is the CME activity provider's responsibility to submit participant completion information to ACCME for the purpose of granting ABIM MOC credit.

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2. Follow the instructions for completing the CME credit application and posttest.
3. Return to your Eligible Credits page to claim the ABIM MOC points (optional).
4. MedStudy will report claimed MOC points directly to the ABIM within 1–2 business days.

Note: For any questions, please email us at cme@medstudy.com or call 1-800-841-0547.

LEARNING OBJECTIVES

As a result of participation in this activity, learners will be able to:

- integrate and demonstrate increased overall knowledge of internal medicine,
- identify and remedy areas of weakness (gaps) in knowledge and clinical competencies,
- describe the clinical manifestations and treatments of diseases encountered in internal medicine and effectively narrow the differential diagnosis list by utilizing the most appropriate medical studies, and
- apply the competence and confidence gained through participation in this activity to both a successful board exam-taking experience and daily practice.

TARGET AUDIENCE

Participants in this MedStudy educational activity are those physicians seeking to assess, expand, and reinforce their knowledge and clinical competencies in internal medicine, focusing their learning on subjects that are directly relevant to clinical scenarios that will be encountered on the ABIM Certification board exam or the Maintenance of Certification (MOC) board exam and the American Osteopathic Board of Internal Medicine (AOBIM) board exams, as well as in the contemporary clinical setting. The content of this activity is intended to help learners assess their own key knowledge and clinical competencies with evidence-based standards of care, as reflected on the board exams, and remedy any potential competency gaps that may exist.

METHOD OF PARTICIPATION

The content of this CME activity is intended to help learners assess their key knowledge and clinical competencies with evidence-based standards of care, which are reflected on the board exams and in day-to-day practice. Internists or other physicians preparing for the ABIM certification or MOC exam—or who simply want to update their knowledge of internal medicine—should:

- Preview the section material the day before a study session by reading the Preview | Review questions and recalling whatever knowledge they might already have.
- Read the Core, paying special attention to yellow-highlighted text, which is the must-know material for the ABIM certification and MOC exams, based on ABIM content outlines. Review tables and figures to reinforce study and to see concise summaries of interrelated facts and clinical examples in key topic areas. Self-test again later by answering Preview | Review questions.
- One to two days after reading the Core, go back to the Preview | Review questions again, and try to recall as much as possible. Repeat this again in 7–10 days, 1–2 months, and 4–6 months to improve knowledge and proficiency and, ultimately, to ensure mastery of the material.
- The learner will be required to complete a posttest as part of the requirements for receiving CME or MOC credit for this product.

Without these people,
the 19th Edition *Internal Medicine Core* wouldn't exist.
Thank You.

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medstudy.com/hub

The Hub contains an online consolidated list of all current guidelines focused on internal medicine. Guidelines on the Hub are easy to find, continually updated, and linked to the published source.

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Endocrinology

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GENERAL PRINCIPLES

PREVIEW | REVIEW

- What is meant by positive and negative feedback regulation in endocrine diseases? Which is most common: positive or negative feedback?

If you want to test for **hypo**secretion of a hormone, try to **stimulate it**. Example: In adrenal insufficiency, adrenocorticotropic hormone (ACTH) fails to stimulate cortisol production (the ACTH stimulation test).

If you want to test for **hyper**secretion of a hormone, try to **suppress it**. Example: In Cushing syndrome, dexamethasone fails to suppress production of cortisol (the dexamethasone suppression test).

Laboratory findings must always be interpreted within a clinical context. Example: In primary hyperparathyroidism, parathyroid hormone (PTH) is expected to be high but may be **inappropriately normal** for the lab range; this **inappropriately normal** PTH level is consistent with PTH hypersecretion because the proper PTH response to hypercalcemia is suppression to a very low level.

Biochemical confirmation of hormonal disease (with labs and dynamic testing) **always** precedes imaging because benign, nonfunctional masses are common in all endocrine glands (incidentalomas). Know what you are looking for before you image!

Important characteristics to know about a hormone:

- What is its function?
- Where is it produced and secreted?
- What stimulates and inhibits its release?
- Where are these controls?
- How is it secreted? Is it diurnal, pulsatile, or under tonic inhibition?

Note: Many endocrine glands respond to feedback mechanisms that regulate hormone secretion by negative and/or positive feedback. Positive feedback stimulates hormone release, whereas negative feedback inhibits or suppresses hormone release. Feedback is important in maintaining homeostasis. Most endocrine glands are under negative feedback control. Example: Excess cortisol inhibits both corticotropin-releasing hormone (CRH) and ACTH production.

Note on plasma vs. serum: **Plasma** is the liquid component of blood that has no cells. **Serum** is plasma with the clotting factors removed. In the body, the liquid component of the blood is plasma. Serum is the liquid in a red-top tube after clotting occurs. You will see these terms used interchangeably, and it is okay because it usually doesn't matter. For example, you are actually measuring plasma osmolality by doing a serum osmolality test. In this section, we generally stick with the term **plasma** when talking about the body and **serum** for lab tests.

PRIMARY, SECONDARY, AND TERTIARY GLANDULAR DISEASES

PREVIEW | REVIEW

- What are the definitions of primary, secondary, and tertiary hormone diseases?

With regard to glandular abnormalities:

Primary glandular disease refers to disease of the gland that secretes the hormone.

Secondary glandular disease refers to disease of the gland that controls the primary gland.

Tertiary glandular disease refers to disease of the gland that controls the secondary gland that controls the primary gland.

Let's look at some examples:

Primary hypothyroidism results from a diseased thyroid gland underproducing thyroid hormone.

Secondary hypothyroidism is caused by a diseased pituitary gland underproducing thyroid-stimulating hormone (TSH). Consequently, the thyroid underproduces thyroid hormone.

Tertiary hypothyroidism begins with a diseased hypothalamus underproducing thyroid-releasing hormone (TRH). Because of this, the pituitary underproduces TSH. As a result, the thyroid underproduces thyroid hormone.

Here are 2 more examples:

Primary hyperaldosteronism results from a diseased adrenal gland overproducing aldosterone. This condition is caused by an aldosterone-secreting tumor or adrenal hyperplasia.

Secondary hyperaldosteronism originates with a diseased kidney overproducing renin. As a consequence, adrenal glands overproduce aldosterone. So, disease is at the level of the kidney: renovascular disease or a renin-secreting tumor.

HYPOTHALAMUS

The hypothalamus sits in the forebrain just below the thalamus and above the pituitary gland. It controls the endocrine function in the body by assessing many bodily and external environmental signals and then using hormones and nerves to output new control signals to the pituitary gland.

Input to the hypothalamus is from the cortex, autonomic nervous system, peripheral endocrine system, and external environment (e.g., temperature and light).

The hypothalamus controls output of the **anterior** pituitary by means of **releasing hormones**, such as CRH and TRH, and inhibiting hormones, such as dopamine. It controls the output of the **posterior** pituitary (i.e., neurohypophysis) by direct **nerve** stimulation.

POSTERIOR PITUITARY GLAND

The pituitary gland is considered the master gland. Functionally, it is composed of the anterior pituitary and the posterior pituitary, which participate in different hormonal axes. Each axis has different positive and negative feedback controls.

It helps to think of the posterior pituitary as an extension of the hypothalamus. The antidiuretic hormone (ADH; a.k.a. vasopressin) and oxytocin synthesized in the hypothalamus are transported and stored in the posterior pituitary. (All other pituitary hormones are made in and secreted by the anterior pituitary gland). The posterior pituitary secretes these hormones in response to nerve stimuli from the hypothalamus.

ADH regulates plasma osmolality. Normal plasma osmolality is 285–295 mOsm/kg (285–295 mmol/kg), and it can be either measured directly or estimated. Be familiar with the formula:

$$\text{Osmolality} = (2 \times [\text{Na}^+]) + (\text{glucose}/18) + (\text{BUN}/2.8)$$

Plasma osmolality is the most important determinant of ADH secretion, and the main effect of ADH is decreasing renal free water excretion in the late distal tubule and cortical collecting duct. Osmoreceptors of the hypothalamus are exquisitely sensitive to small changes in plasma osmolality; small increases in the plasma osmolality sensed in the hypothalamus lead to large increases in ADH secretion, increased renal water retention, and a concentrated urine.

ADH secretion causes the kidneys to conserve water and concentrate the urine (antidiuresis), which prevents hyperosmolarity from getting worse. However, free-water intake is needed to correct hyperosmolarity, even when the urine is maximally concentrated. Hence, high plasma osmolality also stimulates thirst. Thirst produces the needed increase in free-water intake.

The osmotic threshold (i.e., set point) for ADH release is decreased (ADH is released at a lower osmolality) in pregnancy, leading to mild physiologic hyponatremia.

ADH also is released in response to nonosmotic factors; the most potent of these is nausea, which increases ADH levels to several hundred times normal. Other factors that stimulate ADH include pain, medications, lung disorders (including lung cancer), and central nervous system disorders. In these states, ADH impairs free-water excretion, causing hyponatremia—this is termed the syndrome of inappropriate antidiuretic hormone (SIADH). ADH release is also triggered by severely decreased effective arterial blood volume (i.e., true hypovolemia, heart failure, liver cirrhosis).

More on SIADH is in the [Nephrology](#) section.

ANTERIOR PITUITARY GLAND

PREVIEW | REVIEW

- What are the hormones of the anterior pituitary?
- What are the signs and symptoms of a pituitary tumor?
- What is the workup for a pituitary tumor?
- Aside from a prolactinoma, what are the other causes of hyperprolactinemia?
- What is the best initial medical therapy for hyperprolactinemia?
- How do you test for acromegaly?
- Which cancers most commonly metastasize to the pituitary?
- What is the clinical presentation of pituitary apoplexy? What is the treatment?

OVERVIEW

The anterior pituitary produces 6 hormones (and without them, you feel like a **FLAT PiG**):

- 1) Follicle-stimulating hormone (FSH)
- 2) Luteinizing hormone (LH)
- 3) Adrenocorticotropic hormone (ACTH)
- 4) Thyroid-stimulating hormone (TSH)
- 5) Prolactin (PRL)
- 6) Growth hormone (GH)

It secretes these hormones in response to releasing and inhibiting hormones that are made in the hypothalamus and released into the hypophyseal portal system (a specialized portal system that connects the hypothalamus with the anterior pituitary).

The anterior pituitary hormones are controlled by both positive and negative feedback. High plasma hormone levels inhibit hormone production, and low plasma hormone levels stimulate hormone production. This feedback system is termed the hypothalamus-pituitary-target gland axis.

With positive feedback, low hormone levels cause the hypothalamus to produce releasing hormones (e.g., TRH, corticotropin-releasing hormone [CRH]) that induce pituitary hormone secretion (e.g., TSH, ACTH), which, in turn, stimulates target gland hormone production (e.g., thyroxine, cortisol).

With negative feedback, higher-than-normal levels of the target gland hormones (e.g., thyroxine, cortisol) inhibit hormone production in both the pituitary and the hypothalamus. The exception to the rule is prolactin, which is continuously inhibited by dopamine from the hypothalamus. When there is a decrease in dopamine, prolactin increases.

ACTH has a **diurnal variation** with a peak at 6 a.m. and a nadir at midnight. ACTH stimulates the adrenal gland to produce corticosteroids and adrenal androgens, and it has a regulatory effect on production of mineralocorticoids. ACTH increases in response to CRH from the hypothalamus and to physical or psychological stresses, and ACTH is suppressed in response to high cortisol levels.

GH is secreted in a **pulsatile fashion** and is regulated by 2 hypothalamic hormones: growth hormone-releasing hormone (GHRH) and somatostatin (a.k.a. growth hormone-inhibiting hormone). GHRH causes release of GH from the pituitary, and somatostatin tonically inhibits release of GH from the pituitary. Note: **Somatostatin** can also **inhibit** the release of TSH from the pituitary, as well as regulate other neuroendocrine cell activity. Because the release of GH is pulsatile, a random GH level is not useful. As a screen for GH excess or deficiency, measure the more stable GH product, insulinlike growth factor 1 (IGF-1).

LH and FSH regulate sex hormone production. LH and FSH production is regulated by **pulsatile secretion** of gonadotropin-releasing hormone (GnRH) from the hypothalamus. **Inhibin**, produced in the ovary and testis, inhibits **only FSH** secretion.

PRL is different from the other hormones because it is under **tonic inhibition** by hypothalamic dopamine sent down the pituitary stalk. This is an important concept because stalk compression is a cause of **hyperprolactinemia**.

TSH secretion is stimulated by hypothalamic TRH and inhibited by thyroid hormone and **somatostatin**. When thyroid hormone levels are high (i.e., primary hyperthyroidism), TSH levels will be low.

PITUITARY TUMORS

Pituitary tumors can present with symptoms of hormonal hypersecretion, hypopituitarism, and vision loss. They can also be detected as an incidental finding (after imaging of the brain for unrelated symptomatic complaints, such as headache). These are sometimes called incidentalomas. Pituitary tumors are due to the abnormal proliferation of cells of the anterior pituitary.

The **1st step in evaluating** a pituitary tumor is to determine if it is **functional** (secreting hormones). The **2nd step** is to determine if it is causing a **mass effect** leading to anterior pituitary hormone hyposecretion or to vision loss. The size of the tumor determines the evaluation process. A pituitary adenoma > 1.0 cm (macroadenoma) is evaluated for hormonal **hypersecretion**, **hyposecretion**, and vision loss, and those < 1.0 cm (microadenoma) are evaluated only for **hypersecretion** as they are generally not large enough to cause hormone **hyposecretion** or vision loss.

Clinical presentation depends on the type of adenoma:

- **Lactotrophs (prolactinomas):** hyperprolactinemia, resulting in amenorrhea and galactorrhea in women, hypogonadism in men, and infertility in both; the most common **functioning** adenoma

- **Gonadotrophs:** most are clinically silent until they become macroadenomas and cause mass effect and/or pituitary hypofunction; the most common **non-functioning** adenoma
- **Thyrotrophs (TSHoma):** hypersecretion of TSH, resulting in hyperthyroidism; least common adenoma (Labs show a normal/high TSH and high free T₄ [FT₄].)
- **Somatotrophs:** hypersecretion of GH, resulting in acromegaly (best screen = IGF-1)
- **Corticotrophs:** hypersecretion of ACTH, resulting in Cushing disease
- **Mixed cell type:** most often combines somatotrophs + lactotrophs, called **somatomammotrophs**, with cosecretion of both GH and prolactin

Remember: Mixed cell type tumors exist; therefore, it is important to always check a prolactin level in somatotroph tumors and IGF-1 in lactotroph tumors because prolactin- and GH-producing cells are from a common cell line.

Typical mass effect symptoms include headaches, diplopia, or visual field defects (e.g., bitemporal hemianopsia). Less commonly, adenomas can extend and cause CSF rhinorrhea.

Acute hemorrhage into an adenoma causes **apoplexy**, manifesting as acute severe headache, nausea, vomiting, vision impairment and loss, and altered mental status. This is an **endocrine emergency** and requires immediate **corticosteroids** and a neurosurgical consult. Although all types of pituitary hormonal deficiencies can occur, only the sudden loss of ACTH production is life threatening; it stops cortisol production and precipitates an adrenal crisis, which can rapidly progress to shock.

Suspect a pituitary adenoma when a patient presents with multiple hormone abnormalities or a mixture of symptoms, such as low libido, weight loss, anorexia, weakness, and (in women) amenorrhea.

When interpreting FSH and LH levels, always consider whether the levels are appropriate for the reproductive stage of the female (pre- vs. postmenopausal). For example, if a postmenopausal female patient has low or inappropriately normal FSH and LH levels, there is a gonadotropin deficiency. (Remember: Postmenopausal women should have an elevated FSH level, so a normal level is **inappropriately normal**).

Diagnosis: MRI is the imaging of choice for the tumor. When a patient presents with an incidental pituitary tumor, the size of the tumor determines biochemical evaluation.

If < 1 cm, check the following for **hypersecretion**:

- Prolactin level
- IGF-1 to screen for GH excess
- TSH and FT₄ (TSH helps in evaluation if FT₄ is high.)
- Screen for cortisol excess with:
 - 24-hour urine free cortisol,
 - low-dose (1 mg) overnight dexamethasone suppression test, **or**
 - midnight salivary cortisol.
- LH, FSH, and α subunit tests are generally not done.

If > 1 cm, do formal **visual field** testing and check for both **hypersecretion** (with these same tests) and **hyposecretion**. To work up for hyposecretion, do the following:

- ACTH stimulation test (screening for cortisol deficiency)
- LH and FSH in postmenopausal women (both are normally high) and testosterone in men to screen for hypogonadism
- IGF-1 to screen for GH deficiency
- TSH and FT_4 (TSH helps in evaluation if FT_4 is low.)
- In premenopausal women, ask about changes in menses. A regular menstrual cycle off OCPs excludes gonadotrophin deficiency.

If the hormone labs are normal, the tumor is nonfunctional and is likely a gonadotroph tumor that is inefficient in making the active hormone β subunit.

Remember: Gonadotropins (LH and FSH), TSH, and human chorionic gonadotrophin (hCG) have an α and a β subunit. The β makes it unique, whereas α subunits are just inactive glycoprotein. Finding high levels of α subunits supports a diagnosis of **gonadotroph or nonfunctional tumor**.

If the tumor is nonfunctional, it does not impinge on the optic nerve or chiasm, and there is no hypersecretion of hormones, then the tumor can be reimaged in about 6 months if it's a macroadenoma or in 1 year if it's a microadenoma. If there is no change in size, then repeat yearly for macroadenomas, and for microadenomas repeat every 1-2 years for the following 3 years.

Indications for surgical removal of a pituitary tumor include:

- visual field or other ophthalmologic defects,
- a lesion in or abutting the optic chiasm or compressing the optic nerve,
- apoplexy, or
- hypersecretion of ACTH, GH, or TSH.

Prolactinomas have their own criteria for surgical removal, which we will cover in **Hyperprolactinemia and Prolactinomas**.

On MRI, other sellar masses can be seen, including craniopharyngiomas, which often present as calcified cystic suprasellar lesions. They are considered benign, but they can cause symptoms secondary to mass effect and impingement on the optic nerve.

Radiologists may occasionally report an "empty sella," which is a description of an imaging finding and not a diagnosis, because the majority of people have normal hormonal function. In empty sella, the pituitary has been displaced and squished by CSF but still **functions normally**; it has been described in **multiparous women**. No treatment is needed for empty sella syndrome if there are no associated hormone deficiencies.

Hyperprolactinemia and Prolactinomas

A serum PRL concentration that is repeatedly elevated (> 20 ng/mL) is termed hyperprolactinemia. This is the most frequent functional abnormality of the pituitary gland.

When hyperprolactinemia is not caused by a prolactinoma, prolactin levels are generally < 200 ng/mL.

Nonprolactinoma causes of hyperprolactinemia:

- Drugs that are dopamine antagonists; i.e., certain antipsychotics (e.g., phenothiazines, haloperidol, risperidone), metoclopramide, and verapamil
- Diseases of the hypothalamus and/or pituitary stalk that interfere with production or transport of dopamine, thus removing the negative inhibition on prolactin production (e.g., sarcoidosis, stalk compression, and trauma). Stalk compression is when a pituitary tumor pushes on the stalk and interferes with transport of dopamine.
- Pregnancy or estrogen use. Pregnancy is the most common cause of physiologic hyperprolactinemia.
- Nipple stimulation (e.g., due to lactation)
- Orgasm: Recommend patients abstain from sexual intercourse for 24 hours prior to test.
- Chest wall injuries, including skin lesions (e.g., piercing, herpes zoster)
- Hypothyroidism (Always check a TSH.)
- Chronic kidney disease

Prolactinoma is the most common functional pituitary tumor. Prolactinomas are usually < 1 cm (**microadenomas**), but they can also be **macroadenomas** causing visual field defects. PRL levels generally correlate with tumor size (> 100 ng/mL for macroadenomas). **Elevated PRL** level inhibits the release of GnRH, **decreasing LH** and **FSH**. Therefore, hyperprolactinemia of any cause results in hypogonadism and erectile dysfunction in men and amenorrhea and galactorrhea in women.

If you see a macroadenoma with only mild hyperprolactinemia (prolactin < 100 ng/mL), then it is not a prolactinoma—the prolactin elevation is likely due to pituitary stalk compression. In this case, dopamine delivery to the lactotrophs is impaired, removing the tonic inhibition of prolactin production.

Note: Watch for the following pitfall in the lab! A markedly elevated prolactin can be masked (falsely low) due to a lab artifact called the "hook effect." If the tumor is ≥ 1 cm and the PRL level is < 100 ng/mL, check a diluted prolactin test before diagnosing stalk effect.

Due to amenorrhea, prolactinomas are diagnosed earlier in women than in men. Decreased libido is the earliest symptom of a prolactinoma in males but is often ignored, so men tend to present later and with larger masses and visual field defects. Galactorrhea occurs in most women with prolactinomas but rarely in men. **Longstanding hypogonadism** is associated with decreased skeletal bone mineralization in both men and women.

Management options for prolactinomas include medical treatment, surgical resection, and observation. Indications for medical or surgical treatment include:

- Tumor size > 1 cm
- Hypogonadal symptoms (e.g., amenorrhea, infertility, erectile dysfunction)
- Galactorrhea affecting the patient's quality of life
- Women with impaired fertility

Always check TSH and pregnancy test (in women) before deciding to treat.

Microadenomas usually do not grow to > 1 cm, so observation alone can be an appropriate option for certain groups: postmenopausal women, premenopausal women who do not desire fertility and do not have or are not troubled by galactorrhea, and men who are not interested in fertility. Conservative management should include estrogen replacement in premenopausal women (oral contraceptive pills [OCs]), testosterone replacement in men, and observation in postmenopausal women. Follow with serial MRIs and prolactin levels to assess any change in size. Stable prolactin levels predict a stable tumor size.

Prolactinomas are extremely sensitive and responsive to medical treatment. For most patients, treatment with dopamine agonists is the best initial option. Dopamine agonists decrease both the PRL level and tumor size. Cabergoline is 1st line because of its efficacy and safety profile. Cabergoline can cause increased cardiac valvulopathy when administered at a very high dosage, as in the treatment of Parkinson's. Cabergoline is contraindicated in patients with known lung, heart valve, and retroperitoneal fibrotic disease. Bromocriptine is the 2nd line agent; it causes more nausea and orthostatic hypotension than cabergoline.

Transsphenoidal surgery is only used when the patient cannot tolerate drug therapy, or when it is ineffective. Postoperatively, an elevated PRL level is indicative of persistent or recurrent disease, particularly in the case of macroadenomas. Radiation is usually reserved for post-surgical cases to eradicate any remaining tumor.

When a woman on drug therapy for a prolactinoma becomes pregnant, stop the medication and monitor clinically for symptoms, physical exam, and visual field testing. Do not check prolactin levels; they are expected to increase with pregnancy. About 1/3 of macroadenomas enlarge during pregnancy; however, a normal pituitary also enlarges during pregnancy. MRI is only recommended if there is clinical evidence of growth, such as new headaches or visual field changes. If the tumor enlarges enough to cause symptoms, cabergoline or bromocriptine can be restarted. If vision is threatened, surgery is a therapeutic option. Both bromocriptine and cabergoline appear to be safe in early pregnancy, but data on fetal effects with long-term exposure are limited.

Acromegaly

Growth hormone (GH) is required for normal growth. GH production is suppressed by hyperglycemia and somatostatin and is stimulated by hypoglycemia.

When excess GH presents in childhood before growth plates are closed, it is termed gigantism. When it occurs in adulthood, it is termed acromegaly because the growth plates are closed; there is not excessive linear growth, but there is acral growth (i.e., hands, feet).

> 99% of acromegaly cases are due to a benign, well-defined adenoma, which is recognized on CT or MRI. Affected patients typically become symptomatic in their late 30s to mid 40s. Signs and symptoms of acromegaly include:

- Enlarging hands and feet
- Coarsening of the facial features
- Deepening of the voice
- Carpal tunnel syndrome, often bilateral
- Acanthosis nigricans
- Skin tags
- Pronounced jaw growth (which leads to multiple dental problems)
- Excessive sweating, body odor

Acromegaly has an insidious onset associated with an increased mortality when untreated. The most important long-term problem associated with acromegaly is cardiovascular disease. Patients have increased risk of:

- Ischemic heart disease
- Cardiomyopathy
- Diastolic dysfunction
- Hypertension
- Left ventricular hypertrophy
- Stroke

Acromegaly is also associated with obstructive sleep apnea, insulin resistance/diabetes mellitus, colon polyps, and colorectal cancer.

Screen for acromegaly by checking an IGF-1 level. Do not order a random GH level because a single value of GH is not useful in diagnosing acromegaly; its secretion is pulsatile, and levels in the blood can vary greatly in a healthy individual. IGF-1 is produced by the liver and mediates the growth-promoting effect of GH. Unlike GH, IGF-1 levels are stable throughout the day. A normal age-adjusted IGF-1 level almost always excludes the diagnosis of acromegaly. If the IGF-1 level is elevated, confirm the diagnosis by demonstrating a failure of GH to suppress after a 75-g oral glucose load (via an oral glucose tolerance test [OGTT]). A post-OGTT GH level > 1 ng/mL (1 µg/L) is diagnostic of acromegaly. Also check prolactin levels (elevated due to cosecretion in 25% of GH tumors). If the tumor is > 1 cm, check for visual field deficits and for other hormonal deficiencies.

Order a screening colonoscopy and echocardiogram on all patients diagnosed with acromegaly, regardless of age.

Treat all patients with transsphenoidal surgery, even if they are asymptomatic. Some experts recommend medical therapy with somatostatin analogs as initial therapy prior to surgery for a better chance for a cure and possibly safer intubation.

Radiation is used as initial therapy only in poor surgical candidates.

Medical treatment may be used as adjuvant therapy in patients with residual tumor after surgical resection and in poor surgical candidates. Options include somatostatin analogs (e.g., octreotide) +/- dopamine agonists (e.g., cabergoline or bromocriptine), and GH receptor antagonists (i.e., pegvisomant).

Other Pituitary Tumors

We mentioned **gonadotroph adenomas** under **Pituitary Tumors** on page 1-3. Recall that they are the most common type of nonfunctioning adenomas, usually macroadenomas. Gonadotroph tumors can present variably:

- Incidentally on imaging and hormonally silent
- Mass effect and hormonally silent
- Mass effect with symptoms of hypogonadism/partial panhypopituitarism
- Mass effect with symptoms of gonadotropin excess (very, very rare)

A diagnosis of gonadotroph adenoma is usually supported by finding an increase in free α subunits (inactive) or rarely, high levels of FSH and/or LH.

Transsphenoidal surgery is indicated for **symptomatic** nonfunctioning or functional gonadotroph adenomas.

For asymptomatic patients with preserved endocrine function and a normal visual field assessment, observation with serial imaging studies is appropriate.

Radiation is an option for certain types of tumors but primarily is used postsurgically to contain residual tumor mass. Patients who have had pituitary radiation need life-long monitoring of anterior pituitary function for adrenal insufficiency and secondary hypothyroidism.

Pituitary hyperplasia is expected in **pregnancy** and can mimic a pituitary tumor if imaging is done (for more on pituitary adenoma during pregnancy, see the **Women's and Men's Health** section). **Severe primary hypothyroidism** (disease of the thyroid gland) can also cause pituitary hyperplasia as the pituitary thyrotrophs become hyperplastic from the over demand for TSH; imaging shows a pituitary mass. Clinically, the patient is hypothyroid; biochemically, the FT_4 is low and the TRH and the TSH are high. The elevated TRH suppresses dopamine, causing an increase in PRL; thus, the patient can be mistakenly diagnosed with a prolactinoma. Treatment with thyroxine replacement causes the thyrotrophs to shrink and PRL levels to normalize.

Metastatic cancer can be seen in the pituitary; the posterior part of the gland is most often involved. These metastases can present as isolated central **diabetes insipidus** (DI; absent or deficient ADH production). Breast and lung cancer metastases are most common. Infiltrative diseases, such as sarcoidosis, can also cause isolated DI. Lymphoma and leukemia can present as primary cancer of the pituitary.

Acquired Hypopituitarism

Pituitary apoplexy is a **neurosurgical emergency** caused by hemorrhage into a pituitary mass, usually an adenoma. Suspect apoplexy in the patient who presents with severe headache, N/V, diplopia, +/- altered mental status. Symptoms can begin suddenly ("mule kick in the head" or "the worst headache of my life") or can develop over 1-2 days. Diabetes with microvasculature changes, radiation therapy, and current warfarin use are risk factors. The patient's history may include indications or a diagnosis of an adenoma causing hormone excess or deficiency.

Pituitary hormones are abnormal in apoplexy. Apoplexy causes hypopituitarism, which can cause a decrease in all the pituitary hormones, the most life-threatening of which is ACTH. No ACTH means no cortisol (i.e., secondary adrenal insufficiency), shock, and death. Apoplexy can be difficult to distinguish from subarachnoid hemorrhage (SAH) occurring in the same area; however, in SAH, pituitary hormones are normal.

Suspect pituitary apoplexy when the patient has the acute symptoms mentioned above; the diagnosis is confirmed by finding a dense pituitary mass on CT or MRI. Test pituitary hormones (remember: the most critical one is ACTH), along with a cortisol level. Again, urgent recognition and treatment of secondary adrenal insufficiency is necessary to prevent life-threatening hypotension.

Treatment: If the symptoms are mild, only corticosteroids are necessary. Edema can cause a mass effect and require emergent decompression. Consult a neurosurgeon to make the call on whether to use corticosteroids alone or take the patient to surgery.

Sheehan syndrome (1/10,000 deliveries) is **postpartum** hypopituitarism. It always involves the anterior pituitary and sometimes also affects the posterior pituitary, but it rarely causes central diabetes insipidus (i.e., low ADH from posterior pituitary).

Severe cases can manifest with symptoms of adrenal insufficiency and/or hypothyroidism (e.g., weakness, lethargy, anorexia, hypotension).

Sheehan syndrome results from hypovolemic shock following severe obstetrical bleeding that causes necrosis of the enlarged anterior pituitary of pregnancy. This classic form of Sheehan syndrome nowadays occurs rarely in medical resource-rich countries. Instead, patients may present with failure to lactate, postpartum amenorrhea, or **chronic** hypopituitarism.

Acute postpartum hypopituitarism may indicate underlying unsuspected pituitary disease, e.g., autoimmune hypophysitis with resulting cortisol deficiency, growth hormone deficiency, and hypoglycemia (especially seen with growth hormone deficiency). Confirm cortisol deficiency by measuring the serum cortisol level. Hypoglycemia can also be due to the sudden increase in insulin sensitivity that occurs immediately postpartum.

Treat all causes of acute hypopituitarism emergently with high doses of hydrocortisone as well as IV glucose as needed to correct any hypoglycemia. If the patient is hypothyroid, delay thyroid therapy until the patient has been stabilized with hydrocortisone. Treating with thyroid hormone first can precipitate an adrenal crisis.

Other causes of hypopituitarism include pituitary and parasellar tumors, radiation, infections, inflammation, and infiltrative processes, such as sarcoidosis, hemochromatosis, and histiocytosis X.

Remember: If one anterior pituitary hormonal deficiency is found (independent of the etiology), all other anterior pituitary hormones should be assessed for concomitant deficiencies.

DIABETES INSIPIDUS (DI)

PREVIEW | REVIEW

- What happens to the urine osmolality and serum Na^+ during water deprivation in a patient with diabetes insipidus?

DI occurs when the kidneys are unable to retain **free water**, causing a dilute urine despite progressively increasing plasma osmolality. It is characterized by thirst (with polydipsia) and the production of large volumes of dilute urine (usually $> 3 \text{ L/day}$). Serum Na^+ is normal if the patient has access to water, but hypernatremia occurs if access to water is limited. Nocturia typically is the 1st symptom of DI. Volume depletion rarely occurs, as long as there is an intact thirst mechanism and patients have access to water. Infants, nursing home patients, and those who are unconscious are vulnerable to these complications.

DI can be **central** (decreased ADH **production**) or **nephrogenic** (renal **resistance** to the effect of ADH).

Neurogenic DI (a.k.a. central DI) is either acquired or congenital. Acquired central DI occurs when there is disease or damage to the posterior pituitary. It can be caused by brain cancer or metastases, trauma, neurosurgery, or systemic infiltrative diseases (e.g., eosinophilic granuloma, sarcoidosis, granulomatosis with polyangiitis).

Figure 1-1 shows what's going on with ADH and plasma osmolality in central DI. Normally, as plasma osmolality increases (e.g., when there is lack of access to water),

plasma ADH increases. In central DI, plasma ADH does not increase with rising plasma osmolality. The kidneys do not get the signal (ADH) to conserve water, urine osmolality stays low, and, unless the patient drinks, hypernatremia will get worse.

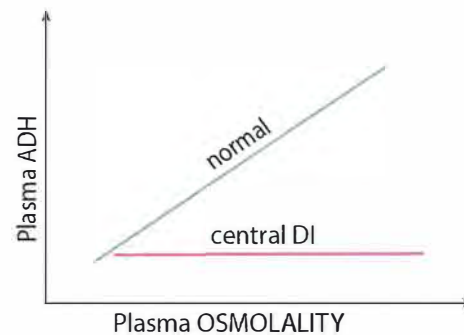


Figure 1-1: Central DI

Nephrogenic DI (a.k.a. ADH-resistant DI) can be acquired or due to gene mutations in the ADH receptor or in an aquaporin. (Aquaporins are transmembrane proteins that increase water permeability of the renal collecting tubule in response to ADH.) **Important causes of acquired nephrogenic DI:**

- Drugs (especially **lithium**)
- Hypercalcemia (serum $\text{Ca}^{2+} > 11 \text{ mg/dL}$ [2.75 mmol/L])
- Chronic hypokalemia (serum $\text{K}^+ < 3 \text{ mEq/L}$ [3 mmol/L])
- Intrinsic renal disease (especially **Sjögren syndrome**)

Figure 1-2 illustrates the pathogenesis of nephrogenic DI. Normally, as plasma ADH rises in response to rising plasma osmolality, ADH acts on the kidneys to increase urine osmolality. High urine osmolality means high renal water reabsorption, which helps correct the hypernatremia. With **nephrogenic DI**, ADH increases appropriately; however, the kidney does not respond, and the urine osmolality remains low.

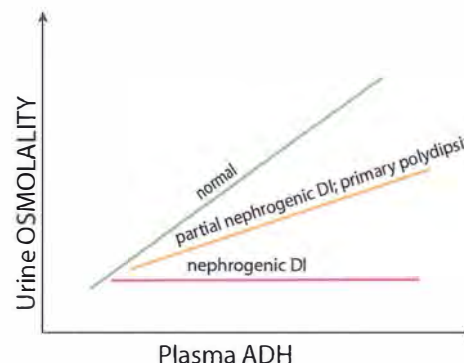


Figure 1-2: Nephrogenic DI

Both central and nephrogenic DI can be complete or partial. In partial central DI, the ADH release in response to hyperosmolality is present but inadequate. In partial nephrogenic DI, there is a blunted renal response to the effects of ADH. In both cases, disease is milder than in the complete forms.

Diagnose central vs. nephrogenic DI with the **water restriction test**. This test ideally should be done in the hospital; it can be done in the office only when there is access to phlebotomy and quick turnaround on lab results.

Note: Do **not** restrict water if the serum Na^+ is already high ($> 145 \text{ mEq/L}$ [145 mmol/L])! These patients have already self-restricted; measure plasma and urine osmolality and skip to desmopressin administration.

If serum Na^+ is **not** already high, the first step is to restrict water/fluid intake. Then measure the urine osmolality, plasma osmolality, and serum Na^+ every 2 hours. If the urine osmolality rises to $> 600 \text{ mOsm/L}$ (600 mmol/kg), you are done: the patient does not have DI, so there is no need to give desmopressin. If the urine osmolality remains $< 600 \text{ mOsm/L}$, wait until the serum Na^+ rises to $144\text{--}145 \text{ mEq/L}$, then give desmopressin (i.e., synthetic ADH). Assess the renal response to desmopressin by measuring the urine osmolality every 30 minutes for 2 hours.

When interpreting the results of the water restriction test, refer to [Figure 1-1 on page 1-7](#) and [Figure 1-2 on page 1-7](#).

In central DI, ADH does not increase in response to a rising plasma osmolality, so the urine osmolality remains low (i.e., the urine remains dilute). However, the kidneys respond normally to exogenous desmopressin with an increase in urine osmolality. Therefore, diagnose central DI when the urine does not concentrate with water deprivation but **does** concentrate after desmopressin administration.

In nephrogenic DI, exogenous desmopressin has no (or little) effect. So, diagnose nephrogenic DI if the urine does **not** concentrate with water restriction or desmopressin administration.

Primary polydipsia (a.k.a. psychogenic polydipsia) mimics DI; consider it in patients with polydipsia and polyuria +/- psychiatric illness. The water restriction test quickly differentiates psychogenic polydipsia from DI because patients with psychogenic polydipsia concentrate the urine normally with water restriction. Also, psychogenic polydipsia patients will never have hypernatremia; in fact, they are at risk for hyponatremia due to excessive water ingestion.

Treat **central** DI with either subcutaneous or intranasal **desmopressin**, a synthetic vasopressin analog. Desmopressin effectively reduces polyuria and

nocturia. Because the kidneys immediately respond to ADH, giving desmopressin results in a quick increase of the urine concentration and reduction in urine output. The intranasal preparation is more potent than the oral; injectable is the most potent. Be careful to titrate the dose properly and counsel the patient to drink only when thirsty because hyponatremia can easily occur (i.e., drug-induced SIADH). **Mild** cases of partial central DI can occasionally be managed with an oral drug that stimulates ADH (e.g., chlorpromazine, carbamazepine) or with thiazides and salt restriction, but desmopressin acetate (DDAVP) is preferred.

In **nephrogenic** DI, the urine is persistently dilute, even when ADH is high. Giving desmopressin does not increase the concentration of the urine. Treat nephrogenic DI with a low-solute diet first, then add thiazide diuretics or amiloride if needed. NSAIDs are used to treat rare hereditary forms.

Note: In central DI, if the thirst center and ADH osmoreceptors are damaged, which can occur with a hypothalamic lesion (e.g., craniopharyngioma), the patient can have recurrent hypernatremic dehydration without thirst (adipsic hypernatremia). These patients are often very difficult to treat.

Remember: **DI** typically presents as polyuria/polydipsia, with or without **hypernatremia**, with normal volume status. SIADH usually presents as **hyponatremia**, also with normal volume status.

SIADH

PREVIEW | REVIEW

- What are the urine osmolality, urine Na^+ , serum Na^+ , and serum osmolality in a patient with syndrome of inappropriate secretion of antidiuretic hormone?

The syndrome of inappropriate secretion of antidiuretic hormone (**SIADH**) is sometimes idiopathic but may be caused by CNS trauma or infection, pulmonary disease, drugs, and ectopic hormone production, especially with **small cell lung cancer**.

These patients have hyponatremia with normal volume status. High ADH causes renal free-water reabsorption, which lowers **serum** osmolality. Urine osmolality is inappropriately high, and urine Na^+ concentration is also **high**. Remember to always rule out hypothyroidism and adrenal insufficiency, because these can present similarly to SIADH.

Treat SIADH with fluid restriction.

See the [Nephrology](#) section for further discussion of SIADH.

THYROID GLAND

PREVIEW | REVIEW

- What is the 1st screening test of choice for hyper- and hypothyroidism?
- What is the difference between the thyroid uptake and the thyroid scan? What do the different tests tell you?
- What are common signs and symptoms of hypothyroidism? Lab tests?
- How do you make a diagnosis of secondary or tertiary hypothyroidism?
- What are the risks of overtreating hypothyroidism?
- What are signs and symptoms of myxedema coma?
- What is the treatment for myxedema coma?
- What is apathetic hyperthyroidism?
- What specific physical findings confirm the diagnosis of Graves disease?
- What is the result of the thyroid uptake and scan in a patient with Graves'?
- What are side effects of medications used to treat Graves'?
- What are the precipitating events leading to thyroid storm?
- In addition to propylthiouracil or methimazole, β -blockers, and iodine, which other drug is given to patients to treat thyroid storm?
- What is the presumptive cause of subacute thyroiditis?
- What are the results of the thyroid uptake in patients with thyroiditis (all causes)?
- In which situations is it appropriate to check a sick patient's thyroid function?
- Workup of which nodule—a hot or cold one—can cease after the uptake and scan test?
- Which cold nodules do not require biopsy?
- List some characteristics associated with malignant nodules.
- What are the 4 histologic types of thyroid cancer? Which is the most aggressive?
- Which type is the most common thyroid cancer?
- What is the hormone released by medullary thyroid cancer?
- Multiple endocrine neoplasia 2A (MEN2A) and MEN2B are associated with which histologic type of thyroid cancer?
- Thyroid lymphoma is associated with which autoimmune disease?

NORMAL PHYSIOLOGY

TRH is made and secreted by the **hypothalamus**, which stimulates the **anterior pituitary** to make and secrete TSH, which in turn stimulates formation and secretion of thyroid hormone by the **thyroid gland**. The majority of the thyroid hormone produced is thyroxine (T_4), but it does make a small amount of triiodothyronine (T_3). T_3 is considered the more active hormone, and the majority is produced locally by deiodination of T_4 in the peripheral tissues. T_4 binds very tightly to TBG (thyroxine-binding globulin) and weakly to albumin. T_3 also binds to these proteins but not as strongly. Only a very small fraction of the total T_4 and total T_3 is unbound and, therefore, free and active (i.e., FT_4 , FT_3). The FT_4 free component (in addition to the TSH) is generally the fraction that you want to measure when testing for thyroid disorders.

The activity of the thyroid gland is regulated by a negative feedback process in which the serum levels of T_4 and T_3 stimulate or inhibit TRH production by the hypothalamus (Figure 1-3).

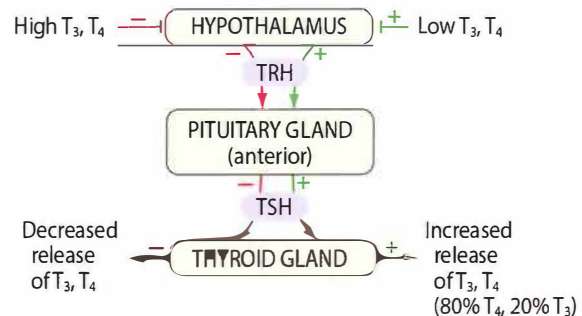


Figure 1-3: HTH-pituitary-thyroid axis

THYROID FUNCTION TESTS

Thyroid **function** tests (TFTs) include TSH, FT_4 , and sometimes FT_3 . The FT_4 assay has replaced the T_3 resin uptake test.

When screening for primary thyroid disease, start with a **TSH** to detect abnormalities of thyroid function—both **hyper-** and **hypothyroidism**. If the TSH is high, then order a FT_4 to assess for hypothyroidism. If the TSH is low, then order a FT_4 to assess for hyperthyroidism (Table 1-1 on page 1-10). Remember that 80% of the thyroid hormone production by the thyroid is T_4 whereas the majority of T_3 is production is by extrathyroidal deiodination of T_4 peripherally. Note: If the patient is being treated with a thyroid axis altering drug (thioamides or thyroid hormone), the pituitary hormone (TSH) may have some delay in returning to physiological levels compared to the thyroid hormones (T_3 and T_4).

During the 1st trimester of pregnancy, you can expect a physiological TSH drop due to elevation in hCG (remember, they both have a common α subunit so HCG can stimulate the receptor). Do **not** confuse this with hyperthyroidism! As a rule of thumb, the lower limit of normal TSH in pregnancy is $0.1 \times$ the trimester of pregnancy (1st trimester is 0.1 mU/L; 2nd trimester is 0.2; 3rd trimester is 0.3).

Table 1-1: Overview of Thyroid Function Tests		
TSH	FT ₄	Diagnosis
High	Low	Primary hypothyroidism
	Normal	Subclinical hypothyroidism
	High	Pituitary (secondary; TSH-induced) hyperthyroidism Thyroid hormone resistance syndromes
Low	High	Primary hyperthyroidism Subacute or silent thyroiditis
	Normal	Subclinical hyperthyroidism Euthyroid sick syndrome
	Low	Pituitary (secondary) hypothyroidism Severe euthyroid sick syndrome

OTHER THYROID TESTS

Uptake and Scan

If primary hyperthyroidism is diagnosed (with a low TSH and high FT₄), the next step is to determine its cause. Two tests, the radioactive iodine uptake (RAIU) and **thyroid scan** (also called “scintigraphy”), help to establish a diagnosis by measuring the degree and pattern of iodine uptake by the thyroid. In clinical practice, these tests are often referred to as “the thyroid uptake and scan,” but recognize these are 2 different tests (the uptake; the scan). The RAIU measures the degree of iodine uptake (given as a percent uptake) by the thyroid. The scintigraphy scan assesses the pattern of iodine uptake (takes a “picture”), showing a diffuse, focal, or multifocal distribution.

RAIU: The patient is given a small dose of radioactive iodine; and then later, a radiation detector over the thyroid determines the percentage of the dose that was taken up by the gland. Know the uptake results (**high**, **low**, or **normal**) for various causes of thyroid disease.

RAIU is **increased** in:

- Graves disease
- TSH-secreting pituitary tumor
- Hot nodules (solitary or toxic multinodular goiter [MNG]), if hot enough
- High hCG states, such as an hCG-secreting tumor and gestational thyrotoxicosis (due to the hCG activating the TSH receptor)
- Iodine deficiency

RAIU is **decreased** in:

- Thyroiditis (“dumping” of thyroid hormone)
- Excess exogenous T₄ or T₃
- Iodine excess (e.g., contrast dye, diet, amiodarone)
- Factitious hyperthyroidism

Thyroid scan (scintigraphy): The patient is given a dose of technetium-99m or radioactive iodine and a scintillation scanner produces a rough **picture** indicating how these isotopes localize in the thyroid (**Figure 1-4**). The scan gives information on the size, shape, and overall activity of the gland and shows **hot** (hyperfunctioning) and **cold** (underfunctioning) spots. In Graves’, the scan shows diffuse increased uptake, in a hot nodule it’s local.

The thyroid RAIU and scintigraphy scan are essential in determining the cause of **hyperthyroidism** and are **never** used in the workup of a **hypothyroid** or **euthyroid** patient. Thyroid scintigraphy can be used in the evaluation of thyroid nodules, but only if the TSH is low (If the TSH is normal, then ultrasound is the best way to determine if a thyroid nodule biopsy is needed.) Hyperfunctioning (hot) nodules are rarely malignant and do not require biopsy.

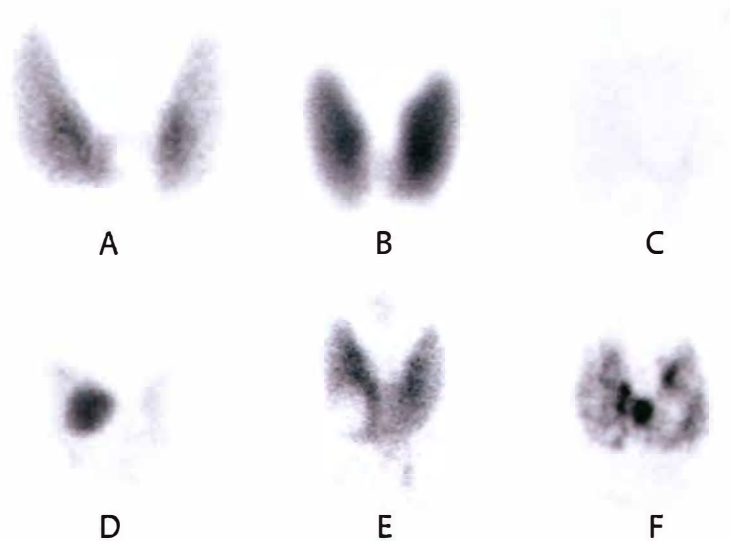


Figure 1-4: Thyroid scintigraphy (i.e., thyroid scan). (A) Normal thyroid: normal diffuse uptake. (B) Graves disease: diffusely increased uptake. (C) Painless thyroiditis: very low uptake. (D) Hot (autonomous) nodule: discrete area of increased uptake, sometimes with suppression of the surrounding gland. (E) Cold (nonfunctioning) nodule: area of reduced or absent uptake. (F) Toxic multinodular goiter: several areas of increased uptake.

Ultrasound

Thyroid ultrasound (U/S) is used to:

- Determine the size and **number** of nodules.
- Determine whether a nodule is **cystic or solid**.
- Stratify a nodule's malignancy **risk** by U/S characteristics (low, medium, or high).
- Localize a nodule for fine needle aspiration.
- Follow up a nodule's size over time.
- Follow up in a patient after thyroid cancer resection.

When a patient presents with a **palpable nodule** and is **hyperthyroid**, an RAIU and scintigraphy should always precede a thyroid U/S. If the palpable nodule is "hot" (functional), then no biopsy is needed; consider radioactive iodine (^{131}I) therapy. When a patient presents with a **palpable nodule** and is **hypothyroid** or **euthyroid**, the next step in the workup is to go directly to U/S to see if the nodule meets criteria for a biopsy. This is discussed further under **Nodule Workup on page 1-17**.

Biopsy

Fine needle aspiration (FNA) is a biopsy method used to evaluate a thyroid nodule (also discussed under **Nodule Workup on page 1-17**) and results dictate the next step.

HYPOTHYROIDISM

Findings

Symptoms of hypothyroidism are nonspecific but include:

- Cold intolerance
- Weight gain
- Fatigue
- Menstrual irregularities; infertility
- Mental slowness and concentration issues
- Depressed mood
- Constipation
- Puffiness in the face
- Extremity swelling
- Hoarseness
- Coarse hair/alopecia
- Brittle nails
- Dry skin
- Decreased tolerance to exercise
- Carpal tunnel syndrome

Signs on physical exam include:

- Goiter
- Cool/pale skin
- Coarse hair
- Periorbital and nonpitting edema
- Tongue enlargement (severe cases)
- Bradycardia
- Delayed reflexes

In addition to a high TSH and a low FT_4 , abnormal labs/studies include:

- Hyponatremia (euvolemic)
- Macrocytic anemia
- Hyperlipidemia (increased total cholesterol and LDL)
- Pericardial effusion on echocardiograms (rare)
- Increased prolactin level

Hypothyroidism is a cause of hyperprolactinemia, amenorrhea and galactorrhea. If a woman has an elevated prolactin and amenorrhea, check thyroid function after confirming that she is not pregnant. If symptoms are due to hypothyroidism, the elevated prolactin, amenorrhea, and galactorrhea resolves with thyroxine treatment.

Diagnosis of Hypothyroidism

The best screening test for hypothyroidism is the TSH, which is elevated. Add an FT_4 if secondary (pituitary) or tertiary (hypothalamic) hypothyroidism is suspected:

- High TSH and low FT_4 = primary hypothyroidism.
- High TSH and normal FT_4 = "subclinical" hypothyroidism.
- Low or inappropriately normal TSH and low FT_4 = secondary (problem with pituitary) or tertiary (problem with hypothalamus) hypothyroidism or euthyroid sick syndrome.

Our understanding of **subclinical hypothyroidism** is still evolving. We know TSH normally drifts up with age. Patients with TSH 5-10 mU/L (mildly elevated) develop overt hypothyroidism at a rate of about 4% per year, which is low, so not everybody needs to be treated. A family history of autoimmune thyroid disease and positive anti-thyroid peroxidase (**anti-TPO**) antibodies are risk factors for subclinical disease.

Low or inappropriately normal TSH with a low normal FT_4 is secondary or tertiary hypothyroidism except in hospitalized, sick patients who may have euthyroid sick syndrome. (See **Euthyroid Sick Syndrome on page 1-16**.) Less than 1% of those with hypothyroidism have central hypothyroidism (i.e., secondary or tertiary). Secondary hypothyroidism is due to TSH deficiency and tertiary hypothyroidism is due to TRH deficiency. Suspect **secondary/tertiary disease** when you see a deficiency of **multiple** hormones (e.g., adrenal insufficiency and hypothyroidism occurring in the same patient) or in patients with a history of pituitary mass, pituitary surgery, or traumatic brain injury. (Isolated hypothyroidism due to pituitary or hypothalamic dysfunction is very rare and is usually genetic in nature.)

Secondary and tertiary hypothyroid diseases are differentiated by **imaging** the sella. **Routine TRH** stimulation test is **not** done because management is the same: Replace thyroid hormone to achieve a normal FT_4 level (not a TSH level).

Treatment of Hypothyroidism

Treatment for hypothyroidism is **levothyroxine** (T_4) alone. Adding T_3 might help with some neuropsychological symptoms, but multiple randomized trials have shown **no** benefit of combined T_3/T_4 beyond that achieved with T_4 monotherapy. In addition, T_3 therapy is harder to regulate due to its short half-life and may cause hyperthyroid effects, such as atrial fibrillation and bone loss. T_3 is not recommended in the treatment of hypothyroidism.

T_4 has a long half-life and takes weeks to equilibrate. In most cases, you can start patients on 50–100 mcg/day or 1.6 mcg/kg/day while fasting (an hour before breakfast). For patients with the potential for **coronary artery disease**, especially the **elderly**, start low (50 mcg/day) and slowly titrate up. Adjust the dose of levothyroxine every 6 weeks in increments of 12.5–25 mcg.

For primary hypothyroidism, the main treatment target is the TSH: Keep the level within the lower half of the normal reference range for your laboratory. Allow enough time for the blood level to come to a steady state, so do not check the TSH again until a full 6–8 weeks after a dose adjustment. Do not overtreat because you risk inciting complications of **hyperthyroidism**, such as **atrial fibrillation** and **osteoporosis**.

Know that a TSH elevation $> 10 \mu\text{U/mL}$ (10 mU/L) in a patient prescribed $> 200 \text{ mcg/day}$ of T_4 is most commonly due to **nonadherence**.

Watch out for food, drinks, and drugs that interfere with absorption of thyroxine (e.g., iron/calcium/aluminum supplements and bile acid sequestrants), raise TBG levels (estrogens), or increase the metabolism of T_4 . These, in addition to malabsorption (think celiac), cause persistently elevated TSH despite therapeutic dosages of T_4 .

If a patient is hypothyroid and needs emergent surgery for another reason, do it! Otherwise, try to restore euthyroidism before surgery.

Always treat pregnant hypothyroid patients and follow their TSH levels every 4 weeks during pregnancy because their requirements increase (the dose needs to be adjusted upwards $\geq 50\%$ over the prepregnancy dose). The goal in pregnancy is to keep TSH in the lower half of the trimester-specific reference range (approximately $< 2.5 \mu\text{U/mL}$ [2.5 mU/L]). Failure to treat maternal hypothyroidism during pregnancy can adversely affect the baby. For more on hypothyroidism during pregnancy, see the **Women's and Men's Health** section.

Treating **subclinical** hypothyroidism is controversial. In clinical practice, the decision to treat is individualized. American Association of Clinical Endocrinologists/American Thyroid Association guidelines (2012) generally recommend treatment for patients with a TSH $> 10 \mu\text{U/mL}$ (10 mU/L) and **no** treatment for patients with TSH $< 10 \mu\text{U/mL}$. When to start thyroid hormone for a TSH $< 10 \mu\text{U/mL}$: in pregnancy, in those attempting pregnancy, in the presence of a large goiter, and, most controversially, when symptoms suggest hypothyroidism + anti-TPO antibodies.

Myxedema Coma

Myxedema coma is 1 of 2 **thyroid emergencies** (the other being thyroid storm). Mortality is 30–40% and is higher in the elderly and in those with heart disease. It is a **clinical** and not a biochemical diagnosis, so the diagnosis depends on recognition of the classic signs and symptoms—**not** on the absolute value of T_4 or elevation of TSH.

Any cause of hypothyroidism can lead to myxedema coma. Undiagnosed, longstanding hypothyroidism can progress to myxedema coma. In patients with known but inadequately treated hypothyroidism, myxedema coma can be precipitated by infection, exacerbation of heart disease, opiates, or cold temperature.

Patients usually present with a history of progressive hypothyroid symptoms. Decreased mentation, bradycardia, and hypothermia (even body temperatures down to 74°F [23.3°C]!) are classic findings. Other signs indicate a **generalized slowing of systemic processes**: hypoventilation, hypoglycemia, and hypotension.

For the patient who presents to the emergency department obtunded with multisystem failure, quiz relatives for possible antecedent signs and symptoms of thyroid dysfunction.

Other symptoms depend on why the patient has thyroid disease:

- If the disease is primary, there may be no other symptoms, but be aware that rarely, primary autoimmune processes can affect both the thyroid and the adrenal, called **Schmidt syndrome**.
- If the disease is secondary, the patient may have symptoms of other hormone deficiencies; **adrenal insufficiency** is **especially important**.
- Patients may have a pericardial effusion.
- Up to 25% of patients have seizures.

Other lab abnormalities include hyponatremia, hypoglycemia, anemia, and hyperlipidemia.

Diagnose myxedema coma by history and physical examination in combination with hypothyroidism on labs. If the patient is stable, assess for adrenal insufficiency with an ACTH stimulation test prior to treating with thyroid hormone. (See **Steroid Synthesis on page 1-20**.) If the patient is unstable, just empirically treat with **glucocorticoids** without doing the ACTH stimulation test.

Give **empiric stress-dose glucocorticoids** until adrenal insufficiency is excluded by ACTH stimulation testing. Note: This should **always** be done prior to giving thyroid hormones because giving thyroid hormones first can precipitate adrenal crisis.

Treat myxedema coma with thyroid hormone. Optimal treatment is controversial; options include:

- T_3 (advantages: rapid onset and decreased conversion of T_4 to T_3 during acute illness), **or**
- intravenous T_4 (due to reduced absorption with oral), **or**

- **combined T₃ and T₄** (preferred by most experts) using a loading dose and a smaller daily dose thereafter.

Give empiric broad-spectrum antibiotics until infection is excluded. Pay particular attention to gradually warming the body temperature, maintaining adequate blood pressure with IVF and/or vasopressors, and normalizing the serum Na⁺.

Know that the mortality of myxedema coma is directly related to the degree of hypothermia and that **passive rewarming** (i.e., with blankets) is one of the most important elements of supportive care. Active rewarming can worsen hypotension (due to vasodilation) and should be avoided.

HYPERTHYROIDISM

Etiology

The **most common** cause of hyperthyroidism is autoimmune **Graves disease** (see **Graves Disease**). Most other causes occur in the context of **nodular disease** or **thyroiditis** and are discussed under **Thyroid Nodules and Cancer** on page 1-17 and **Thyroiditis** on page 1-15, respectively. Causes of hyperthyroidism:

- Toxic multinodular goiter (MNG)
- Toxic adenomas
- Thyrotoxicosis due to autoimmune thyroiditis (hashitoxicosis)
- Factitious thyrotoxicosis (exogenous thyroid hormone ingestion)
 - Thyroglobulin is a protein made by thyroid cells. Thyroglobulin levels are used mainly for thyroid cancer surveillance but can also be used when factitious thyrotoxicosis is suspected. Thyroglobulin is elevated in all endogenous hyperthyroidism etiologies (including thyroiditis) and low in factitious thyrotoxicosis.
- Iodine-induced hyperthyroidism (e.g., amiodarone, contrast)
- Subacute (i.e., painful) thyroiditis
- Postpartum thyroiditis
- TSH-producing adenoma (rare)

A good history and a thyroid scan and uptake will often get you the right diagnosis.

Findings

Symptoms of hyperthyroidism, regardless of cause, include:

- Anxiety and restlessness
- Irritability
- Insomnia
- Impaired concentration (even confusion or psychosis)
- Weight loss
- Diarrhea/hyperdefecation (increased frequency of stools with normal consistency)

- Heat intolerance
- Alopecia
- Onycholysis
- Dyspnea
- In women: menstrual irregularities (oligomenorrhea or amenorrhea, impaired fertility)
- In men: gynecomastia, decreased libido, infertility, and/or erectile dysfunction

Exam may reveal:

- Goiter
- Warm skin
- Exophthalmos (the “hyperthyroid stare”) in patients with Graves disease
- Lid lag
- Tremor
- Tachycardia
- Atrial fibrillation or ectopy in up to 20% of patients (more common in **elderly**)

Note: β -blockade (propranolol) is indicated in the setting of symptomatic hyperthyroidism, even prior to establishing the cause of hyperthyroidism, because β -blockade can control the symptoms of thyrotoxicosis (palpitations/anxiety) and decrease peripheral T₄ to T₃ conversion.

Abnormal general labs/studies (in addition to a low TSH and elevated FT₄):

- Low total cholesterol and LDL
- Normochromic, normocytic anemia
- Hypercalcemia with increased bone alkaline phosphatase
- Osteopenia/osteoporosis
- Dilated cardiomyopathy

Consider the diagnosis of hyperthyroidism in elderly patients with **new-onset atrial fibrillation** or depression without classic symptoms of hyperthyroidism—this is termed **apathetic hyperthyroidism**. Hyperthyroidism in the elderly can look like failure to thrive with apathy, anorexia, and weight loss. You may need to distinguish thyroid disease from polymyalgia rheumatica and clinical depression or adjustment disorder.

Graves Disease

Graves disease is the most common cause of thyrotoxicosis. It is caused by thyroid-stimulating immunoglobulins, IgG antibodies that bind to and stimulate the TSH receptors in the thyroid gland.

Physical findings **specific** for Graves disease (in addition to those listed in **Findings**; also see **Figure 1-5 on page 1-14**):

- A diffuse, soft, symmetric goiter (See **Nontoxic Goiter on page 1-19**.)
- Presence of bruit on thyroid auscultation
- Ophthalmopathy: proptosis and periorbital edema with impaired extraocular movements $\rightarrow$ diplopia, corneal ulcerations, visual impairment. Know that the risk of Graves ophthalmopathy (GO) is **increased** in

both **active and passive smokers** and **after radioactive iodine (RAI) therapy**. Smoking is also associated with progression of GO **after** RAI therapy and adversely affects the course of GO **during** treatment with steroids and orbital radiotherapy. Know that 90% of patients with Graves' have ocular involvement on MRI or CT. Clinically apparent GO requires formal eye testing and imaging to determine the degree of eye inflammation. If a patient with mild-to-moderate GO decides on RAI treatment, pretreatment with steroids is warranted in order to prevent the progressions of GO. RAI is **contra-indicated** in patients with **severe** eye inflammation.

- Dermopathy: Pretibial myxedema is a thickening and redness of the dermis due to a **lymphocytic** infiltrate that gives it a *peau d'orange* appearance (looks different from the myxedema seen in hypothyroid patients).



Figure 1-5: Graves disease: proptosis and lid retraction

Diagnosis

To diagnose Graves', use a good clinical exam (GO +/- goiter with a bruit) + TFTs + thyroid uptake and scan. TSH is low (usually $< 0.01 \mu\text{U/mL}$ [0.01 mU/L]), FT_3 and FT_4 are elevated (rarely, only FT_3 is increased with normal or low FT_4), and the thyroid uptake and scan shows an enlarged gland with **diffusely increased uptake** (see Figure 1-4 on page 1-10). Other common lab abnormalities: elevated alkaline phosphatase, hypercalcemia, anemia, and thrombocytopenia. Autoantibodies are generally not measured unless the diagnosis is unclear or a thyroid uptake and scan cannot be done (e.g., pregnant, recent contrast), but TSI (thyroid-stimulating immunoglobulins, a.k.a. thyroid receptor antibodies) are specific for and positive in $> 90\%$ of cases of Graves disease.

Treatment

Treatment options for Graves disease are antithyroid drugs (i.e., methimazole [**MMI**] or propylthiouracil [**PTU**]), radioactive iodine, or surgery.

MMI is the preferred drug in **nonpregnant** patients because of a lower toxicity than PTU. PTU received an **FDA boxed warning** for increased risk of death due to acute liver failure or severe liver injury, so PTU is no longer the 1st line therapy in nonpregnant patients and children. Vasculitis and lupus-like side effects have also been reported. PTU is still the 1st line treatment for **thyroid storm and in the 1st trimester** of pregnancy.

The most serious side effects of PTU and MMI are hepatic toxicity and agranulocytosis, which are rare and unpredictable. LFTs and CBCs do **not** require monitoring. Check only if the patient becomes symptomatic (e.g., jaundice,

dark urine, prolonged fever/sore throat), and discontinue the drug at that time. Side effects almost always disappear when the drug is discontinued. Mild side effects include skin rash and polyarthritis.

β -blockers can be used independent of the etiology of the hyperthyroidism to help with adrenergic symptoms, including tremor, tachycardia, and anxiety, while waiting for PTU or MMI to take effect.

Remission in Graves' is seen in 30% of patients after 1-2 years on antithyroid medication; relapse is common. Relapse is much less likely if thyroid stimulating immunoglobulins disappear with treatment, but this happens in a small minority of cases—usually young, female patients with relatively small thyroid glands.

In the United States, most patients with Graves disease receive definitive treatment with thyroid ablation using ^{131}I . Pretreat virtually all patients with β -blockers, and many with MMI (or PTU), prior to radioactive iodine ablation. Remember to rule out pregnancy in female patients (as radioiodine is contraindicated in pregnancy), and counsel patients to avoid pregnancy for 6 months to 1 year after thyroid ablation. Most patients become hypothyroid in response to ^{131}I therapy; it can take several months for the TSH to normalize and then become elevated.

Surgery may be indicated in patients who are pregnant (2nd trimester is optimal; for more on hyperthyroidism during pregnancy, see the **Women's and Men's Health** section), in patients with an associated cold nodule and a concerning FNA, relapse after radiation, or severe allergic reactions to antithyroid drugs and in some young patients with a large goiter. **Complications** of surgery include loss of all parathyroids and damage to recurrent laryngeal nerves. Remember, all patients need lifelong thyroid hormone therapy after surgery.

Thyroid Storm

Thyroid storm is the 2nd thyroid emergency that carries a **high mortality rate** (the other is myxedema coma). Thyroid storm is often precipitated in patients with undiagnosed or inadequately treated hyperthyroidism. Precipitating events include surgery, infections, or an iodine load, such as amiodarone or contrast dye.

Symptoms of thyroid storm are similar to symptoms of hyperthyroidism, only more severe: tachycardia, heart failure, fever, psychosis, or delirium. Some patients have GI symptoms of nausea, vomiting, and diarrhea. As with myxedema coma, thyroid storm is a **clinical** rather than a biochemical diagnosis, so the diagnosis depends on recognition of the classic signs and symptoms, **not** on the severity of T_4 or TSH abnormalities. Suspect thyroid storm with clinical presentation of fever, tachycardia, and altered mental status in the context of overt hyperthyroidism. In virtually all cases, **TSH is very low** and **FT_4 is markedly increased**.

Thyroid storm is characterized by severe metabolic stress that the patient can no longer tolerate. This

severe stress results in a **relative adrenal insufficiency**, even though the adrenal glands may be functioning perfectly and secreting a large amount of cortisol. Patients in thyroid storm die from cardiovascular collapse. A very important aspect of treatment is **supraphysiologic doses** of **glucocorticoids**.

Treatment of thyroid storm includes the following:

- Glucocorticoids, as described above
- Interrupt the physiologic response to excess thyroid hormone: IV **propranolol** or esmolol
- Block **new** hormone synthesis: high-dose thioamide (PTU preferred)
- Block release of **preformed** hormone from the gland: stable iodide
- Block peripheral conversion of T_4 to T_3 : iodinated contrast agent, propranolol, and corticosteroids. PTU—but not MMI—also does this, although the clinical relevance of this is unknown.
- Give empiric broad-spectrum **antimicrobial** coverage until infection is excluded.
- Provide **supportive** care in the ICU with diligent attention to volume status, temperature, and heart rate.

THYROIDITIS

Thyroiditis (thyroid inflammation) can be the result of multiple disease processes, each causing a different type of inflammation in the thyroid gland. All causes of thyroiditis that completely resolve follow a typical pattern of changes in thyroid function: from hyperthyroidism (caused by inflammation-induced cell death) to euthyroidism (as the inflammation resolves) to hypothyroidism and then back to euthyroidism again at the end of the healing process (see Figure 1-6). Some types do not completely resolve and lead to persistent hypothyroidism (mainly Hashimoto's).

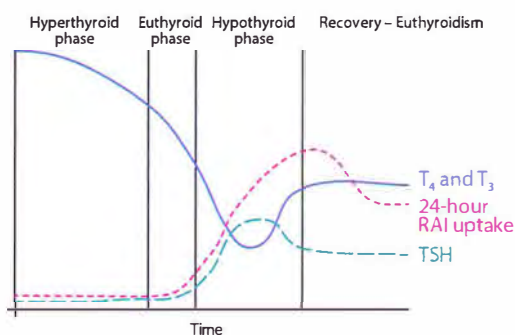


Figure 1-6: Normal course of a thyroiditis that completely resolves

Review of the labs during the phases of thyroiditis:

- 1) Hyperthyroidism: High FT_4 and FT_3 ; TSH is suppressed; high ESR; RAIU is low because low TSH is suppressing production. (High FT_4 and FT_3 are due to thyroid destruction.)
- 2) Euthyroid: all labs normal

- 3) Subclinical hypothyroidism: normal FT_4 , high TSH (typically 5–10 mU/L)
- 4) For those that go to overt hypothyroidism: low FT_4 , high TSH (typically > 10 mU/L)
- 5) Back to euthyroid state: all labs normal

The most inflammatory disease processes cause the most pain and tenderness and indicate a need for a quicker workup. So let's review thyroiditis from this standpoint—painful vs. painless.

Painful and Tender

Subacute thyroiditis (a.k.a. granulomatous or de Quervain thyroiditis) is a common problem in 30- to 50-year-olds and in females > males (~4:1) and is the most common cause of a painful and tender thyroid. Subacute thyroiditis is presumed to be caused by a **viral** infection. Pathology shows thyroid inflammation and granulomas; fibrosis can occur but eventually resolves with a return to normal histology. Patients complain of a **tender and painful anterior neck** with pain that can radiate to the ear; they also often have constitutional symptoms including fever, chills, sweats, and malaise. On occasion, constitutional symptoms dominate the presentation.

Subacute thyroiditis follows the typical pattern of changes in thyroid function: from hyperthyroidism to euthyroidism to subclinical hypothyroidism to either complete normalization with euthyroidism (~85%) or long-term overt hypothyroidism (~15%).

Subacute thyroiditis is typically (85%) **self-limited** and usually does not require treatment other than NSAIDs for the inflammatory symptoms. When NSAIDs are not sufficient, give **glucocorticoids** as an 8-week taper. Occasionally, a patient may need β -blockers for thyrotoxic symptoms or levothyroxine for overt hypothyroidism. Reevaluate periodically until the patient's thyroid function normalizes.

Infectious thyroiditis (a.k.a. suppurative thyroiditis) is a rare problem that is most commonly the result of a staph or strep infection, and much less commonly, fungal or other bacterial infections. It usually occurs in children and can have an acute or chronic presentation. With the acute presentation, patients typically have severe pain, fever, and unilateral swelling. Do an ultrasound and fine needle aspiration with a Gram stain and C+S. Treat with the appropriate antibiotic.

Radiation thyroiditis can develop shortly (7–10 days) after exposure to radiation, which may be in the form of radioactive iodine treatment, radiotherapy of head and neck cancer, or accidental exposure (e.g., nuclear accident). Note that radiation thyroiditis is **painful**, but it **resolves** without therapy.

Painless and Nontender

Hashimoto thyroiditis (a.k.a. chronic autoimmune thyroiditis) is the **most common thyroiditis** (4% of the population, women:men 8:1) and the most common

cause of hypothyroidism in the U.S. (Worldwide, iodine deficiency is the most common cause.) Both genetic and environmental factors are part of Hashimoto's; however, this is not well understood. Cases are clustered in families, and the thyroiditis is sometimes associated with other autoimmune diseases, such as Type 1 diabetes, primary adrenal insufficiency, pernicious anemia, and vitiligo.

Hashimoto thyroiditis is characterized by a painless, chronic, lymphocytic infiltration of the gland causing a **firm and often irregular goiter**, which sometimes is confused for multiple nodules (ultrasound helps distinguish).

Up to **95%** of patients with Hashimoto's have measurable **anti-TPO antibodies**. Immune-mediated thyroid cell apoptosis is the ultimate cause of hypothyroidism, but how these antibodies specifically cause cell death is unclear.

Virtually all patients become hypothyroid over time as the gland is gradually destroyed, but some present with thyrotoxicosis ("Hashitoxicosis"). Presenting symptoms, therefore, are variable and depend on what phase of the disease they have on presentation. Most patients present with persistent hypothyroidism and are treated with levothyroxine.

Painless thyroiditis (a.k.a. silent thyroiditis, subacute lymphocytic thyroiditis) can present as hyper- or hypothyroidism. The disease process generally starts with a hyperthyroid stage (2–4 weeks), which progresses to a hypothyroid stage (4–12 weeks). Most patients recover. The gland is nontender and may be enlarged. Thyroid scans done during the hyperthyroid phase show diffusely low uptake (**Figure 1-4 on page 1-10**). This is helpful in distinguishing painless thyroiditis from Graves disease, in which uptake is high. **50%** of these patients later develop chronic autoimmune hypothyroidism associated with anti-TPO antibodies.

Postpartum thyroiditis is fairly common, affecting up to **10–15%** of postpartum women within 1 year of delivery. Patients present with hyper- or hypothyroid symptoms and a painless goiter. ESR is normal, but many patients do have anti-TPO antibodies. RAIU is decreased. Treat

symptomatic hypothyroidism with low-dose levothyroxine, and treat symptomatic hyperthyroidism with β -blockers. Patients usually recover completely, although some stay hypothyroid. Those that recover need annual follow-up because of the risk of overt hypothyroidism later.

Because many of those with anti-TPO antibodies progress to overt hypothyroidism, painless thyroiditis and postpartum thyroiditis are considered variants of Hashimoto's.

See **Table 1-2** for a comparison.

Remember: RAIU helps distinguish Graves' from thyroiditis as a cause for hyperthyroidism. RAIU is **high** in Graves' and **low** in patients who are hyperthyroid due to thyroiditis, **iodine excess**, **exogenous T_4 or T_3 ingestion**, and **struma ovarii** (thyroid tissue in an ovarian teratoma).

EUTHYROID SICK SYNDROME

Euthyroid sick syndrome (a.k.a. nonthyroidal illness syndrome) is seen in seriously ill or starving patients and can be confused with secondary hypothyroidism. In states of significant illness, the body does not need much FT_3 (the active hormone). Instead, the body converts FT_4 to **reverse T_3 (rT_3)**, an inactive compound. The FT_3 is very low while both the FT_4 and TSH are low or low-normal. In addition to low T_4 and T_3 , thyroid-binding globulins are also decreased.

Clinically, you see a severely ill, hospitalized patient with a mildly decreased FT_4 and low-normal TSH.

Patients with euthyroid sick syndrome are **not** given thyroid supplementation. Do **not** check TFTs in sick patients unless their acute illness is possibly due to a thyroid emergency (i.e., thyroid storm or myxedema coma).

Generally, the diagnosis of euthyroid sick syndrome is presumptive because central hypothyroidism is a very rare entity. In the recovery phase, the TSH can be elevated, but a TSH level $> 20 \mu U/mL$ ($20 mU/L$) makes it very unlikely to be a finding in euthyroid sick recovery and more likely to indicate overt hypothyroidism.

Table 1-2: Types of Thyroiditis and Their Treatments

Symptoms	Type	Antibody	T_4 Levels	Treatment
Painful and tender	Subacute	–	Hyper to hypo to eu	Resolves without therapy; NSAIDs for pain
	Infectious	–	Variable	Resolves after infection treated; NSAIDs prn
	Radiation	$\pm$	Hyper to hypo to eu	Resolves without therapy; NSAIDs prn
Painless and nontender	Hashimoto's	Anti-TPO	Hypo!	Levothyroxine
	Painless	Anti-TPO, anti-Tg	Hyper to hypo to eu	Treat hyper with β -blockers; hypo with low-dose thyroxine.
	Postpartum	Anti-TPO	Hyper to hypo to eu	Treat hyper with β -blockers; hypo with low-dose thyroxine.

THYROID NODULES AND CANCER

Thyroid nodules are common, especially in females and in the elderly. Incidental thyroid nodules are seen in > 50% of patients who undergo ultrasound, CT, or MRI to evaluate anterior carotid disease! < 10% of these nodules are **malignant**; however, these incidentomas require the same evaluation as nodules that present clinically (see below). Incidental thyroid nodules can also be found on PET scan; up to 40% of nodules found on PET scan in patients with a normal TSH are malignant, and workup is indicated. (Note: Diffuse thyroid uptake on PET is more suggestive of Hashimoto's than malignancy.)

Nodules can be multiple or single, hot or cold. Most solitary nodules are cold, and most of those are benign. Virtually all **hot** or **purely cystic** nodules are **benign**.

A malignant nodule can be primary thyroid carcinoma or a metastasis. Neck radiation as a child (especially with > 100 rads) is a major risk factor for malignant nodules (mostly papillary carcinoma), as well as nonmalignant nodules (colloid adenomas).

So, the task for the internist is to determine which nodules are malignant and which ones aren't, keeping in mind that **most nodules are not malignant**.

Basic evaluation of thyroid nodules: First, check the TSH and ultrasound. If the TSH is low, do a thyroid scan (scintigraphy) to see if the nodule is hyperfunctioning (i.e., hot). If TSH is normal or high, possibly do a fine needle aspiration to rule out malignancy based on U/S results. More on this is found in [Nodule Workup](#).

Here are some helpful generalities:

- Autonomously functioning nodules (hot nodules) are **rarely** malignant, so a single hot nodule does not require a biopsy if U/S is low suspicion. Histology from a **hot** thyroid nodule can be **indistinguishable** from a **follicular** thyroid malignancy, which can lead to false-positive biopsies and unnecessary surgery or RAI. In general, **hot** nodules should not be biopsied!
- The majority of nodules are cold, and the majority of these are benign, but **thyroid malignancies** also present as **cold nodules**.
- Cold** nodules in a patient with **Graves'** are still evaluated with a biopsy because they can be malignant.
- Multinodular goiters** (MNGs) can have **both** hot and cold nodules. As with solitary nodules, do a thyroid scan only if the TSH is low. If the thyroid scan shows cold areas, use the thyroid U/S to determine if a biopsy is warranted. If the TSH is normal or high, a thyroid scan is not needed, and the U/S alone will dictate if an FNA is needed. See also [Multinodular Goiter – Nontoxic and Toxic on page 1-19](#).
- Purely cystic nodules may appear as cold nodules on a thyroid scan but do not need a biopsy because they have a low malignancy risk. Always confirm cold nodules with a thyroid ultrasound prior to biopsy.

- All nodules should have an U/S to evaluate for suspicious characteristics and help determine if FNA is needed.

Risk Factors for Thyroid Cancer

The following risk factors increase the likelihood that a nodule is malignant:

- Hx of head/neck irradiation
- Family Hx of thyroid cancer
- New nodules in those < 20 or > 70 years of age
- Male
- Growing nodule (If the rate of growth is rapid, you must rule out a thyroid lymphoma.)
- Firm or hard consistency
- Lymphadenopathy
- Fixed
- Symptoms of compression in a patient without comorbid goiter: dysphonia, dysphagia, and cough
- Suspicious U/S features (See [Nodule Workup](#).)
- Hypermetabolic nodule detected by PET scan (focal uptake; diffuse thyroid uptake is consistent with autoimmune thyroiditis)

Nodule Workup

Thyroid nodules can be discovered by the patient, by routine physical examination, or incidentally during imaging done for another indication (incidentoma). Nodules can be solitary, or with multinodular goiter. The 2015 American Thyroid Association (ATA) thyroid nodule guidelines determine the need for FNA based on risk factors, U/S features, and nodule size. General rule: If a thyroid nodule (single, multiple, or within an MNG) has any suspicious characteristics by U/S or there is clinical concern, refer for FNA.

Know the workup for thyroid nodules. Start with a good history and physical exam with focus on risk factors for malignancy, including prior neck radiation and a family history of thyroid cancer. Then, check the TSH and thyroid U/S:

- Normal or high TSH:** Check a thyroid **U/S** (even if the nodule was found on CT or MRI). If the nodule has suspicious ultrasound features (see below), perform an FNA. Patients with high TSH also require evaluation for hypothyroidism (see [Hypothyroidism on page 1-11](#)).
- Low TSH** indicates that the nodules may be hyperfunctioning. In addition to U/S, do a thyroid **scan** (scintigraphy; [Figure 1-4 on page 1-10](#)). Patients with low TSH should also be evaluated for hyperthyroidism (see [Hyperthyroidism on page 1-13](#)).
 - In the context of a low TSH, hot nodules with low suspicion U/S are rarely malignant and do not require FNA. Histologically, hot nodules can look very similar to cancer, and biopsies often lead to false-positive results.
 - If the nodule is cold and U/S criteria are met, proceed with FNA.

Ultrasound criteria for biopsy (FNA) are as follows:

- High-risk U/S findings (biopsy high-risk nodules if they are ≥ 1 cm in size):
 - Solid or hypoechoic
 - Irregular margins
 - Microcalcifications
 - Taller-than-wide shape
 - Rim calcifications
 - Extrathyroidal extension
- Low-risk U/S findings:
 - Partially cystic, hyperechoic, or isoechoic
 - None of the high-risk U/S features above

Biopsy low-risk nodules only if ≥ 1.5 – 2 cm in size.

Purely cystic nodules (i.e., with no solid component) are benign and generally not biopsied/drained unless there are compressive symptoms or for cosmetic reasons.

What you do after FNA of thyroid nodules depends on what the **pathology** shows. Malignant or suspicious pathology goes to surgery. Nondiagnostic and follicular lesion of undetermined significance (FLUS) pathology goes for repeat FNA. Follicular neoplasm generally gets a hemithyroidectomy or repeat FNA with molecular markers. Benign nodules are followed with repeat U/S.

Benign Nodular Disease

In euthyroid patients with nodules and/or an MNG established as benign on FNA, consider surgery only if compressive symptoms develop, such as difficulty breathing or swallowing. Consider repeat biopsy if there is significant growth or development of high-risk U/S features. Recurrence of a cystic nodule after several aspirations is considered to be an indication for surgical excision, as is persistent patient anxiety and concern about cosmetic appearance.

Toxic Adenoma

A toxic thyroid adenoma is a benign area of **autonomous** hyperfunctioning thyroid tissue. Most occur as a single hyperfunctioning nodule within normal tissue that grows slowly, eventually becoming large enough to suppress TSH production. The end result is an autonomous, hyperfunctioning nodule in the midst of “turned-off” thyroid tissue (i.e., a **hot nodule**). These are usually diagnosed by TFTs, which demonstrate overproduction of FT_3 and FT_4 with suppression of TSH, and are confirmed on thyroid scan (focal uptake in hot nodule; see [Figure 1-4 on page 1-10](#)).

Treatment of thyroid adenomas: If the patient is hyperthyroid, 1st line therapy is radioactive iodine for **ablative** treatment or surgical resection. If the thyroid adenoma is compressing underlying structures or is cosmetically problematic, surgery is the best treatment.

Antithyroid drugs work but are not curative, so they generally are not offered.

For the euthyroid patient with a thyroid adenoma, **do not** use suppressive therapy with thyroxine because the risks of overt hyperthyroidism outweigh the benefits of mild shrinkage.

Percutaneous ethanol injection of autonomous functioning thyroid nodules is an alternative to surgery and RAI (e.g., in patients who are not a candidate for either), with restoration of normal thyroid function in the majority of cases. This treatment is not routinely done in the U.S.

To review RAIU and scan findings in hyperthyroid disorders:

- Hyperthyroidism with high RAIU. Distinguish these three with a thyroid scan!
 - **Graves** disease
 - Toxic multinodular goiter
 - Toxic adenoma
- Hyperthyroidism with a decreased RAIU
 - **Thyroiditis**
 - Overmedication with thyroxine supplements
 - Medications containing iodine (e.g., amiodarone)

Thyroid Carcinoma

Thyroid cancer is the most common endocrine cancer and incidence rates are increasing. There are 4 histologic types of carcinoma:

- 1) **Papillary**: most common; well-differentiated; usually indolent; spreads via lymphatics to local lymph nodes, and later to bone/lungs
- 2) **Follicular**: less common; differentiated; spreads hematogenously to bone/lungs/CNS. Capsular and/or vascular invasion is crucial in differentiating a follicular carcinoma from a benign adenoma. This is why a hemithyroidectomy is necessary after a biopsy showing follicular neoplasm. If surgical pathology confirms carcinoma, then a completion thyroidectomy is performed.
- 3) **Anaplastic**: rare; highly undifferentiated and highly malignant; death within 6 months of diagnosis; no good treatment available
- 4) **Medullary**: associated with hyperplasia of parafollicular C cells and elevated serum calcitonin. It can be sporadic or inherited with ~ 15% occurring as a component of multiple endocrine neoplasia syndromes (i.e., MEN2A and MEN2B) and familial medullary thyroid cancer (FMTC) syndrome. MEN cases are associated with point mutations in the *RET* protooncogene. If *RET*+, always screen for pheochromocytoma; if confirmed, resect the pheo before resecting the medullary thyroid cancer.

Note: You do not need to know the specific staging systems of the various thyroid cancers.

Treatment of the thyroid cancer is usually a near-total thyroidectomy, which always leaves part of the posterior capsule around the recurrent laryngeal nerve intact. A thyroid **lobectomy** can be done as treatment for **papillary** cancer that is very small and limited to one lobe.

Frequently, a small amount of residual thyroid tissue also remains after near-total thyroidectomy. **Postoperative RAI therapy** can be given to higher-risk patients to destroy any remaining normal cells (remnant ablation) and any thyroid cancer cells.

There is higher risk of **recurrence** with:

- Incomplete tumor resection
- Extrathyroidal extension
- Distant metastases
- Poor tumor differentiation or advanced tumor grade
- Mediastinal or bilateral cervical lymph node metastases (if papillary cancer)
- Extensive capsular and vascular invasion (if follicular cancer)

The decision to treat with RAI, as well as the dose of ^{131}I used, is individualized, but patients with risk factors for recurrence definitely should receive postoperative RAI. Following surgery, thyroxine therapy is necessary but sometimes is not started immediately after thyroidectomy if RAI is going to be given. Instead, the TSH is allowed to rise over several weeks; once the TSH level is $> 25 \mu\text{U/mL}$ (25 mU/L), RAI is given. After RAI, thyroid hormone is started. If thyroid hormone withdrawal is not the best option (mostly for patients with comorbidities), then increase the TSH with recombinant human thyrotropin alfa (Thyrogen). If Thyrogen is used, then thyroid hormone therapy can be started immediately after surgery—even if RAI is going to be given.

Once thyroid hormone is started, use **suppressive doses** of **thyroxine** in higher-risk cancers. Most **differentiated** thyroid cancers remain **responsive** to TSH, so keeping the TSH suppressed slightly below the lower limit of normal helps prevent recurrence. Suppression of TSH can increase the risk of hyperthyroid complications (e.g., atrial fibrillation, dilated cardiomyopathy, osteoporosis); therefore, target the TSH to be around $0.1 \mu\text{U/mL}$ (0.1 mU/L) for cancers with higher risk of recurrence while maintaining a normal FT_4 .

Long-term follow-up usually involves one or more of the following: neck ultrasound, total body scans, and/or thyroglobulin levels (as long as the patient does not have antithyroglobulin antibodies to interfere with the assay). Thyroglobulin is only expressed by thyroid tissue (both cancer and noncancerous cells), so thyroglobulin levels following surgery and RAI therapy should be undetectable. Any rise in thyroglobulin levels suggests recurrent disease. Do not check the thyroglobulin immediately after surgery, as it has a long half-life (> 60 hours) and levels can be elevated up to 25 days post-op.

Thyroid **lymphoma** is associated with chronic autoimmune thyroiditis. Think about this in a patient with chronic autoimmune thyroiditis who develops a **fast-growing thyroid mass**. The most common tumor type is a diffuse large B-cell lymphoma, which is treated with chemotherapy and external beam radiation. Surgery is used only for biopsy and diagnosis.

Nontoxic Goiter

Simple, nontoxic goiter is a diffuse enlargement of the thyroid gland with a normal TSH and FT_4 . It can be caused by a lack of iodine or ingestion of a goitrogen (e.g., cassava root, Brussels sprouts, cauliflower, cabbage), but many cases are idiopathic. Diagnose nontoxic goiter with thyroid function tests; FT_4 and TSH are normal.

Treatment: Remove any goitrogens from the diet. If the cause is low iodine, iodine supplements help.

Multinodular Goiter — Nontoxic and Toxic

Nontoxic multinodular goiter (MNG) is fairly common and occurs more often in **women**. Cause is multifactorial. Nodules of varying sizes are distributed throughout the gland, but patients are generally asymptomatic and euthyroid with a normal TSH. They come to attention because of the size of their gland or because (rarely) the gland gets large enough to compress surrounding structures.

Suspect this diagnosis when various-sized nodules are palpated in a goiter. After obtaining a normal TSH, perform U/S to look for any nodules with features suspicious for malignancy. If concerning features are present, do a biopsy (see the U/S criteria for FNA biopsy under **Nodule Workup** on page 1-17). If no biopsy is needed or the results of the FNA are benign, then nontoxic MNG is generally managed conservatively but has 2 main indications for treatment:

- 1) Symptomatic compression of key structures (e.g., trachea or esophagus)
- 2) Cosmetic: surgical correction of a disfiguration

Standard surgical treatment of nontoxic MNG, if indicated, is bilateral subtotal thyroidectomy. If the patient is not a surgical candidate, radioiodine therapy can be used for goiter shrinkage. These nodules are typically **benign**. Benign nodules remain benign, and they do not change size. Thyroxine suppressive therapy is **not** used because it is not very effective and long-term thyroxine therapy increases the risk of osteoporosis and atrial fibrillation.

Toxic MNG refers to an MNG with **thyrotoxicosis**. TSH is suppressed, and FT_3 and FT_4 are often increased. The thyroid scan (see **Figure 1-4** on page 1-10) usually shows ≥ 1 **hot** nodule.

Toxic MNG can be treated with antithyroid medications (e.g., methimazole) in urgent or emergent clinical situations to control the hyperthyroidism, but 1st line treatment is usually ablative therapy with radioactive iodine since it is curative. This does not destroy all the nodules, but it does destroy those that are hyperfunctioning. Most patients end up euthyroid after RAI. Surgery is used in cases that are refractory or in symptomatic cases when compression symptoms are present.

ADRENAL GLAND

PREVIEW | REVIEW

- Name 3 different hormones that are produced in the adrenal cortex. (Also see [Figure 1-8](#).)
- What is produced in the adrenal medulla?
- What do mineralocorticoid hormones do?
- What are the mineralocorticoid effects of excess cortisol?
- How does a woman who overproduces adrenal androgens present?
- Which gene defect is most commonly associated with congenital adrenal hyperplasia?
- What is the difference between Cushing syndrome and Cushing disease?
- What is the adrenocorticotropic hormone (ACTH) level in Cushing disease?
- What are your choices for initial tests to evaluate a patient who may have Cushing syndrome?
- In which clinical situations does pseudo-Cushing syndrome occur?
- How does adrenal insufficiency (both primary and secondary) present?
- Abnormal K^+ levels occur in which type of adrenal insufficiency? Why?
- How do aldosterone levels affect serum Na^+ and K^+ ?
- Which syndrome should you be concerned about in a patient with difficult-to-treat hypertension and low K^+ ?
- What is the best screening test for primary hyperaldosteronism? How do you interpret it?
- Hypoaldosteronism is usually due to which acquired problem?
- Which screenings are employed to test for pheochromocytoma?
- What are the 1st steps in working up adrenal incidentalomas?

OVERVIEW

Cortisol, adrenal androgens, and aldosterone are made in the cortex of the adrenal gland from cholesterol.

The adrenal **cortex** has 3 zones (remember “**GFR**” as the sequence and “the deeper you go, the sweeter it gets”):

- 1) The outer zona **glomerulosa** (aldosterone = salt)
- 2) The middle zona **fasciculata** (cortisol = sugar)
- 3) The inner zona **reticularis** (androgens = sex)

The adrenal **medulla** makes **epinephrine** in chromaffin cells.

Hypothalamic corticotropin-releasing hormone (CRH) is secreted in response to a low serum cortisol, stress, and circadian rhythm. CRH causes the release of adrenocorticotropic hormone (ACTH) from the anterior pituitary, which stimulates the adrenal gland to release glucocorticoids (**cortisol** and precursors), adrenal androgens (mainly dehydroepiandrosterone sulfate [**DHEA-S**]), and to a lesser extent, mineralocorticoids (**aldosterone** and precursors), because aldosterone production is mostly regulated by the renin-angiotensin system. ACTH has **no effect** on epinephrine production from the adrenal medulla. See [Figure 1-7](#).

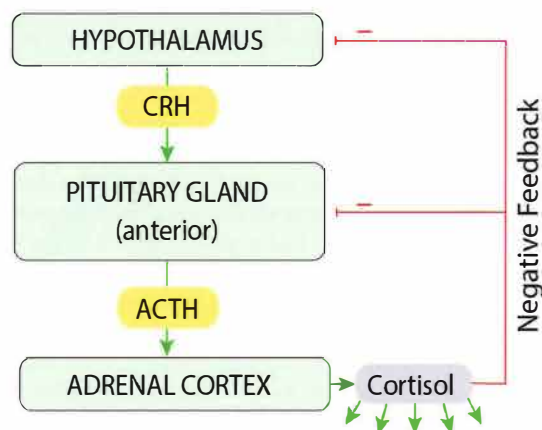


Figure 1-7: HTH-pituitary-adrenal (HPA) axis

STEROID SYNTHESIS

Refer to the adrenal steroid synthesis diagram ([Figure 1-8](#)). It gives you all you need to know for those mind-boggling conditions of congenital adrenal hyperplasia.

Remember: In response to ACTH, the adrenal gland takes cholesterol and forms 3 products—**mineralocorticoids** (aldosterone), **cortisol**, and **androgens** (DHEA-S)—through a series of enzyme actions.

In [Figure 1-8](#), the solid green line represents normal pathways of steroid synthesis. The ovals are the genes that code for important enzymes:

- *CYP17* → 17 α -hydroxylase
- *CYP21A2* → 21-hydroxylase
- *CYP11B1* → 11 β -hydroxylase

An “X” over the oval represents a defect in the gene, with subsequent impairment of the enzyme for that step of synthesis. The color of the X matches the color of the pathway that increases if that enzyme is blocked. For example, a defect in either *CYP11B1* or *CYP21A2* results in increased DHEA-S and decreased aldosterone and cortisol. Not only that, but it causes a buildup in the hormone right before it. For example, a defect in *CYP11B1* causes a buildup of 11-deoxycortisol, and a defect in *CYP21A2* causes a buildup of 17-hydroxyprogesterone.

Recognize that whenever a pathway is blocked, precursors to the blocked point build up. Levels of these precursor hormones are measured clinically to diagnose the particular enzyme deficiency. If you know the effects of the final product of each pathway, then you can easily deduce the clinical presentation of deficiencies and excesses that arise when any pathway is blocked and rerouted into other pathways.

Now, let's go over the actions of the 3 ultimate products and their effects:

- 1) Mineralocorticoids (e.g., **aldosterone**) increase renal Na^+ reabsorption and K^+/H^+ excretion, so high levels cause hypertension, hypokalemia, and metabolic alkalosis. Although ACTH does stimulate aldosterone production, the major regulator is **angiotensin II**.
- 2) Glucocorticoids (e.g., cortisol) stimulate lipolysis and gluconeogenesis by the liver, and they release amino acids from the muscles. They also weaken bones by decreasing the protein matrix. Cortisol inhibits all stages of the inflammatory process. Its immunosuppressive effect is on T cells and their associated cell-mediated immunity and delayed hypersensitivity. Excess cortisol can also stimulate mineralocorticoid receptors with the clinical appearance of aldosterone excess (i.e., hypertension, hypokalemia, and alkalosis) even though the aldosterone level is low!
- 3) The main androgen produced by the adrenals is DHEA-S.
 - In normal males, adrenal androgens are overshadowed by the production of **testicular** androgens.
 - Normally, in females, the adrenals **contribute half** of the **circulating testosterone** (ovaries contribute the other 50%). Together with adrenal DHEA-S, these androgens slightly virilize the normal female

(e.g., pubic and axillary hair). In excess, the clinical effects depend on whether exposure occurs in utero (causing ambiguous genitalia in females) or postnatally (causing virilization, hirsutism, and abnormal menses). Bottom line: Anytime virilization is noted in a female, think about overproduction of androgens by either the **adrenals** or **ovaries**. You can tell where androgens are coming from by the DHEA-S level because DHEA-S is only produced by the adrenal gland; this is unlike testosterone, which can be from either adrenals or ovaries. So, high DHEA-S = adrenal origin!

Virilization is the development of male secondary sex characteristics (e.g., male hair growth, male pattern baldness, increased muscle bulk) in a female.

Refer again to the synthesis diagram (Figure 1-8) and note the following:

- With defective *CYP21A2* and *CYP11B1*, the increased precursors force the reactions along the purple line with enhanced production of adrenal androgens (DHEA-S).
- If *CYP17* is defective, the reaction is forced along the pink line, and more mineralocorticoids are produced.

CONGENITAL ADRENAL HYPERPLASIA (CAH)

CAH is a congenital, autosomal recessive mutation that causes a decrease in cortisol production. CAH is caused by defects in 1 of the 3 genes previously mentioned:

- *CYP21A2* (enzyme = 21-hydroxylase)
- *CYP11B1* (enzyme = 11 β -hydroxylase)
- *CYP17* (enzyme = 17 α -hydroxylase)

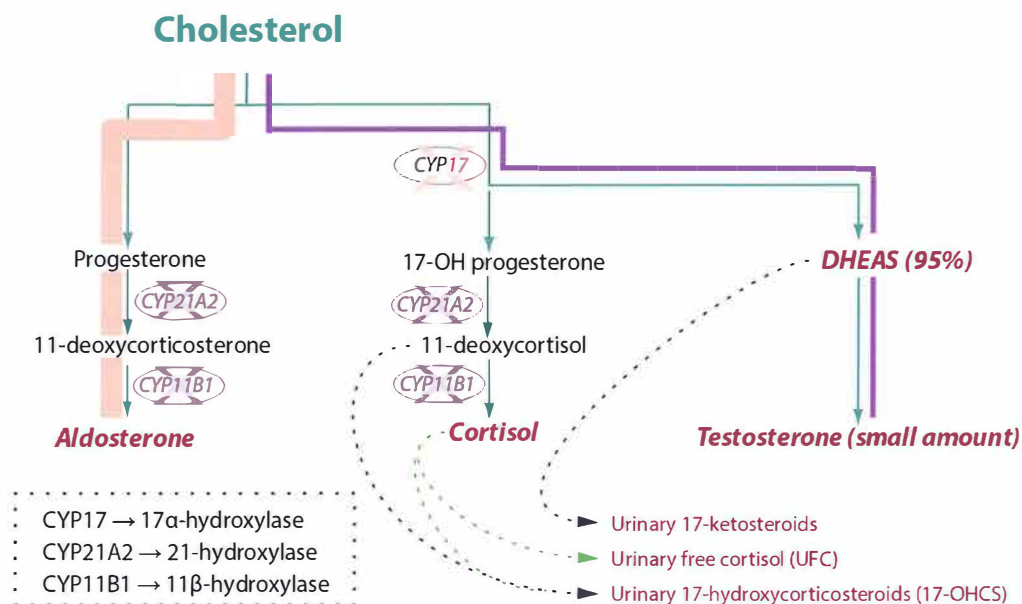


Figure 1-8: Adrenal steroid synthesis pathways

95% of all CAH is due to mutations in **CYP21A2**, causing a deficiency of 21-hydroxylase such that 17-OH progesterone is not converted to 11-deoxycortisol (and thus 17-OH progesterone accumulates and is the screening test). This mutation/deficiency blocks **cortisol** (and aldosterone) production and the high precursors lead to increased androgen production. These mutations have variable expression and can result in severe, moderate, or mild clinical syndromes. The elevated ACTH that occurs in response to the low cortisol causes adrenal hypertrophy ("hyperplasia"). Note: These patients will require long-term glucocorticoid and mineralocorticoid therapy.

Severe 21-hydroxylase deficiency causes the classic "salt-losing" form of CAH. The newborn can present in **adrenal crisis** with hyponatremia and hyperkalemia. Females with this salt-losing type are born with **ambiguous genitalia**. This occurs because the impairment of 21-hydroxylase during gestation forces an increase in DHEA-S and testosterone (purple line on diagram), which causes not only the ambiguous genitalia in newborn girls but also subsequent virilization in boys and girls.

Moderate 21-hydroxylase deficiency causes the classic "simple virilizing" form of CAH. These patients have 1–2% of normal 21-hydroxylase enzyme activity. This is just enough to make sufficient cortisol and aldosterone, but there is still a buildup of precursors that cause an elevated DHEA-S so females have **prepubertal** virilization and males have precocious puberty.

Mild 21-hydroxylase deficiency causes the nonclassic "late onset" form of CAH. Females have **postpubertal** virilization. Labs show an **early morning elevation** of blood **17-hydroxyprogesterone**, and increased blood DHEA-S. Late-onset CAH must be differentiated from polycystic ovary syndrome (PCOS). Confirm with a markedly elevated, 17-hydroxyprogesterone level after ACTH stimulation. Combination estrogen-progesterone oral contraceptive pills (OCPs) are first-line therapy, similar to polycystic ovary syndrome (PCOS) management. Spironolactone can be added. Glucocorticoids are effective but are not used as first-line agents for late-onset CAH, due to the need for long-term therapy and the possible side effects of long-term glucocorticoid use. However, glucocorticoids can be used for a short time to assist with infertility/anovulation in late-onset CAH when fertility is desired.

Less commonly, CAH is due to a genetic defect in **CYP11B1** with 11 β -hydroxylase deficiency. This leads to elevated **11-deoxycortisol** and **11-deoxycorticosterone** (DOC). DOC is a mineralocorticoid precursor but it also has its own mineralocorticoid activity. As with 21-hydroxylase deficiency, cholesterol is shunted along the purple line of the diagram into producing excess DHEA-S and testosterone. As a result, patients with 11 β -hydroxylase deficiency have both virilization and signs of mineralocorticoid excess, even though aldosterone levels are low! Thus, the clinical presentation is hypertension, hypokalemia, and metabolic alkalosis due to DOC; and hirsutism and menstrual irregularities from the elevated DHEA-S.

Mutations in **CYP17** are the rarest of all, accounting for < 1% of all CAH. Here, deficiency in 17 α -hydroxylase pushes the pathway into formation of only mineralocorticoids (primarily DOC). Clinical features are hypertension, hypokalemia, alkalosis (due to DOC), and hypogonadism (due to androgen deficiency). Aldosterone is suppressed by the hypokalemia and renin is low, due to the hypervolemic state. Diagnose with a high DOC and corticosterone, with low cortisol, androgens, and estrogens.

CUSHING SYNDROME

Cushing syndrome occurs when there is an **excess of glucocorticoid in circulation** causing easy fatigability, proximal muscle weakness, easy bruising, weight gain, and emotional lability (sometimes frank psychosis). In women, it additionally causes amenorrhea, hirsutism, and acne. Physical exam reveals facial plethora (a.k.a. moon facies; i.e., a round, red face); thin skin; thick (at least 1.0 cm), bright **purplish** striae (**Figure 1-9**); cervicodorsal fat pad ("buffalo hump"); and truncal obesity. Cortisol in high concentrations can stimulate mineralocorticoid receptors, leading to edema, hypertension, hypokalemia, and metabolic alkalosis in some patients. Comorbid diagnoses include insulin resistance (20% have Type 2 diabetes) and osteoporosis.



Figure 1-9: Abdominal striae in Cushing syndrome

Causes of Cushing syndrome:

- Iatrogenic glucocorticoid administration (e.g., prednisone); the most common cause
- ACTH-secreting **pituitary** adenoma (Cushing **disease**); the most common cause of ACTH-dependent cortisol excess
- **Ectopic ACTH-secreting tumor**: bronchogenic, pancreatic, or thymic carcinoma (Small cell lung cancer is the most common cause of **ectopic** Cushing's syndrome in patients > 60 years of age!)
- Bilateral adrenal hyperplasia
- Adrenal adenomas or carcinomas

Cushing **syndrome** caused by pituitary adenomas is termed Cushing **disease**. Next to exogenous steroids, Cushing disease is the **most common** cause of Cushing syndrome.

Know the following:

- The ACTH level is elevated or inappropriately normal in Cushing disease.
- Recall that ACTH increases the synthesis of not only **cortisol**, but also **adrenal androgens** (Figure 1-8 on page 1-21). So, in Cushing disease (pituitary disease) and ectopic ACTH production, elevated ACTH stimulates production of adrenal DHEA-S, and females can present with hirsutism, virilization, and acne. This is in contrast to non-ACTH-mediated cortisol excess, in which the ACTH and DHEA-S are both low.

In clinical practice, Cushing's can have subtle nuances, but typical exam question scenarios are straightforward when you use the following workup.

Cushing Syndrome Workup

The suspicion of Cushing syndrome comes from recognizing the typical clinical features (i.e., moon facies, buffalo hump, and central obesity).

Before starting the following workup for hypercortisolism, be sure to exclude exogenous glucocorticoid administration, including factitious (i.e., surreptitious) ingestion. Patients on glucocorticoids should not be worked up for Cushing syndrome because you cannot assess for endogenous cortisol excess while on glucocorticoids. All glucocorticoids, including steroid inhalers, topical steroids, and injectable steroids will suppress ACTH and endogenous cortisol secretion.

Step 1: Document the presence of cortisol excess with one of the following initial tests:

- 24-hour urinary free cortisol (**UFC**),
- late-night **salivary cortisol**, and/or
- **low-dose (1 mg) dexamethasone** suppression test (DST).

Confirm an abnormal test either by repeating it or with one of the other 2 tests. A random cortisol is affected by multiple factors and is not useful to evaluate for cortisol excess.

The majority of plasma cortisol is bound to cortisol-binding globulin (CBG), and < 5% is free and physiologically active. Be aware that estrogen (OCPs) raises CBG, which raises serum cortisol and can give a false-positive DST. The urinary and salivary cortisol tests measure free cortisol and do not result in false-positives with estrogen use.

If the patient is depressed, obese, alcoholic, or has uncontrolled diabetes, think **pseudo-Cushing's** before attributing the clinical scenario to true Cushing syndrome. Identify pseudo-Cushing's with the low-dose DST or salivary cortisol levels. Patients with pseudo-Cushing's usually have normal cortisol suppression after treatment

with dexamethasone, and they maintain their diurnal rhythm on salivary cortisol testing. Do not use a UFC because it can often be elevated in pseudo-Cushing's. If a screen for excess cortisol production is abnormal, make an endocrine referral.

Remember: Cushing **syndrome** is the general description for any state of excess cortisol and includes the specific diagnosis of Cushing **disease**, which refers to an ACTH-secreting pituitary tumor.

Step 2: Determine if the Cushing syndrome is ACTH-dependent or ACTH-independent.

Once you have identified a patient with true Cushing syndrome with a Step 1 test, check the **ACTH** level. Normally, a high cortisol state completely suppresses ACTH production. Thus, **any** measurable **ACTH** indicates ACTH-dependent Cushing syndrome—either Cushing disease or ectopic ACTH production. Go to Step 3a.

A suppressed ACTH indicates ACTH-independent Cushing syndrome—**adrenal** hyperplasia, adrenal nodule, or adrenal carcinoma. Go to Step 3b.

Step 3a (ACTH-dependent Cushing syndrome):

ACTH-dependent Cushing syndrome means the cause is either a pituitary tumor (Cushing disease) or an ectopic, ACTH-secreting tumor. Again, ACTH level is elevated or inappropriately normal in both, but Cushing disease is much more common.

See the algorithmic approach for ACTH-dependent vs. ACTH-independent workup (Figure 1-10 on page 1-24).

As Cushing disease is more common than ectopic secreting tumors in ACTH-mediated cortisol excess, the next step is to image the **pituitary** with a **gadolinium-enhanced MRI** and refer the patient to a neurosurgeon if you see a pituitary tumor.

Some ACTH-producing microadenomas are not visible on MRI due to their very small size, so pituitary etiology of cortisol excess is verified with inferior petrosal sinus venous sampling (**IPSS**; detects local production of ACTH). If the IPSS does not confirm a pituitary source, the patient likely has an ectopic ACTH-producing tumor, such as primary lung or carcinoid tumor; look for these with **high-resolution CT** of the **chest** and **abdomen**.

Step 3b (ACTH-independent Cushing syndrome):

When the patient has a high cortisol and low ACTH, there is most likely an **adrenal tumor** (hyperplasia, adenoma or carcinoma) that is secreting cortisol. Image the adrenals with a contrast-enhanced CT. If a mass is found, refer to a surgeon for adrenalectomy.

Consider ordering DHEA-S concentration. Since patients with cortisol-producing adrenal **adenomas** have **low** ACTH, the DHEA-S level will also be low. In contrast, **carcinomas** can make all adrenal products, and they can have **high** DHEA-S, cortisol, aldosterone, and **urine 17-ketosteroids** despite a low ACTH.

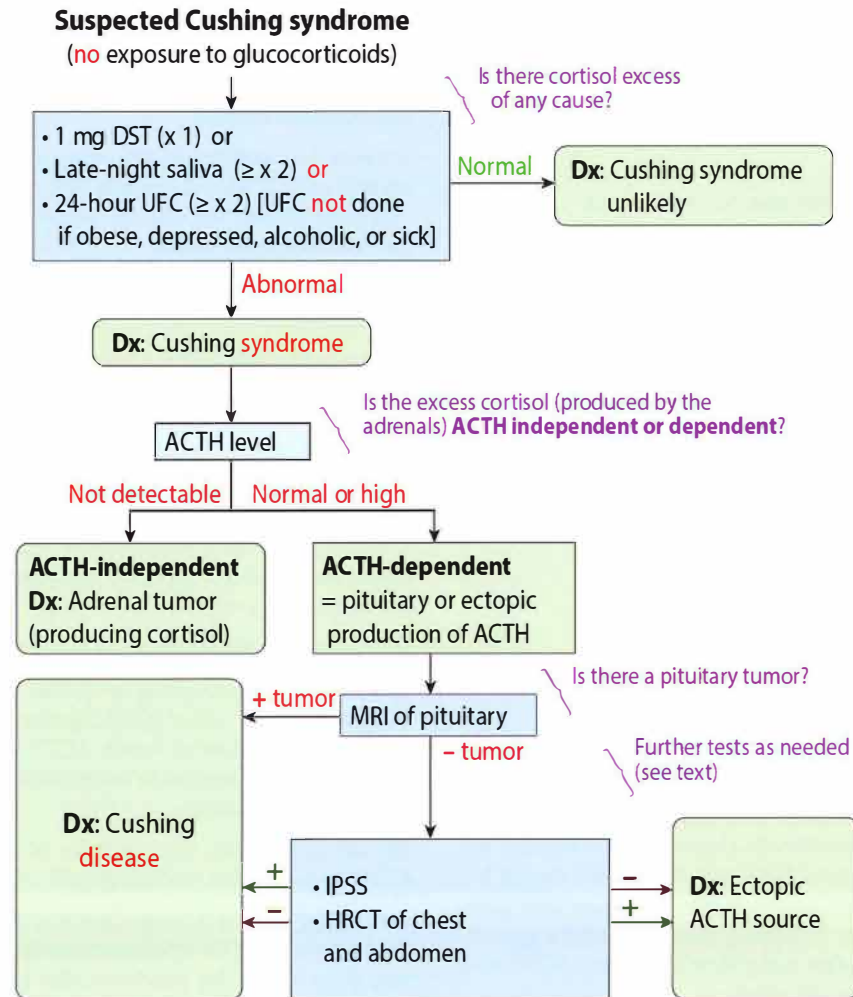


Figure 1-10: Cushing syndrome workup

ADRENAL INSUFFICIENCY (AI)

AI can be **primary** (i.e., Addison disease = dysfunction of the adrenal gland itself) or **secondary** (pituitary) disease. When AI presents acutely, it is an endocrine emergency (adrenal crisis).

In industrialized countries, **primary** AI is most often the result of autoimmune adrenalitis (which is sometimes seen in polyglandular autoimmune syndromes 1 and 2), but it can also be caused by granulomatous and infiltrative diseases, (e.g., HIV/AIDS, CMV, TB, amyloidosis, sarcoidosis). The most common cause of **secondary** AI is rapid withdrawal of chronic exogenous glucocorticoids.

Polyglandular autoimmune syndrome 1 is autosomal recessive (defective *AIRE* gene). Key manifestations include chronic mucocutaneous candidiasis, hypoparathyroidism, and adrenal insufficiency. Other findings can include malabsorption/pernicious anemia, hepatitis, alopecia, chronic autoimmune thyroiditis, and premature gonadal failure.

Polyglandular autoimmune syndrome 2 includes ≥ 2 of the following: Addison disease, chronic autoimmune thyroiditis, premature ovarian failure, and Type 1 diabetes. Less common findings include pernicious anemia, vitiligo, alopecia, sprue, and myasthenia. Schmidt syndrome is the Type 2 syndrome with primary adrenal insufficiency and autoimmune thyroid disease (and often Type 1 diabetes). Know that you must **replace cortisol first** because giving thyroid replacement prior to glucocorticoid replacement can precipitate an adrenal crisis.

Remember that autoimmune diseases often occur together.

Signs and symptoms of AI: The preeminent symptom of adrenal insufficiency is **weakness**. As the disease worsens, patients can become bed-bound. Other symptoms include anorexia, weight loss, N/V, vague abdominal pain, hypoglycemia, and moodiness. Hypercalcemia occurs in 20% of patients (mechanism is unknown). Eosinophilia is unusual but, if present, can be a clue.

Since primary AI affects the entire cortex in addition to cortisol deficiency and low DHEA-S level, there is aldosterone deficiency leading to hyperkalemia, a. Hyponatremia is often seen in primary AI. **Hyperpigmentation** may be evident on physical exam and is due to cosecretion of ACTH and melanin precursor.

Secondary AI (disease of the **pituitary**; e.g., postpartum hypopituitarism [a.k.a. Sheehan syndrome]): **Low ACTH** is **not** due to diseased adrenal glands; thus, because aldosterone is normal and hyponatremia and hyperkalemia are not seen, the zona glomerulosa can still make aldosterone in response to the renin-angiotensin system. The renin-angiotensin system is the major regulator of aldosterone production, not ACTH. It is not associated with hyperpigmentation. Here, the DHEA-S is low due to lack of ACTH stimulation.

Diagnosis and treatment of AI: If the patient has **acute adrenal insufficiency**, it needs to be **treated immediately**. Your first task is simply to recognize that AI exists and treat it. You can sort out etiology later.

Treatment of adrenal crisis: If the patient is in **shock** and you suspect adrenal shock, check a random cortisol, give IV fluids with glucose if the patient is hypoglycemic and dexamethasone. Perform an ACTH stimulation test **after** the patient **stabilizes**. **Dexamethasone** is potent, does **not interfere** with the cortisol assay, and does not cause endogenous adrenal suppression for a few hours, so the ACTH stimulation test is reliable. Dexamethasone does suppress the ACTH level, so if you have time, draw a serum ACTH prior to instituting treatment.

Treatment of stable patients with AI: In patients who are hemodynamically stable, perform an ACTH stimulation test: First, draw a baseline cortisol and ACTH level, then give **cosyntropin** (synthetic ACTH) 0.25 mg IM/IV, and recheck cortisol at 30 and 60 minutes. Normally, the cortisol level increases with cosyntropin stimulation. If the stimulated cortisol is $< 18\text{--}20\text{ }\mu\text{g/dL}$ ($496\text{--}552\text{ nmol/L}$), your patient has AI. The ACTH level determines whether the disease is in the adrenals (primary; high ACTH level) or the pituitary (secondary; low ACTH level).

You may not need the cosyntropin (ACTH) test in 2 types of patients when AI is suspected: those whose 8 a.m. cortisol is $< 3\text{ }\mu\text{g/dL}$ (83 nmol/L) with clear-cut clinical findings of adrenal insufficiency and those with chronic glucocorticoid use or recent high-dose glucocorticoid therapy, because the test is impossible to interpret.

Note: The cosyntropin stimulation test is abnormal (lower than expected increase in cortisol) in **both** primary and secondary adrenal insufficiency. In primary AI, endogenous ACTH levels are already high and administration of cosyntropin has little effect. In longstanding secondary/tertiary AI (disease in pituitary or hypothalamus), the adrenal glands do not respond to

ACTH stimulation even though they are not diseased (because they are atrophied).

If the cosyntropin test is abnormal, you can check an ACTH level and a serum aldosterone. In primary AI, the ACTH level is high while the serum aldosterone is low.

Summary of interpretation of labs in AI:

- **Primary AI** = **abnormal** cosyntropin stimulation, **high** ACTH level, and **low** aldosterone (because multiple layers of adrenal are affected by the disease process). Hyperkalemia occurs in $> 20\%$ of cases, but its absence does not rule out primary AI. Low DHEA-S.
- **Secondary/Tertiary AI** = abnormal cosyntropin stimulation, low or low-normal ACTH level, and normal aldosterone. Low DHEA-S. Image the pituitary (sella) with MRI if no history of steroid use.

Although longstanding secondary/tertiary AI causes an abnormal cosyntropin stimulation test, acute causes of central adrenal insufficiency (e.g., after pituitary surgery, intracranial trauma/bleeding) can have a normal cosyntropin test because the adrenal glands haven't had time to atrophy (so they respond normally to ACTH stimulation). Consider treating empirically and wait several weeks before checking the cosyntropin test in these patients.

After the acute phase of treatment of AI, these patients need long-term glucocorticoid therapy. Remember to instruct the patient about stress dosing (doubling their baseline steroid therapy in case of illness), and the importance of having a medical ID form with them at all times describing their disease. Also, remember that in **primary AI**, there is usually an associated **mineralocorticoid deficiency**, so for long-term care you need to also replace mineralocorticoids with fludrocortisone.

MINERALOCORTICIDS

Aldosterone is discussed extensively in the **Nephrology** section. It increases Na^+ resorption and, hence, K^+ and H^+ excretion in the distal tubules, causing hypokalemia and a metabolic acidosis. Increased Na^+ resorption means increased water retention and the tendency for hypertension. The release of aldosterone is mainly controlled by both the renin-angiotensin system and the K^+ level, but ACTH does have some effect.

To recap, renin is released by the **healthy** kidney from the juxtaglomerular apparatus in response to at least 3 independent factors:

- 1) Perceived volume depletion, as measured by the juxtaglomerular cells. These are specialized myoepithelial cells cuffing the afferent arteriole.
- 2) Decreased levels of filtered Na^+ , as measured by the efferent macula densa cells
- 3) Sympathetic nervous system stimulation, which stimulates release of renin in response to assuming the upright posture

Renin converts **angiotensinogen** to **angiotensin I**, which is then converted to **angiotensin II** by the angiotensin-converting enzyme (ACE)—mainly in the lungs. Angiotensin II has pressor effects and stimulates aldosterone release from the **zona glomerulosa** in the adrenal glands.

Hyperaldosteronism

Primary hyperaldosteronism (disease in the adrenal) is associated with **low renin**, hypertension, hypokalemia, and metabolic alkalosis.

Secondary hyperaldosteronism (disease in the kidney) is a **high renin** state. Decreased renal blood flow from either renal artery stenosis or fibromuscular dysplasia → increased renin → increased angiotensin II → increased aldosterone.

Situations other than aldosterone excess that can cause hypertension and hypokalemia are licorice ingestion and Cushing syndrome.

See the **Nephrology** section for more on when and whom to screen for hyperaldosteronism.

Figure 1-11 summarizes the screening and confirmatory tests and how to determine the source of the aldosterone.

The best **screening test** for primary hyperaldosteronism is a paired plasma aldosterone concentration (PAC) and plasma renin activity (PRA). This is often presented as a PAC:PRA ratio. Know that aldosterone blockers (i.e., spironolactone, eplerenone) interfere with the PAC:PRA ratio **and must be stopped 4 weeks prior to performing this test**. All other antihypertensive medications can be continued. Low K^+ decreases the aldosterone production and can give a false-negative PAC:PRA ratio, so correct hypokalemia with oral K^+ before the test. Interpret the results this way:

- **Primary hyperaldosteronism:** aldosterone (PAC) elevated and renin (PRA) suppressed → elevated PAC:PRA ratio (of at least 20:1). Think adrenal disease (aldosterone-producing adenoma or primary adrenal hyperplasia).

Suspected Primary Hyperaldosteronism

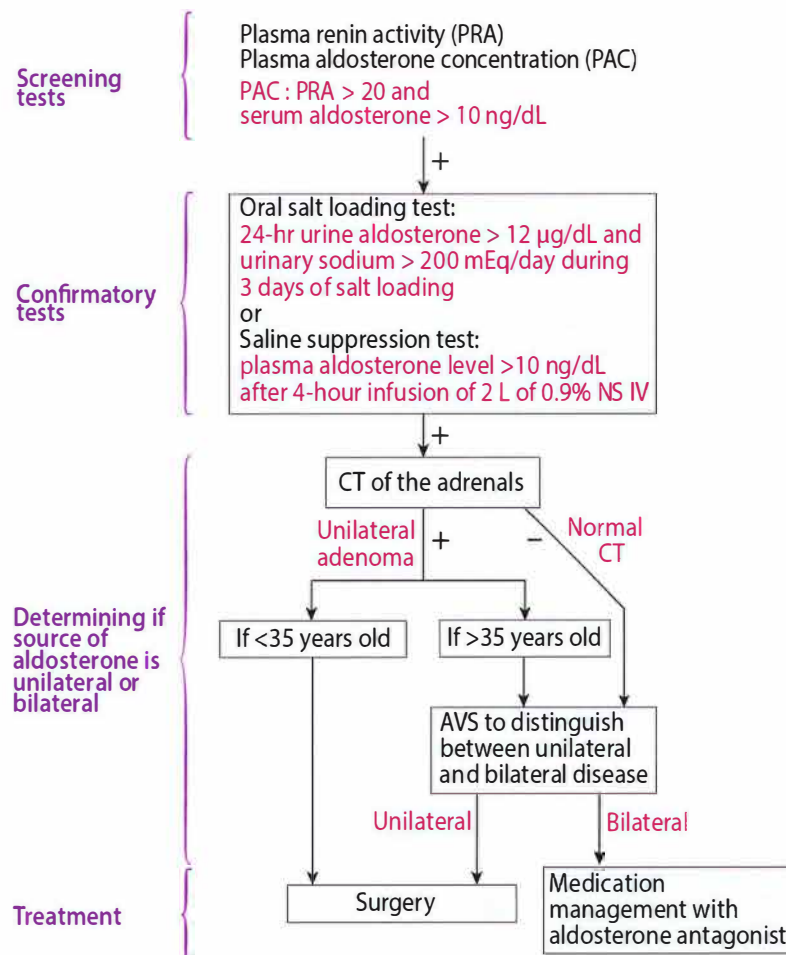


Figure 1-11: Primary hyperaldosteronism workup

- **Secondary hyperaldosteronism:** PAC and PRA both elevated, with PAC:PRA usually < 10. Think renovascular disease (common) or renin-secreting tumor (rare).
- **Cushing's** (cortisol activates mineralocorticoid receptor) and chronic consumption of **black licorice** (increases mineralocorticoid effect of glucocorticoids): PAC and PRA both low, with PAC:PRA either normal or elevated

Confirmatory tests: If the labs support primary hyperaldosteronism (PAC high, PRA low, and PAC:PRA high), **confirm** the diagnosis by **trying to suppress** aldosterone production. In saline suppression testing, give 2 L normal saline IV over 3–4 hours to the recumbent patient. Nonsuppression of PAC indicates primary hyperaldosteronism. Alternatively, you can give an oral Na⁺ load for 3 days, then measure the 24-hour urine aldosterone excretion. (Again, nonsuppression suggests adrenal disease.) These tests are not as easy as they seem. In patients with significant hypertension, giving saline or a high-salt diet runs the risk of dangerously increasing blood pressure.

Remember, if the aldosterone level is not high (at least > 10 ng/dL [277.4 pmol/L]), it is not hyperaldosteronism, even when the PAC:PRA is high. The renin activity can be very low for other reasons (e.g., high salt consumption, essential hypertension), giving a misleadingly high PAC:PRA ratio.

Once primary hyperaldosteronism is confirmed, the next step is to determine if it is due to an aldosterone-producing adenoma (APA) or primary adrenal hyperplasia (PAH). With this workup, keep in mind that while APA can be treated surgically, both APA and PAH can be treated medically. If the patient is not a surgical candidate, or surgical treatment is not preferred, you can stop here—just treat with an aldosterone antagonist!

If the patient is a surgical candidate and wishes to pursue surgical treatment, proceed as follows. First, **image** the adrenals with either high-resolution CT or MRI to see if there is an adrenal adenoma.

If there is a unilateral adrenal nodule on CT/MRI, the next step depends on the age of the patient:

- < 35 years of age: Go straight to surgical adrenalectomy. Nonfunctioning adrenal adenomas are rare in this age group.
- > 35 years of age: Perform adrenal vein sampling (AVS) to prove the adenoma is functional (i.e., an APA). If AVS is consistent with APA (lateralization of high aldosterone to the side with the tumor), proceed to surgery.

If imaging does **not** reveal an adrenal nodule, there still may be an APA that is too small to detect on imaging. Regardless of age, perform AVS. If there is lateralization of aldosterone production, you can proceed with adrenalectomy.

If AVS shows no lateralization (i.e., no APA), the primary aldosteronism is due to PAH and treatment is with aldosterone antagonists (i.e., spironolactone, eplerenone).

Hypoaldosteronism

The most common cause of hypoaldosteronism is decreased production of **renin** in **diabetic** patients with mild renal failure (**hyporeninemic hypoaldosteronism**, a.k.a. Type 4 renal tubular acidosis [RTA]). It is also seen in patients with chronic interstitial nephritis, chronic NSAID use, and heparin therapy. More severe hypoaldosteronism is seen with primary adrenal insufficiency (i.e., Addison disease).

Suspect hypoaldosteronism in patients with **hyperkalemia** and **normal** anion gap metabolic **acidosis** out of proportion to the renal disease (low aldosterone leads to failure to excrete H⁺/K⁺ in the distal tubule). Patients are unable to retain Na⁺ in states of volume contraction, and they develop **postural hypotension**.

Start the workup by excluding AI as a cause of the hyperkalemia and hypotension because, clinically, they can look similar; perform an ACTH stimulation test. Next, measure renin and aldosterone levels during upright posture and salt restriction (renin is low in this diagnosis but high in AI). Treat with a mineralocorticoid (fludrocortisone). If hypertension and edema are present, do not use fludrocortisone; treat with a low-potassium diet and a loop diuretic.

PHEOCHROMOCYTOMA

In 2014 the Endocrine Society published the 1st clinical practice guidelines for pheochromocytoma. Our discussion is based on these guidelines.

Pheochromocytoma (pheo) is a rare catecholamine-secreting tumor that arises from chromaffin tissue of the adrenal medulla. They are called paragangliomas when they arise in extraadrenal sympathetic ganglia. Symptoms are due to secretion of catecholamines: epinephrine, norepinephrine, and dopamine. Symptoms are typically paroxysmal and described as “spells.” The classic triad is headaches, sweating, and tachycardia. Rule of thumb: 10% are extraadrenal, 10% are bilateral, 10% are **malignant**, and 10% are **genetic/familial**.

The **risk of malignancy** is **higher** in **extraadrenal pheo** and in certain genetic mutations. 5–15% of patients with these tumors do **not** present with hypertension and many have sustained, not paroxysmal hypertension.

The differential diagnosis includes labile essential hypertension, anxiety, hyperthyroidism, hypoglycemia, and menopausal flushing—all are more common than pheo. Medications and drugs (e.g., cocaine, pseudoephedrine, amphetamines) can also cause similar symptoms. Carcinoid tumor can mimic pheo but is quite rare.

Suspect a pheo in patients who have **spells** of headaches, sweating, and tachycardia. The likelihood of a pheo increases with these risk factors:

- Orthostatic hypotension (volume depletion)
- Refractory HTN
- HTN in a young person without a family Hx

- Adrenal incidentaloma
- Dilated cardiomyopathy of unknown cause
- HTN during procedures or with ingestion of tyramine-containing foods
- Paroxysmal HTN
- Atypical results when using certain classes of medications (e.g., MAO inhibitors, sympathomimetics, opioids, dopamine receptor antagonists, β -blockers)
- Family Hx of pheochromocytoma (particularly high risk)
- Family Hx of MEN2, neurofibromatosis (NF), or von Hippel-Lindau (VHL) disease (particularly high risk)

Start the pheo workup with the following biochemical screening tests:

- **24-hour urinary fractionated metanephrines:** This screening test is very sensitive and specific but cumbersome. It's usually the best test in patients with low pretest probability of pheo. Wean patients off tricyclic antidepressants and cyclobenzaprine 2 weeks before testing because these meds interfere with the results. (SSRIs are okay.)
- **Plasma free metanephrines:** Simple to do, and sensitivity is high, so a negative test excludes disease. However, specificity is lower, and false-positive results are common, especially in patients with low pretest probability of disease. Plasma free metanephrines is most appropriate in high-risk patients: those with MEN2/NF/VHL, incidentaloma with characteristics of pheo, or family history of pheo.
- Do not measure plasma catecholamines or vanillyl-mandelic acid (VMA)—these tests have proven to be less accurate than the above tests.
- If screening test confirms pheo ($> 3 \times$ ULN) then image; if not, then confirmatory testing needs to be done with a clonidine suppression test.

If the biochemical tests confirm a pheo, perform CT or MRI to localize the tumor.

If imaging does not show a tumor and you still suspect one given the screening tests and history, look for the tumor using a PET scan, total body MRI, or radioactive tracer (^{123}I , metaiodobenzylguanidine [MIBG] scintigraphy, a norepinephrine analog that concentrates in adrenals and pheos).

Discuss genetic testing with all patients with pheochromocytoma, but prioritize the following patient groups:

- Young age (< 45 years)
- Paranglioma: familial paragangliomas due to germline mutations of genes encoding succinate dehydrogenase subunits B, C, and D (SDHB, SDHC, SDHD), which increase malignancy risk
- Those with a family Hx of pheo or paraganglioma
- Those with multifocal, bilateral, or metastatic disease

Always treat pheos with surgical resection. Laparoscopic adrenalectomy is usually appropriate, but open resection

should be considered for large (> 6 cm) or invasive tumors. Treat all patients with preoperative α -adrenergic receptor blockade (phenoxybenzamine or doxazosin) for at least 7–14 days prior to resection. A CCB or β -blocker can be added if blood pressure cannot be controlled with α -blockade alone.

Remember to **never** use a β -blocker without first treating with an α -blocker, because it leads to unopposed α stimulation, which can cause hypertensive crisis. Patients with pheo tend to have depleted intravascular volume; replace preoperatively using intravenous saline or a high-sodium diet.

Although most pheos are benign, approximately 10% are malignant. For those with malignant, metastatic disease and positive ^{123}I -MIBG scintigraphy, treatment with ^{131}I -MIBG can be effective. For rapidly expanding lesions or those with negative ^{123}I -MIBG scintigraphy, a chemotherapy regimen of cyclophosphamide, vincristine, and dacarbazine can provide up to 50% tumor regression.

Patients with an undiagnosed pheo who go to surgery for an unrelated condition have a high mortality rate. Severe adverse reactions to anesthesia include hypertensive crisis, cardiac arrhythmia, and death.

OTHER ADRENAL MASSES

Many adrenal masses are “incidentalomas”—masses > 1.0 cm and discovered by accident on an imaging study done for another reason, such as abdominal pain. Prevalence of incidentalomas increases with age and can reach 10%. Up to 15% of patients with an incidentaloma have bilateral masses.

90% of incidentalomas are nonfunctioning adenomas. $< 3\%$ are cancerous unless the patient has a known diagnosis of malignancy, in which case the mass has a 50% chance of being malignant.

Without a history of malignancy, the 2 questions to ask yourself are:

- 1) Is it making hormones?
- 2) Is it cancerous (primary adrenocortical carcinoma [ACC] or metastatic)? ACC is suspected with lesions > 4 –6 cm.

All patients with adrenal incidentaloma should have the following tests:

- **Low-dose overnight dexamethasone suppression test** for all patients; this test evaluates for subclinical Cushing syndrome, the most common hormonal abnormality.
- **Plasma free or urinary fractionated metanephrines** for all patients; this test evaluates for pheochromocytoma, the most dangerous hormonal abnormality.
- **Blood pressure and serum K^+** for all patients. Only check PAC:PRA if hypertension or hypokalemia is present. These tests evaluate for primary hyperaldosteronism.

- Only check adrenal sex hormones if females have virilization (DHEA-S) or males have feminization (estradiol).

If the results of these tests are normal and the mass is < 4 cm, observation is appropriate with repeat imaging in 6–12 months and repeat hormonal testing for cortisol excess yearly for a few years, depending on the clinical setting. Know that FNA is **never** used to determine whether an adrenal mass is an adenoma or an ACC because cytologic features may not distinguish between them. However, FNA **may** be used to differentiate an adenoma from **metastatic** disease. Remember to rule out pheochromocytoma before doing any procedure on an adrenal mass!

There are 3 indications for **adrenalectomy** of an incidentaloma:

- 1) Tests indicate a functioning tumor (namely cortisol or catecholamine production, because aldosterone excess can be treated medically or surgically).
- 2) Mass is > 4–6 cm.
- 3) Imaging characteristics are suspicious for malignancy (e.g., irregular margins, calcifications, inhomogeneous density, growth over time).

HORMONES OF REPRODUCTION

PREVIEW | REVIEW

- What is the definition of primary amenorrhea, and what are the common causes?
- A female patient with short stature, primary amenorrhea, and little or no breast development probably has which genetic defect?
- What is the definition of secondary amenorrhea, and what are the common causes?
- What are the initial labs for the workup of secondary amenorrhea, once pregnancy is excluded?
- What do elevated follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels in an amenorrheic woman tell you?
- Which testing is done for a woman with secondary amenorrhea who has low FSH and LH levels?
- What is the most common cause of primary hypogonadism in males?
- Differentiate Kallmann syndrome from Klinefelter's.
- In which situations do you see gynecomastia as a normal finding? As part of a disease state?

FEMALES

Normal Physiology

Follow along in [Figure 1-12 on page 1-30](#).

The menstrual cycle is a complex series of changes required for the production of an oocyte, and for the preparation of the uterus for pregnancy. The cycle is divided into two phases: follicular and luteal. The follicular phase begins with the onset of menses (day 1 of the menstrual cycle) and ends at ovulation (some say it ends on the day before the LH surge). The follicular phase can last 14 to 21 days. The luteal phase, which consistently lasts 14 days, begins after ovulation (some say on the day of the LH surge) and ends at the onset of the next menses.

The hypothalamus secretes gonadotropin-releasing hormone (GnRH) in a pulsatile fashion (60- to 90-minute cycle), which stimulates the anterior pituitary to then pulse out two gonadotropins, luteinizing hormone (LH) and follicle-stimulating hormone (FSH).

LH stimulates androgen formation within the theca cells. FSH regulates the new ovarian follicle granulosa cells to produce 2 hormones: **estrogen** from the androgen precursors (builds up the lining of the uterus) and **inhibin** (suppresses secretion of FSH). Estrogen normally **inhibits** FSH and LH production; however, at **midcycle**, estrogen has a **positive** feedback effect causing a **surge** in the LH and FSH, which then stimulates ovulation.

After ovulation, the follicle becomes a corpus luteum that secretes estradiol (main estrogen) and progesterone. Progesterone, in turn, prepares the lining of the uterus for possible implantation and **suppresses** gonadotropin release.

In women, the ovaries and adrenals share the task of producing testosterone—each producing 50%. Differentiate where androgen excess is from by checking a DHEA-S, because sulfation of DHEA only occurs in the adrenal glands (not the ovaries). The major effect of testosterone in females is androgenization with normal hair development in the pubic and axillary regions.

Amenorrhea

Amenorrhea is the absence of menses and can be intermittent or permanent, depending on the etiology.

Primary Amenorrhea

Primary amenorrhea is the absence of menses by 16 years of age in the presence of normal growth and secondary sexual characteristics. It is commonly the result of a genetic cause or an anatomical problem.

To determine etiology, think of the organs affecting the menstrual cycle:

- Hypothalamus (e.g., anorexia, constitutional delay of puberty, GnRH deficiency)
- Pituitary (e.g., hypopituitarism, hyperprolactinemia, hypothyroidism)
- Ovary (e.g., PCOS, Turner syndrome gonadal dysgenesis)
- Uterus (e.g., Müllerian agenesis)
- Vagina (e.g., transverse vaginal septum)

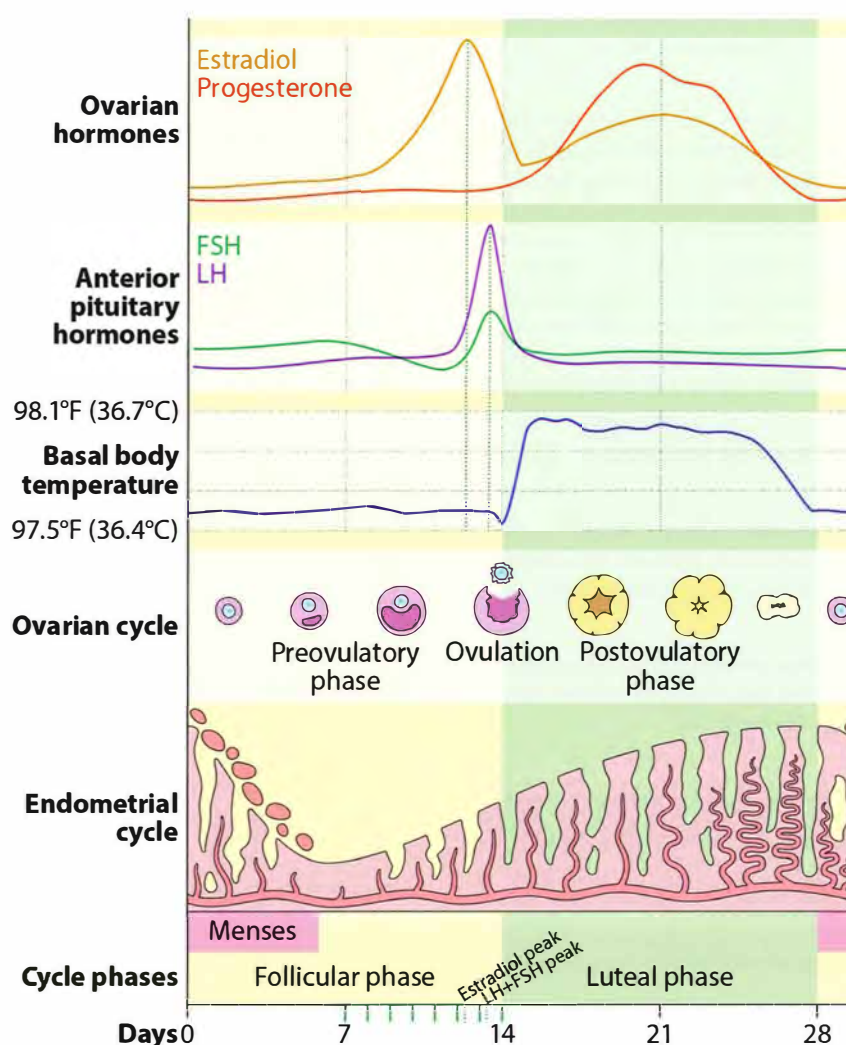


Figure 1-12: Menstrual cycle

An abnormality at any one of these locations can cause primary amenorrhea.

Primary amenorrhea is **rare**, and evaluation is often undertaken by pediatricians; however, know the following important diagnoses:

- If a patient with primary amenorrhea has short stature, widely spaced nipples, little breast development, webbed neck, and decreased pubic and axillary hair, think of **Turner syndrome** (karyotype 45,X).
- If you see a female with **no palpable cervix** and **no uterus**, but there are normal secondary sex characteristics, including breasts and pubic and axillary hair, consider congenital absence of the uterus.
- If you see a female with **no palpable cervix**, **no uterus**, and **no pubic and axillary hair**, but there are **breasts**, consider androgen insensitivity syndrome (an insensitivity to androgens in a **karyotypic 46,XY**). In this condition, testosterone levels are in the normal male range.

Secondary Amenorrhea

Secondary amenorrhea is the absence of menses for:

- ≥ 3 months in a woman who previously had regular menstrual cycles or
- ≥ 6 months in a woman who has had irregular menses.

The most common causes of secondary amenorrhea are pregnancy, PCOS, and functional hypothalamic amenorrhea.

Know that erratic menstrual cycles are common in the first years after menarche and in the last years prior to menopause. Secondary amenorrhea is most often caused by **pregnancy**; once that is excluded, think about the other causes.

In initial labs, include a pregnancy test (always!), FSH, LH, prolactin (PRL), and thyroid-stimulating hormone (TSH). If the woman is hirsute, and particularly if she is virilized (e.g., deepening voice, balding), measure serum total testosterone and DHEA-S. Also consider 17-OH progesterone.

Increased FSH and LH levels in the amenorrheic woman tell you that there is ovarian failure. See [Figure 1-13](#). If the woman is < 40 years of age, this is called primary ovarian insufficiency (POI), and, if the woman is > 40 years of age, it is called menopausal ovarian failure. (The median age of menopause is 51 years.) In POI cases, consider mosaic Turner syndrome (get a karyotype), fragile X, or autoimmune polyglandular syndrome. Note, though, that POI does occur idiopathically in many women.

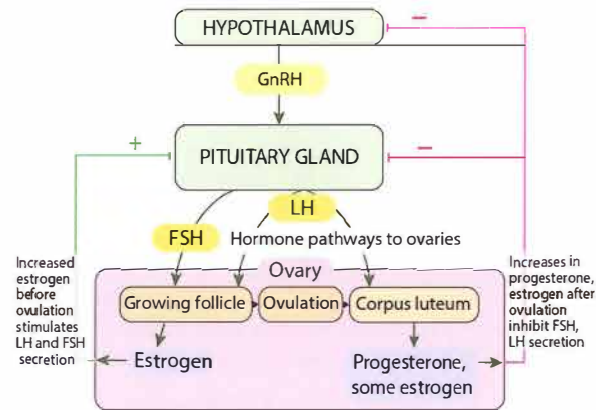


Figure 1-13: HTH-pituitary-gonadal axis in women

Low FSH and LH levels in the amenorrheic woman tell you that the pituitary is not making the hormones, either because it is diseased or because the hypothalamus is not sending out GnRH. This is called “**hypogonadotropic hypogonadism**,” and it has several causes. Etiologies include hyperprolactinemia, hypothyroidism, infiltrative disorders, celiac disease, and **functional** hypothalamic amenorrhea.

Functional hypothalamic amenorrhea (FHA) is caused by **stress** from an eating disorder and/or prolonged, intense exercise; e.g., long-distance running. **FSH/LH** and **estrogen** are **decreased**. Measure PRL and TSH to exclude hyperprolactinemia and hypothyroidism before making this diagnosis.

So, check the following for the secondarily **amenorrheic** woman with **low FSH and LH**:

- Prolactin level
- TSH level
- MRI of the pituitary gland

If there is a question as to the estrogen status (LH and FSH are “normal” with secondary amenorrhea), a progesterone challenge test can be done. If withdrawal bleeding occurs, it signifies the presence of endogenous estrogen exposure—consider adding progesterone for endometrial protection. Absence of menses after progesterone withdrawal confirms a low or absent estrogen state. Order a brain MRI and consider starting estrogen to prevent long-term complications.

Amenorrhea with Hirsutism

The **amenorrheic** woman with **virilizing** signs needs a good history (duration of symptoms), physical exam, and labs: **DHEA-S**, **testosterone**, and **17-OH progesterone** levels.

The major diagnoses that cause **amenorrhea** and **virilization** are **polycystic ovary syndrome (PCOS)**, congenital adrenal hyperplasia, and, rarely, **tumors** of the **adrenal** or **ovary**. Recall from the discussion in [Steroid Synthesis on page 1-20](#) that, in the female, both the ovaries and the adrenals contribute to androgen production, almost equally. Usually, normal androgen production causes only growth of pubic and axillary hair. **Excess** growth of hair in these areas and/or other “masculinizing” signs prompt concern about either PCOS or adrenal/ovarian tumors.

Polycystic Ovary Syndrome

For a discussion of polycystic ovary syndrome, see the [Women's and Men's Health](#) section.

Hirsutism

This topic is simply a more targeted discussion of hirsutism—a specific virilizing sign ([Table 1-3](#)). Hirsutism is when a woman grows coarse hair in places they typically either do not grow hair or only have very fine hair (e.g., moustache area, chin, torso, back). The history and physical exam are keys to evaluating a hirsute woman. Rapid onset and progression are always more worrisome for a tumor. Always ask the patient about the hair distribution in family members (mother/sister) to distinguish from normal ethnic/genetic hirsutism. Objectively assess hair growth and distribution during the physical.

Idiopathic hirsutism refers to hirsutism with no identifiable cause in a woman with no other signs of virilization (e.g., clitoromegaly, deepening of the voice, male-pattern

Table 1-3: Hirsutism Workup — Laboratory Findings

Disorder	Testosterone	DHEA-S	LH:FSH Ratio	17-OH Progesterone
Adrenal carcinoma	Normal/↑	↑↑↑	Normal	Normal/↑
Ovarian carcinoma	↑↑↑	Normal	Normal	Normal
Congenital adrenal hyperplasia	Normal/↑	Normal/↑	Normal	↑↑↑
Polycystic ovary syndrome	Normal/↑	Normal/↑	> 2	Normal

balding, increased muscle mass) and with normal menstrual cycles, hormone levels, and weight. The best treatment to slow hair growth is spironolactone, which is an aldosterone and androgen receptor antagonist. Birth control pills may also slow hair growth and should be used in conjunction with spironolactone (since spironolactone is contraindicated in pregnancy!).

A scoring system (**Ferriman-Gallwey**) can be useful to determine whether a patient truly has worrisome features. The scale shows photos of hair growth in parts of the body subject to androgens: upper lip, chin, chest, abdomen, pelvis, upper arms, thighs, upper back, and lower back. For each location, the amount of hair is assessed and graded on a scale of 0 to 4. A score > 8 merits further evaluation, especially when the hirsutism is associated with other virilizing signs/symptoms (e.g., deepening of the voice, increased muscle bulk).

In truth, the scoring system is not used much in practice, as hirsutism is not typically pathologic. It's the presence of virilization and rapidly worsening hirsutism that are concerning.

The workup for the **virilized female** includes evaluation of ovarian and adrenal androgens: **testosterone**, **DHEA-S**, the **LH:FSH** ratio, and **17-OH progesterone** (Table 1-3 on page 1-31).

Recognize the lab results below, which are seen in the **virilized woman**:

- **Mild** elevations of DHEA-S and/or testosterone are consistent with **PCOS**.
- **Elevated** testosterone and **very high** DHEA-S are consistent with an **adrenal carcinoma**.
- **Very high** testosterone with normal DHEA-S is consistent with an **ovarian stromal tumor** (e.g., Sertoli-Leydig tumor = < 1% of ovarian cancers).

Remember that hirsutism can also be due to **late-onset, partial congenital adrenal hyperplasia**, which is usually caused by a **CYP21A2** gene defect (→ 21-hydroxylase deficiency). Labs show elevated blood 17-hydroxyprogesterone and blood DHEA-S (Figure 1-8 on page 1-21).

Cushing disease (in the pituitary) and **prolactinoma** are uncommon causes of hirsutism. Drugs causing hirsutism include minoxidil, cyclosporine, and phenytoin.

MALES

In men, luteinizing hormone stimulates Leydig cells (**L stimulates L**) to produce testosterone, which in turn inhibits FSH and LH secretion. FSH stimulates the Sertoli cells to secrete inhibin B and also secrete androgen-binding protein (ABP), which in turn binds to testosterone and moves into the seminiferous tubules. ABP-testosterone is less lipophilic and concentrates within the luminal fluid of the seminiferous tubules, enabling spermatogenesis in these tubules and sperm maturation in the epididymis. Hence, both FSH and LH are required for spermatogenesis. See Figure 1-14 for the hypothalamus-pituitary-gonadal axis in men.

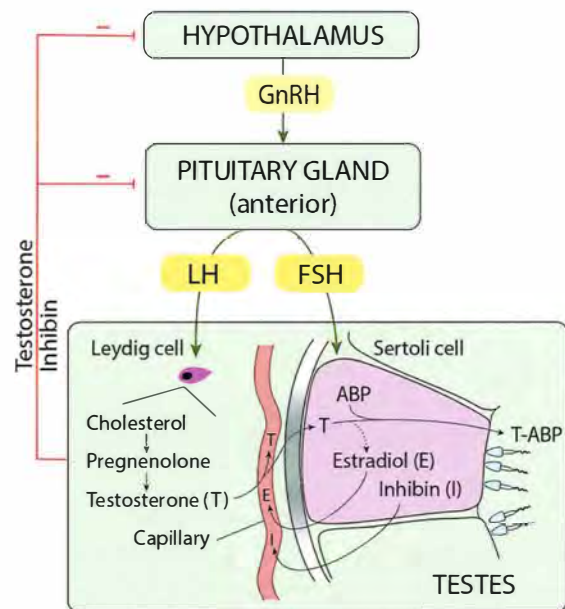


Figure 1-14: HTH-pituitary-gonadal axis in men

Primary hypogonadism (testicular failure) is usually due to **Klinefelter syndrome** (47,XXY or mosaic 46,XY/47,XXY). The genetic abnormality results in **defective testosterone synthesis** by the Leydig cells. The testes do not grow properly, and they fail to adequately produce androgens. Clinical features include small testes, long arms and legs, infertility, lack of virilization (sparse hair growth and muscle mass), and gynecomastia. Some patients have learning disabilities. The expression of this genetic abnormality is variable. Occasionally, mosaic individuals are fertile. Testosterone is decreased, and serum LH and FSH are markedly elevated. Diagnose with a karyotype. Treat Klinefelter syndrome with testosterone. Infertility can be addressed with in vitro techniques harvesting spermatozoa from the testes.

Secondary hypogonadism is due to an **abnormal hypothalamic-pituitary-gonadal axis**, so testosterone level is low and FSH and LH are low or inappropriately normal. Causes of secondary hypogonadism are acquired or congenital.

Acquired causes are more common and include:

- Hyperprolactinemia
- Longstanding use of exogenous testosterone or abuse of anabolic steroids
- Excessive glucocorticoids from any source
- Infiltrative disorders
- Chronic opioid use
- Aging
- Obesity

The workup for hypogonadism in men is summarized in Figure 1-15.

Kallmann syndrome is an example of a congenital gonadotropin deficiency. It is characterized by GnRH deficiency + anosmia (inability to smell). It is associated with midline

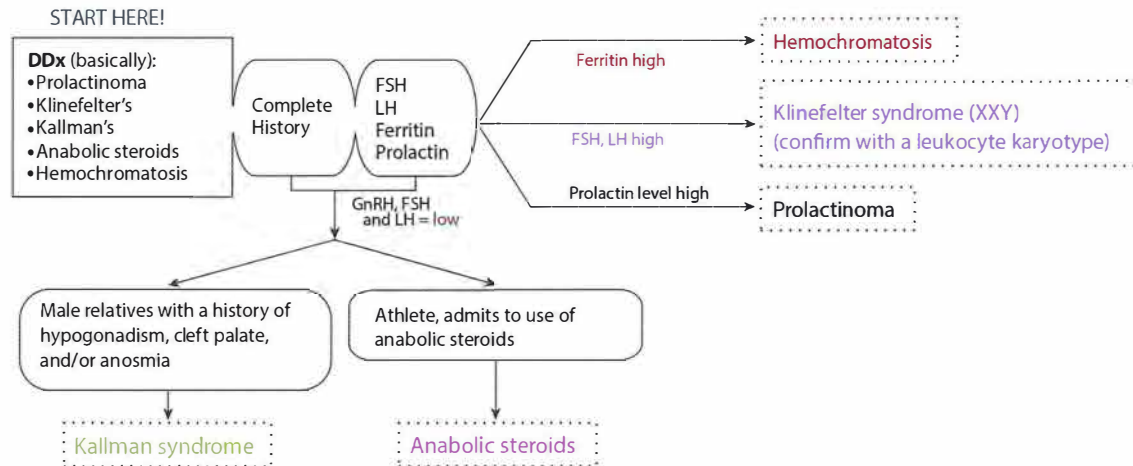


Figure 1-15: Hypogonadism workup for men

defects, such as cleft palate and horseshoe kidney. It is X-linked recessive, so male relatives on the maternal side may be affected. In Kallmann syndrome, FSH and LH levels are low (distinguishing it from Klinefelter syndrome, where LH and FSH are high).

Erectile dysfunction is discussed in the [Women's and Men's Health](#) section.

Gynecomastia results from an increased **estrogen-to-androgen** ratio. Unilateral or bilateral gynecomastia is **normal at puberty** and tends to **regress after 1-2 years**. It is found in males who have increased aromatization of circulating androgens into estrogen. Also, conditions that produce excess testosterone (such as DHEAS-secreting adrenal adenoma) can result in excess estradiol because of peripheral aromatization.

Gynecomastia is also seen in advanced age, obesity, renal failure, cirrhosis, hyperthyroidism, Klinefelter syndrome, germ cell tumors, and hyperprolactinemia. It can be brought on by certain drugs (think spironolactone!), including anabolic steroids (additional clues to anabolic steroid use include a very muscular physique, small testes, and infertility), and certain supplements. A healthy male with chronic stable nontender gynecomastia, normal history and physical exam does **not** require further workup.

Labs for gynecomastia include TSH, estradiol, prolactin, testosterone, LH:FSH, and hCG levels. In males with gynecomastia and an elevated hCG and/or high estradiol levels, check a testicular ultrasound for a tumor. Testicular cancers are discussed further in the [Oncology](#) section.

DIABETES MELLITUS

OVERVIEW

The U.S. is seeing an epidemic of metabolic syndrome and diabetes mellitus that **parallels** the epidemic of U.S. **obesity**. For those born in 2000, the lifetime risk of developing

any kind of DM is **33%** (males) and **39%** (females)! Diabetic patients have **2×** the **death rate** of nondiabetic patients from cardiovascular disease (CVD). The life span of diabetic patients is reduced by 12 years (males) and 19 years (females), as compared with nondiabetic individuals. **Early** initiation of excellent glycemic control reduces the risk of CVD and microvascular complications in patients with Type 1 and Type 2 diabetes.

Classification of diabetes is based on the **mechanism of dysfunction** (Type 1 or 2), not on whether the patient requires insulin for treatment.

The American Diabetes Association (ADA) and the American Association of Clinical Endocrinologists (AACE) have practice guidelines for management. Fortunately, they pretty much agree on the major items!

CLASSIFICATION

PREVIEW | REVIEW

- What are the categories of diabetes mellitus?
- List 3 medications that can induce diabetes or impair insulin action.
- Define maturity-onset diabetes of the young and latent autoimmune diabetes in adults.

Know these categories:

- **Prediabetes** includes both impaired glucose tolerance (IGT) and impaired fasting glucose (IFG).
- **Type 1 DM** (T1DM; < 10% of DM): previously called insulin-dependent DM (IDDM) and juvenile-onset DM. The term IDDM is **not** used anymore. T1DM is most commonly immune mediated but can be idiopathic (antibody negative).
- **Type 2 DM** (T2DM; > 90% of DM): previously non-insulin-dependent DM (NIDDM) and adult-onset DM. The term NIDDM is **not** used anymore.

- **Gestational DM:** diabetes or glucose intolerance with pregnancy
- Specific types of DM due to **other causes:**
 - Drug-induced or chemical: Certain drugs can induce T2DM in patients with insulin resistance or impair the action of insulin (especially niacin, steroids, thiazides, oral contraceptives, β -blockers, and statins).
 - Endocrinopathy-induced: Cushing syndrome, acromegaly, pheo
 - Exocrine pancreas-induced: trauma, surgery, pancreatitis, cystic fibrosis (termed cystic fibrosis-related diabetes [CFRD])
 - Posttransplant diabetes
 - Genetic defects of the β -cells: Maturity-onset diabetes of the young (MODY) is a group of rare monogenetic autosomal dominant defects that cause ineffective production and/or release of insulin by the β -cells in the pancreas. If the patient does not have evidence of T1DM (negative T1DM antibody test), consider MODY if there is a strong family history of diabetes and the patient does not have risk factors for T2DM (obesity, acanthosis, HTN).
 - Latent autoimmune diabetes in adults (LADA): A late onset of an immune-mediated diabetes mellitus, LADA is also referred to as Type 1.5 DM. These patients are generally > 30 years of age and often nonobese adults. LADA can be initially controlled on orals but will require insulin over time. Distinguish from T2DM with a positive T1DM antibody test.

DIAGNOSIS AND SCREENING

PREVIEW | REVIEW

- What are the criteria for the diagnosis of prediabetes?
- Which diseases can result in a misleading value of hemoglobin A1c?
- When are finger stick glucoses useful? When should they not be used?

The recommendations in this section are based on the 2020 American Diabetes Association “Standards of Medical Care in Diabetes,” which we refer to as the 2020 ADA guidelines.

Normal fasting plasma glucose (FPG) is < 100 mg/dL (5.6 mmol/L).

Diagnosis of prediabetes (use 1 of the following):

- 1) Impaired fasting glucose (IFG) = FPG 100–125 mg/dL (5.6–6.9 mmol/L)
- 2) Impaired glucose tolerance (IGT) = 2-hour plasma glucose of 140–199 mg/dL (7.8–11.0 mmol/L) after a 75-g oral glucose load; i.e., during an oral glucose tolerance test (OGTT)
- 3) HbA1c of 5.7–6.4%

The OGTT is more sensitive than FPG for diagnosing prediabetes and is considered the best test by the AACE, but it is rather impractical in most offices—and the screening guidelines take this into account.

Diagnosis of diabetes (use 1 of the following):

- 1) FPG $\geq$ 126 mg/dL (7.0 mmol/L)
- 2) Random plasma glucose $\geq$ 200 mg/dL (11.1 mmol/L) with symptoms (polyuria, polydipsia)
- 3) HbA1c $\geq$ 6.5%
- 4) 2-hour plasma glucose $\geq$ 200 mg/dL after a 75-g OGTT

Confirm diagnosis by **retesting** at least once unless there are clear signs of metabolic decompensation (i.e., diabetic ketoacidosis [DKA], hyperosmolar coma).

Know that the best test for diagnosing T2DM is the fasting plasma glucose (FPG). About 20% of patients screened with the HbA1c have false-negative tests, compared to using the FPG or OGTT.

Additionally, the HbA1c result can be misleading in some patient groups; e.g., those with hemoglobinopathies and thalassemias, patients with iron deficiency or hemolytic anemias, and those with hepatic or renal diseases.

Finger stick (capillary whole blood) glucoses are not equivalent to serum/plasma glucoses. Finger sticks obtain whole blood from capillaries, and capillary whole blood glucoses are subject to much variability. **Finger sticks** are acceptable for **self-monitoring** of known diabetic patients, but only use **plasma or serum** for **diagnosis** of diabetes.

Screen **all** patients for DM at **3-year intervals**, beginning at 45 years of age, and screen younger patients if overweight (2017 ADA guidelines define overweight as a BMI $\geq$ 25 kg/m² or BMI $\geq$ 23 kg/m² in Asian Americans) with any of the following risk factors:

- 1st degree relative with diabetes
- CVD
- Acanthosis nigricans, PCOS, nonalcoholic fatty liver disease
- Sedentary
- High-risk ethnicity (e.g., African American, Latino, Native American, Asian American, Pacific Islander)
- Metabolic syndrome
- HTN or on therapy for HTN
- Dyslipidemia (HDL < 35 mg/dL [0.9 mmol/L]; triglycerides [TG] > 250 mg/dL [2.8 mmol/L])
- Hx of gestational diabetes or of delivery of infant > 9 lb
- Antipsychotic therapy (for schizophrenia or bipolar disorder)
- Chronic glucocorticoid exposure

PREDIABETES

PREVIEW | REVIEW

- What is the significance of diagnosing prediabetes?

Prediabetic patients have a **6-fold increased risk** of developing overt T2DM; 1/3 of them do, 1/3 stay prediabetic, and 1/3 normalize. The condition is quite important to discover because some prediabetic patients **develop microvascular disease**. Also, overt diabetes increases a patient's risk of CVD by 50%!

Goals and Types of Treatment

Promoting a “healthy lifestyle” is your best bet for helping the prediabetic patient. Weight loss of 5–10% decreases the risk of developing overt diabetes by 50%, as do regular exercise (30–60 minutes, moderate intensity, 5 days/week) and a low-sodium/high-fiber diet (low in saturated and trans fats) with moderation of alcohol.

No drugs are FDA approved yet for the treatment of prediabetes, although metformin, acarbose, glitazones, and GLP-1 agonists have been studied, with strong evidence in their favor. Per the ADA and other experts, metformin is indicated in high-risk patients to decrease the rate of progression to T2DM by 30%. (Note: There was a 50% decrease with 5–7% weight loss!)

Lipid and blood pressure goals and aspirin therapy should be the same as for the diabetic patient (see [Ancillary Management on page 1-41](#)).

The 2020 ADA guidelines recommend yearly screening of patients with prediabetes for the development of diabetes and assessment of modifiable CVD risk factors.

TYPE 1 DM

PREVIEW | REVIEW

- Which autoimmune diseases are associated with Type 1 diabetes mellitus (T1DM)?
- What is the primary treatment for T1DM?
- Explain the honeymoon effect and the dawn phenomenon.
- What is the best way to treat morning hyperglycemia?

T1DM accounts for 5–10% of diabetes and is caused by cell-mediated β -cell destruction that leads to an absolute insulin deficiency. **90%** of patients have **autoantibodies** against:

- islet cells,
- insulin,
- glutamic acid decarboxylase [GAD], and/or
- tyrosine phosphatases IA-2 and IA-2 β .

Test patients with prediabetes, IGT, or IFG yearly.

95% of patients with T1DM have HLA DR3 or DR4, indicating a genetic predisposition. Certain environmental factors, such as viruses, may also be important.

The rate of β -cell destruction is quite variable, being rapid in some individuals (mainly infants and children)

and slow in others (mainly adults). When there is slowly progressive autoimmune diabetes with an adult onset, it is often called latent autoimmune diabetes in adults (LADA).

T1DM patients are prone to ketosis, depending on how much insulin is being produced or taken. Do not forget that T1DM is associated with other autoimmune diseases. Autoimmune diseases associated with T1DM include Hashimoto thyroiditis, primary adrenal insufficiency, celiac disease, vitiligo, pernicious anemia (B_{12} deficiency due to autoantibodies), and myasthenia gravis. (Note: In T2DM, screen for B_{12} deficiency if on long term metformin.)

Treatment of T1DM

Treatment of hyperglycemia in T1DM reduces micro- and macrovascular complications.

Treat with **insulin**. Oral hypoglycemics are ineffective. See [Table 1-4 on page 1-36](#).

Multiple daily injection (MDI) insulin regimens include agents in 2 main groups:

- 1) Basal—**long-acting insulin** to cover fasting needs (about 50% of the daily insulin):
 - Glargine
 - Detemir (Levemir)
- 2) Bolus or prandial—**short-acting insulin** to cover meals (about 50% of the daily insulin):
 - Regular (HumuLIN R, NovoLIN R)
 - Lispro (Humalog)
 - Aspart (NovoLOG)
 - Glulisine (Apidra)

Intermediate-acting insulin can also be used to cover fasting and meals: NPH (neutral protamine Hagedorn; HumuLIN N, NovoLIN N) is not used as much as the basal and bolus insulins in the above list. It is generally only used when cost is an issue. Timing of the evening NPH dose can be tricky and is generally given with dinner. If there is nocturnal hypoglycemia or early morning hyperglycemia, the evening NPH dose can be changed from dinner to bedtime to shift the insulin peak from overnight to morning.

Premixed insulin combinations (e.g., “70/30” of NPH/R) are generally **not** recommended to treat patients with T1DM.

Fixed daily doses of each type of insulin do not always correct hyperglycemia, especially in patients whose intake of carbohydrates varies dramatically. The approach is to use nutritional counseling to teach patients how to effectively **carbohydrate count** (i.e., estimate the grams of carbohydrate in their next meal). Then, they use a preestablished insulin:carbohydrate (I:C) ratio to calculate the dose of their premeal short-acting insulin. For example, if using rapid acting insulin and the patient's individualized I:C ratio is 1:15, then when the intake is estimated at 60 g of carbs, the dose is 60/15, or ~ 4.0 units of short-acting insulin premeal. This dosing method gives patients a little

Table 1-4: Insulin Preparations

Type	Duration of Action	Drug (Brand Name)	Onset	Peak	Duration	Relative Cost	Miscellaneous
Human insulin preparations	Intermediate	NPH (Humulin N, NovoLIN N)	2 hours	4–10 hours	10–16 hours	\$	Peaks and duration do not simulate natural basal and post-meal insulin activity as well as insulin analogs.
	Short	Regular (Humulin R, NovoLIN R)	30–60 minutes	2–4 hours	5–8 hours	\$	
Insulin analogs	Long	Glargine	2 hours	None!	20–24 hours	\$\$\$	Less nocturnal hypoglycemia compared to NPH
		Detemir (Levemir)	2 hours	3–9 hours	6–24 hours*	\$\$\$	
	Short	Lispro (Humalog)	5–15 minutes	30–75 minutes	3–5 hours	\$\$\$	Less hypoglycemia compared to Regular
		Aspart (NovoLOG)	5–15 minutes	30–75 minutes	3–5 hours	\$\$\$	
		Glulisine (Apidra)	5–15 minutes	30–75 minutes	3–5 hours	\$\$\$	

*Duration of action for detemir is dose-dependent.

more dietary flexibility and still prevents hyperglycemia. The counseling aspect is important because it is difficult to estimate the carbohydrate content of most meals. The use of mobile device apps has greatly improved patients' ability to accurately count carbohydrates.

Alternatively, patients can be treated with a continuous pump that provides rapid-acting insulin at a basal rate throughout the day. Patients then enter a premeal glucose level and the amount of carbs to be eaten. The pump then delivers a bolus that provides an appropriate insulin correction and the meal dose of insulin. The pumps appear to slightly improve glucose control over MDI injections, decrease hypoglycemic events, and allow for greater flexibility in timing of meals.

Pumps and intensive insulin regimens carry a danger of **hypoglycemia**, and this can be fatal if it occurs at night or is otherwise unrecognized. Malfunction of the pump can result in quick ketoacidosis. Sensor-augmented therapy with continuous glucose monitoring can be useful in decreasing the number and severity of hypoglycemic events.

Know that **nocturnal hypoglycemia** is a problem, not only because it is potentially lethal, but also because episodes lead to feeling poorly the next day with marked fatigue and a measurable decrease in productivity.

Notes for T1DM

Labile DM: T1DM is a difficult condition, because so many factors impact glucose levels (e.g., food, exercise, stress, sleep). Labile DM (a.k.a. brittle diabetes) reflects very hard-to-control diabetes with marked variability in glucose reading, which leads to overt hyper and hypoglycemia. Labile DM is so unstable that patients are often unable to maintain a normal life and have frequent hospitalizations.

Female patients tend to have complicated pregnancies. **Labile T1DM** occurs in 3/1,000 patients with T1DM, most of whom are young women. Hypoglycemia and DKA seem unpredictable. Contributing causes include defective insulin action or delayed food absorption. For example, increased growth hormone in puberty causes increased insulin resistance. An important cause is delayed gastric emptying (a.k.a. gastroparesis; from autonomic neuropathy). Malabsorption, antipsychotic meds, and alcohol use can also contribute to labile diabetes. Factitious (i.e., self-induced) lability is sometimes seen, resulting from some combination of cognitive, behavioral, and psychosocial factors. Management depends on etiology, but those with profound recurrent hypoglycemia without a modifiable cause may benefit from pancreas transplantation.

The **honeymoon effect** refers to an improvement of hyperglycemia after diagnosis and institution of treatment. Sometimes, patients can be removed from insulin entirely for a short while. Eventually, however, they require reinstitution of treatment. The **dawn phenomenon** refers to increased blood glucose between 4:00 and 7:00 a.m. with no preceding hypoglycemia. It also can occur in healthy nondiabetic people. The cause is transient, mild insulin resistance due to the normal early-morning rise in cortisol and growth hormone (GH).

In diabetic patients, early-morning hyperglycemia can also be due to the evening long-acting insulin dose wearing off. Increase the basal (long-acting) insulin in the evening to target a normal fasting glucose level.

The **Somogyi effect**: It was hypothesized that nocturnal hypoglycemia causes early morning hyperglycemia, and the suggested treatment had previously been to decrease the evening insulin to prevent the nocturnal hypoglycemia. This theory has been disproven! Thus, it is **incorrect to reduce** the evening basal insulin in patients with morning hyperglycemia.

TYPE 2 DM

PREVIEW | REVIEW

- Which mechanisms lead to the development of Type 2 diabetes mellitus (T2DM)?
- Which conditions are associated with acanthosis nigricans?
- What are the initial drugs used to treat newly diagnosed T2DM?
- What are the mechanisms of action of the main classes of oral hypoglycemics?
- What are the metformin side effects and contraindications? Thiazolidinediones?
- In which T2DM situations should patients be prescribed insulin early in treatment?

Etiology

More than 90% of diabetes cases are due to T2DM. T2DM is characterized by impaired glucose handling at many sites. The disease has a strong **hereditary** component (multifactorial and polygenic), and several candidate genes have emerged in various populations. Concordance of T2DM in monozygotic twins is 70–90%. Obesity increases insulin resistance, and ~ 80% of patients with T2DM are obese. T2DM patients with central obesity, HTN, and dyslipidemia are said to have **metabolic syndrome**. For more information, see **Obesity** on page 1-46.

Know the mechanisms that lead to T2DM:

- Insulin resistance in muscle and fat tissues
- Gradual reduction in insulin secretion by the pancreas
- Dysregulated hepatic gluconeogenesis and glucagon secretion
- Reduction in gastrointestinal incretins (glucagon-like peptide 1 and glucose-dependent insulinotropic polypeptide)

Note: Insulin resistance is also associated with **acanthosis nigricans**. This velvety, dark rash in flexural areas occurs in conditions associated with insulin resistance, such as PCOS, Cushing's, certain medications (e.g., niacin, corticosteroids), and acromegaly. Rapid onset of widespread acanthosis nigricans in the older patient suggests GI malignancy.

Treatment of T2DM

Metformin monotherapy, in addition to therapeutic lifestyle changes (**TLC**; i.e., diet and exercise, weight loss) is recommended as initial treatment for most patients with T2DM, unless there are contraindications (e.g., glomerular filtration rate [GFR] < 30 mL/minute). Agents from other classes are added later as needed to achieve glycemic control. Use a patient-centered approach to guide the choice of add-on pharmacologic agents. Consider cardiovascular comorbidities and hypoglycemia risk, as

well as impact on weight, cost, risk for side effects, and patient preferences. Management of T2DM is covered under **Approach to Drug Therapy in T2DM** on page 1-39. First we will go over the different agents and their classes. In the following, focus particularly on **metformin**, **GLP-1 receptor agonists**, and **insulin**.

Medications used to treat T2DM:

- Secretagogues (i.e., sulfonylureas, meglitinides)
- Sensitizers:
 - Biguanide (metformin)
 - Thiazolidinediones/glitazones (rosiglitazone, pioglitazone)
- α -Glucosidase inhibitors
- Amylin analogs (pramlintide)
- Glucagon-like peptide-1 (GLP-1) receptor agonists (i.e., exenatide, liraglutide, albiglutide, lixisenatide, and dulaglutide)
- Dipeptidyl-peptidase 4 inhibitors (DPP4I; i.e., alogliptin, linagliptin, saxagliptin, sitagliptin)
- Sodium-glucose cotransport (SGLT-2) inhibitors (canagliflozin, dapagliflozin, empagliflozin)
- Insulin

See **Approach to Drug Therapy in T2DM** on page 1-39 for details on when and how to initiate these agents.

For general competency and for exam questions, it is important to know the mechanisms of action of each class of oral hypoglycemic drugs. Note the maximum efficacy in lowering HbA1c for metformin and sulfonylureas is 1–2%; the efficacy is lower for the other medications.

The **sulfonylureas** and **meglitinides** are **insulin secretagogues**: they **both** increase insulin secretion but do so by different, although similar, mechanisms of action.

Sulfonylureas

2nd generation sulfonylureas include **glipizide**, **glyburide**, and **glimepiride**. Glyburide's half-life is very long, and patients (especially the **elderly**) are at risk for **severe hypoglycemia**. The use of glyburide is no longer preferred by the ADA; **use glipizide and glimepiride instead**. Sulfonylureas are rarely used, except when cost is an issue.

Sulfonylureas are approved for use in combination with most other drugs **except** meglitinides. **Weight gain** and hypoglycemia are common side effects of sulfonylureas.

Hypoglycemia can persist for several days in states of overdose or renal impairment. Severe hypoglycemia caused by an **overdose** of sulfonylureas mandates an admission to the hospital because the resultant persistent hypoglycemia may require:

- close observation for several days,
- IV dextrose initially to reverse the hypoglycemia, and
- octreotide (usually IM or SQ, q 6 hours $\times$ 24 hours).

Octreotide is a long-acting somatostatin analog that markedly inhibits insulin secretion.

Use sulfonylureas with caution in the elderly and in patients with declining renal function; glipizide has a relatively shorter half-life and is safer in these conditions.

Meglitinides

Meglitinides are also insulin secretagogues. These are rapid-acting drugs with a very short half-life. Examples are **repaglinide** and **nateglinide**. The major effect is on postprandial glucose.

As with sulfonylureas, weight gain is a common side effect of the meglitinides. As a group, there is less evidence of their effect with regard to macro- or microvascular outcomes.

Use secretagogues with caution in patients with **chronic kidney disease**. Rarely used, because they need to be taken with each meal.

Biguanides

Biguanides are insulin sensitizers and reduce hepatic glucose production.

Metformin is the only biguanide on the market in the U.S. It is the **1st line medication** in most diabetes management guidelines, unless the patient has an indication for immediate insulin (more information is under **Insulins**). Start with 500 mg bid and gradually increase to a maximum of 2,000 mg/day in divided doses. Many other formulations are available, such as extended-release metformin and metformin in combination with glyburide as a single tablet.

There are fewer side effects with metformin monotherapy than with sulfonylureas. There is no weight gain, and hypoglycemia is rare.

Also favorable: Metformin decreases LDL and TGs and may decrease cardiovascular events, according to the United Kingdom Prospective Diabetes Study [UKPDS]).

Be aware of side effects and conditions that sometimes limit the use of metformin:

- Dose-related abdominal pain and diarrhea
- Metformin is contraindicated in patients with severe **renal** dysfunction (GFR < 30 mL/minute/1.73 m²), decompensated heart failure (HF), and acute or chronic metabolic acidosis.
- In acutely **ill** patients and in those scheduled for **contrast** procedures or surgery, hold the metformin due to the increased risk of lactic acidosis. (The supposed propensity of metformin to cause lactic acidosis is not supported by evidence; however, it is still in the package insert, and you may be tested on it.)
- Potential for B₁₂ deficiency

Thiazolidinediones (TZDs)

TZDs (a.k.a. **glitazones**) are also insulin sensitizers. They act on adipose, muscle, and liver to increase glucose utilization and decrease glucose production and may help

preserve some function of pancreatic β -cells. There are 2 approved in the U.S.: **rosiglitazone** and **pioglitazone**.

Favorable effects: modest reduction in blood pressure, increased HDL, and decreased TGs.

Serious adverse effects include fluid retention, exacerbation of stable heart failure, and weight gain, so avoid thiazolidinediones in those with or at risk for HF. (There is an FDA black box warning of HF for these medications.) There is also an **increased risk of fractures** (definitely in women, probably in men). Pioglitazone may be associated with bladder cancer. Rare hepatotoxicity has been reported, so obtain baseline liver tests and monitor periodically. There is low risk of hypoglycemia.

α -Glucosidase Inhibitors (AGIs)

AGIs (**acarbose** and **miglitol**) delay carbohydrate absorption in the gut. They are not used often. The biggest effect is on postprandial glucose. Common side effects are flatulence, diarrhea, and abdominal bloating. AGIs are approved as monotherapy and in combination with sulfonylureas.

Amylin Analogs

Amylin is a hormone secreted by pancreatic β -cells, along with insulin, which regulates glucose influx by suppressing glucagon and slowing stomach emptying.

Pramlintide is an amylin analog given as an injection before meals. It is intended to be used **with prandial insulin** because it helps insulin work more effectively. Based on the complexity of the regimen, it is not used often.

Cut the insulin dose by 50% when initiating treatment with pramlintide. Gastroparesis and insensitivity to hypoglycemia are contraindications.

Glucagon-Like Peptide-1 (GLP-1) Receptor Agonists

GLP-1 drugs are called **incretin** mimetics. Incretin hormones are secreted by the gut (GLP-1 is an example) and regulate glucose by stimulating insulin release, inhibiting postprandial glucagon release, slowing nutrient absorption, and accelerating satiety.

Exenatide was the 1st GLP-1 injection approved for diabetes treatment, with a bid injection. Extended-release exenatide is available for **once-weekly injection**. It can be combined with MET, sulfonylureas, and TZDs as well as basal insulin. Other GLP-1 receptor agonists are **liraglutide**, **dulaglutide**, **albiglutide**, and **lixisenatide** injections.

Side effects include vomiting and diarrhea, which can be significant.

Acute pancreatitis has been reported in association with GLP-1 receptor agonist treatment, but there is not sufficient data to know if there is a causal relationship.

There is an FDA black box warning of the risk of thyroid C-cell tumors. All GLP-1 receptor agonists are contraindicated in patients with a family history of medullary

thyroid cancer, including MEN2 syndromes, because of C-cell hyperplasia (seen only in rodents so far and not in humans). Exenatide should not be used in patients with $\text{GFR} < 30 \text{ mL/minute/1.73 m}^2$, but other GLP-1 can be used cautiously in CKD.

GLP-1 receptor agonists are useful add-ons to metformin to promote weight loss and to minimize hypoglycemia risk.

GLP-1 receptor agonists with demonstrated cardiovascular disease benefit (liraglutide, semaglutide, dulaglutide) should also be strongly considered, independent of A1c, in those who have established atherosclerotic cardiovascular disease or indicators of high risk, established kidney disease, or heart failure.

Dipeptidyl-Peptidase 4 Inhibitors (DPP4Is)

DPP4Is slow the breakdown of endogenous **incretins**, such as GLP-1, thereby increasing its concentration. Representative drugs are: **sitagliptin**, **saxagliptin**, **vildagliptin**, **linagliptin**, and **alogliptin**. They can be used alone or in combination with metformin or TZD.

The biggest effect is on decreasing postprandial hyperglycemia. DPP4Is do not tend to cause hypoglycemia. The glycemic lowering is less than GLP-1 agonists. DPP4Is are effective in patients with chronic kidney disease; some will need dose adjustments. Rarely, these drugs cause severe skin reactions, such as blistering, angioedema, and anaphylaxis. The concerns about increased pancreatitis with DPP4Is seem not to have panned out, similar to the situation with GLP-1 agonists.

Like GLP-1 agonists, DPP4Is are **useful add-ons to metformin**, **sulfonylureas**, or **TZDs** to minimize weight gain and minimize hypoglycemia risk.

Sodium-Glucose Cotransport (SGLT-2) Inhibitors

SGLT-2 inhibitors are an important class of oral hypoglycemic agents. They block renal reabsorption of Na^+ and glucose in the proximal tubule, increasing urinary excretion of glucose. These drugs do not cause hypoglycemia, and they lead to modest weight loss.

Canagliflozin was the 1st agent in this class. It is an oral agent approved as monotherapy and in combination with metformin, sulfonylureas, glitazones, and insulin. **Empagliflozin** and **dapagliflozin** are other approved SGLT-2 inhibitors. They not approved for use in Type 1 diabetes or in patients with a $\text{GFR} < 45 \text{ mL/minute/1.73 m}^2$. Common side effects are dehydration, renal impairment, urinary tract infections, and genital mycotic infections. This class of drugs may increase the risk of euglycemic DKA in T2DM patients! There is an FDA black box warning about the risk of amputation with canagliflozin.

Strongly consider SGLT-2 inhibitors, independent of A1c, in patients who have ASCVD to reduce the risk of major adverse cardiovascular events in those with T2DM. In

patients with ASCVD, multiple risk factors for ASCVD, or diabetic kidney disease, SGLT-2 inhibitors appear to reduce risk of heart failure hospitalization and progression of kidney disease.

Insulins

Most patients with T2DM eventually require insulin therapy. The same insulins used in T1DM are used in T2DM. Although they may cause less nocturnal hypoglycemia, the **insulin analogs** (long- and short-acting) are **not** more effective at lowering HbA1c than the older human insulins (NPH and regular); however, human insulin is much less expensive for patients. The fixed insulin preparations (e.g., “70/30” of NPH/regular) are also used in T2DM patients. (See [Table 1-4 on page 1-36](#).)

As in patients with T1DM, patients with T2DM who take insulin can sometimes benefit from using the **carbohydrate:insulin ratio** to calculate premeal insulin doses.

Nocturnal hypoglycemia can lead to poor daytime functioning in patients with T2DM, just as in patients with T1DM.

According to both the ADA and the AACE, add insulin to the treatment regimen when there is persistent hyperglycemia on oral drugs, **except** in the following special situations, in which you should institute insulin **early**:

- Consistently high random plasma glucoses ($> 300\text{--}350 \text{ mg/dL}$ [$16.6\text{--}19.4 \text{ mmol/L}$])
- $\text{HbA1c} > 10\text{--}12\%$
- $\text{HbA1c} > 9\%$ with symptoms
- Severe symptoms of hyperglycemia or history of DKA

In these situations, oral agents can be added later, after the glucoses have stabilized with insulin—and, eventually, you may be able to stop the insulin entirely.

Both the ADA and the AACE suggest waiting to add insulin (meaning, use oral agents 1st), except in the above groups, because of the side effects of weight gain ($\sim 2\text{--}4 \text{ kg}$) and hypoglycemia associated with insulin use.

The ADA-preferred regimen for insulin is **basal-bolus** dosing, where patients are given a long-acting insulin that keeps glucoses controlled during the fasting state, and short-acting insulin is given preprandially (just before meals). In patients who are hospitalized, or are fasting for whatever reason, do **not** discontinue their basal insulin simply because they are not eating. Stop the rapid-acting prandial (mealtime) insulins, but **continue** the **basal insulin** because its function is to deal with the hyperglycemia that occurs regardless of whether food is present or not, though the dose might need to be reduced by 30–50%.

Approach to Drug Therapy in T2DM

Along with lifestyle changes, metformin is the preferred initial treatment in all patients with T2DM unless a contraindication exists or the patient cannot tolerate it.

Intensify treatment if the HbA1c is $\geq 7\%$ (6.5% per the AACE) after **3 months**.

The 2020 ADA guidelines recommend the following approach based on hemoglobin HbA1c at presentation:

- HbA1c $< 9\%$ = **metformin monotherapy**.
- HbA1c $> 9\%$ = **dual therapy**: metformin + one of the following: sulfonylurea, GLP-1 agonist, DPP4I, TZD, SGLT-2 inhibitor, or basal insulin.
- HbA1c $> 10\%$, blood glucose > 300 mg/dL (16.65 mmol/L), or marked symptoms = combination injectable therapy (usually basal insulin + rapid-acting insulin) + metformin.

If the HbA1c is not at goal after **3 months**, intensify therapy with an additional agent from another class. Add-on medication choice is governed by comorbidities, as well as hypoglycemia, weight gain, and cost concerns.

If ASCVD or multiple risk factors for ASCVD, choose a GLP-1 receptor agonist with demonstrated cardiovascular benefit. If CKD or heart failure, consider an SGLT-2 inhibitor with demonstrated heart failure reduction and/or CKD progression benefit.

If hypoglycemia is a concern, consider GLP-1 agonist, DPP4 inhibitor, TZD, or SGLT-2 inhibitor. To minimize weight gain or promote weight loss, consider GLP-1 agonist or SGLT-2 inhibitor. Only choose SU or TZD if cost is a major issue.

Insulin pumps are not a quick fix but are good for patients who require multiple injections and are motivated to learn carbohydrate counting. Insulins are described under [Treatment of T1DM on page 1-35](#).

Keep in mind that bariatric surgery is an option with a BMI > 35 kg/m², per the ADA.

GLYCEMIC TREATMENT GOALS

PREVIEW | REVIEW

- What are the treatment goals for glucose and hemoglobin A1c (HbA1c)?
- Describe the relationship between HbA1c and pre- and postprandial blood glucoses.

For both T1DM and T2DM, keep the glucose level as close to normal as possible while avoiding significant hypoglycemia. Recommendations between the advisory groups differ only slightly in targets. The ADA recommends a target HbA1c $< 7\%$ for many nonpregnant adults; the AACE recommends $< 6.5\%$. However, treatment targets should be individualized.

Note: Data has emerged (ADVANCE, VADT, and ACCORD studies) showing that **intensive** glycemic control (compared to standard control) may have **no** long-term benefit or actually **cause harm** in some groups of patients.

Therefore, the target HbA1c may be loosened to **$< 8\%$** for the following groups:

- History of severe hypoglycemia or hypoglycemic unawareness
- Limited life expectancy
- Advanced vascular complications
- Extensive comorbidities
- Longstanding DM with difficulty attaining low HbA1c despite optimal and aggressive management attempts.

If the HbA1c remains elevated but the FPG are controlled, start checking postprandial glucose levels.

Also know that preprandial hyperglycemia contributes more to high average blood glucose when the HbA1c is elevated. Once the HbA1c is $< 7.5\text{--}8\%$, postprandial hyperglycemia contributes more to high average blood glucose and is linked to macrovascular complications.

When using insulin to treat DM, consider checking the postprandial glucose periodically, even when the HbA1c is at a target, so you do not miss periods of hyperglycemia.

Some patients who are hospitalized get worse when their blood glucoses are tightly controlled (80–110 mg/dL [4.4–6.1 mmol/L]); therefore, these are the recommendations:

- Noncritically ill patients: Keep FPG < 140 mg/dL (7.8 mmol/L) and random glucoses < 180 mg/dL (10 mmol/L) using the patient's typical basal regimen and a titrated prandial regimen. A corrective dose of insulin is appropriate if needed to correct prandial hyperglycemia, but use of the sliding scale is discouraged.
- Critically ill patients: Keep glucose at 140–180 mg/dL using an IV insulin infusion as needed.

DIABETIC COMPLICATIONS

PREVIEW | REVIEW

- Name 3 diabetic microvascular complications and characterize their screening and treatment.
- Which microvascular complication usually occurs first in diabetic patients, retinopathy or nephropathy?
- Discuss the major diabetes studies that show a correlation between reducing blood glucoses and subsequent micro- and macrovascular complications.
- Which tests make up the annual monitoring for a known diabetic patient?

Diabetes causes **microvascular** disease (e.g., retinopathy, nephropathy, neuropathy) and **macrovascular** disease (e.g., coronary and peripheral atherosclerosis $\rightarrow$ CVD, stroke, and PAD). Tobacco use greatly accelerates macrovascular complications.

Start screening for microvascular complications immediately at diagnosis because T2DM may already have been present for 5–10 years. The following 3 microvascular complications usually appear 10–15 years after the onset (not diagnosis) of DM:

- 1) **Retinopathy** correlates with duration and control of DM. Early findings include dot hemorrhages. Macular edema and neovascularization (proliferative retinopathy) are late findings. Treatment options include intravitreal anti-vascular endothelial growth factor (anti-VEGF) and photocoagulation (laser treatment). Retinopathy can worsen transiently with initiation of tight glycemic control.
- 2) **Nephropathy** is usually heralded by persistent albuminuria (urine albumin:creatinine ratio > 30 mg/g). Note: Albuminuria in the range of 30–300 mg/g was previously called microalbuminuria. Treat with either ACEI or ARB to **decrease** the rate of nephropathy progression (by decreasing intraglomerular pressure). Retinopathy almost universally precedes nephropathy. If a diabetic patient without retinopathy develops nephrotic-range proteinuria, evaluate the patient for other causes of nephrotic syndrome.
- 3) **Neuropathy** includes autonomic neuropathy, axonal (Schwann cell) degeneration, symmetric polyneuropathy (“stocking and glove”), erectile dysfunction, and gastroparesis. Both alcohol and tobacco use increase the risk and severity of neuropathy. Diabetic mononeuropathy usually affects the 3rd and 6th cranial nerves, the peroneal nerve (foot drop), and the radial nerve (wrist drop). Strict glycemic control decreases the risk of neuropathy and improves nerve conduction. The pain associated with diabetic sensory dysfunction is difficult to treat. Recommended drugs include amitriptyline, venlafaxine, duloxetine, gabapentin, and pregabalin. Remember: Before diagnosing a neuropathy due to diabetes, check B₁₂ levels if on metformin.

Know the major diabetes studies and how glycemic control affects diabetic complications:

- Tight blood glucose control reduces **microvascular** complications in both T1DM and T2DM. This was demonstrated for T1DM by the Diabetes Control and Complications Trial (DCCT) and for T2DM by the UKPDS, the Japanese Kumamoto study, and the ACCORD study.
- A reduction in **macrovascular** complications (cardiovascular disease) has been harder to show, particularly for T2DM. A 10-year follow-up of intensively treated (HbA_{1c} ~ 7%) UKPDS and DCCT patients (the EDIC trial) showed improved cardiovascular outcomes. Although the difference was not statistically significant at the time of the original studies, the benefit emerged as the patients aged. However, ACCORD, ADVANCE, and VADT did not show any benefit of tighter glycemic control on cardiovascular outcomes in patients with T2DM.

Monitoring

All diabetic patients need **annual** evaluations for microvascular complications (5 years after diagnosis in T1DM and immediately at diagnosis in T2DM).

Be sure to do the following:

- Urine spot albumin:creatinine ratio as a test for nephropathy. Normal is < 30 mg of albumin per gram of creatinine. Moderately increased albuminuria is 30–300 mg/g. Severely increased albuminuria is > 300 mg/g.
- Check creatinine and estimated **GFR**.
- Refer patient to an **ophthalmologist** for a retinal exam and rapidly refer macular edema or proliferative retinopathy. Macular edema can lead to vision loss if not treated. It is acceptable to use fundus photography in clinical situations when experienced ophthalmologists are unavailable.
- Inspect the **feet** and perform a sensory evaluation using 10-g monofilament, pinprick, temperature, and vibration. Know that loss of vibratory sense and sensation to the 10-g monofilament predicts foot ulcers.
- Do **not** routinely screen asymptomatic diabetic patients for ischemic heart disease. Outcomes are unchanged with intervention in asymptomatic patients, provided you are treating their CVD risk factors.

ANCILLARY MANAGEMENT

PREVIEW | REVIEW

- Which antihypertensives are recommended for diabetic patients with hypertension?

Hypertension

Although blood pressure targets are individualized in hypertensive patients with diabetes, the 2020 ADA Standards of Medical Care recommends medication in addition to lifestyle changes for pressures ≥ 140/90 mmHg. For those patients at high cardiovascular risk a target of < 130/80 mmHg, may be appropriate, but only if it can be safely attained.

The 2020 ADA Standards of Medical Care in Diabetes, which are consistent with the 2019 ACC/AHA High Blood Pressure guidelines, say to treat diabetic patients with albuminuria (albumin:creatinine ratio > 30 mg/g) 1st with an **ACEI** or an **ARB**. Next, add a thiazide diuretic (e.g., chlorthalidone)—and/or dihydropyridine calcium channel blocker (e.g., amlodipine) if needed—to reach the BP target. Remember: Avoid combination ACEI + ARB! ONTARGET (2008) showed this combo increases risk of hypotensive symptoms, hyperkalemia, and acute kidney injury, with no cardiovascular benefit.

For the rare patient with DM who is not hypertensive, use an ACEI or an ARB if albuminuria is present. There is no

evidence to support the use of ACEI or ARB for primary prevention in diabetic patients without albuminuria or hypertension.

Dyslipidemia

The ADA Standards of Medical Care in Diabetes—2020 include recommendations on statin initiation. Recommendations are risk based (“statin benefit group”), not LDL based (“treat to target”).

Treat diabetic patients 40–75 years of age:

- With a moderate-intensity statin
- With a high-intensity statin if at high risk

Every 39 mg/dL (1.0 mmol/L) LDL-C decrease causes a 21% decrease in major vascular events. Treatment of dyslipidemia is discussed in detail in the Cardiology section.

Know that triglyceride levels are very dependent upon glycemic control. The worse the diabetes control, the higher the triglycerides. Also know that even if the triglycerides are high and the LDL is normal, the initial lipid therapy is a statin (“statin benefit group”).

Aspirin

Aspirin use in diabetic patients is controversial because not all diabetic patients have the same risk for heart disease, despite DM being listed as a CVD risk-equivalent. Per the 2020 ADA recommendation, aspirin therapy (75–162 mg/day) may be considered as a primary prevention strategy in those with diabetes who are at increased cardiovascular risk, after a comprehensive discussion with the patient on the benefits versus the comparable increased risk of bleeding. Give diabetic patients with known cardiovascular disease a daily aspirin as secondary prevention. ASA-allergic patients can take clopidogrel.

HYPERGLYCEMIC EMERGENCIES

PREVIEW | REVIEW

- List the symptoms of diabetic ketoacidosis (DKA).
- Which lab abnormalities occur in the patient with DKA?
- What is the formula used for correction of pseudohyponatremia due to hyperglycemia?
- When is HCO₃⁻ given to treat DKA?

Ketoacidosis

Diabetic ketoacidosis (DKA) is sometimes the initial presentation of T1DM, but it can also occur in T2DM. It is caused by a state of complete or partial insulin deficiency leading to massive lipolysis. Lipolysis causes a release of free fatty acids and ketone bodies (β-hydroxybutyrate and acetoacetate). These products, high anion gap acidosis (because ketones are acids),

and the associated hyperglycemia cause volume depletion from massive osmotic diuresis.

Symptoms include nausea, vomiting, abdominal pain, polyuria, and lethargy. Ask about symptoms of infection (e.g., pneumonia, UTI) and nonadherence with diabetes medications, the two most frequent precipitating conditions for DKA.

On clinical exam, hypotension can occur due to severe volume depletion. Fruity breath and a Kussmaul respiratory pattern suggest ketoacidosis. Severe cases are marked by confusion or obtundation.

Diagnosis: DKA is diagnosed by a high anion gap acidosis, ketosis, and, most of the time, hyperglycemia (see Table 1-5). Secondary derangements include deficits in total body K⁺ and phosphorus (even though both can be normal in serum measurements at presentation because of the acidosis and hemoconcentration). Serum Na⁺ is usually decreased because of the osmotic shift of water from inside cells to the intravascular space caused by the hyperglycemia, a phenomenon referred to as pseudohyponatremia. Correct for this by adding 2.0 mEq/L (2 mmol/L) to the measured serum Na⁺ for every 100 mg/dL (5.6 mmol/L) increase in blood glucose over 100 mg/dL.

Table 1-5: Diagnostic Criteria for Diabetic Ketoacidosis (DKA) vs. Hyperglycemic Hyperosmolar State (HHS)

Parameter	DKA	HHS
Usual glucose at diagnosis	> 250 mg/dL (13.88 mmol/L)	> 600 mg/dL (33.3 mmol/L)
Arterial pH	< 7.3	> 7.3
Serum HCO ₃ ⁻	< 18 mEq/L (18 mmol/L)	> 18 mEq/L (18 mmol/L)
Urine ketones	Positive	"Small" or negative
Serum ketones	> 3 mmol/L	< 0.6 mmol/L
Effective serum osmolality	Variable	> 320 mOsm/kg (320 mmol/kg)
Anion gap	> 10 mEq/L (10 mmol/L)	Variable
Mental status	Varies with severity	Stupor/Coma

Adapted from: Kitabchi, A. E., G. E. Umpierrez, J. M. Miles, and J. N. Fisher. 2009. Hyperglycemic crises in adult patients with diabetes. *Diabetes Care*. 32(7):1335–1343.

Treatment:

- Treat precipitating causes (e.g., infection, infarction).
- Start aggressive volume replacement; give normal saline (~ 2–3 L), then either continue the normal saline or switch to 0.45% saline if the corrected serum Na⁺ is > 135 mEq/L (135 mmol/L).
- Start IV insulin at 0.1 units/kg/hour. When glucose is < 200 mg/dL (11.1 mmol/L), add D5 (5% dextrose) to the IV fluids to avoid hypoglycemia while insulin

is infusing. Keep the IV insulin going until the acidosis is resolved and the anion gap is normal; the insulin is required to stop production of the ketoacids.

- If the K^+ is < 5.0 mEq/L (5.0 mmol/L) at the start of treatment, give potassium chloride (KCl) immediately because there is usually a several-hundred mEq K^+ deficit despite normal serum K^+ concentration.
- In cases of very low K^+ (< 3.3 mEq/L [3.3 mmol/L]), give KCl and hold insulin until the K^+ is ≥ 3.3 mEq/L.

More on K^+ : It falls with treatment of DKA because of shifting into the cells from both the reversal of acidosis and the action of insulin. This can further aggravate hypokalemia and lead to cardiac arrest or respiratory muscle weaknesses. Also monitor the heart-wave morphology and rhythm for any hypokalemic changes, such as T-wave amplitude flattening (1st change), ST-segment depression, T-wave inversions, PR-interval prolongation, and, finally, an increase in amplitude of U waves.

Bicarbonate (HCO_3^-) is controversial but can be given when pH is < 7.0 , especially if the patient is having respiratory or hemodynamic collapse.

The standard urine ketone test (and older plasma tests) react with acetoacetate, but not β -hydroxybutyrate. With severe ketoacidosis, β -hydroxybutyrate levels can be much higher than acetoacetate levels. In this situation, urine ketone testing can underestimate the presence or severity of the DKA.

If the patient is being treated for DKA and seems to be getting better but the ketones start rising, the β -hydroxybutyrate is being converted to acetoacetate as the acidosis resolves. Clinically, you can follow resolution by monitoring the pH and anion gap. The anion gap reflects both types of ketones. Plasma β -hydroxybutyrate concentration can be checked directly with point of care testing, and it is sensitive and more specific than the urine tests.

Hyperglycemic Hyperosmolar State (HHS)

HHS is one of the most serious acute complications of T2DM. It can lead to coma and death and has many precipitating factors, including volume depletion, infection, drugs (e.g., glucocorticoids), and any serious illness.

HHS is caused by partial insulin deficiency and decreased intake of fluids. The patient is usually elderly and has a preceding history of lethargy, weight loss, and polyuria.

Exam is consistent with severe volume depletion and confusion, stupor, or coma. These patients are not severely acidotic, so they do not have fruity breath or Kussmaul respirations.

Labs show severe hyperglycemia (typically > 600 mg/dL [33.3 mmol/L]) and evidence of azotemia, dehydration, and volume depletion. If an anion gap metabolic ketoacidosis is present, it is generally mild.

See [Table 1-5](#) for a comparison of diagnostic criteria in DKA vs. HHS.

Treat HHS similarly to DKA, with IV fluid resuscitation and insulin bolus + infusion. Be sure to correct the serum Na^+ for the hyperglycemia to determine if a free-water deficit exists, then replace it gradually over the next 24–48 hours. K^+ replacement is usually required.

DIABETES IN PREGNANCY

See the [Women's and Men's Health](#) section.

HYPOGLYCEMIA

PREVIEW | REVIEW

- What is the Whipple triad?
- Which laboratory tests help you determine if someone is factitiously self-injecting insulin to induce hypoglycemia?

OVERVIEW

The diagnosis of hypoglycemia is not based on a low blood glucose level alone; it requires fulfillment of the **Whipple triad**:

- 1) Signs and symptoms consistent with hypoglycemia
- 2) Associated low **plasma** glucose level (< 55 mg/dL [3.0 mmol/L])—do not measure with a home glucose monitor.)
- 3) Relief of symptoms with supplemental glucose

Symptoms are autonomic (e.g., palpitations, tremor, sweating, paresthesias) and neuroglycopenic due to CNS glucose deprivation (e.g., confusion, impaired consciousness, seizures). Usually, autonomic symptoms happen first. Signs of hypoglycemia are nonspecific (e.g., hunger, sweating, anxiety, tremor, altered mental status).

Divide your patients into 2 groups—hypoglycemic patients without diabetes and hypoglycemic patients with diabetes—and then treat accordingly. See [Hypoglycemia in Patients without Diabetes](#) next and [Hypoglycemia in Patients with Diabetes](#) on page 1-45 for details.

HYPOGLYCEMIA IN PATIENTS WITHOUT DIABETES

Etiology

Causes of hypoglycemia in nondiabetic patients include:

- **Drugs:** insulin, insulin secretagogues (e.g., glyburide), oral hypoglycemic agents, alcohol. Be sure to think about accidental, surreptitious, and malicious ingestion of sulfonylureas or insulin, especially in patients in the health care field or with a diabetic family member (see [Genetic Causes of Hypercalcemia](#) on page 1-48).

- **Hormone deficiencies:** cortisol, glucagon, epinephrine
- **Critical illness:** heart failure, renal failure, liver failure, sepsis, severe malnutrition
- **Islet cell tumors:** insulinoma, insulinlike growth factor (IGF)-secreting tumor
- **Non-islet cell tumors:** Rarely, other tumors (e.g., hepatocellular carcinoma, fibrosarcomas) can cause hypoglycemia via overproduction of insulinlike growth factor-2 (IGF-2).
- **Functional B-cell disorders:** post gastric bypass, non-insulinoma pancreatogenous hypoglycemia (usually postprandial hypoglycemia)
- **Autoimmune:** endogenous antibodies to insulin or insulin receptor (rare)

Diagnostic Approach

After the diagnosis of hypoglycemia has been established (using Whipple's triad), begin your diagnostic evaluation. First, do a careful history (especially medications) and physical exam, looking for clues to one of the causes listed in [Etiology on page 1-43](#). If the patient is seemingly well, always evaluate for exogenous, accidental, surreptitious, or malicious ingestion or administration of sulfonylureas (SUs) or insulin before doing any further testing. Consider adrenal insufficiency, even though it is rare that this would cause hypoglycemia without other clinical features. Finding an isolated low cortisol during a hypoglycemic event does not necessarily mean the patient has primary adrenal insufficiency because recurrent hypoglycemia lowers the baseline of cortisol secretion; i.e., the hypoglycemia may be causing the low cortisol. If the etiology is not apparent, proceed with laboratory testing.

There are 2 classifications of hypoglycemia: **reactive** (sometimes called postprandial) and **nonreactive** (sometimes called fasting).

Reactive Hypoglycemia

Reactive hypoglycemia (a.k.a. postprandial hypoglycemia) develops in response to a **nutrient challenge**. Significant postprandial hypoglycemia has been documented in postoperative gastric bypass patients due to islet cell hypertrophy. This must be distinguished from traditional dumping syndrome in postoperative bariatric surgery patients, where there are hypoglycemic-type symptoms but no hypoglycemia after a meal. Initial treatment for both includes small, frequent meals that are high in protein and fiber and low in carbs. Postoperative bariatric surgery patients with refractory severe hypoglycemia due to abnormal islet cells may require surgery (pancreatectomy or reversal of the bypass).

Postprandial hypoglycemia in patients without gastric bypass also needs to be evaluated. The test of choice is a nonliquid mixed meal that the patient believes will trigger the hypoglycemia. In the past, postprandial hypoglycemia was diagnosed based on hypoglycemia after an OGTT.

This diagnosis has been discredited over time due to poor reproducibility and poor correlation between hypoglycemic symptoms and documented low blood glucose. **Never** order an OGTT to work up hypoglycemia. On exams, OGTT is a typical distractor from the correct answer.

All reactive hypoglycemia requires fulfillment of the Whipple triad to be a true diagnosis warranting additional evaluation.

Nonreactive Hypoglycemia

In nonreactive hypoglycemia (a.k.a. fasting hypoglycemia), the patient is unable to maintain glucose levels with fasting. The most common causes in hospitalized patients are alcohol abuse, drugs (e.g., oral hypoglycemics, pentamidine), and sepsis.

The causes of nonreactive hypoglycemia in seemingly healthy patients (and that are most commonly tested on exams) are causes of hyperinsulinism. The workup for nonreactive hypoglycemia is summarized in [Figure 1-16](#).

Factitious Hypoglycemia

Factitious hypoglycemia is hypoglycemia in a nondiabetic patient caused by ingestion of antidiabetes medications. Insulin and insulin secretagogues are the typical culprits; other classes of antidiabetic medications do not usually cause hypoglycemia. Ingestion can be accidental, surreptitious, and/or malicious. Evaluate for and exclude this diagnosis before any imaging to look for an insulinoma. Review the patient's medication list, and search for pharmacy/medication errors. Suspect surreptitious or malicious etiologies if a patient or family members are in the health care fields or have knowledge/access to glucose-lowering medications.

Endogenous Hyperinsulinism

Endogenous hyperinsulinism is a group of diseases that includes insulinomas, β -cell disorders (such as may occur after gastric bypass), antiinsulin antibodies, and the use of secretagogues in those without diabetes.

If the patient has a spontaneous hypoglycemic event, first confirm the hypoglycemic value with a plasma glucose (capillary/fingerstick glucose values are unreliable and should not be used for hypoglycemia diagnosis), and pair the glucose with a C-peptide, proinsulin, insulin level, and a sulfonylurea (SU) screen.

If insulinoma is suspected but Whipple's triad has not yet been documented, it can be induced by a supervised fast (gold standard: 72-hour fast). The following labs should be obtained at the time of hypoglycemic symptoms (prior to treatment):

- 1) Serum proinsulin (always paired with a glucose)
- 2) C-peptide (always paired with a glucose)
- 3) Urinary/Plasma SU screen
- 4) Serum insulin (always paired with a glucose)

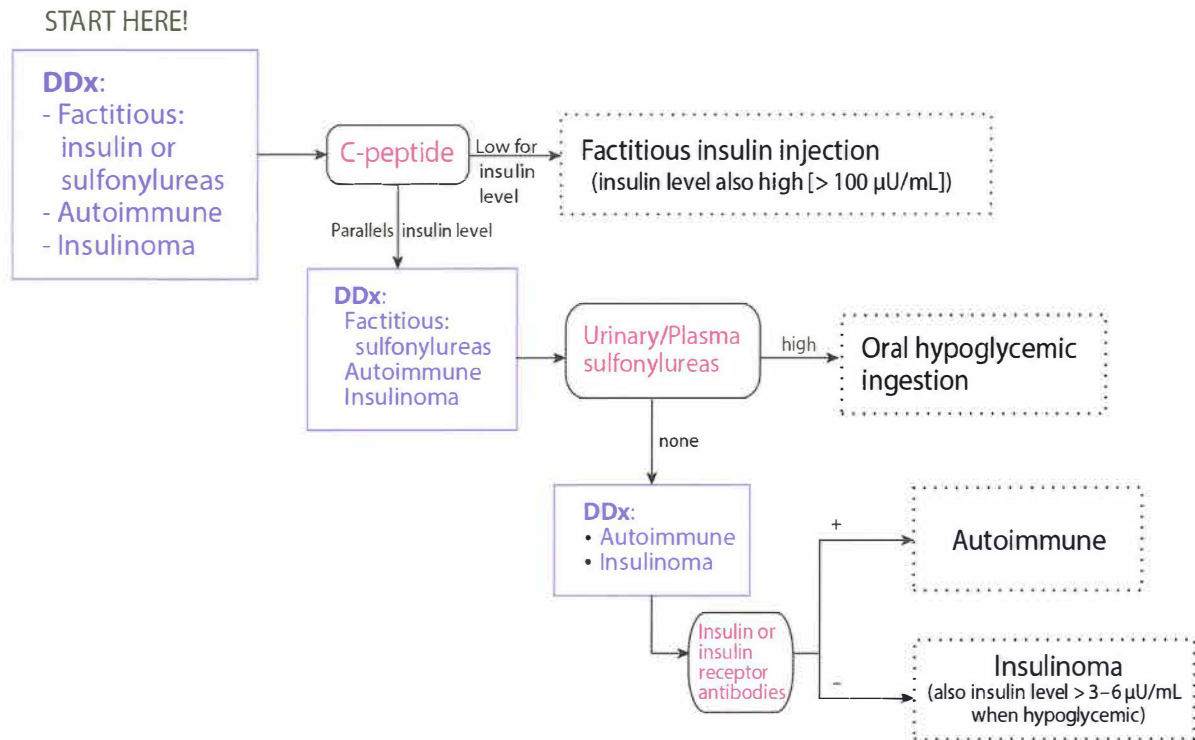


Figure 1-16: Nonreactive hypoglycemia workup

Proinsulin (the precursor of insulin): Insulinomas tend to cause a high ratio of proinsulin to total insulin in the serum. The normal level is 10% of total insulin. With **insulinomas** the level is > 20%, and often 30–40%. With exogenous insulin use, it is low.

C-peptide is produced in a 1:1 ratio with insulin when they are both cleaved from proinsulin. Therefore, with endogenous insulin production (sulfonylurea-induced and insulinoma), the C-peptide level parallels serum insulin values and is high or inappropriately normal during a hypoglycemic event. **C-peptide is low** with exogenous **insulin** injection.

A **urinary/plasma sulfonylurea** test rules in or out factitious hypoglycemia from SU use. Do not proceed to any imaging for insulinoma until a negative SU screen is documented.

Insulin is high or inappropriately normal during the hypoglycemic episode in the following situations:

- Exogenous insulin administration: Insulin levels can be high (sometimes > 100 µU/mL [694.4 pmol/L]) due to self-administration, but the C-peptide is low!
- SU ingestion: Insulin, C-peptide, and proinsulin levels are all high, but the SU screen is positive.
- Insulinoma: Insulin, proinsulin, and C-peptide levels are usually high during an episode of hypoglycemia; SU screen is negative.

- Autoimmune etiologies (antibodies to insulin and insulin receptors): These conditions can cause hypoglycemia **or** hyperglycemia.

HYPOGLYCEMIA IN PATIENTS WITH DIABETES

Hypoglycemia caused by medications is by far the most frequent cause of hypoglycemia in patients with diabetes. Do **not** test diabetic patients for rare causes of hypoglycemia until after extensively reviewing diabetes management and adjusting antidiabetic medications appropriately.

Remember that, in T1DM, other comorbidities (e.g., adrenal insufficiency, celiac disease) can increase the risk of hypoglycemia. In longstanding T2DM and diabetes patients with comorbidities (e.g., heart failure, renal failure, liver failure), agents that are not typically associated with hypoglycemia (i.e., biguanides, TZDs, GLP-1 analogs, DPP4 inhibitors) can still be the cause of hypoglycemia, especially if they are combined with insulin therapy.

Treatment of hypoglycemia, regardless of the etiology, is generally oral carbs (15–20 g) if the patient is able to take them. If not, options are IV dextrose if an IV is in place, or IM/SQ/nasal glucagon if the patient does not have an IV.

OBESITY

OVERVIEW

The prevalence of obesity has increased significantly in the U.S. over the last 30 years: 40% of adults in the U.S. are now obese (BMI > 30 kg/m²), and 7.7% are severely obese (BMI > 40 kg/m²). Obesity is associated with the development of diabetes, hypertension, fatty liver, dyslipidemia, cardiovascular disease, degenerative joint disease, and obstructive sleep apnea.

EVALUATION AND CLASSIFICATION

Screen every patient for obesity by measuring their body mass index (BMI, in kg/m²). Normal BMI is 18.5–24.9 kg/m², BMI 25.0–29.9 kg/m² is overweight, and BMI ≥ 30 kg/m² is obese. Note that BMI will overestimate obesity in individuals with high muscle mass (e.g., body-builders) and underestimate obesity in individuals with low muscle mass (e.g., older adults).

Measure waist circumference—it's an additional cardiovascular risk factor if > 102 cm for men and > 88 cm for women.

MANAGEMENT

Most obesity-associated diseases and complications improve with only a 5–10% weight reduction. Remember to manage the patient's weight loss expectations and focus on healthy lifestyle, not on weight loss alone.

Every patient with overweight/obesity should be offered a lifestyle management plan consisting of 3 components:

- Meal plan: Recommend a diet 500–750 kcal/day less than the daily requirement, and individualize the plan to the patient's preference and culture.
- Physical activity: Recommend aerobic exercise that progresses to 150 minutes/week on 3–5 separate days, with 2–3 resistance exercise sessions 2–3×/week.
- Behavioral modification: Recognize and control environmental cues and stimuli that promote unhealthy eating and sedentary lifestyle. Include self-monitoring, education, stress reduction, and goal setting that requires participation of others.

For obese patients, and overweight patients with ≥ 1 weight-related disease or complication, offer weight-loss medications if lifestyle management therapy has failed.

Weight-loss medications, which can be used alone or in combination, include serotonin agonists (lorcaserin), diabetes medications (liraglutide), sympathomimetics (phentermine), antidepressants (bupropion), anticonvulsants (topiramate), and inhibitors of fat digestion (orlistat). Most of them produce an average of 6–8 kg of weight loss, with around 50–60% of patients reaching a 5% weight loss. All weight-loss medications are contraindicated in pregnancy.

Consider bariatric surgery in patients with BMI > 40 kg/m² or BMI > 35 kg/m² with ≥ 1 severe weight-related diseases/complications who have not met weight-loss goals with exercise, diets, and meds.

BONE / CALCIUM DISORDERS

PREVIEW | REVIEW

- A normal intact parathyroid hormone level in the setting of hypercalcemia suggests which diagnosis?
- How can you differentiate familial hypocalciuric hypercalcemia from primary hyperparathyroidism?
- What are the indications for surgical treatment of primary hyperparathyroidism?
- What monitoring is needed in patients with primary hyperparathyroidism who are being medically managed?
- What are the common causes of secondary hyperparathyroidism?
- Define tertiary hyperparathyroidism. When is it likely to be seen?
- Which vitamins and medications can cause hypercalcemia?
- Which malignancies are associated with hypercalcemia?
- What is the treatment for hypercalcemia?
- What is osteomalacia? How does it present?
- What is the most common cause of vitamin D deficiency?
- Which lab value is used to measure vitamin D levels?

NORMAL CALCIUM PHYSIOLOGY

Ca²⁺ is absorbed from the duodenum, stored in the bone, and excreted by the kidneys. Ca²⁺ levels are tightly regulated by multiple hormones to keep serum Ca²⁺ in a normal range.

When serum Ca²⁺ is low, 2 endogenous hormones are responsible for **increasing** serum Ca²⁺ levels: parathyroid hormone (PTH) and 1,25-(OH)₂-vitamin D (a.k.a. 1,25-(OH)₂-D, calcitriol).

PTH increases Ca²⁺ in the blood through the following:

- Stimulates release of bone Ca²⁺ stores by indirect stimulation of osteoclasts (c = chew bone)
- Increases renal tubular Ca²⁺ reabsorption and renal tubular phosphorus excretion
- Increases activity of kidney 1α-hydroxylase, which increases the production of 1,25-(OH)₂-D and, thereby, increases Ca²⁺ and phosphorus absorption from the gut

Vitamin D is either ingested or is made in the skin after a reaction with sunlight, but it is inert until it is sequentially hydroxylated, first in the liver to form 25-OH-D, and then in the kidney to form 1,25-(OH)₂-D. 1,25-(OH)₂-D increases Ca²⁺ and phosphorus absorption from the gut. 25-OH-D is the stored (measured) vitamin D, and 1,25-(OH)₂-D is the active vitamin D, which acts as a hormone.

High serum free Ca²⁺ feeds back to suppress PTH secretion and, subsequently, 1,25-(OH)₂-D. Low serum Ca²⁺ and vitamin D deficiency increase PTH production.

Calcitonin, from the thyroid parafollicular cells (C cells), can be considered a PTH antagonist. It slows down the osteoclasts, causing a decrease in bone resorption and increase in renal Ca²⁺ clearance (calciuria).

Other hormones also can influence Ca²⁺ levels and bone health. Normal levels of **glucocorticoids** help maintain osteoblast (b = build bone) function, but excess levels increase bone resorption, decrease bone formation, and cause calciuria.

HYPERCALCEMIA

Hyperparathyroidism

Primary hyperparathyroidism (PHPT) is often found incidentally after noting high serum Ca²⁺ on screening laboratory studies. 80% of cases are caused by solitary parathyroid adenomas. Complications of untreated PHPT include low bone density (measured in the distal radius), fractures, kidney stones, and hypercalcemia.

Although most patients are asymptomatic, the classic signs and symptoms of PHPT have been described as “bones, stones, abdominal moans, and psychic groans.”

Bones refer to both increased risk of fractures and the presence of bone aches and pains. There is an increased risk of calcium-containing kidney **stones** and nephrocalcinosis. **Abdominal moans** refer to the multiple GI symptoms (e.g., constipation, nausea, anorexia, abdominal pain, peptic ulcer) linked to hypercalcemia.

Psychic groans can include confusion, memory loss, and delirium. As helpful as this mnemonic is, remember

that most symptomatic patients have mostly vague, nonspecific symptoms, like generalized fatigue, attention/concentration deficits, depression, and weakness.

On the ECG, expect to find a shortened ST segment.

Subperiosteal bone resorption (a.k.a. osteitis fibrosa cystica) with a **moth-eaten** appearance to the radial side of phalangeal cortices on **finger** radiographs is the classic finding, indicating prolonged PTH excess. This finding is now rare, probably due to earlier recognition. If an exam question shows you radiographs of a patient's hands, think about primary hyperparathyroidism.

The diagnosis of PHPT is made by finding an **elevated** or **inappropriately normal** intact PTH (iPTH) with an **elevated Ca²⁺** (see Table 1-6). A normal iPTH in the setting of hypercalcemia is compatible with the diagnosis of primary hyperparathyroidism because, normally, high Ca²⁺ suppresses iPTH. Serum phosphorus is usually low-normal to low (see Table 1-6).

Know that patients with drug-induced hypercalcemia caused by lithium or thiazides may present with PTH levels above normal; ask about these meds, and stop thiazides for 3 months before the hypercalcemia evaluation is done.

Differentiate hypercalcemia due to PHPT from benign familial hypocalciuric hypercalcemia (FHH) by measuring 24-hour urinary Ca²⁺ and Cr excretion and calculating the Ca²⁺/Cr clearance ratio:

$$\text{Ca}^{2+}/\text{Cr clearance ratio} = \frac{[24\text{h urine Ca}^{2+} \times \text{serum Cr}]}{[24\text{h urine Cr} \times \text{serum Ca}^{2+}]}$$

Urinary Ca²⁺ excretion is very low in FHH (Ca²⁺/Cr clearance ratio < 0.01) and normal to high in PHPT. FHH does not need treatment (see [Genetic Causes of Hypercalcemia on page 1-48](#)).

Remember: If a patient with PHPT is taking hydrochlorothiazide (HCTZ) or lithium or has coexisting vitamin D deficiency, the 24-hour urine Ca²⁺ (and the Ca²⁺/Cr clearance ratio) can be low. Screen patients with PHPT for vitamin D deficiency by checking the 25-OH-D level (not 1,25-(OH)₂-D).

Table 1-6: Labs in Diseases Affecting Calcium

Calcium-Related Diseases	Ca ²⁺	PO ₄ ³⁻	Alkaline Phosphatase	iPTH	25-OH-D	1,25-(OH) ₂ -D
Primary hyperparathyroidism	↑	Normal/↓	Normal/↑	Normal/↑	Normal/↓	N/A
Hypercalcemia of malignancy due to lytic bone lesions	↑	Normal/↑	↑	↓	Normal	Normal (except in lymphoma, where it is ↑)
Humoral hypercalcemia of malignancy (i.e., due to PTHrp)	↑	Normal/↓	↑	↓ (but PTHrp is ↑)	Normal	Normal
Chronic kidney disease	Normal/↓	↑	N/A	↑	Normal/↓	Do not check (but it is ↓).
Osteomalacia from vitamin D deficiency	↓	↓	↑	↑	↓	Do not check.

PHPT is a biochemical diagnosis (made by labs); imaging is not necessary for the diagnosis but is often done to localize the adenoma. Imaging can include sestamibi scans and ultrasound.

Once the diagnosis of PHPT has been established biochemically, determine if parathyroidectomy is indicated. Indications for surgical **parathyroidectomy** include:

- Symptomatic PHPT (remember “bones, stones, abdominal moans, psychic groans”)
- eGFR < 60 mL/minute/1.73 m² (CKD Stage 3 or higher)
- Serum Ca²⁺ > 1 mg/dL (0.25 mmol/L) above the upper limit of normal
- T-score of ≤ -2.5 at lumbar spine, femoral neck, total hip, or distal 1/3 radius; Z-score of ≤ -2.0 in premenopausal women and men < 50 years of age
- < 50 years of age
- Vertebral fracture by x-ray, CT, MRI, or DEXA (dual energy x-ray absorptiometry)
- Kidney stone, either clinically or on imaging, or nephrocalcinosis
- 24-hour urine Ca²⁺ > 400 mg (> 10 mmol) and increased stone risk by urine biochemical stone risk profile

Monitoring and management of asymptomatic PHPT patients **who do not undergo surgery** includes:

- Measure serum Ca²⁺ and creatinine yearly.
- Obtain **bone density scans** every 1-2 years.
- Check 25-OH-D level, and supplement if < 20 ng/dL (480 pmol/L).
- Measure 24-hour urinary Ca²⁺. If the urinary Ca²⁺ is > 400 mg/day, then do a complete urinary biochemical stone profile.
- Diet advice is the same as for patients without primary hyperparathyroidism (i.e., goal = Ca²⁺ intake of 1,000 mg/day). Do **not** tell patients to restrict their Ca²⁺ intake—just avoid excessive supplementation.

No specific drug is recommended by the 2014 Guidelines for the Management of Asymptomatic Primary Hyperparathyroidism because long-term efficacy data are scarce. However, **cinacalcet** (Sensipar) is approved for the medical management of PHPT. Cinacalcet can be useful in patients who are not candidates for, or refuse, surgical parathyroidectomy. Note that this agent controls hypercalcemia alone and does not address bone loss or hypercalciuria. **Bisphosphonates** can be used to build bone in the lumbar spine and hips, but they do not decrease serum Ca²⁺ or urine Ca²⁺ excretion in the long term. Therefore, the clinical situation determines whether and which medication to use. A patient with fractures or severe osteoporosis requires bisphosphonates, while symptomatic hypercalcemia requires cinacalcet. If neither of these situations apply, do **not** give these medications. Hypercalciuria and kidney stones can only be addressed by parathyroid surgery.

Secondary hyperparathyroidism is the overproduction of parathyroid hormone secondary to a chronic abnormal stimulus inducing its production. Ca²⁺ is usually normal. Typically, this is due to chronic kidney disease and/or vitamin D deficiency. In chronic kidney disease, there is reduced renal 1-hydroxylation (i.e., activation) of 25-OH-D, leading to low levels of active 1,25-(OH)₂-D. This leads to lower Ca²⁺ and high PTH. Phosphate (PO₄³⁻) is high due to poor renal excretion (see [Table 1-6 on page 1-47](#) and the [Nephrology](#) section for further discussion).

Tertiary hyperparathyroidism is seen in patients with end-stage renal failure (ESRD) and chronic, poorly controlled secondary hyperparathyroidism. There is progression from 4-gland hyperplasia to autonomous PTH production. It can persist after renal transplantation if the autonomous, hypertrophied parathyroid glands continue to oversecrete parathyroid hormone, causing elevated serum Ca²⁺ levels. In the setting of ESRD +/- transplant, labs show a markedly elevated PTH and high Ca²⁺. Surgery is generally needed for severe tertiary hyperparathyroidism.

Summary: Hypercalcemic patients with elevated or normal iPTH and low phosphorus = **primary** hyperparathyroidism. If symptomatic (e.g., kidney stones, CKD, low bone density), do surgery. **Secondary** hyperparathyroidism with a normal Ca²⁺ = consider vitamin D deficiency and CKD as the cause. **Tertiary** hyperparathyroidism = ESRD or kidney transplant with hyperparathyroidism + hypercalcemia.

Other Causes of Hypercalcemia

Vitamins and Medications

Vitamin D excess, **vitamin A excess** (causes Ca²⁺ release from bones), **thiazide diuretics** (decreases Ca²⁺ excretion), and **lithium** (increases PTH threshold by requiring Ca²⁺ to be at a higher level to shut off PTH production) can cause hypercalcemia.

Genetic Causes of Hypercalcemia

Benign familial hypocalciuric hypercalcemia (FHH) is autosomal dominant with normal or slightly elevated iPTH and elevated serum [Ca²⁺].—the same laboratory pattern as in primary hyperparathyroidism. The problem is in the calcium-sensing receptor, which requires a higher Ca²⁺ level before turning off PTH secretion. FHH requires **no** treatment, so it is important to differentiate from other causes of hypercalcemia (especially primary hyperparathyroidism). If FHH is suspected, measure Ca²⁺ and creatinine in the serum and urine, then calculate the Ca²⁺/Cr clearance ratio. If the ratio is < 0.01, the diagnosis is FHH; if > 0.02, FHH is excluded, and the diagnosis is most likely primary hyperparathyroidism. Remember that this is a very rare disease, so **verify** that there are no factors that are causing a falsely low urine Ca²⁺ (especially vitamin D deficiency, malabsorption, celiac disease). Also recognize that FHH is genetic and not acquired. Thus, if there were normal calcium levels in the past, it is not FHH.

Hypercalcemia of Malignancy

Mechanisms of hypercalcemia of malignancy (non-PTH mediated) are:

- osteolytic bone lesions,
- PTH-related protein (PTHrP) production, or
- extrarenal 1α -hydroxylase production to make $1,25\text{-(OH)}_2\text{-D}$ (active vitamin D).

Types of cancer that cause hypercalcemia: myeloma, some solid tumors, tumors with bone metastases, and lymphoma.

Some solid tumors (e.g., breast, renal, squamous cell) secrete a **PTHrP**, in which the *N*-terminal (amino) end is identical to iPTH. But the mid- and carboxy-terminal portions are different, so it is not measured by the iPTH assay. The elevated Ca^{2+} inhibits production of PTH by the parathyroid glands, so PTH levels are suppressed. Make the diagnosis by measuring PTHrP levels.

Bone metastases (e.g., breast cancer and multiple myeloma) account for 1/2 of all patients with elevated Ca^{2+} and malignancy; they produce local osteoclast activation substances, causing breakdown of bone.

Lymphoma can have macrophages and lymphocytes with unregulated production of **1α -hydroxylase**, the enzyme that normally converts 25-OH-D into $1,25\text{-(OH)}_2\text{-D}$ in the kidney. This extrarenal source of 1α -hydroxylase causes an increase in $1,25\text{-(OH)}_2\text{-D}$ and hypercalcemia. Make the diagnosis by measuring $1,25\text{-(OH)}_2\text{-D}$ (**calcitriol**) levels.

More information on hypercalcemia of malignancy can be found in the [Oncology](#) section.

Granulomatous Diseases

Several **granulomatous** diseases, including sarcoidosis, tuberculosis, berylliosis, histoplasmosis, and leprosy, can cause hypercalcemia by stimulating macrophages to increase $1,25\text{-(OH)}_2\text{-D}$ production (similar to lymphoma). Macrophages (and lymphocytes) have unregulated 1α -hydroxylase activity, which converts 25-OH-D into $1,25\text{-(OH)}_2\text{-D}$. If suspected, measure $1,25\text{-(OH)}_2\text{-D}$ (**calcitriol**) levels.

Immobilization

Immobilization can cause elevated Ca^{2+} . High bone turnover states (e.g., hyperthyroidism, Paget disease, adolescence) increase the risk, but immobilization-induced hypercalcemia can occur without those comorbidities. The high Ca^{2+} level causes a **decrease in iPTH**.

Treatment of Hypercalcemia

For **severe** hypercalcemia, immediately give 3–4 L of **normal saline** to treat volume depletion (remember, hypercalcemia causes renal salt wasting and nephrogenic DI). **Calcitonin** is added to increase renal calcium excretion and inhibit bone turnover. **Loop diuretics**

should be used only if the patient develops fluid overload from saline resuscitation (monitor electrolytes and volume status).

Bisphosphonates inhibit bone resorption in areas of high turnover, such as sites of malignancy, and usually are used in conjunction with saline infusions and calcitonin to treat **moderate-to-severe** hypercalcemia.

Pamidronate and **zoledronic acid** are the bisphosphonates favored by most because of their rapid onset of action (48 hours) and intravenous formulation. Know that these drugs can cause **osteonecrosis of the jaw** in patients with multiple myeloma and metastatic bone disease.

Give glucocorticoids to treat hypercalcemia caused by sarcoidosis and other granulomatous diseases (see [Granulomatous Diseases](#)), myeloma, and lymphoma.

Mobilize patients as much as possible with physical therapy, home health assistance, and help of family.

HYPOCALCEMIA

Signs and Symptoms

Hypocalcemia can cause nonspecific symptoms, including fatigue, anxiety, and depression. The hallmark of hypocalcemia is neuromuscular irritability (i.e., tetany). Patients report paresthesias, especially in the fingers and toes and around the mouth, and muscle cramps. On physical exam, try to elicit Trousseau sign (inflate a blood pressure cuff above systolic BP for 3 minutes; the muscles of the hands will spasm) and Chvostek sign (tap the facial nerve just in front of the ear; the facial muscles will spasm).

Severe hypocalcemia can cause seizures. Know that alkalosis exacerbates hypocalcemic seizures, and acidosis is protective. In a patient with hypocalcemia and metabolic acidosis, always correct the hypocalcemia before you correct the acidosis!

Causes of Hypocalcemia

Low serum Ca^{2+} is caused by the following:

- Hypoparathyroidism—decreased PTH secretion (clue: high PO_4^{3-} + low Ca^{2+}):
 - Primary hypoparathyroidism
 - Thyroid surgery with **loss of parathyroid glands**
 - Severe **hypomagnesemia** ($\text{Mg}^{2+} < 0.8 \text{ mEq/L}$ [0.4 mmol/L]); Mg^{2+} is required for PTH release and its effect on target organs. This can be seen in patients with bowel disease or alcohol abuse.
- Vitamin D deficiency
- Severe, acute pancreatitis: precipitation of Ca^{2+} salts in the abdominal cavity
- Acute, severe **hyperphosphatemia**, whereby Ca^{2+} is chelated by the phosphorus
- “Hungry bone” after parathyroidectomy (clue: low PO_4^{3-} + low Ca^{2+} + high pre-op alkaline phosphatase)

- **Pseudohypoparathyroidism** (Types Ia, Ib, Ic, II) is due to PTH resistance. It is a rare genetic disease due to a mutation in a gene involved in PTH receptor function. These patients have an appropriately elevated PTH (in response to the hypocalcemia). In addition to hypocalcemia, patients with Type Ia have short 4th metacarpals and short stature.

When patients with shortened 4th metacarpals and short stature have a normal serum Ca^{2+} , they may have **pseudo-pseudohypoparathyroidism**. These patients are heterozygous for the Ia mutation, and have the physical phenotype of pseudohypoparathyroidism Type Ia, but normal Ca^{2+} homeostasis.

Osteomalacia

Osteomalacia is a condition of decreased mineralization of normal bone at sites of bone turnover. It typically presents with symptoms of bone pain, but occasionally presents with hypocalcemia (see Table 1-6 on page 1-47). It is most commonly caused by vitamin D deficiency. In children, osteomalacia is called rickets; it causes listlessness, irritability, and bowing of the legs. Older patients present with **bone pain** and **proximal muscle weakness**. Patients of all ages have diffuse decreased bone mineral density.

These patients have an elevated **alkaline phosphatase** due to compensatory osteoblastic activity. This is a good lab clue!

In adults, bilateral symmetric pseudofractures (i.e., narrow radiolucent lines, most commonly in the femoral neck and femoral shaft) establish the diagnosis. An iliac crest bone biopsy with tetracycline double-labeling can provide a definitive pathologic diagnosis, but usually osteomalacia is diagnosed clinically without a biopsy.

Once the diagnosis is established, work up the cause (many possibilities). Again, vitamin D deficiency is the most common case in adults. The usual cause of vitamin D deficiency is inadequate intake and/or malabsorption. It's quite common in the elderly and in northern latitudes. Vitamin D deficiency is also more typical in people who use a lot of sunscreen, have darker skin, and/or avoid sunlight.

Studies link vitamin D deficiency with falls, fractures, cancer, and CVD. Look for osteomalacia in older patients with prolonged hospitalizations, who develop bone pain with radiographs that show hairline fractures.

If you suspect vitamin D deficiency, check the 25-OH-D level, **not** the $1,25\text{-(OH)}_2\text{-D}$ level! In osteomalacia due to vitamin D deficiency (the most common cause), the 25-OH-D level will be low.

Renal osteodystrophy and adynamic bone disease are discussed in the **Nephrology** section. Osteoporosis is discussed in the **General Internal Medicine** section.

MULTIPLE ENDOCRINE NEOPLASIA (MEN)

MEN syndromes: All are autosomal **dominant** but with varying expression! See Table 1-7. The types are categorized as MEN1, MEN2A, and MEN2B.

Table 1-7: Multiple Endocrine Neoplasia Syndromes

Type	Clinical
MEN1	Primary hyperparathyroidism Pituitary adenomas Pancreatic islet cell tumors
MEN2A	Primary hyperparathyroidism Medullary thyroid cancer Pheochromocytoma
MEN2B	Medullary thyroid cancer Pheochromocytoma Developmental abnormalities*

*Marfanoid body type, skeletal deformations, mucosal neuromas (especially lips and tongue ["blubbery lips"])

MEN1: Symptoms are caused by hyperplasia, adenomas, and/or cancers of the parathyroid, pituitary, or the islet cells of the pancreas (think "**PPP**"). **Primary hyperparathyroidism** due to multiple parathyroid adenomas is typical. **Prolactinoma** is the most common pituitary tumor, and **gastrinoma** is the most common symptomatic pancreatic tumor. Suspect MEN1 in a patient with hyperprolactinemia and hypercalcemia. There is often a strong family history of peptic ulcer disease (undiagnosed gastrinoma) or primary hyperparathyroidism. Phenotypic expression within a family might be quite variable.

Aside from gastrinomas, the pancreatic tumors in MEN1 can also be insulinomas, VIPomas (which secrete vasoactive intestinal peptide), or glucagonomas. **Insulinomas** can cause hypoglycemic episodes and are diagnosed by documenting inappropriately high serum insulin levels. **VIPomas** present with secretory diarrhea. Diagnose with a high serum VIP level.

Glucagonoma is a very rare malignant tumor of pancreatic islet cells that produces glucagon and can cause a blistering dermatitis, hyperglycemia +/- diabetes, cheilitis (inflammation of the lips), diarrhea, weight loss, and cognitive impairment. The skin and tongue changes are due to a glucagon-induced amino acid deficiency. Think about it in patients with a family history of MEN1 who present with a triad of mild hyperglycemia, glossitis with a "beefy red tongue," and a distinctive blistering erythematous rash that is often found in the groin region (termed migratory necrolytic erythema).

Diagnose glucagonoma by measuring a glucagon level—one of the rare instances when it is useful to perform a randomly timed hormone assay! A level **> 500 pg/mL** (500 ng/L) is supportive. Image the pancreas with a helical CT if glucagon levels are high. In

the majority of patients, glucagonoma is metastatic (to liver, lymph nodes, bone, adrenals, kidney, and/or lung) at diagnosis.

MEN2A: **Medullary thyroid cancer** occurs in virtually all patients with MEN2A (and MEN2B) and often occurs early in life. **Pheochromocytoma** occurs frequently; **primary hyperparathyroidism** occurs in 25–50%.

MEN2B: Like MEN2A, they have **medullary thyroid carcinoma**, and 1/2 of patients have **pheochromocytoma**. Unlike MEN2A, they do not have primary hyperparathyroidism. This type is easy to differentiate from the others because of the **mucosal neuromas** seen on physical exam.

Remember: Both MEN2A and MEN2B have medullary thyroid cancer and pheochromocytoma.

Table 1-7 summarizes the classic clinical findings in MEN1, MEN2A, and MEN2B. Remember:

- **Primary hyperparathyroidism** (parathyroid hyperplasia) causes hypercalcemia but generally no symptoms.
- **Pituitary adenomas** can cause prolactinomas, acromegaly, or Cushing disease but can also be nonfunctional.
- **Pancreatic islet cell tumors** can present with hypoglycemic episodes (insulinoma) or peptic ulcer disease (gastrinoma).
- **Medullary thyroid cancer** is characterized by a high calcitonin level; diagnosis is with fine needle aspiration (FNA) biopsy.
- **Pheochromocytoma** can present with “spells” of headache, palpitations, sweating, and hypertension but usually is asymptomatic.

If a patient with an elevated iPTH has a family history of one brother having “medullary cancer” and another having a “parathyroid tumor,” what tests do you run on the patient?

Answer: Think MEN2A. Check calcitonin and free plasma metanephrines. In an exam setting, you may see only one of these in the answer choices.

The **RET protooncogene** test for hereditary medullary thyroid cancer (MTC) can also be very useful and offers the potential for prophylactic surgical intervention prior to the development of MTC in family members who are at risk. **Calcitonin** elevation correlates with **tumor burden** and may be the 1st sign of recurrent disease. Calcitonin doubling time is accurate in predicting **prognosis**. Elevated calcitonin levels can cause symptoms, such as flushing, diarrhea, and weight loss.

Treatment of MTC is surgical resection. For disease persistence or recurrence options, include observation, surgery, external beam radiation, and tyrosine kinase inhibitors.

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Allergy & Immunology

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IMMUNOLOGIC HYPERSENSITIVITY REACTIONS

PREVIEW | REVIEW

- What mediates immediate hypersensitivity reactions?
- When does the late phase of a Type 1 hypersensitivity reaction occur? Why does it occur?
- What is the difference between the late phase of Type 1 hypersensitivity reaction and the delayed Type 4 hypersensitivity reaction?
- What is the treatment for anaphylaxis?
- Which antihypertensive medication is relatively contraindicated in someone at risk for anaphylaxis? Why?
- Which diseases are mediated by Type 3 immune complex hypersensitivity reactions?

OVERVIEW

Immunologic hypersensitivity reactions reflect **immune-mediated** tissue injury seen in allergies, autoimmune disease, and other inflammatory diseases. These immune responses are the staggeringly important basis for disease prevention in the body, and are the **normal** reaction to a foreign antigen. There are 2 general dysfunctions in which these normal defense mechanisms cause disease:

- 1) An overexuberant response to a foreign antigen
- 2) Autoimmune disease develops, in which the body sees a self-antigen as foreign

So, as we go through the following mechanisms of immunologic hypersensitivity responses, remember that these are also the mechanisms of our normal immune responses to foreign antigens. We tend to forget that!

There are 4 types of immunologic hypersensitivity reactions (per Gell and Coombs):

- **Type 1:** IgE-mediated—immediate (anaphylactic, atopic)
- **Type 2:** IgG- or IgM-mediated cytotoxic
- **Type 3:** Immune complex-mediated (i.e., antibody-antigen mediated)
- **Type 4:** T Cell-mediated—delayed, 4 subtypes (a, b, c, d)

TYPE 1 — IgE-MEDIATED IMMEDIATE HYPERSENSITIVITY REACTION

The “classic” allergies are IgE-mediated Type 1 immediate hypersensitivity reactions. Almost all of these reactions are triggered by **foreign** allergens. Examples include hives/urticaria, allergic rhinitis, allergic asthma, and reactions to insect stings, drugs (e.g., penicillin [PCN]), or foods (e.g., eggs, peanuts, tree nuts, shellfish, soy).

Type 1 — Acute Response

The **acute** phase of an **immediate hypersensitivity reaction** occurs **within minutes to hours** after exposure. Mast cell degranulation (especially producing histamine) is the cause of the symptoms. This reaction is **IgE** mediated. The IgE reaction is antigen-specific and occurs only in response to **previous exposure** to the same allergen.

The base (Fc portion; see [Antibodies on page 2-22](#)) of IgE binds to a receptor on mast cells. This receptor is not specific, so there are many IgEs (each with its own antigen specificity) bound to a mast cell. Typically, no reaction occurs when IgE binds to a mast cell; however, when IgE attaches to its specific allergen, the same antigen reacts with ≥ 2 IgE molecules, interlinking them. Degranulation of the mast cell occurs with this complicated activation process, releasing histamine and stimulating the synthesis and secretion of other mediators like leukotriene, prostaglandin D₂ (PGD₂), and cytokines. Histamine is responsible for most of the acute symptoms. Mast cells also release other products that have chemotactic effects, and some of them are enzymes (e.g., chymase, tryptase). We can measure tryptase levels to confirm anaphylactic reactions because unlike histamine, which is broken down rapidly after release, tryptase is stable for up to a few hours after mast cell degranulation. See [Mastocytosis on page 2-13](#).

A quick review—histamine interacts with 4 receptors:

- **H₁** activation causes the **wheal** and flare, **bronchoconstriction**, and **pruritus**.
- **H₂** activation results in increased **gastric acid** secretion.
- **H₃** activation causes decreased histamine synthesis and release (negative feedback).
- **H₄** activation is immunomodulatory and affects eosinophil and mast cell chemotaxis.

Type 1 — Late-Phase Response

The late-phase response (LPR) occurs **3–12 hours** after the acute response in $< 25\%$ of cases and can last from **hours to days**. The LPR is caused by the initial immediate IgE reaction that stimulates the synthesis of cytokines and the subsequent cellular recruitment of eosinophils and basophils. This results in an **eosinophilic inflammatory infiltrate**.

In the airways, the LPR is a cause of airway hypersensitivity seen in asthmatic patients.

Type 1 — Anaphylaxis

Anaphylaxis is a potentially life-threatening allergic reaction that presents with symptoms such as urticaria, angioedema, abdominal pain, hypotension, and respiratory compromise. It is rapid in onset and can cause death. Anaphylaxis may begin within 5–30 minutes after antigen exposure, but can be delayed up to 2 hours.

The term “anaphylaxis” was traditionally associated only with the IgE-mediated set of symptoms we discuss under [Type 1 – Acute Response on page 2-1](#), and the term “anaphylactoid” was used for all other causes of this same set of symptoms. In 2014, the World Allergy Organization proposed new terminology that has been widely adopted. **Anaphylaxis** is now the **only** term used for this set of symptoms. Anaphylaxis, as with hypersensitivity reactions, is further categorized as immunologic or nonimmunologic.

Immunologic anaphylaxis includes:

- IgE-mediated reactions
- Complement activation with the release of anaphylatoxins C3a, C4a, and C5a

Nonimmunologic anaphylaxis includes all those previously termed “anaphylactoid,” in which the medication or substance itself directly triggers histamine and tryptase release from mast cells. Examples of **nonimmunologic** anaphylaxis are:

- Radiocontrast media (RCM) reactions
- Certain drug reactions:
 - Vancomycin (red man syndrome)
 - Opioids (especially codeine or meperidine)

Immunologic anaphylaxis is usually the result of an extreme IgE-mediated form of an immediate hypersensitivity reaction and this is the focus of the rest of this topic. IgE causes the release of the cytoplasmic granules with histamine and tryptase from mast cells (and maybe basophils). These released cytoplasmic granules cause an immediate reaction causing anaphylactic symptoms.

There are many causes of IgE-mediated anaphylaxis. The most common include:

- Drugs (especially penicillins and non-ASA NSAIDs)
- Insect stings (especially bees, wasps, and yellow jackets)
- Foods (especially peanuts, tree nuts, and shellfish)

A person may be sensitive to insect stings/bites and sustain a large, local reaction. But this does **not** increase the risk of anaphylaxis and further workup is **not** necessary. Of course, insect-sting anaphylaxis requires further evaluation with venom skin testing and serum venom-specific IgE. Refer to [Stinging-Insect Allergy on page 2-11](#).

The diagnosis of anaphylaxis is solely based on blood pressure and the patient's symptoms—as outlined in [Table 2-1](#). It involves at least 2 organ systems. Recognition and timely treatment of anaphylaxis is essential. Remember that hypotension is not necessary for the diagnosis of anaphylaxis!

Biphasic phase of anaphylaxis (late phase): Up to ~ 20% of patients experiencing IgE-mediated anaphylaxis have a 2nd episode within 1–30 hours after the initial event. This 2nd phase is believed to be caused by recruitment of inflammatory cells, including eosinophils, lymphocytes, and basophils, which is similar to

Table 2-1: Anaphylaxis Diagnosis

Anaphylaxis is diagnosed when any 1 of the following 3 criteria is fulfilled:

- 1) Sudden onset with involvement of the skin or mucosal tissue and either:
 - Sudden respiratory symptoms, or
 - Hypotension
- 2) ≥ 2 of the following occur suddenly after exposure to a likely allergen:
 - Skin or mucosal tissue involvement
 - Respiratory involvement
 - Hypotension
 - GI symptoms
- 3) Hypotension after exposure to a known allergen

the LPR of Type 1 hypersensitivity. Patients treated for anaphylaxis must be observed for the biphasic response or provided with emergency self-medications (e.g., epinephrine autoinjectors) if discharged. While difficult to predict, certain factors may increase the likelihood of the biphasic phase:

- Delayed initial epinephrine administration
- Severe initial symptoms
- Delayed resolution of initial symptoms
- Coexistence of asthma
- Oral ingestion of allergens
- β-blocker medication

Type 1 — Treatment

Treatment for immediate hypersensitivity includes avoidance of the allergen, antihistamine therapy (occasionally glucocorticoids), and allergen-specific immunotherapy (**3 As**). Advise all patients who have had prior anaphylaxis—especially those at high risk for recurrent exposure to its cause, such as **beekeepers**—to get an epinephrine autoinjection kit. Provide an anaphylaxis action plan and instructions on how/when to use epinephrine. Immunotherapy can take up to 1 year to show an effect and is not available for all causes of anaphylaxis. Effective immunotherapy causes an increase in regulatory T-cell secretion of IL-10 and blocking antibodies of the IgG isotype, among many other effects. Only IgE-mediated reactions benefit from immunotherapy treatment.

Anaphylaxis treatment:

- Administer 0.2–0.5 mL IM of epinephrine (1:1,000 dilution) in the lateral thigh muscle (fastest site of systemic absorption). The maximum dosage is 0.5 mg (0.5 cc of 1:1,000). Do not give the dose by IV due to adverse cardiovascular effects, and do not give SQ because absorption is slower compared to IM. Repeat dosing can be given every 10–20 minutes as needed. Note: Do not use the IV solution for IM treatment. Giving 0.5 mL of the 1:10,000 IV solution of epinephrine would grossly underdose the patient,

resulting in the administration of 0.05 mg (in 0.5 mL), 10× less than the intended dose of 0.5 mg.

- H₁ and H₂ antagonists (commonly diphenhydramine and cimetidine, respectively) can also be given for urticaria and pruritus.
- Give inhaled albuterol if bronchospasm develops.
- Ensure that the patient remains recumbent until they are completely asymptomatic. Deaths have occurred from patients being prematurely raised to a sitting position.
- For refractory hypotension: Administer 0.5 mg of epinephrine (5 mL of the 1:10,000 dilution) by IV every 5–10 minutes. Use caution and hemodynamic monitoring whenever using IV epinephrine due to risk of cardiac arrhythmia. Intravascular volume expansion (normal saline preferred) should also be given to patients who do not respond initially to IM epinephrine. Lastly, vasoactive agents such as dopamine, norepinephrine, and vasopressin may be needed for anaphylaxis refractory to epinephrine.

IV or PO glucocorticoids should be administered as part of the initial treatment. They are not effective for acute cases but may decrease likelihood of delayed response. Do not send patients home without making provisions for emergency self-treatment of the biphasic phase, even if they are given systemic glucocorticoids. Intramuscular epinephrine is 1st line treatment for all causes of anaphylaxis! The failure to recognize the symptoms of anaphylaxis and to promptly administer epinephrine has led to preventable fatalities.

Epinephrine affects the α- and β-adrenergic systems, resulting in bronchial relaxation, vasoconstriction, and decreased vascular permeability. The effect of epinephrine is blunted in patients on β-blockers. Therefore, in patients at risk for anaphylaxis (primary treatment is epinephrine), the use of β-blockers is relatively contraindicated. Glucagon slow infusion (5 mg slow IV bolus over 5 minutes) can be used in patients on β-blockers with anaphylaxis refractory to epinephrine; however, epinephrine should always be used first, even for patients on β-blockers. **Again:** Epinephrine is always 1st line treatment! At discharge, refer patients to an allergist, and prescribe epinephrine autoinjector.

TYPE 2 — IgG- OR IgM-MEDIATED CYTOTOXIC HYPERSENSITIVITY

Type 2 cytotoxic hypersensitivity is the main mechanism of autoimmune diseases that cause tissue or cell damage. Type 2 reactions occur when IgG or IgM binds to a fixed target tissue antigen or cell receptor, causing either dysfunction or inflammatory destruction. Most of Type 2 reactions are autoimmune—that is, directed at self-antigens. Extrinsic allergens can cause this reaction when they attach to cell surfaces. Penicillin is an example of an extrinsic agent that can cause both immediate IgE-mediated reactions and delayed IgG-mediated reactions.

The binding of the antibody results in target cell **destruction** by various means:

- Complement activation causes cells to be lysed by membrane attack complexes (MACs). This is discussed under [The 3 Complement Pathways on page 2-23](#).
- Complement activation may result in opsonization from the production of C3b. Phagocytes have a receptor for C3b and readily attack opsonized C3b-coated cells.
- Phagocytes also have a receptor for the Fc portion of the antibodies and readily attack opsonized antibody-coated cells.

Examples of target cell receptors:

- Platelets (immune thrombocytopenia [ITP], formerly known as immune thrombocytopenic purpura)
- RBCs (autoimmune hemolytic anemia)
- RBCs when penicillin binds to them, causing them to be recognized as foreign
- Foreign RBCs (hemolytic disease of the newborn)

Examples of Type 2 reactions targeting fixed tissue antigens:

- Goodpasture syndrome (basement membrane of the kidney and lung)
- Bullous pemphigoid, pemphigus vulgaris
- Rheumatic fever
- Graves disease (TSH receptor)
- Myasthenia gravis (acetylcholine receptor on muscle cells)

Do not get Type 2 cytotoxic hypersensitivity mixed up with the **T-cell-mediated** cytotoxic damage seen in Type 4 hypersensitivity reactions.

TYPE 3 — IMMUNE COMPLEX HYPERSENSITIVITY

Anytime you see a **vasculitis**, think of Type 3 hypersensitivity reactions. Type 3 reactions are seen in **autoimmune** diseases and in reactions to **drugs**. Immune complexes (ICs) form when antibodies combine with an antigen (self or foreign). A hypersensitivity reaction occurs when antibody (usually IgG) reacts with a target antigen to form ICs, which, in certain conditions, precipitate and activate complement with subsequent small vessel inflammation and necrosis.

Remember: Just because an antibody reaction occurs and ICs are formed, it does not necessarily mean there is precipitation. Significant precipitation occurs only when there is **slight antigen excess** in relation to the antibody.

Review: When the antibody response initiates, there is a **huge** excess of **antigens** compared to antibodies (Ag:Ab >> 1). The ICs that are formed are small, soluble, and are quickly **cleared**.

Within 1–2 weeks, as exceedingly more antibodies are produced, a point is reached when there is only **slight antigen excess**. This allows the ICs to interlace and become bigger and less soluble. These large ICs **precipitate** in the small vessels and activate complement, which starts a cascade—causing the release of more cytokines and the gathering of more inflammatory cells. This process ultimately results in necrosis of the small vessels in any organ. This small vessel vasculitis is also termed hypersensitivity vasculitis and leukocytoclastic vasculitis.

The pathologic hallmark skin finding in a patient with leukocytoclastic vasculitis is **palpable purpura** (Figure 2-1). See more on leukocytoclastic vasculitis in the **Rheumatology** section.



Figure 2-1: Confluent palpable purpura in severe leukocytoclastic (small vessel) vasculitis
Source: James Heilman, MD

As the antigen is cleared, there comes a point when there is **antibody excess**. The formed ICs are large, and are quickly **cleared** by circulating phagocytes (e.g., monocytes, macrophages).

There are 2 possible clinical consequences:

- 1) **Serum sickness** is a systemic reaction in which a large amount of antigen is injected into a nonimmunized host and **within 1–2 weeks**, you see a necrotic vasculitis similar to the one just discussed. Other symptoms include fever and joint pain.
- 2) **Arthus reaction** is a local reaction that occurs when a patient is first hyperimmunized (so there are many circulating IgGs) and then given a small intradermal injection of the target antigen. Many ICs are made **at the injection site** and they induce the complement cascade and inflammation. **Within 4–12 hours**, a painful, indurated lesion appears and may progress to a sterile abscess.

Serum sickness and Arthus reaction are generally self-limited, and patients usually **fully recover**. Occasionally, glucocorticoids are given.

Type 3 reactions play a role in the following autoimmune diseases and their associated antigen(s):

- SLE—nuclear materials, such as dsDNA and Smith antigen
- Chronic autoimmune thyroiditis (a.k.a. Hashimoto's) and chronic lymphocytic thyroiditis—thyroglobulin
- Pernicious anemia—intrinsic factor
- Rheumatoid arthritis—rheumatoid factor

External antigens:

- Hepatitis antigen-associated serum sickness
- Tetanus and diphtheria immunization
- Local insulin reactions
- Treat external antigen reaction by stopping the exposure to the antigen.

TYPE 4 — DELAYED T-CELL-MEDIATED HYPERSENSITIVITY

Type 4 delayed T-cell-mediated hypersensitivity is a CD4+ helper-cell-driven response and is not mediated by antibodies, unlike the other 3 hypersensitivity reactions. Previously sensitized **CD4+ helper cells** migrate to, and interact with a foreign antigen, and overproduce cytokines (signaling proteins) which initiate an inflammatory reaction with an overabundance of macrophages, eosinophils, cytotoxic T8+ cells, or neutrophils. The reaction peaks in 24–72 hours—hence, the common name of “**delayed-type hypersensitivity**.”

Gell and Coombs classification further divides **delayed cell-mediated hypersensitivity** into 4 subtypes dependent upon the effector cells that cause tissue damage and specific disease:

- **Type 4a: monocytes/macrophages** (seen in contact dermatitis and granulomatous reactions like tuberculin skin test, tuberculosis, and leprosy)
- **Type 4b: eosinophils** (seen in chronic asthma, chronic allergic rhinitis, maculopapular exanthema with eosinophilia, and drug reaction with eosinophilia and systemic symptoms [DRESS])
- **Type 4c: cytotoxic T8+ cells** (seen in contact dermatitis and skin sloughing reactions such as Stevens-Johnson syndrome/toxic epidermal necrolysis)
- **Type 4d: neutrophils** (seen in pustular exanthema reactions like Behçet disease)

Clinically, hypersensitivity reactions can be a combination of types:

- Contact dermatitis often has 4a and 4c features.
- Chronic allergic asthma and chronic allergic rhinitis can have Type 1 (i.e., IgE) and Type 4b mechanisms.
- Allergic bronchopulmonary aspergillosis (ABPA) has components of Type 1, 3, and 4.
- Hypersensitivity pneumonitis (HP) starts out as a Type 3 reaction and then becomes more of a Type 4 reaction.

Do not confuse the **delayed-type** hypersensitivity reaction of Type 4 with the **late-phase** response of Type 1!

URTICARIA

PREVIEW | REVIEW

- What is the difference between acute and chronic urticaria?
- What precipitates cholinergic urticaria?
- What is the difference between acute urticaria and urticarial vasculitis?

Acute urticaria presents as superficial, blanching, transient, pruritic wheal-and-flare reactions (hives) that last < 6 weeks (Figure 2-2). Common causes include allergies to food, insects, latex, and drugs. If the patient has isolated urticaria, treat with antihistamines. Look for other systemic symptoms (i.e., respiratory, cardiovascular, GI) that indicate more severe anaphylaxis. Allergy testing is guided by the clinical history. Refer to [Skin vs. Serum Allergy Testing](#) on page 2-12.



Figure 2-2: Urticaria
Source: john

Chronic urticaria (CU) is hives that last ≥ 6 weeks. Up to 50% of patients with CU are allergic to their own IgE receptors, 10% are allergic to their own IgE, and 10% have antithyroid antibodies. Although there is an association between CU and autoimmune disorders, routine tests to diagnose autoimmune diseases are not recommended in the absence of a clinical history suggestive of autoimmune disease.

No diagnostic testing is required for most patients with CU. However, limited routine laboratory testing can be performed to provide reassurance and to exclude underlying causes. These may include a CBC with differential, erythrocyte sedimentation rate (ESR), and/or C-reactive protein, liver enzyme, and thyroid-stimulating hormone measurement.

Treatment of urticaria involves addressing pruritus and swelling. Use H_1 antihistamines (e.g., hydroxyzine) or newer 2nd generation H_1 antihistamines (e.g., cetirizine), which are less sedating. H_2 antihistamines and glucocorticoids are reserved for refractory urticaria or angioedema.

There are also several **nonallergen-mediated** causes of urticaria:

- **Dermatographism** (a.k.a. dermatographia) simply means “writing on the skin.” Exaggerated wheals and flares arise after the skin is stroked or gentle pressure is applied (Figure 2-3).
- **Acquired cold urticaria** is mediated by either **cryoglobulins** or IgE. Shock can occur if the patient is immersed in cold water! Diagnose with a 5-minute skin ice-cube challenge.
- **Familial cold urticaria** is an **autosomal dominant inflammatory disease** characterized by urticaria, myalgias, fever, and joint pain after cold exposure.
- **Cholinergic urticaria** is precipitated by **heat** (e.g., hot showers, a hot day, exercise). It usually presents as punctate lesions that are very pruritic. The exact etiology is unknown, but mast cell hypersensitization is most likely. Treat symptoms with a 1st generation antihistamine, such as hydroxyzine, or a 2nd generation antihistamine, such as cetirizine.
- **Pressure urticaria** commonly causes swelling and burning of areas exposed to heavy pressure. Diagnose by placing 15 pounds (6.8 kg) of weight suspended over a patient’s shoulder for 15 minutes and monitoring for development of swelling.
- **Urticarial vasculitis (UV)** can clinically resemble acute urticaria. However, patients report hives lasting ≥ 24 hours in a fixed location (in contrast to acute urticaria, which resolves in minutes to hours or migrates to other areas). Patients often complain that the hives are nonpruritic, burn, and are painful. Other red flags include skin **ecchymosis**, **purpura**, **petechiae**, or elevated ESR, which are not seen in acute urticaria. Diagnose UV by skin biopsy. Although the mainstay of UV treatment is glucocorticoids, other agents are options depending on the severity of clinical signs and symptoms:
 - Pruritus— H_1 antihistamines
 - Arthralgia/Arthritis—NSAIDs
 - Mild/Moderate—dapsone, hydroxychloroquine, colchicine
 - Severe—methotrexate, azathioprine, cyclosporine A



Figure 2-3: Dermatographia
Source: R1carver

ATOPIC DERMATITIS (ECZEMA)

PREVIEW | REVIEW

- What is the 1st line treatment for atopic dermatitis?
- What do you do if you encounter an adult patient with new-onset recalcitrant eczema?

Atopic dermatitis occurs in ~ 1–3% of adults and is due to dysfunctions in the innate and adaptive immune systems and skin barrier abnormalities. It typically presents as a very pruritic, dry, thickened, scaly rash on the flexural skin surfaces (Figure 2-4). When severe, the rash becomes thick scaling plaques. Symptoms are lifelong and there is no known cure.



Figure 2-4: Atopic dermatitis
Source: James Heilman, MD

There is a layered treatment approach:

- **Moisturizers** are the 1st layer of therapy. There should be aggressive application of emollients multiple times a day and every time after the patient gets wet (showers, baths, sweating, and swimming). Moisturizers are less effective if applied to dry skin.
- **Immunomodulatory creams** are the 2nd layer of therapy. Topical corticosteroids or topical calcineurin inhibitors (i.e., pimecrolimus, tacrolimus) should be applied to problem areas of the skin to decrease inflammation. Although topical corticosteroids are the 1st line antiinflammatory agents, they can cause skin atrophy. Use on the face, axilla, and genitalia should be avoided. Topical calcineurin inhibitors do not cause skin atrophy.
- **Antihistamines** are the 3rd layer of therapy. 1st generation antihistamines are more effective than the later generations, but they have some degree of sedation. This can be useful for patients who are unable to sleep because they are constantly scratching their skin at night. It is important to break the scratch-itch-scratch cycle. Avoidance of common irritant triggers, such as harsh soaps, detergents, wool, and chemicals is recommended.

Oral corticosteroids should only be used for temporary control of an acute flare. They should not be used for chronic control because cessation can lead to rebound disease. **Antibiotics** are used if the patient shows signs of infection. Treat these infections with topical or oral antibiotics. Most patients with atopic dermatitis are colonized with *Staphylococcus aureus*, and superinfection is fairly common.

Know! For new-onset adult eczema that is recurrent and refractory to conventional therapy, refer the patient to dermatology to rule out cutaneous T-cell lymphoma (e.g., mycosis fungoides).

For more information on atopic dermatitis, see the [Dermatology](#) section.

CONTACT DERMATITIS

PREVIEW | REVIEW

- What should you do if you have a patient with a linear itchy rash just below the umbilicus where the belt buckle touches the abdomen?

Poison oak and poison ivy cause contact dermatitis in most individuals (Figure 2-5). Other agents, such as nickel (found in some jewelry), rubber components, perfumes, hair products, and makeup can cause contact dermatitis in sensitized individuals.

Remember that contact dermatitis often has features of hypersensitivity Types 4a and 4c.



Figure 2-5: Poison ivy contact dermatitis
Source: Britannic124

Order **patch testing** if the patient has a rash in a pattern that suggests their makeup, hair product, nickel-containing jewelry, or a belt buckle caused the rash. Once the allergen or irritant is identified, recommend avoidance of the offending agent. For additional information, see the [Dermatology](#) section.

RHINITIS

PREVIEW | REVIEW

- What are the 1st line therapies for mild vs. moderate-to-severe allergic rhinitis?
- Which class of medication for the treatment of allergic rhinitis is avoided during the 1st trimester of pregnancy?
- What is rhinitis medicamentosa? How is it treated?
- What is atrophic rhinitis? How is it treated?

There are 2 broad categories of rhinitis: allergic and nonallergic. The most common type of rhinitis is **viral** rhinitis, followed by **allergic** rhinitis.

ALLERGIC RHINITIS

There are 2 main types of **allergic rhinitis**:

- 1) Seasonal—provoked by seasonally present pollens
- 2) Perennial (year-round)—provoked by dust mites, molds, or animal dander

Symptoms of allergic rhinitis include congestion, sneezing, rhinorrhea, and nasal itching. Once initiated, patients have **nonspecific** hypersensitivity to many irritating stimuli. Patients demonstrate sensitization to allergens when tested by skin prick or a serum assay for specific IgE antibodies. See **Skin vs. Serum Allergy Testing** on page 2-12.

Eosinophils appear on nasal smear only when the patient is **symptomatic**. Patients with perennial allergic rhinitis can have a high nasal eosinophil count year-round. In patients with a positive allergen testing, a nasal eosinophil count > 3/HPF is very specific but not very sensitive for allergic rhinitis.

Treatment of allergic sinusitis: Intranasal glucocorticoids are the **1st line** therapy for mild allergic rhinitis. For moderate-to-severe symptoms or symptoms not controlled with intranasal glucocorticoids alone, use an intranasal antihistamine or a combination of intranasal glucocorticoid plus intranasal antihistamine.

Other drugs include the oral form of the 2nd generation less-sedating antihistamines. Of these 2nd generation antihistamines, fexofenadine and bilastine (not available in the U.S.) do not cross the blood-brain barrier and are completely nonsedating. The other 2nd generation antihistamines (e.g., cetirizine, levocetirizine, loratadine, desloratadine) are somewhat sedating because they partially cross the blood-brain barrier.

The 1st generation antihistamines (e.g., diphenhydramine, chlorpheniramine, hydroxyzine) are generally not used and are never given to the elderly. They easily cross the blood-brain barrier and cause sedation, blurry vision, dry mouth, and urinary retention.

Cromolyn sodium is sometimes used for mild symptoms.

Treatment of allergic sinusitis during pregnancy:

- For mild symptoms not controlled by avoidance, cromolyn ophthalmic drops are the treatment of choice.
- For moderate-to-severe symptoms, an intranasal glucocorticoid spray is the treatment of choice; **budesonide** is preferred.
- If intranasal budesonide is not effective enough, chlorpheniramine is commonly added on. It has a long safety record in pregnant women. If sedation is an issue with chlorpheniramine, use 2nd generation antihistamines—especially loratadine or cetirizine.
- Allergy shots are not started during pregnancy, but if a woman has already started allergy shots and becomes pregnant, she can continue without dose escalation.

- **Avoid** oral decongestants in the 1st trimester of pregnancy! They increase the risk of congenital malformations, such as gastroschisis and atresia of the small intestine.

NONALLERGIC RHINITIS

There are many nonallergic categories of rhinitis: infectious, vasomotor [idiopathic], nonallergic with eosinophilia, medicamentosa, and atrophic. Unless there is an overlap, patients with nonallergic rhinitis do **not** demonstrate sensitization to allergen when tested by skin prick or serum assay (i.e., IgE is not involved).

Infectious rhinitis is an acute rhinitis caused by a viral, bacterial, or fungal infection. Viral infections (e.g., common cold, flu) are **by far the most common cause** of any type of rhinitis. Classic symptoms are self-limited with sneezing and a watery nasal drainage.

Vasomotor rhinitis (a.k.a. idiopathic rhinitis) is the usual noninfectious cause of nonallergic rhinitis. It tends to occur in the middle-aged. It is thought to be neurogenic—a reaction to a specific stimulus. Patients have sneezing attacks, followed by nasal congestion and rhinorrhea when exposed to cold, sunlight, certain foods, or various other stimuli. Treatment is with intranasal glucocorticoids; intranasal anticholinergic sprays are effective when rhinorrhea is the predominant symptom. As with all the other causes of nonallergic rhinitis, these patients do **not** demonstrate sensitization to allergen when tested by skin prick or a serum assay.

NARES—nonallergic rhinitis with eosinophilia syndrome—is an inflammatory rhinitis that causes year-round symptoms of rhinorrhea, sneezing, and occasionally, loss of smell. NARES is not a Type 1 hypersensitivity reaction. **Eosinophils** are found in nasal secretions. Negative allergy screening along with a nasal smear showing 5–20 eosinophils/HPF makes NARES likely.

Rhinitis medicamentosa is rebound congestion caused by prolonged use of vasoconstricting nasal drops (i.e., phenylephrine, oxymetazoline). A beefy, red nasal mucosa is the diagnostic finding in the setting of persistent nasal congestion and continued use of an α -adrenergic nasal spray. Treat by stopping use of adrenergic nasal sprays. Use intranasal glucocorticoids prn to help with recovery.

Atrophic rhinitis is characterized by **atrophy** of the nasal mucosa, **crusting**, dryness, **fetor**, and **loss of smell** (anosmia). Patients are typically **younger** and from warmer climates. Some are colonized with *Klebsiella ozaenae*. Secondary causes include excessive nasal/sinus surgeries, granulomatous disease, and exposure to radiation. Treat atrophic rhinitis initially with **nasal saline lavage**.

Note that other causes of chronic nasal congestion rhinitis include deviated septum, foreign body (typically unilateral and with malodorous discharge), tumors, and drug reactions (especially with propranolol and α -methyl dopa). Persistent nasal symptoms may accompany pregnancy, hypothyroidism, or testosterone deficiency (hormonal rhinitis).

RHINOSINUSITIS

PREVIEW | REVIEW

- What are the characteristic symptoms and the duration of acute rhinosinusitis?
- When are antibiotics used to treat acute rhinosinusitis?
- How long must symptoms last before the diagnosis of chronic rhinosinusitis can be made?
- How is chronic rhinosinusitis treated?

Note: The term rhinosinusitis is now used instead of sinusitis because inflammation of the sinuses is almost always accompanied by inflammation of the nasal mucosa. **Acute rhinosinusitis** is defined as rhinorrhea, nasal congestion, facial pain, and sinus tenderness lasting **< 4 weeks**. Diagnosis is made clinically; do not order a sinus CT or other imaging for uncomplicated acute rhinosinusitis. Sinus CT or x-rays cannot distinguish between bacterial and viral infections; the vast majority of cases are caused by viral infections, which do not require antibiotics.

Initially treat acute rhinosinusitis symptomatically with nasal saline washes and intranasal glucocorticoids. Treat pain with acetaminophen or with NSAIDs (only if not sensitive).

So, **when** are antibiotics needed? Give antibiotics only in the following scenarios:

- Severe initial symptoms with high fever ($> 102.0^{\circ}\text{F}$ [38.9°C]), purulent nasal discharge, and facial pain
- Worsening symptoms after initial improvement (a.k.a. "double sickening")
- Persistent symptoms with no improvement after 7–10 days

The 1st line treatment is **amoxicillin + clavulanic acid**. Use doxycycline for PCN allergy.

Recurrent episodes of acute bacterial sinusitis may indicate a B cell defect or selective IgA deficiency.

Chronic rhinosinusitis (CRS) occurs when symptoms last **> 12 weeks**. It can occur with or without nasal polyps and can have eosinophils, neutrophils, or both in the nasal mucosa. Depending on the H&P, workup can include evaluation for allergens, immunodeficiency, cystic fibrosis, sinus CT, and referral to ENT for possible surgery in recalcitrant cases.

CRS diagnosis requires all the following history and findings:

- Duration of disease for > 12 weeks
- Presence of 2 of the following (MOPS):
 - Mucopurulent discharge
 - Obstruction/Congestion
 - Pain over paranasal sinus areas of face
 - Loss of smell (anosmia)

- Evidence of sinusitis on CT scan or evidence of mucopurulent discharge from ostiomeatal complex (visualized by rhinoscope) in posterior area of nasal cavity

Manage CRS by restoring ostiomeatal patency/drainage of sinuses with topical glucocorticoids and nasal saline lavage.

Know! Do not obtain sinus x-rays. They are not helpful in the workup of acute or chronic rhinosinusitis.

ASTHMA

Asthma is an important disease in the Allergy & Immunology subspecialty. However, for the sake of concision, asthma is extensively covered solely in the [Pulmonary Medicine](#) section.

DRUG HYPERSENSITIVITY REACTIONS

PREVIEW | REVIEW

- When is drug desensitization indicated? Give 2 examples of when penicillin desensitization is required.
- What is DRESS syndrome? Name a few drugs that commonly cause this reaction.
- What is the difference between Stevens-Johnson syndrome and toxic epidermal necrolysis?

OVERVIEW

Here we talk about drug hypersensitivity reactions. Remember that these are quite different from drug side effects, listed on the drug information sheet, and from the effects of a drug overdose. The timing and type of reaction provide clues as to which type of drug reaction is occurring. If a drug is given intravenously and an **immediate** reaction with **urticaria** develops within **minutes to an hour**, a Type 1 immediate **IgE-mediated** reaction has most likely occurred.

If a reaction is delayed up to **24–72 hours**, a **Type 4 delayed** hypersensitivity reaction is likely. An **exanthematous** (maculopapular or morbilliform) eruption also suggests a delayed hypersensitivity reaction.

More severe skin manifestations include Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and DRESS syndrome. (See more on these three manifestations under [Stevens-Johnson Syndrome \(SJS\) and Toxic Epidermal Necrolysis \(TEN\)](#) on page 2-10 and under [DRESS Syndrome](#).) These manifestations usually appear **> 72 hours** after exposure to the drug. For more details on SJS and TEN, see the [Dermatology](#) section.

Besides skin manifestations, other problems can occur, including fever, arthritis, and vasculitis, as well as GI,

neurologic, and pulmonary findings. Prior exposure to the drug is necessary for an immunologic reaction to occur.

Laboratory testing is generally **not** helpful. Peripheral blood eosinophilia is suggestive but **not** conclusive of a drug allergy. PCN skin testing is helpful if you suspect an IgE-mediated mechanism (i.e., Type 1 hypersensitivity reaction).

Also see [Immunologic Hypersensitivity Reactions on page 2-1](#).

β-LACTAM ANTIBIOTICS

β-lactam antibiotics are the **most common** cause of drug allergy, and PCN is by far the most common of these. Despite this, PCN allergy is exceedingly overdiagnosed. About 5–10% of patients report a history of PCN allergy. However, 80–95% of patients with a reported PCN allergy are found **not** to be allergic, leaving us with an actual prevalence between 0.25% and 2%.

Confirm PCN allergy with skin testing; a negative skin test has a negative predictive value of > 95% and thus makes a future anaphylactic reaction to PCN very unlikely. For those who are confirmed PCN allergic by skin testing and require treatment with PCN, desensitization is available. (See [Drug Desensitization](#).)

PCN itself does not cause an allergic reaction. It is the degradation products when linked to self-proteins (i.e., when tissue-bound) that are allergenic. The **major** determinant used in skin testing reagents is **penicilloyl-polylysine** (PPL). 75% of those with a PCN allergy react to this reagent.

Other skin testing reagents, to which fewer people react, are called **minor** determinants. These are:

- Benzylpenicillin (penicillin G)
- Penicilloate
- Penilloate

One study suggests that those who react to minor determinants are more likely to have more severe reactions. It is ideal to include both the major and minor determinants when testing for PCN allergy. Unfortunately, in the U.S., only penicillin G is available.

A negative allergy test does **not** rule out an allergic reaction to PCN because it is only about 75% sensitive. Remember: All allergy skin testing (PCN testing included) checks only for IgE-mediated reactions (i.e., Type 1 only; not Types 2, 3, and 4).

Like PCN allergy, PCN cross-reactivity also appears to be overdiagnosed. In the past, PCN was thought to cross-react with cephalosporins at a rate of as much as 20%, but data shows that cross-reactivity between PCN and 3rd generation cephalosporins is extremely low (< 2%). Cross-reactivity between PCN and 1st and 2nd generation cephalosporins may be higher as cross-reactivity involves similarities of side chains. Cross-reactivity between β-lactams and carbapenems

is very low. Aztreonam does not cross-react with other β-lactams except for ceftazidime. (They both share a common R-group side chain.)

To treat any drug allergy, **stop** the drug. For anaphylaxis, give epinephrine without delay and ensure that the patient is in a recumbent position until recovered and asymptomatic. See [Type 1 – Treatment on page 2-2](#).

DRUG DESENSITIZATION

Following a drug desensitization protocol in the appropriate situation allows for a **temporary** state of tolerance to the drug, as long as the person continues to take the specific drug.

Desensitization can be done for any patient with a Type 1 **IgE**-mediated hypersensitivity reaction to a medication. It is effective in this group for those with immediate or late-phase reactions. Common antibiotics that can cause this reaction are the β-lactams, quinolones, and clindamycin.

Know! Desensitization is necessary if the drug is the only known clinically effective therapy or all other effective treatments are unavailable.

Desensitization is **contraindicated** for serious **non-IgE**-mediated reactions, such as SJS, TEN, or DRESS syndrome.

A typical desensitization procedure (e.g., for PCN allergy) starts with very tiny oral or IV doses of approximately 1/10,000 of the full therapeutic dose—with increased dosage every 15 minutes. After 4–8 hours, a full dose is reached, and a temporary tolerance to the drug is achieved. The patient can then be given the full course of the antibiotic. This tolerance is rapidly lost once the drug is stopped, so the procedure must be repeated if the drug is ever given again.

Note: Generally, oral doses are the preferred method—but even with oral doses, the patient must be in a monitored setting where treatment for anaphylaxis (injectable epinephrine and other drugs) is available at the bedside.

Scenarios where drug desensitization is required:

- A **pregnant woman** with syphilis who has a PCN allergy
- A patient with **neurosyphilis** who has a PCN allergy

Both cases require desensitization because PCN is the only known effective therapy. After desensitization, give PCN for the duration of therapy. Again, if PCN is required in the future, desensitization therapy must be repeated.

DRESS SYNDROME

DRESS stands for drug rash with eosinophilia and systemic symptoms. DRESS syndrome is a Type 4b (i.e., with eosinophils) hypersensitivity reaction. Patients typically develop a polymorphic drug rash, peripheral eosinophilia, and systemic symptoms—which include

fever, lymphadenopathy, and multiorgan involvement (e.g., liver, kidney, heart). It commonly occurs 2–8 weeks after exposure to the offending drug, usually aromatic antiseizure medications, minocycline, and allopurinol. Reactivation of human herpesvirus 6 and other viruses has been implicated.

Treat DRESS by **stopping** the offending drug. (Symptoms may initially worsen or persist.) Treatment is with glucocorticoids and IVIG. The disease may be progressive even after discontinuation of the offending agent. When there is organ involvement, such as cardiac myopathy, corticosteroids must be weaned with extreme caution. These patients are at risk for cardiac failure and should be managed by clinicians experienced with DRESS syndrome.

STEVENS-JOHNSON SYNDROME (SJS) AND TOXIC EPIDERMAL NECROLYSIS (TEN)

SJS and TEN are part of a single disease spectrum. It is a Type 4c (i.e., with cytotoxic CD8+ T cells) hypersensitivity reaction. There is **severe sloughing** of the skin, equivalent to a 3rd degree burn! **Mucosal** involvement of the eyes, mouth, and lips almost always occurs (Figure 2-6).



Figure 2-6: Stevens-Johnson syndrome
Source: Thomas Habif, MD

Nikolsky sign is positive and refers to the removal of the epidermis with slight tangential pressure.

Diagnosis depends on the extent of epidermal detachment according to body surface area (BSA):

- SJS (< 10% BSA)
- Overlap syndrome (10–30% BSA)
- TEN (> 30% BSA)

Treat SJS and TEN with supportive care in a burn unit. Of course, stop the offending drug. **IVIG** may be beneficial. **Glucocorticoids** are **contraindicated in TEN**; use of glucocorticoids in SJS is controversial. Mortality is high.

For more information on SJS and TEN, see the **Dermatology** section.

RADIOCONTRAST MEDIA (RCM) REACTIONS

RCM reactions are almost always **nonimmunologic** reactions to parenteral iodine or gadolinium contrast media. These reactions are caused by the **direct** interaction of contrast with mast cells; i.e., they are not immunoglobulin-mediated or cell-mediated. Incidence of this reaction has decreased recently with the use of nonionic and hypoosmolar contrast media. Symptoms are usually mild (but can be severe) and range from flushing, hives, and laryngeal edema to angioedema and outright anaphylaxis. Onset of symptoms can occur quickly (within 1 hour) or be delayed for days.

Immediate, severe symptoms are indistinguishable from those of an IgE-mediated anaphylactic reaction and are termed **nonimmunologic anaphylaxis** (for more on this recent change in terminology, see [Type 1 – Anaphylaxis on page 2-1](#)). Rather than an IgE mediation of effects, this nonimmunologic anaphylactic reaction is caused by the media **directly activating** mast cells, basophils, or both. The resulting release of mediators such as histamine and tryptase cause the severe clinical reaction. Rarely, RCM causes an IgE-mediated immediate allergic response.

Know that RCM reactions are **not** associated with seafood or iodine allergies. Risk factors for RCM reactions include female gender, asthma, and prior reaction to RCM. Use of β -blockers or underlying cardiovascular disease increases the risk for more serious RCM reactions.

Decrease the likelihood of RCM reactions by giving **nonionic** or **hypoosmolar** radiocontrast and pretreat with the following regimen:

- Prednisone (50 mg): 13, 7, and 1 hour prior to procedure
- Diphenhydramine (50 mg): 1 hour prior to procedure

The nonimmunologic anaphylaxis category includes all those previously termed “anaphylactoid” in which the medication or substance itself directly triggers the release of histamine and tryptase from mast cells.

Other causes of nonimmunologic anaphylaxis are **vancomycin** (red man syndrome) and **opioids** (especially codeine and meperidine). For a dermatologic discussion of radiocontrast media cutaneous drug reaction, see the [Dermatology](#) section.

VANCOMYCIN HYPERSENSITIVITY

Vancomycin hypersensitivity (a.k.a. **red man syndrome**) is a common adverse drug reaction due to **nonimmunologic, direct mast cell degranulation**. Treat by decreasing the infusion rate, not by decreasing the dose.

Although vancomycin can also cause an IgE-mediated immediate hypersensitivity reaction, this is rare.

STINGING-INSECT ALLERGY

Insect stings from the order Hymenoptera (e.g., bees, wasps, yellow jackets, hornets, fire ants) are the most common cause of insect allergy. These allergic reactions are a Type 1 IgE-mediated immediate hypersensitivity reaction.

A large local reaction to a sting or bite is not an allergic reaction and needs no workup. Even generalized hives do **not** increase the risk of anaphylaxis and need no workup. Of course, anaphylaxis itself does require workup with allergy skin tests and serum allergy tests. Identifying the correct stinging insect by history is notoriously unreliable.

Give venom immunotherapy (venom allergy shots) to **patients with anaphylaxis** with confirmed positive insect allergy tests. This treatment has a success rate of 98%! Prescribe an epinephrine autoinjector and recommend insect avoidance.

FOOD ALLERGY

The prevalence of food allergies is about 4% in the adult population. The most common food allergens are peanuts, tree nuts, fish, shellfish, and soy. Food allergies are a Type 1 IgE-mediated immediate hypersensitivity reaction.

Patients need to learn how to avoid the food(s) they are allergic to. Teach patients how to ask the right questions in restaurants and how to read food labels to avoid exposure. Patients with severe food allergies should receive an epinephrine autoinjector and receive training on its proper administration.

LATEX ALLERGY

Latex is natural rubber tapped from the sap-like fluid of rubber trees. Latex allergy is due to sensitization to highly allergenic proteins—primarily **hevein**—on the surface of the latex products. This is a true allergic reaction, like those to stinging insects and food, and is a Type 1 IgE-mediated immediate hypersensitivity reaction.

Before latex alternatives were available, latex allergy was a frequent cause of **anaphylaxis** in patients in hospitals and among health care workers. Now, development of latex allergy is uncommon unless patients have a condition that gives them an increased exposure to latex-containing products (e.g., spina bifida, urologic problems).

The main risk factors for development of latex allergy in patients with spina bifida are the number of surgeries, total serum IgE, presence of a ventriculoperitoneal shunt, and a personal history of atopy. The greatest risk factor for patients (not just those with spina bifida) is multiple surgeries at an early age.

Interestingly, several fruits and vegetables have proteins that are **cross-reactive** with latex allergens. While these patients can show a high IgE level to multiple fruits, vegetables, and nuts, the main ones that show clinical relevance are **PKB PACT** (peekaboo PACT):

- Papaya, kiwi, banana (fruits)
- Potato, avocado, chestnut, tomato (vegetables, fruits, and nuts)

Patients with spina bifida have more cross-reactivity to potatoes, and health care workers have more cross-reactivity to kiwis, bananas, and avocados.

Evaluate for latex allergy by inquiring about a history of prior reactions and getting a latex-specific IgE antibody immunoassay. A negative immunoassay essentially rules out latex allergy.

Skin test reagents (for skin prick tests) are not commercially available in the U.S. They are used successfully in many places outside the U.S.

Treat by providing a latex-free environment, which many hospitals and clinics have adopted.

HYPERSENSITIVITY LUNG DISEASE

Both allergic bronchopulmonary aspergillosis (ABPA) and hypersensitivity pneumonitis (HP) are discussed in more detail in the [Pulmonary Medicine](#) section.

HYPERSENSITIVITY PNEUMONITIS (HP)

HP (a.k.a. extrinsic allergic alveolitis) is a very complex disease with variable presentation that can be caused by many organic agents—as suggested by its many common names, including ventilation pneumonitis, farmer's lung, bird fancier's lung, maltworker's lung, and mushroomworker's lung. **Thermophilic actinomyces** species are thought to be the culprit in many instances, especially farmer's lung. HP is initiated by a **Type 3 immune complex-mediated** hypersensitivity reaction, with an IgG precipitin developing against a specific allergen, and eventually develops a **Type 4 cell-mediated** hypersensitivity reaction (again, HP = Types 3 and 4).

Presentation of HP is acute, subacute, or chronic:

- Acute: Symptoms start within hours of exposure and include chest tightness, dyspnea without wheezing, fever, and chills.
- Subacute: gradual onset of cough and dyspnea with fatigue and weight loss
- Chronic: insidious onset of cough and dyspnea with fatigue and weight loss

Diagnosis of HP is usually made with a suggestive history, an HRCT of the lung that reflects the presentation, and results of antigen avoidance. Occasionally bronchoalveolar lavage (BAL) or lung biopsy is done. Note that skin tests are **not** a helpful diagnostic test (this is not an IgE-mediated reaction!). HRCT findings:

- Acute: infiltrates with a ground glass pattern of attenuation (may be fleeting)
- Subacute: ground glass infiltrates, centrilobar nodules, darker lobar areas due to decreased attenuation and vascularity
- Chronic: spotty ground glass infiltrates, centrilobular nodules, larger upper lobe decreased attenuation (darker areas) mainly due to air trapping. Eventually HRCT looks more like idiopathic pulmonary fibrosis.

Treatment of HP is mainly allergen avoidance. Consider a trial of glucocorticoids in chronic disease with an inflammatory component (ground glass infiltrates or BAL with > 20% lymphocytosis).

ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS (ABPA)

ABPA is almost exclusively limited to patients with **asthma** (prevalence 1–2%) or **cystic fibrosis** (CF; prevalence 2–9%). There are 3 hypersensitivity reactions involved in the reaction of atopic individuals to aspergillus: Type 1 IgE-mediated, a **Type 3 immune complex-mediated (with IgG)**, and **Type 4 cell-mediated** (again, ABPA = Types 1, 3 and 4).

ABPA manifests as asthma symptoms with recurrent, sometimes severe exacerbations. Early symptoms are mild fever, wheezing, dyspnea, and coughing up sputum with brownish flecks. With severe exacerbations, the patient can have fever, bronchial plugging, dyspnea, hemoptysis, and coughing with expectoration of the brownish bronchial plugs.

Treatment for severe exacerbations includes glucocorticoids and antifungal therapy with itraconazole or voriconazole. A typical dosing regimen with prednisone is 0.5 mg/kg/day for 2 weeks followed by gradual tapering over 4–6 weeks.

Immunotherapy treatments (allergy injections) do not work with ABPA; they actually worsen it. APBA involves multiple types of hyperreactivity to multiple proteins of *Aspergillus fumigatus*, and can also involve IgE to other related allergens—so specific immunotherapy can’t hit all the targets.

SKIN vs. SERUM ALLERGY TESTING

PREVIEW | REVIEW

- What are the benefits of skin testing?
- When is serum antigen-specific IgE testing indicated?

Skin testing is quicker and has a slightly better negative predictive value (NPV) than serum-specific IgE testing. When testing for **food allergens**, both serum and skin tests have only 50–60% positive predictive value (PPV). A positive test only demonstrates sensitization to a particular allergen and does not guarantee clinical reactivity. Therefore, only order food allergy testing when there is a compatible history of food allergy.

For the serum specific IgE test, scoring is done with either a radioallergosorbent assay (RAST) or the newer fluorescent enzyme immunoassay (FEIA), which uses the College of American Pathologists scoring scheme. There are cut-off levels that have a high PPV for a limited number of foods (Table 2-2).

Table 2-2: Serum-Specific IgE Cut-Off Levels

Food	IgE Concentration (kU/L)	PPV
Egg	7	95%
Milk	15	95%
Peanut	14	100%
Codfish	20	100%
Soy	30	73%
Wheat	26	74%

Regarding inhalant allergens, skin testing has high PPV and NPV, especially when combined with positive history of reactions to inhalants. There is less data on accuracy of using antigen-specific serum IgE tests for inhalant allergies; they have good PPV, but their NPV is not as good as skin testing.

Serum testing is often done in lieu of skin testing for both food and inhalant allergens when there is:

- Extensive skin disease
- Dermatographism
- Anaphylactic sensitivity to the allergen
- Ongoing antihistamine use that cannot be withheld for 1–2 weeks (Antihistamines depress the skin test response.)

Remember: Positive results on both allergy skin testing and a serum allergy testing only **suggest** sensitivity to a potential allergen, but a **negative test** is strong evidence **against** allergy to that substance.

VACCINES

PREVIEW | REVIEW

- What should be done if your patient needs the influenza vaccine but gets hives with egg ingestion?
- Which vaccines are contraindicated in pregnancy? Which should be given?
- How long should you wait to give the measles, mumps, and rubella vaccine after your patient has received a transfusion of packed red blood cells?

INFLUENZA VACCINE AND EGG ALLERGY

Large trials have proven that even confirmed egg-allergic patients can safely receive the injectable inactivated influenza vaccine (IIV) as a single dose. The recommendation is the same for those with an egg allergy and for everybody else. The previously recommended staggered dosing of 10% then 90% is no longer done; nor is vaccine skin testing; nor is the 30-minute postvaccination observation period.

IMMUNODEFICIENCY AND LIVE VACCINES

Live viral vaccines include the following:

- Rotavirus
- Measles, mumps, rubella (MMR)
- Live attenuated influenza vaccine (LAIV)
- Varicella
- Zoster
- Yellow fever (YF)
- Smallpox
- Oral polio vaccine (OPV)
- Live oral typhoid vaccine (LOTV)
- Bacille Calmette-Guérin (BCG)

Live vaccines are **contraindicated** in the following conditions:

- HIV: CD4 < 200 cells/ μ L (0.20×10^9 /L)—all live vaccines
- B-cell deficiency: all live vaccines
- T-cell deficiency: all live vaccines
- Complement deficiency: no vaccine contraindications
- Phagocyte dysfunction: LOTV and BCG (the live bacterial vaccines), LAIV, OPV, YF, MMR
- Chemotherapy or high doses of immunosuppressive therapy: all live vaccines
- Chronic glucocorticoid use (i.e., prednisone > 20 mg/day)

PREGNANCY AND VACCINES

Vaccines should be given before conception when possible. When administered during pregnancy, vaccine

benefit to the mother and fetus should outweigh any risk. Most toxoid, inactivated vaccines are safe, while live virus vaccines may be harmful and are contraindicated.

Know:

- Vaccines recommended in pregnancy: **Tdap** (tetanus, diphtheria, and acellular pertussis); **inactivated influenza** vaccine—give with each pregnancy
- Vaccines contraindicated in pregnancy: All live attenuated vaccines including **varicella**, **MMR**, **zoster** live virus vaccine, intranasal live influenza vaccine, rotavirus, and yellow fever. Note that Shingrix (an inactivated vaccine) has replaced zoster live vaccine, but because sufficient testing has not been done, the CDC recommends that pregnant patients who have had shingles wait until after pregnancy and breastfeeding to take the vaccine.

IMMUNOGLOBULIN THERAPY AND LIVE VACCINES

Only 2 vaccines have been shown to have a significant interaction with immunoglobulin products:

- 1) Measles-containing vaccines (MMR and MMRV)
- 2) Varicella-containing vaccines (varicella and MMRV)

The following are the recommended intervals between administering measles or varicella vaccine and immunoglobulin-containing products:

- IVIG: 8–11 months, depending on dose
- Whole blood: 7 months
- Plasma, platelets, packed red blood cells (PRBCs): 6 months
- Measles immunoglobulin: 6 months
- Varicella immunoglobulin: 5 months
- Rabies immunoglobulin: 4 months
- Tetanus, hepatitis A, and hepatitis B immunoglobulins: 3 months

MASTOCYTOSIS

PREVIEW | REVIEW

- Which physical finding is pathognomonic for urticaria pigmentosa?

Mastocytosis is a rare disorder characterized by abnormal mast cell proliferation and accumulation in various organs. The degree of involvement determines the extent of the disease.

There are 3 types of mastocytosis:

- 1) **Cutaneous mastocytosis** results from increased mast cells only in the **dermis**. There are characteristic brownish macules called **urticaria pigmentosa**. Formation of a wheal upon gentle stroking of the macule (**Darier sign**) is pathognomonic.

- 2) **Systemic mastocytosis** is caused by increased mast cells in tissues, organs, and skin. These patients have generalized symptoms dependent upon the degree of involvement.
- 3) **Malignant mastocytosis** causes severe systemic symptoms but often **no** skin changes. Physical exam may reveal hepatosplenomegaly and lymphadenopathy.

Screen with **elevated tryptase ≥ 20 ng/mL**. Remember that mast cells secrete tryptase. Therefore, if you have a lot of mast cells, the tryptase levels are high. Diagnosis of systemic mastocytosis is based on the presence of the major criterion plus 1 minor criterion, or the presence of 3 out of the 4 minor criteria (Table 2-3).

Table 2-3: Diagnosis of Systemic Mastocytosis

Major Criterion (plus 1 minor)	Minor Criteria (3 out of 4 required)
Mast cell aggregates in bone marrow and/or extracutaneous organs	1) Atypical/Spindle-shaped cells in bone marrow or other extracutaneous tissue 2) Tryptase level > 20 ng/mL 3) Presence of <i>c-kit</i> gene point mutation 4) Expression of surface markers CD2, CD25, or both

Patients who have typical episodic clinical symptoms accompanied by transient elevations in serum tryptase but do not meet the diagnostic criteria for mastocytosis have mast cell activation syndrome.

Advise patients to stay away from cold, heat, alcohol, ASA, and opiates. Oral cromolyn may help GI symptoms. Various chemotherapy regimens have been used in the treatment of systemic and malignant mastocytosis. Unfortunately, chemotherapy has not been particularly successful.

EOSINOPHILIC ESOPHAGITIS (EoE)

EoE is characterized by persistent eosinophil infiltration of the esophagus. **Solid food dysphagia** and **food impaction** are the most common presenting symptoms. Other symptoms include chest pain, heartburn, and upper abdominal pain. Patients often have other allergic conditions, including asthma, allergic rhinitis, and atopic dermatitis.

Diagnose by endoscopy and biopsy of the esophagus looking for > 15 eosinophils/HPF.

Treatment is individualized and involves ≥ 1 of the following:

- Proton pump inhibitors
- Swallowed inhaled glucocorticoids
- 6-food elimination diet: milk, eggs, soy, wheat, fish/shellfish, and peanuts/tree nuts

For additional information on EoE, see the [Gastroenterology](#) section.

HUMAN LEUKOCYTE ANTIGEN (HLA) DISEASES

PREVIEW | REVIEW

- Which rheumatologic disorders have a positive human leukocyte antigen B27?

There are many diseases associated with certain HLAs; this makes sense, as the HLA complex is the **backbone** of immune surveillance. Autoimmune disease arises when there is immune dysfunction. Many **rheumatic** disorders are accompanied by HLA-B27; they include ankylosing spondylitis, acute anterior uveitis, reactive arthritis, **psoriatic spondyloarthropathy**, and **juvenile idiopathic arthritis** (but **not** adult rheumatoid arthritis [RA]).

RA is associated with the HLA-DR4 antigens. See the [Rheumatology](#) section.

IMMUNODEFICIENCIES

PREVIEW | REVIEW

- Which immune deficiency has no mature B cells? What are its symptoms?
- What is the most common Ig deficiency? How frequently does it occur?
- With what disorders do symptomatic IgA deficient patients present?
- What is Wiskott-Aldrich syndrome?
- Know the infections associated with solid organ transplants and when each is likely to occur.
- Name some factors that affect whether a patient with neutropenia develops an infection.

NOTE

The most important thing when thinking of immunodeficiency is to remember that HIV is not the only cause. If you see a patient with severe, recurrent, or atypical infections who does not have HIV, you are not done with your workup. Consider other diagnoses, such as common variable immune deficiency (CVID), uncontrolled diabetes, cystic fibrosis, and 22q11.2 deletion (DiGeorge) syndrome.

Also see [Complement Deficiencies](#) on page 2-24.

IMMUNOGLOBULIN DEFICIENCIES

Immunoglobulin (Ig) deficiencies can be inherited (e.g., agammaglobulinemia, CVID, IgA deficiency) or acquired (e.g., multiple myeloma, acute lymphocytic leukemia [ALL], chronic lymphocytic leukemia, HIV/AIDS, asplenia).

Inherited Immunoglobulin Deficiencies

Congenital agammaglobulinemia (a.k.a. Bruton's or X-linked agammaglobulinemia [XLA]) patients have **increased susceptibility** to pyogenic and encapsulated organisms (e.g., *Staphylococcus*, *Streptococcus*, meningococcus, *Haemophilus*); hence, they have recurrent **sinopulmonary** and ear infections. Some may also develop bacteremia with *Ureaplasma*, *Mycoplasma*, *Helicobacter*, *Campylobacter jejuni*, and *Pseudomonas* species. Enteroviral infections with echovirus is suggestive of agammaglobulinemia.

Diagnosis: Ig assay shows very low or no Igs. There are also no B cells (i.e., no SmIg+ cells, CD19+ cells).

Prognosis is good if the condition is caught early. Test all the patient's brothers and male cousins on the mother's side.

Treatment: exogenous IVIG or SQIG. Prophylactic antibiotics are required for some patients.

Common variable immunodeficiency (CVID) is the most clinically significant immunodeficiency in adults after HIV, yet it is highly underdiagnosed! CVID is a deficiency of IgG accompanied by deficiencies of IgA and/or IgM. Like XLA, patients have increased susceptibility to **encapsulated** organisms (e.g., *S. pneumoniae*, *H. influenzae*). Patients have recurrent **sinopulmonary infections** and **bronchiectasis**; they also tend to get **giardiasis** and **enterovirus infections**. Multiple pulmonary symptoms are common and are the leading cause of death in patients with CVID. Diarrhea is the most common presenting symptom for related GI disease. Giardiasis and enteritis with *Campylobacter jejuni* and salmonellosis are common enteric infections.

There is an **increased** incidence of autoimmune disease and malignancy, especially lymphoma.

Diagnosis: Ig assay shows low IgG with low IgA and/or low IgM. Unlike XLA, CVID patients have mature **B cells present** (CD19+).

Treatment: exogenous IVIG or SQIG. Some patients may require prophylactic antibiotics. Monitor for signs of disease-associated autoimmune complications and malignancy.

Selective IgA deficiency is the **most common Ig deficiency**, with an incidence as high as 1/300! Fortunately, ~ 2/3 of patients are asymptomatic. The ~ 1/3 with symptoms present with 1 or more of:

- Autoimmune disorders (e.g., rheumatoid arthritis, lupus, celiac disease, chronic autoimmune thyroiditis)
- Allergies
- Recurrent sinopulmonary infections (e.g., rhinosinusitis, pneumonia; often caused by encapsulated organisms [e.g., *S. pneumoniae*, *H. influenzae*])
- GI infections (especially giardiasis)
- Celiac disease

Know these 4 important facts about selective IgA deficiency:

- 1) Women can have false-positive serum pregnancy tests. (Urine pregnancy test is normal.)
- 2) In patients with celiac disease, IgA deficiency can cause false negative results in the 2 standard serologic tests for celiac disease—tissue transglutaminase (TTG) IgA antibody and antiendomysial IgA antibody. Thus, it is essential to also order a total serum IgA level at the same time either of these markers is checked. If the patient is IgA deficient, check for IgG TTG antibody.
- 3) Blood transfusion is associated with a higher-than-normal risk of **anaphylaxis** and should be avoided if possible. These patients have anti-IgA antibodies, and transfused blood contains small amounts of IgA. For more on anaphylactic reactions to transfused blood, see the **Hematology** section.
- 4) IVIG and plasma infusions are contraindicated for the same reason as blood transfusion.

Treat patients who have recurrent infections with prophylactic antibiotics.

Wiskott-Aldrich syndrome (WAS) presents with low IgM and IgG, elevated IgA, and elevated IgE. The triad of findings is eczema, immunodeficiency, and thrombocytopenia. Remembering that it is **X-linked** makes for a nice mnemonic: "Wisk" through the **EXIT**. Leukemia and B-cell lymphoma (associated with Epstein-Barr virus) are malignancies found in young males with WAS. Infection with bacteria having polysaccharide capsules (e.g., *Streptococcus pneumoniae*) is dangerous in patients with WAS. Bone marrow transplantation may be a successful cure.

Acquired Immunoglobulin Deficiencies

Acquired Ig deficiencies secondary to **malignancy**, **collagen vascular disease**, and **chemotherapy** (such as rituximab) are common clinical scenarios for the general internist. Infections arise because either effective antibodies are not produced, or B and T lymphocytes are not communicating effectively with one another. Most of these diseases are associated with **hypogammaglobulinemia** (reduction in levels of specific IgA, M, and G) but with a relative polyclonal increase in the gammaglobulin fraction. That is, patients produce an excess of fairly useless antibodies that are **not** specific for an antigen, are usually ineffective, and may cross-react with normal body components, such as RBCs and platelet surface receptors.

Patients with acquired **humoral** deficiencies are predisposed to infections with **encapsulated** organisms and **giardiasis**. See **The Adaptive Immune System** on page 2-18 for more information.

The spleen clears out bacteria and is the site for **formation of opsonizing antibodies**. Opsonizing antibodies are important in defending the host from infection with **encapsulated** organisms, especially **pneumococcus**.

Splenectomy and functional asplenia increase the risk of overwhelming **pneumococcal**, **malarial**, and **babesial** infections. The latter 2 are intra-RBC protozoan parasites.

IgA blocks viral attachment to mucosal surfaces, and IgG blocks viral attachment to host cells.

Other secondary immunodeficiency states to consider include diabetes mellitus, liver failure, renal failure, chronic glucocorticoid use, and malnutrition.

T-CELL DEFICIENCIES

Etiology

T-cell-deficient patients have decreased cellular immunity. These patients present with **opportunistic infections** (OIs; infections that do not usually present in immunocompetent patients), such as *Pneumocystis jirovecii* pneumonia, CMV colitis, and cryptococcal meningitis. Patients are found to have either low T-cell levels or poor T-cell function.

T-cell defects occur in the following:

- HIV/AIDS
- 22q11.2 deletion (DiGeorge) syndrome
- Hodgkin lymphoma (if T-cell derived)
- T-cell variant of ALL
- Prolonged glucocorticoid use
- Solid organ transplantation (because of immunosuppressant medications)

Associated Infections

Patients with T-cell defects are more susceptible to routine **community-acquired** bacteria and viruses (e.g., pneumococcus, *Mycoplasma*, *Legionella*, *Listeria*, *Salmonella*, influenza, respiratory syncytial virus [RSV]), as well as **OIs** with the following pathogens:

- Bacteria (e.g., *Nocardia*, *Rhodococcus equi*, mycobacteria)
- Viruses (especially new infections with cytomegalovirus [CMV], herpes simplex virus [HSV], or varicella-zoster virus)
- Fungi (e.g., *Pneumocystis*, *Cryptococcus*, *Aspergillus*, endemic fungi)
- Parasites (e.g., *Strongyloides*)

Patients also frequently reactivate protozoal and viral diseases that they have previously held in check (for example, *Toxoplasma gondii* and HSV, respectively).

HIV/AIDS is an acquired T-cell deficiency, discussed in the **Infectious Disease** section.

22q11.2 deletion syndrome (a.k.a. DiGeorge syndrome, congenital **thymic hypoplasia**) is a T-cell deficiency due to an early intrauterine malformation of the embryo that can affect several tissues and organs, including the thymus, parathyroids, heart and great cardiac vessels, and face.

A mnemonic for these findings is “**CATCH-22**” (cardiac, abnormal facies, thymic hypoplasia, cleft lip, hypocalcemia, chromosome 22).

There is a wide range of symptoms and variable decrease in T-cell function related to the variable decrease in thymic tissue. In many patients, a microdeletion in chromosome 22q11.2 is demonstrated. In rare circumstances, severely affected infants (complete DiGeorge syndrome = no thymus and no T cells) receive thymic transplantation. Note that some patients reach adulthood, although most adults with DiGeorge have fewer cardiac anomalies but more craniofacial defects and psychiatric illnesses.

Solid Organ Transplantation

Patients who have received a solid organ transplant are at risk for infections carried by the donor organ, as well as nosocomial infections. Additionally, they can reactivate infections that had been previously controlled by their immune system. Some of these infections are mentioned in **Associated Infections** but also include endemic fungi and mycobacteria.

Infections caused by immunosuppressive drugs tend to arise predictably, based on the length of treatment.

Know the following **classic 3** posttransplantation time periods and their associated infection risks:

- **Month 1:** infections from the donor; nosocomial infection (i.e., specific to the type of surgery performed)
- **Months 2–6:** Immunosuppressant medication is starting to take effect, and patients are at risk for the OIs described in **Associated Infections** (e.g., CMV from donor+ and recipient– solid organ transplant recipients).
- **> 6 months:** community-acquired infections

However, the use of routine prophylaxis with trimethoprim/sulfamethoxazole (TMP/SMX) and valganciclovir has shifted the time of onset for some OIs. For instance, CMV may not occur until after valganciclovir is stopped in these patients.

COMBINED T- AND B-CELL DEFICIENCIES

Combined T- and B-cell deficiencies present with infections—usually opportunistic infections. It is difficult to separate this group from the **T-Cell Deficiencies** because you cannot have normally functioning B cells without normally functioning T cells. These patients are found to have both low Ig and low T-cell numbers (or low T-cell function). These defects usually present in infancy and are universally fatal without stem cell transplantation.

Severe combined immunodeficiency (SCID) is a deficiency in both T- and B-cell numbers or function. SCID is either autosomal recessive or X-linked. It is always fatal in infancy unless treated with stem cell transplantation.

Ataxia-telangiectasia is an **autosomal recessive** disorder that causes both **cellular** and **Ig deficiency**. This results in recurrent sinopulmonary infections, bronchiectasis, and progressive telangiectasias. Patients also have a progressive **neurologic** deterioration of uncertain etiology, characterized by cerebellar ataxia and progressive mental deterioration. Survival into adulthood is not common.

NEUTROPENIA

In neutropenia, the absolute neutrophil count (ANC) is $< 1,500$ cells/ μ L (1.5×10^9 /L). Neutropenia occurs in the following scenarios:

- Normal low-variant populations who are asymptomatic (Only 4% of African Americans have ANC $> 1,500$.)
- Decreased bone marrow production due to medications, nutritional deficits, collagen vascular disease, or malignancy
- Congenital neutropenias, such as neutrophil elastase and HAX1 deficiency, usually present in childhood but may be seen in adults during initial presentation (in rare cases).
- A shift from general circulation to other organs like the spleen (e.g., hypersplenic conditions)
- Immune destruction of neutrophils (e.g., in autoimmune disease)

Neutrophils help to fight disease by disrupting or consuming disease-producing cells and microorganisms. Neutropenia can hinder the body's ability to fight disease, resulting in infection. Most often, sepsis is caused by flora that colonize the patient and enter the bloodstream across disrupted gut mucosa (via an IV catheter) or through the oropharynx into the lungs and/or sinuses. Neutropenic infections can be caused by both gram-negative and gram-positive bacteria.

The most common gram-positive organisms causing neutropenic infections are *S. aureus*, *S. epidermidis*, and streptococcal species. More and more infections are caused by the less common gram-positive organisms, such as *Corynebacterium* species, *Cutibacterium acnes* (previously known as *Propionibacterium acnes*), *Bacillus* species, and *Leuconostoc*. These are important to remember because some are **not** effectively treated with **vancomycin**.

Common gram-negative infections include *Pseudomonas* species and Enterobacteriaceae (e.g., *E. coli*, *Klebsiella* species, *Enterobacter*).

Fungi, including yeasts such as *Candida* and molds such as *Aspergillus* species, are important pathogens in patients with prolonged neutropenia. Infections with *Fusarium* species and agents of mucormycosis are especially **deadly** and are being seen more frequently. Not all fungi are equally susceptible to all antifungal drugs. When a patient with neutropenia develops fever and/or an infection while receiving an empiric antifungal drug, it is very important to know which organisms are resistant to that antifungal. (See the discussion of antifungal agents in the **Infectious Disease** section.)

The risk for infection in the patient with neutropenia is directly proportional to the degree and duration of neutropenia.

Other factors that increase risk are:

- Comorbidities
- Presence of catheters
- Concomitant use of immunosuppressive drugs, such as monoclonal antibodies and glucocorticoids (increases risk of *Pneumocystis* and tuberculosis)

A patient with severe neutropenia (< 500 neutrophils) is at a much higher risk than a patient with mild neutropenia (500–1,500 neutrophils); however, **function** of cells is as important as **number** of cells in resisting infection. Even with an adequate number of cells, patients can develop infection if the granulocytes that are present do not function properly. Suspect granulocyte **dysfunction** (e.g., **chronic granulomatous disease**) if the patient has an adequate ANC but has a history of recurrent staphylococcal skin infections, lung infections, and/or lymphadenitis. The duration of neutropenia is also key: An ANC < 500 for > 7 days greatly increases the risk of infection.

For febrile neutropenia, see the **Infectious Disease** section.

HIGHLIGHTS

Know the associations of the following inherited and acquired immunodeficiencies.

Inherited humoral deficiency:

- Recurrent sinopulmonary infections with encapsulated organisms
- Enteroviral infections
- Giardiasis
- Risk of autoimmune disease
- Risk of malignancy

Inherited selective deficiency of IgA:

- Mostly asymptomatic
- Food and inhalant allergies
- False-positive **serum** pregnancy tests
- Anaphylaxis with blood transfusion and IVIG
- Association with autoimmune diseases

Acquired humoral deficiencies can be seen in patients with splenectomy, leukemias, lymphomas, myeloma, HIV/AIDS, and encapsulated organisms.

Classical early complement deficiencies can be found in patients with sinopulmonary infections with encapsulated organisms and C2 deficiency associated with SLE.

Terminal complement deficiencies are associated with infections with encapsulated organisms and *Neisseria meningococcus*.

T-cell defects are associated with patients with HIV/AIDS, after transplantation, treatment with glucocorticoids, and infections with fungi, acid-fast bacteria, viruses, and parasites.

THE IMMUNE SYSTEM

PREVIEW | REVIEW

- What is the 1st line of defense of the immune system?
- Which part of the immune system is rapid and nonspecific?
- Which part of the immune system is slow and specific?
- How is cellular messaging used oppositely in innate and adaptive immunity?

THE INNATE IMMUNE SYSTEM

The innate immune system is the 2nd line of defense against pathogens, after the skin (which is the 1st line).

Characteristics of the innate immune system include:

- Rapid acting
- Nonspecific
- No memory

Its components include:

- Complement
- Macrophages
- Natural killer (NK) cells

THE ADAPTIVE IMMUNE SYSTEM

The adaptive immune system is the 3rd line of defense against pathogens and is activated by the innate immune system. Unlike the innate immune system, the adaptive system is:

- much slower to get started,
- very specific, and
- has memory.

The adaptive immune system can be broken down into 2 main components:

- 1) **Humoral:** B cells, plasma cells, and immunoglobulins (Igs). Activated B cells become plasma cells, which make Ig.
- 2) **Cell-mediated:** T cells

INNATE vs. ADAPTIVE IMMUNITY

The innate immune system is the foundation on which the more sophisticated adaptive immune system sits. The innate system not only protects the body while the adaptive system gears up, but it also helps direct the response. The innate immune system, in general, needs messages to **prevent** it from killing pathogens, while the adaptive immune system needs messages (usually from the innate immune system) to **allow** it to kill pathogens.

The key difference between the 2 systems can be found in their receptors:

- **Innate** immune system receptors are generic, ready-made receptors (e.g., toll-like receptors). These receptors allow a quick but nonspecific response—one that is rapid but does not recognize distinct pathogens. Think of these as the “first responders” to a new attack. The cells that carry out most innate immune functions are myeloid cells.
- **Adaptive** immune system receptors are custom-made receptors (T-cell receptors [TCRs] and Igs) that are refined to be as **specific** as possible for the pathogen. They provide the immune system with the ability to recognize a seemingly infinite variety of pathogens. Once these custom-made receptors have served their purpose, the body keeps a few of them around in case it needs them again in the future, enabling a quicker reaction based on memory. The cells that carry out most adaptive immune functions are lymphoid cells.

Summary: The innate immune system provides a quick, generic response, while the adaptive provides a slower—but more powerful and specific—response to the foreign pathogen. Thanks to immunologic memory, if the pathogen is encountered again in the future, the adaptive system can mount a quicker and more robust response.

INNATE AND ADAPTIVE OVERLAP

There is significant overlap between the innate and adaptive immune systems:

- The classical pathway of the innate complement system requires C1 to bind to an immune (antibody-antigen) complex formed by the adaptive immune system to initiate its activity.
- C3b, made by all pathways of the innate complement system and continuously generated by the alternative pathway, opsonize pathogens and immune complexes—coating and tagging them for phagocytosis. Phagocytes like macrophages and dendritic cells are also professional antigen presenting cells (APCs) and present these antigens to the T-helper cells, which in turn initiate or accelerate the adaptive immune response of B cells. (Whew!)
- Macrophages and NK cells initially function as part of the innate system; when they become further activated by T cells, they can subsequently act as part of the adaptive immune system.

INNATE-LIKE CELLS

There are cells that are part of the adaptive immune system but are innate-like. They show overlap because they are more rapid-acting and less specific than the other lymphocytes. Examples of innate-like immune cells are:

- $\gamma\delta$ T cells
- Natural killer T (NKT) cells
- B-1 cells (an innate-like version of B cells)

CELLS OF THE IMMUNE SYSTEM

There are 2 major cell types in the immune system:

1) Lymphoid cells

- Lymphocytes
 - T cells
 - $\alpha\beta$ T cells
 - CD4+ T cells (a.k.a. helper T cells, T-helper cells [Th cells])
 - CD8+ T cells (a.k.a. cytotoxic T cells)
 - $\gamma\delta$ T cells (innate-like)
 - NKT (natural killer T cells; innate-like)
 - B cells
 - B-1 cells (innate-like, found mainly in peritoneal and pleural cavities)
 - B-2 cells (a.k.a. conventional B cells; the workhorses of the immune system that produce all Igs)
 - Marginal B cells (innate-like, found mainly in the spleen)
- NK cells (natural killer cells; do not confuse with the similarly named T cells!)

2) Myeloid cells

- Granulocytes
 - Neutrophils
 - Eosinophils
 - Basophils
- Professional antigen-presenting cells (APCs)
 - Monocytes/Macrophages
 - Dendritic cells
 - B cells are APCs that are not myeloid
- Other
 - Mast cells
 - Erythrocytes
 - Megakaryocytes/Platelets

HUMAN LEUKOCYTE ANTIGENS (HLAs)

PREVIEW | REVIEW

- What are Class I human leukocyte antigens (HLAs)? What type of cells do they appear on?
- What are Class II HLAs? What type of cells do they appear on?
- What is major histocompatibility complex restriction?

The HLA complex is a group of genes that code for unique proteins, specific for that individual, that are expressed on cell surfaces. The immune system uses a class of these proteins (Class I) to determine if the cell is self (okay) or

nonself (not okay—terminate!). It uses another class, Class II, to make sure that a cell presenting foreign antigen is a professional antigen presenting cell (APC). Many species have this system, and it is identified as the major histocompatibility complex; human leukocyte antigen (HLA) complex is the same system in humans. The HLA gene complex is located on the short arm of chromosome 6. There are 3 classes of HLA. In the following, remember only the **class**—not any of the subclasses.

Class I HLAs (HLA-A, -B, and -C) are expressed on **all** nucleated cells and are used to determine if the cell is self or nonself. The Class I HLA protein on these cells complex with and present foreign antigens to the cytotoxic **CD8+ (killer) T cells**. Class I HLAs play a major role in **transplant rejection, neoplasms, and viral infections**.

In contrast to these “generalist” APCs, there are other specialized cell types that present antigen as a main function. These are called **professional** APCs.

Class II HLAs (HLA-DP, -DQ, and -DR) are expressed on the surface of the professional APCs, which include monocytes/macrophages, dendritic cells (including Langerhans cells), and B cells. The expressed Class II HLAs complex with foreign antigens and present them to **CD4+ (helper) T cells**. Class II HLAs mediate the reactions among macrophages, T cells, and B cells.

Class III HLAs code for peptides involved with inflammation such as tumor necrosis factor (TNF), heat shock proteins, and certain complement proteins.

T cells can recognize antigens only if the antigen is complexed with the proper HLA protein. HLA I presents antigen to CD8+ T cells, and HLA II presents antigen to CD4+ T cells (mnemonic: $8 \times 1 = 8$ and $4 \times 2 = 8$). This is the key concept of MHC restriction.

LYMPHOID CELLS

PREVIEW | REVIEW

- What are the functions of T cells?
- Which antigens do CD4+ helper T cells recognize? CD8+ T cells?
- What is the important distinction between the way natural killer cells and natural killer T cells kill other cells?
- Which immunoglobulins are present on the surface of mature B cells?

LYMPHOCYTES

T Cells

Clusters of differentiation (CD) markers are like “ID tags” that can be identified by monoclonal antibodies in labs.

They are useful in immunophenotyping lymphocytes, which allows us to differentiate one immune cell from another. For example:

- CD45+: all leukocytes (i.e., granulocytes, monocytes, lymphocytes)
- CD3+: T-helper cells and cytotoxic T cells
- CD4+: T-helper cell only
- CD8+: cytotoxic T cells only
- CD19+ and CD20+: mature B cells
- CD16+ and CD56+: NK cells

Interleukins (IL) are the “language of the immune system” and allow immune cells to communicate with one another. For example:

- Secretion of IL-7 causes an inflammatory response.
- Secretion of IL-4, IL-5, and IL-13 causes an allergic response.
- Secretion of IL-10 causes immune suppression.

Functions of T cells:

- Destroy intracellular and other bacteria (especially gram-negatives), viruses, fungi, parasites, and mycobacteria
- Regulate Ig production by B cells
- Activate other immune cells, such as macrophages, by secreting cytokines

All T cells have T-cell receptors (TCRs), which are antigen-specific binding sites composed of 2 subunits (the majority being alpha and beta, and a minority being the innate-like gamma and delta). The TCR is always complexed with CD3, which allows intracellular signaling.

Again: CD4 cells recognize antigen **only** if it is presented along with a Class II HLA antigen. CD8+ T cells recognize an antigen only if it is presented with a Class I HLA, whereas CD4+ T cells recognize an antigen only if it is presented with a Class II HLA. This is the key concept of MHC restriction.

CD4+ T Cells

CD4+ T-helper (Th) cells are the primary defense against extracellular threats. They are divided into several subsets:

- **Th1** activates macrophages and CD8+ cytotoxic T cells, leading to a **cell-mediated** immune reaction.
- **Th2** activates mature B cells to produce antibody, resulting in a **humoral** immune reaction.
- **Th17** induces local inflammation by secreting IL-17 which stimulates local tissue cells to express chemokines and attract inflammatory cells.

Again: Th cells are activated **only** by antigen presented in association with Class II HLAs, which only appear on professional APCs, such as B cells, monocytes/macrophages, and dendritic cells (including Langerhans cells).

How are CD4+ T cells **activated**? An APC, such as a macrophage, ingests an extracellular foreign pathogen. This foreign particle is ingested, processed, and presented

along with the Class II HLA to CD4+ helper T cells. These T cells, after being activated, **induce** B cells to convert to plasma cells and produce specific antibodies against that foreign particle.

How does HIV affect the immune system? **HIV** targets all **CD4+** cells, including CD4+ T-helper cells, macrophages, monocytes, and microglial cells. By targeting and attacking CD4+ cells, HIV severely weakens the immune system, allowing opportunistic infections to occur.

CD8+ T Cells

The CD8+ cells are **cytotoxic** T cells (CTLs) and are important in the defense against intracellular threats such as viruses and neoplastic cells. When a cell is infected by a virus or becomes neoplastic, these viral or neoplastic antigens are processed by the infected cell and presented on its surface in combination with **Class I** HLAs. This marks the cell for destruction by the CTLs. All nucleated cells have Class I HLAs, so **most** cell types can present antigen to CD8+ T cells!

T Regulatory Cells

T regulatory (Treg) cells are a specialized subpopulation of T cells that modulate the activity of the immune system. The expression of the transcription factor **FOXP3** controls the development and function of Treg cells. These cells secrete **immunosuppressive cytokines**, such as IL-10 and transforming growth factor β (TGF- β). Treg cells can down-regulate both Th1 and Th2 responses, thereby, reducing allergic inflammation and inducing tolerance against self-antigens. Genetic mutations in **FOXP3** cause an overwhelming systemic autoimmunity known as **IPEX** (immune dysregulation, polyendocrinopathy, enteropathy, **X**-linked).

Natural Killer T Cells

Name alert! Do not confuse natural killer T (NKT) cells with NK cells—the **innate** lymphoid cells with a very similar name.

NKT cells are so named because they share several features with NK cells, such as granzyme production and **CD16** and **CD56** expression. Yet, unlike NK cells, NKT cells have TCRs and require a signal to kill. They are restricted to a type of MHC-like molecules called **CD1**, which primarily recognizes **lipids** and glycolipids (in contrast to the MHC molecules, which primarily recognize protein antigens).

B Cells

B cells not only produce all the immunoglobulins in the body, but also use these same antibodies as receptors bound to the surface of the B cell. These are called B-cell receptors (BCR). In a naive, mature B cell (one that has never seen antigen), these receptors are ready to interact with antigen presented by a T-helper cell or with an antigen itself. A single B cell has about 100,000 of each class of surface Igs that cover its surface.

Progenitors to B cells develop in the bone marrow and become immature B cells (with surface IgM; **IgM only = immature**) which then migrate from the bone marrow to the lymph nodes, where they express surface IgD in addition to the surface IgM—and now are naive mature B cells (**IgM + IgD = naive mature**). These naive, mature B cells wait to become activated by T-helper cells presenting an antigen, or by an antigen itself. The activated B cell—now with a B-cell receptor (**BCR = activated B cell**) whose variable region contains changes due to the antigen DNA—then moves to the germinal center of the lymph node and starts proliferating wildly, while continuously mutating and producing different variable regions to the BCR. Most of the resulting BCRs have low affinity for the antigen and the B cell dies (apoptosis). Occasionally, one will have a receptor with increased affinity for the antigen, and this “high-affinity” BCR+ B cell survives.

When a Th cell connects to this high-affinity BCR on this mature B cell, it will induce the B cell to transform into:

- a **plasma** cell that will then produce the antigen-specific IgM antibodies at a rate of thousands per second or
- a **memory** B cell that will “**class-switch**” the receptors on its surface (e.g., to IgG, IgA, IgE) but keep the same variable region. It (or its clones) hangs around for years. When a memory B cell meets that same antigen, it will immediately proliferate and differentiate into plasma cells that will produce that new class of antibody.

B cells can be stimulated to convert to plasma cells by activated CD4+ T cells or, if there are sufficiently large quantities, by antigen alone. Plasma cells produce specific antibodies that coat the surface of a particular foreign organism. This coating identifies it as edible to the macrophages (**opsonization**) and initiates the complement cascade. Specific antibodies can also **neutralize** bacterial toxins and viruses.

B cells are also APCs and have Class II HLAs on their surfaces, enabling them to present foreign antigens to CD4+ Th cells. The activated T cells can then induce other B cells to convert to plasma cells and produce antibodies.

NATURAL KILLER CELLS

Name alert! Do not confuse these cells of the innate immune system with NKT cells.

Natural killer (NK) cells are lymphoid cells that play a major role in the immune system response to tumors and viruses. They express **CD16** and **CD56** but not TCRs or their associated CD3 molecules. This is an important difference between NK and NKT cells!

NK cells are called natural killers because they are **always in kill mode**. Cells encountered by the NK cells must present themselves appropriately to avoid getting killed. For example, all cells (except mature RBCs) must display Class I **HLA-E** on their cell surfaces in order to **avoid getting killed** by NK cells. This is in contrast to T cells and NKT cells that require a signal in order to kill.

NK cells are an important component of the immune system because some viruses have evolved to reduce Class I HLA expression on the host cell, protecting them from recognition and destruction by T cells. It is precisely this absence or reduction of Class I HLA expression that causes the NK cell to kill the infected cell (typically by inducing apoptosis), which would have been missed by the T cells.

MYELOID CELLS

Granulocytes are WBCs with identifiable granules within their cytoplasm.

Neutrophils are also known as polymorphonuclear leukocytes, polys, PMNs, segs (mature), and bands (immature). They have a multilobed nucleus with 3–5 lobes. PMNs phagocytize microorganisms, especially those coated with antibodies. If PMNs are absent, patients get overwhelming **pyogenic** infections.

Eosinophils are involved in the pathology of **allergic** reactions and in the immunologic defense against **parasites**.

Basophils are involved with the late-phase response of IgE-mediated Type 1 hypersensitivity. See [Type 1 – IgE-Mediated Immediate Hypersensitivity Reaction](#) on page 2-1.

Professional antigen-presenting cells (APCs) are cells that express Class II HLAs, and, like all nucleated cells, also express HLA I. This is an exclusive group of cells consisting of 3 cell types:

- 1) **B cells**: the **most specific** APCs
- 2) **Monocytes/Macrophages** phagocytose opsonized microorganisms, process and present antigens, and secrete interleukin-1 (IL-1; stimulates T cells).
- 3) **Dendritic cells** are scavengers; they change conformation (when they ingest a pathogen), travel to a lymph node, and activate lymphocytes.

Note that phagocytic cells consist of neutrophils, monocytes/macrophages, and dendritic cells. The monocytes/macrophages and dendritic cells together form the **mononuclear phagocyte system**.

Others:

- Mast cells are involved with the early-phase response of IgE-mediated Type 1 hypersensitivity. See [Type 1 – IgE-Mediated Immediate Hypersensitivity Reaction](#) on page 2-1.
- Erythrocytes directly participate in the immune complex reaction (bacteria, complement, and antibody) for enhanced phagocytosis; their primary functions are in oxygenation, balancing blood pH balance, and transporting nutrients and electrolytes. More information on RBC function is in the [Hematology](#) section.
- Megakaryocytes/Platelets are recognized for their clotting properties, but also are active participants in immune defense (with recruitment of neutrophils and cytokine signaling in the lysis of microorganisms). Refer to the [Hematology](#) section for more information on megakaryocyte and platelet functions.

ANTIBODIES

PREVIEW | REVIEW

- Characterize the various immunoglobulins: G, A, M, E, and D.
- Which antibody crosses the placenta?
- Which antibody is produced 1st during an infection?

All antibodies (a.k.a. immunoglobulins [Igs]) have the same basic structure (Figure 2-7). Each monomer is composed of 2 heavy and 2 light chains that are held together by disulfide bonds. There are 5 immunoglobulin isotypes: G, A, M, E, and D. These isotypes are determined by differences in the structure of the constant regions of the heavy chains. All antibodies have 1 of 2 types of light chains, kappa or lambda.

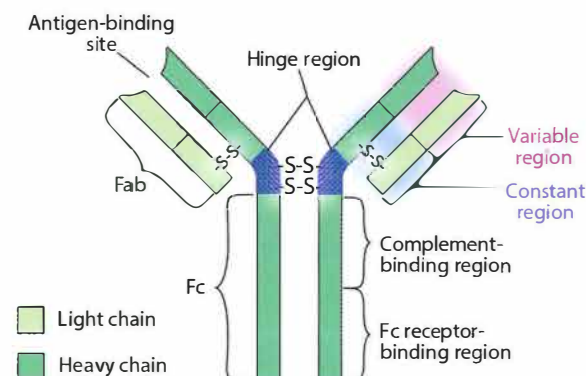


Figure 2-7: Antibody structure

Remember the following key points about immunoglobulins G, A, M, E, and D:

- **IgG** is simplest, smallest, and most abundant Ig in the serum. It is the smallest antibody and the only Ig that can pass through the placental barrier. About 75% of Igs in the serum are IgG. Mechanisms used by IgG to fight pathogens:
 - Immobilize pathogen by mediating their agglutination
 - Opsonize pathogens, making them more susceptible to phagocytosis
 - Activate the classical complement pathway
 - Bind and neutralize bacterial exotoxins and viruses
- A single plasma cell can make IgGs tailored to a specific antigen at a rate of thousands per second! IgG antibodies can cross the placental barrier and provide passive immunity to the fetus (and for the infant's first 6 months of life). IgG is involved with Type 2 IgG-mediated cytotoxic hypersensitivity and Type 3 immune complex hypersensitivity reactions.

- **IgA** is the most abundant Ig produced in the body. It is produced by surface IgA+ plasma cells and is the main Ig in secretions. It is considered our 1st line of defense against pathogens. IgA also is about 15% of Ig in the serum. It is usually in a dimer configuration (2 Igs) with a J (joining) chain connecting the two bases. This dimer configuration automatically attaches to a secretory component, which allows IgA to exit the body via exocrine glands and become part of seromucous secretions. IgA is found in tears, saliva, sweat, and in secretions of the sinuses, respiratory tract, digestive tract, and GU tract. It is the main Ig secreted in breast milk, and is especially high in colostrum. IgA works with the same mechanisms as IgG, but does **not** activate complement.
- **IgM** is the 1st immunoglobulin to develop in the fetus, appearing at ~ 20 weeks. IgM is also the first surface Ig on a developing B cell and the first Ig released by B cells when converted to plasma cells after the initial encounter with a pathogen. IgM is secreted as a pentamer (5 immunoglobulins) in which each monomer is connected at its base by a J chain. Checking for IgM can be useful in diagnosing a current illness and can help distinguish acute vs. chronic infection. IgM has the same mechanisms as IgG, but it is the most effective Ig for complement activation.
- **IgE** is the Ig with the lowest concentration in normal serum (0.05% of Igs) but is a major factor in many allergic conditions, including asthma, allergic rhinitis, atopic dermatitis, and food allergies. It is also used to fight off parasitic infections. In all these cases, plasma IgE levels can be elevated.
- **IgD** is a surface Ig found on B cells, and identifies a B cell as mature. It is involved with the formation of B-cell receptors on B cells that are fundamental in their activation. A tiny amount is found in the serum (~ 0.25% of Igs), but its function in this expressed form is uncertain.

The **variability** in Ig specificity is responsible for the immune system's ability to encounter and then remember an almost limitless number of pathogens. The rearrangement of several regions within the antibody gene makes this possible. Most of the variability is located in the complementarity determining regions, also known as hypervariable regions.

Igs bind specific antigens in the Fab region and then activate either cells or complements (see [Complement Cascade](#)), by means of the Fc region, to destroy the antigen-bearing material.

COMPLEMENT CASCADE

PREVIEW | REVIEW

- What is the cause of hereditary angioedema (HAE)?
- What is the clinical presentation of HAE?

- Which infection is most often seen with terminal complement deficiency?
- What does the CH50 assay measure, and when is it used?

OVERVIEW

The 3 Complement Pathways

The complement system (follow along with [Figure 2-8](#)) is a group of about 30 known plasma factors important in host defense. It has 3 pathways: classical, lectin, and alternative. Through these different pathways, they ultimately perform the same functions:

- Opsonizing target cells with C3b
- Inducing more inflammation with anaphylatoxins C3a, C4a, and C5a
- Building and activating the C5b–C9 membrane attack complex (MAC)

Classical Pathway

IgM and IgG immune complexes (Ig + antigen) activate the **classical pathway**. In this system, we have both the innate (complement) and adaptive (Ig) systems working together. The C1 complex is activated when it attaches to the antibody of an immune (Ag-Ab) complex. Activated C1 cleaves **many** C2s and C4s, subcomponents of which (C4b and C2a) combine and form C4b2a (a.k.a. a C3 convertase). C4b2a, in turn, cleaves **many** C3s.

One IgM pentamer can initiate the classical pathway, but it generally takes at least 2 IgGs or even greater quantities of antigen to perform the same initiation process.

Lectin (or Mannose-Binding) Pathway

Lectins bind mannose on the surface of pathogens. Lectins are also called “mannose-binding lectins” (MBLs) or “mannose (mannan)-binding proteins.” These MBL complexes are produced by an acute phase response and

are fairly nonspecific. Associated proteases then cleave many C2s and C4s, and subsequent steps are similar to the classical pathway.

Alternative Pathway

The alternative pathway is very nonspecific, but acts extremely fast when it is activated by a pathogen or dead tissue to make more C3b to opsonize the pathogen. C3b goes on to stimulate the production of the terminal complement components (C5–C9) which form the membrane attack complex (MAC) on the cell surface of the pathogenic bacteria. C3, the pivotal piece of the complement system, slowly dissociates due to protein factors in the alternative pathway that combine with C3b to make a C3 convertase. The newly produced C3b feeds back into the alternative pathway to repeat the process. This process loop is like an idling motor, and is called **C3 tick-over**—keeping just enough C3b around to immediately opsonize an invading pathogen.

Common Terminal Pathway — C3b Opsonization

Opsonins coat pathogens and mark them for destruction by the immune system. This is typically carried out by macrophages like the Kupffer cells in the liver. The 2 most important opsonins are IgG of the adaptive immune system and C3b of the innate. So, while the slower and more specific adaptive immune system's IgG takes days to mount an appropriate response, the quicker and less specific C3b fulfills this important role more rapidly.

Membrane Attack Complex

C3, when combined with either C4b2a or Factor B, activates C5 and forms the C5-6-7-8-9 **MAC**. This complex forms transplasma membrane channels on the surface of pathogenic bacteria, causing lysis.

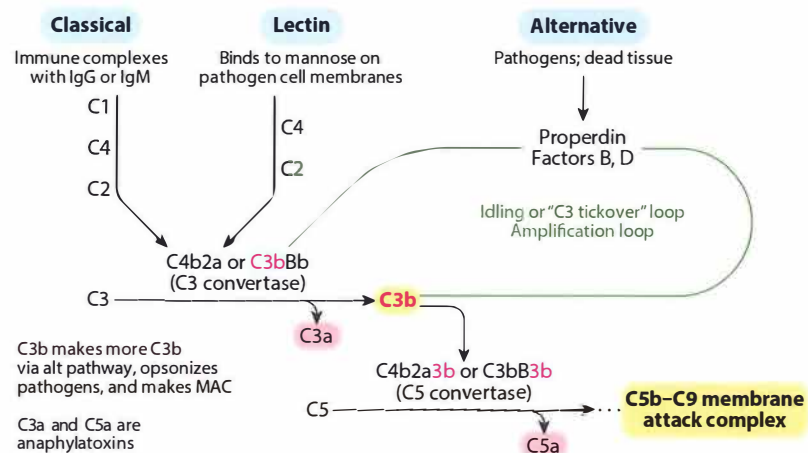


Figure 2-8: The complement cascade

COMPLEMENT DEFICIENCIES

Hereditary Angioedema (HAE)

HAE is an autosomal dominant disorder characterized by recurrent attacks of angioedema caused by a decrease in C1 esterase inhibitor (C1-INH; a.k.a. C1 inhibitor) production or function. While C1-INH is a key inhibitor of the 1st complex in the complement cascade, it is also the principle regulator of bradykinin expression. Lack of C1-INH results in unchecked production of **bradykinin**, the key mediator in HAE attacks. Patients can have either a **decreased C1-INH level** (Type I; 85% of HAE patients) or a nonfunctioning C1-INH (Type II; 15% of HAE patients). Anything that causes an increase in kinins/bradykinins unmasks HAE and precipitates angioedema. Drugs such as ACEIs are recognized causes of angioedema due to the accumulation of bradykinin.

Patients have recurrent angioedema with each episode, lasting 1–3 days. Unlike angioedema/urticaria caused by immediate hypersensitivity reactions, hereditary angioedema is **not** associated with urticaria or itching. Even minor trauma from dental procedures can precipitate attacks! Most patients experience facial swelling, especially lip swelling. The cutaneous symptoms can also affect extremities (Figure 2-9) and genitalia and are rapid in onset. Attacks can include laryngeal swelling with possible stridor and potentially life-threatening obstruction. GI tract attacks are caused by bowel wall swelling and can produce severe abdominal pain, often leading to inappropriate surgeries.



Figure 2-9: Swollen hand during a hereditary angioedema attack
Source: LucyHAE

Diagnosis: Screen by checking for low C4 levels. A normal C4 level during an acute episode of angioedema rules out HAE. A C1-INH functional assay provides definitive diagnosis of HAE:

- If the C1-INH level is low, then it is **Type I HAE**.
- If the C1-INH level is normal, then it is **Type II HAE**.

Treat acute attacks as early as possible with one of the following (in order of preference):

- C1-INH (plasma-derived or recombinant)
- Bradykinin receptor antagonist (icatibant; competes for the bradykinin B receptor)
- Kallikrein inhibitor (ecallantide; decreases bradykinin production)

Trigger avoidance is the first step to prevent acute attacks. Common triggers are trauma to facial and throat areas, oral and dental infections, and certain medications—especially ACEIs and estrogens. If this is not sufficient, then one of the following is given:

- IV or SQ plasma-derived C1 inhibitor replacement (best overall; best if pregnant or lactating)
- Tranexamic acid (limited effect but often tried first because it is given orally)

Note that epinephrine, glucocorticoids, and antihistamines are **not** effective in any HAE therapy.

Acquired Angioedema

Acquired angioedema is clinically similar to HAE, but is defined by low C1-INH (as in HAE) and also a **low C1q**. Synthesis of complement components in the liver and macrophages are inhibited by myelo- and lymphoproliferative diseases like lymphoma. In addition, autoimmune disease can result in the formation of C1-INH autoantibodies. Both instances result in decreased C1-INH and C1q levels. Again, C1q levels are normal in HAE. Acquired angioedema is found in older patients with underlying disease, and treatment is similar to HAE.

C1, C2, and C4 Deficiencies

C1, C2, or C4 deficiencies cause **decreased activation** of complement via the **classical** pathway. C2 deficiency is the most common complement deficiency in North American Caucasians. Most of the complement proteins are inherited as **autosomal recessive** genes. Although the alternative pathway takes up some of the slack, these patients are likely to have recurrent sinopulmonary disease due to **encapsulated** bacteria (such as *Streptococcus pneumoniae*, *Haemophilus influenzae* Type b, and *Neisseria meningitidis*). Patients must undergo prophylactic vaccinations against encapsulated organisms. In patients with 1 abnormal gene, serum complement levels are about 1/2 normal. In these patients, there is an increased incidence of rheumatoid diseases—**especially SLE!**

C3 Deficiency

C3 deficiency (complete absence of its function) is heritable and results in **severe pyogenic** (bacterial) infections.

C5–C9 Deficiency

C5–C9 deficiency (a.k.a. **terminal complement deficiency**) is an autosomal recessive disorder that affects the MAC.

A very rare deficiency of Factor D or properdin in the alternative pathway also decreases the production of terminal complex components and the MAC.

It results in increased *Neisseria meningococcal*/gonococcal infections (especially meningitis or septicemia). Screen for terminal complement deficiency with a CH50 assay. Specific diagnosis is made by assay of these complement components.

CH50 ASSAY

The CH50 (a.k.a. CH100) screening assay measures the total complement activity of the classical pathway. A normal test shows that all factors of the classical pathway (C1–C9) are present. A CH50 is done on a meningococemia patients as a screen for terminal complement deficiency (C5–C9). CH50, C3, and C4 are sometimes used to follow the disease activity of SLE. If the CH50 is very low, check individual complement components (C1–C9 levels) for specific deficiencies. Know that CH50 activity can be normal even when an individual component is 50–80% decreased. For this reason, if the index of suspicion is high for a complement disorder and the CH50 is normal, it may still be necessary to measure individual components.

Immune complexes activate complement to form C3b, which attaches to the Fc portion of IgG. This maintains the solubility of the complexes in the serum and prevents them from cross-connecting and precipitating. IgA does not activate the classical complement pathway and is therefore more susceptible to precipitation. This causes ICs to deposit in small blood vessels and tissues when high levels build up.

See [Type 3 – Immune Complex Hypersensitivity on page 2-3](#).

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medstudy.com/hub

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IMMUNE COMPLEXES

Immune complexes (ICs or antigen-antibody complexes) form during normal day-to-day immune surveillance and are then removed from the serum. As they form, complement is **usually** activated and a C3 component (C3b) attaches to the complex.

The C3b-IC entity is recognized by and attaches to the complement receptor (CR). The main CR1 is found in abundance on RBCs.

Immune complexes are scrubbed off the RBCs by the Kupffer cells in the liver. (Remember that Kupffer cells also remove and destroy C3-coated gram-positive and gram-negative bacteria; see [Common Terminal Pathway – C3b Opsonization on page 2-23](#).) If there are any defects in this elimination process, ICs increase in the serum, as in the following conditions:

- **Hepatic vein thrombosis** (a.k.a. Budd-Chiari syndrome) and cirrhosis cause a decreased clearance of ICs.
- **Paroxysmal nocturnal hemoglobinuria** (PNH) causes decreased binding of ICs; for more information, see the [Hematology](#) section.
- **SLE** causes a decreased amount of CR1 on RBCs.

Note that each of these disorders causes an **increase in ICs** in the serum.

Dermatology

SECTION EDITOR

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COMMON SKIN PROBLEMS

PREVIEW | REVIEW

- What bacterium most commonly infects patients with atopic dermatitis? What virus?
- What is the clinical presentation of seborrhea?
- What is the clinical presentation of intertrigo?
- Allergic contact dermatitis is an example of what type of hypersensitivity reaction?
- What are the serious side effects of isotretinoin?
- How do you distinguish rosacea from acne vulgaris?
- What inflammatory scarring disease affects the axilla, groin, and perianal areas?

OVERVIEW

As the largest organ of the human body, it is no surprise that the skin serves numerous functions that are essential in the maintenance of human health. More specifically, the skin functions to prevent infection using both innate and adaptive immunity, repair injury, protect the integrity of DNA, provide circulation, maintain a barrier for water and temperature regulation, provide sensory communication, and provide nutrition.

The skin is composed of 3 main layers: the epidermis, the dermis, and the subcutaneous tissue. The epidermis is the body's first line of defense and comprises a semipermeable, laminated surface that acts as a barrier to chemical penetration, microbiologic invasion, and fluid and solute loss. The dermis provides structural and nutritional support and is populated by nerves and vasculature. At the dermal-epidermal interface is the basement membrane, which is an area of great interest, because genetic defects of this zone may lead to significant disease. It is also a target of autoimmune attack. The subcutaneous tissue provides thermoregulation and cushioning to prevent injury to underlying structures, such as bone and muscle. Any failure of the skin to function in these capacities can lead to substantial morbidity and mortality.

MedStudy Skin Signs (available at medstudy.com/products/skin-signs-1) provides additional images and examples of various dermatologic conditions.

ATOPIC DERMATITIS (AD)

AD (a.k.a. eczema) is a chronic inflammatory skin condition with a relapsing and remitting course (Figure 3-1). Typically, 60% of cases present in infancy, with > 90% of all cases presenting at < 5 years of age; in 10–30%, the condition persists to adulthood. Onset is rare after 30 years of age, and the disease generally becomes less severe with increasing age.

AD is characterized by **dry skin** and **pruritus**. Subsequent scratching leads to more inflammation and **lichenification**



Figure 3-1: Antecubital fossa with atopic dermatitis
Source: Kimberly Salkey, MD

(i.e., thickening and hardening of the skin, with exaggeration of its normal markings), as well as more itching and scratching (i.e., “itch-scratch” cycle). In adults, the most commonly involved areas are the wrists and the antecubital and popliteal fossae. Patients can also develop erythematous and edematous pruritic patches on the head and neck, which can crust and then “weep,” at least partially as a result of scratching.

There is often a personal or family history of eczema, allergic rhinitis, or asthma, as well as laboratory findings of elevated serum IgE levels and eosinophilia. The combination of AD, allergies, and asthma is referred to as the atopic triad.

Flares can be precipitated by clothing (particularly wool), changes in weather, emotional stress, aeroallergens (dust mites and pollen), and infections. *Staphylococcus aureus* infection is often present in severe cases. Diluted bleach baths can decrease *S. aureus* colonization but have not been shown to reduce flares. Give oral antibiotics or topical mupirocin cream for secondary infections.

Most treatments for AD focus on avoiding exacerbating factors, maintaining a good moisturizing regimen, and using medications when the first 2 methods do not suffice. Hydration, moisture-trapping agents with low water content (emollients), ointments, and topical corticosteroids are the mainstays of treatment for AD. Lotions (high water content) can actually worsen the condition by drying the area through dehydration. Lotions or gels with alcohol are even more drying.

Topical steroids are the mainstay of AD treatment. Use a step-up or step-down strength method depending on the results of treatment. Use mid- or high-potency topical corticosteroids for the trunk and extremities and low-potency topical corticosteroids for the face. However, topical corticosteroids are not recommended for prolonged use on the face or intertriginous areas, because they can cause striae, atrophy, telangiectasias, pigmentary changes, and acneiform skin eruptions. Instruct patients to use steroids twice daily until their skin returns to baseline or up to 2 weeks at a time, whichever occurs first.

Tacrolimus (Protopic) and **pimecrolimus** (Elidel) are topical immunosuppressants (calcineurin inhibitors) that are effective alternatives to topical corticosteroids. Because these do not cause skin atrophy, they are especially good for facial lesions. There is a theoretical risk of skin cancer or T-cell lymphoma (black box warning due to risk with systemic use; no significant topical data yet), so these agents are 2nd line for intermittent treatment of AD. These agents should be avoided in HIV+ patients or anyone with a weakened immune system. Counsel patients about this risk; the risk of severe local side effects from topical steroids may outweigh the risk of calcineurin inhibitors for lesions involving the face.

Eczema is a chronic condition, so patients will need to follow this protocol with each flare. Because patients with AD have a defective skin barrier, they need to use a bland emollient not only during but also after flares to help prevent recurrences. Eczema can run a much more chronic and severe course, which may necessitate a referral to dermatology. Also, educate patients on the avoidance of rubbing or scratching the skin lesions.

Pruritus is a significant component of eczema, and controlling the itch tends to improve the rash. Oral antihistamines (H1 blockers) can be very helpful but generally work at night as a sedative to reduce itching.

Avoid soap, because it can be drying and strips the skin of natural oils.

Crisaborole, which is a phosphodiesterase inhibitor, can be used topically for mild and moderate AD. It is rarely used because it is expensive, but it is a nonsteroidal choice and safe for long-term use on the face and for anyone > 2 years of age. Use oral cyclosporine, azathioprine, mycophenolate mofetil, or methotrexate for severe AD that does not respond to conservative therapy. In 2017, the U.S. Food and Drug Administration (FDA) approved dupilumab (Dupixent), an injectable biologic medication that inhibits interleukin-4 (IL-4) and is indicated for severe or refractory AD. Ultraviolet (UV) light therapy is also used in this setting. Oral corticosteroids are rarely indicated for acute flares and often cause rebound flares when tapered.

Eczema herpeticum is caused by herpes simplex virus, and it can cause a severe disseminated infection. Suspect eczema herpeticum in patients who develop fever and pustular or punched-out lesions that do not respond to oral antibiotics. It is more common in patients who are taking immunosuppressants and needs to be addressed quickly to limit systemic effects. If suspected, treat with oral antivirals or, if the patient is unable to swallow, intravenous (IV) acyclovir while establishing the diagnosis.

SEBORRHEIC DERMATITIS

Seborrheic dermatitis affects 2–5% of the population and is a chronic condition that manifests as a yellow, greasy scale overlying erythematous patches or plaques (Figure 3-2). Pruritus is variable. It affects areas where sebaceous glands are most active and especially involves the scalp (dandruff), eyebrows, paranasal area, and

external auditory canals, although the chest, axilla, and groin areas can also be involved. There is a strong association with *Malassezia furfur*, although the relationship between the resident yeast and seborrheic dermatitis is not entirely clear.



Figure 3-2: Seborrheic dermatitis

Seborrheic dermatitis is common in patients with HIV/AIDS, Parkinson disease and other neurologic disorders, and mood disorders.

Treatment of seborrheic dermatitis: frequent washing and an antidandruff shampoo. The active ingredient in these shampoos is selenium sulfide, zinc pyrithione, or salicylic acid. The antimicrobial shampoos include ketoconazole or ciclopirox.

Use low-potency topical corticosteroids in combination with ketoconazole cream for skin disease. Topical calcineurin inhibitors (**tacrolimus** and **pimecrolimus**) can be used as **steroid-sparing agents**. Sulfur/sulfacetamide cleansers or lotions are effective adjunctive or maintenance therapy for skin disease, especially for the face.

INTERTRIGO

Intertrigo is an **irritant** dermatitis found in intertriginous areas: warm and moist skin folds that rub together and have little air circulation (e.g., inframammary fold, axilla, interdigital, groin). Intertrigo presents as tender, pruritic, macerated, brightly erythematous plaques. Contributing factors include obesity, hyperhidrosis, diabetes, alcohol, and smoking. Skin microbiomes cause secondary infections (e.g., *Candida*, a yeast). Suspect *Candida* when satellite papules extend beyond the main eruption. Tinea cruris and erythrasma can mimic nonspecific intertrigo. These can be ruled out with a potassium hydroxide (KOH)

test and Wood lamp, respectively. The KOH test shows hyphae with dermatophytes and pseudohyphae with candidal infection. Wood lamp shows green with pseudomonal infection and coral red with erythrasma, which is an infection with the bacterium *Corynebacterium* that is treated with erythromycin.

Treat intertrigo with topical antifungals and drying agents (e.g., antifungal powders, aluminum sulfate products, corn starch). Avoid the use of talcum powder in the genital area of women because of the potential increased risk of ovarian cancer.

CONTACT DERMATITIS

Contact dermatitis does not have a single presentation. Its manifestations can vary from slightly dry and erythematous skin to the development of edema, oozing vesicles, or chronic eczema or dermatitis.

Contact dermatitis (Figure 3-3) can be caused by irritant contact dermatitis (80% of cases), or it can be of allergic origin (20% of cases).



Figure 3-3: Contact dermatitis of the hand
Source: James Heilman, MD

The most typical chemical irritants are soapy water, rubbing alcohol, and common household cleaners. Sufficient exposure to these irritants causes dermatitis in every individual. For irritant contact dermatitis, prior sensitization is not required. Dyshidrotic eczema is common in individuals who wash their hands frequently. The finding of highly pruritic vesicles on the sides of the fingers is helpful in making this diagnosis.

The allergic type of contact dermatitis is due to a T-cell-mediated, delayed-type hypersensitivity reaction (Type 4 hypersensitivity) in the skin. Patients must become sensitized to the antigen with 1 or many exposures. After sensitization and upon reexposure, the skin develops a pruritic lesion in 12 hours to 2 days. The most common allergens are nickel, chromium, neomycin, bacitracin, and oleoresin urushiol (poison oak, poison ivy, and poison sumac). Linear and geometric eruptions often reflect an external cause. The distribution can also provide a clue, such as an allergy to nickel in jewelry that occurs on the earlobes or an allergy to jeans buttons that occurs on the abdomen.

Identify and remove the offending allergen or irritant as 1st line treatment. Symptomatic treatment includes cool compresses, topical corticosteroids, and Burow solution (aluminum acetate dissolved in water, 1:40). If the reaction is severe or involves the face, give systemic corticosteroids, usually as a reducing dose over 2 weeks. A shorter course can precipitate rebound reaction. Patch testing is the gold standard to identify contact allergens, especially if there is no obvious precipitating exposure. In patch testing, multiple suspected allergens are applied to the patient's back under occlusive dressings. After 48 hours, the dressings are removed and the area is examined for evidence of delayed hypersensitivity reactions.

STASIS DERMATITIS

Stasis dermatitis is one of the clinical manifestations of chronic venous insufficiency of the lower extremities. Venous hypertension is exacerbated by gravity and valvular incompetence in leg veins and causes distention of capillaries. This distention allows leakage of fluid and plasma into tissue, as well as deposition of hemosiderin and erythrocyte extravasation.

Clinical features include pitting edema of the shin and calf that is more pronounced at the end of the day and resolves overnight, rusty hemosiderin deposition, and eczematous findings such as itchy and dry skin. Over time, the legs start to develop signs of lipodermatosclerosis, characterized by induration and a firm circular cuff that creates an inverted wine bottle appearance. Venous ulcers can develop and increase risk of secondary infection. Scratching may lead to oozing and crusting. Edema and superimposed contact sensitization to self-treatments may lead to blistering.

The mainstay of treatment is management of venous hypertension. Elevation of the legs and compression with stockings or bandaging can improve venous return. Encourage exercise and lifestyle changes. Surgical strategies can be pursued in more severe cases. For symptom control and management of skin changes, topical therapy such as that used for eczema is indicated, including topical corticosteroids and emollient use.

ACNE AND ROSACEA

Acne Vulgaris

Presentation

The clinical manifestations of acne vulgaris are:

- Open (blackheads) and closed (whiteheads) comedones
- Papules
- Pustules
- Cystic lesions

Comedonal acne is noninflammatory acne and develops in early adolescence. The pathogenesis involves occlusion of the follicles.

Inflammatory acne occurs as a reaction to several factors, including *Cutibacterium acnes* (previously known as *Propionibacterium acnes*) within the follicle, ruptured follicular epithelium with leaking of sebum, and the immunologic response to these factors.

Acne severity is genetic and hormonal, with an imbalance between estrogens and androgens. However, most patients with acne do not overproduce androgens. Rather, sebaceous glands that are locally hyperresponsive to androgens are more likely to explain the genetic predisposition. Very severe nodular acne with the development of sinus tracts is called acne conglobata. It usually occurs in young males on the chest and back.

In women with polycystic ovary syndrome (PCOS), however, acne is a common but nonspecific external manifestation of increased serum androgens. PCOS occurs in 5–10% of all women, and about 1/3 of women with acne have PCOS. Women with oligomenorrhea and hirsutism plus acne can be investigated for PCOS with tests for luteinizing hormone (LH), follicle-stimulating hormone (FSH), free and total testosterone, dehydroepiandrosterone sulfate (DHEAS), a lipid profile, glucose tolerance test, and insulin sensitivity. See more on PCOS in the [Women's and Men's Health](#) section.

Factors that can exacerbate acne include cosmetics, oils, repetitive mechanical trauma (e.g., scrubbing), clothing (e.g., turtlenecks, bra straps, sports helmets), humidity, and heavy sweating. Diet is a controversial cause; some studies have shown an association with low-fat milk intake (exacerbating acne). There is no reliable data on high-glycemic-load diet exacerbating acne. Stress appears to worsen acne.

Acne vulgaris differs from rosacea by the presence of comedones (not seen in rosacea) and the lack of telangiectasia (seen in rosacea).

Treatment of Acne Vulgaris

Minimize friction in acne-prone areas (e.g., chin straps, baseball caps) and discontinue aggravating factors (e.g., topical corticosteroids, industrial compounds, certain oral contraceptives, lithium, phenytoin, phenobarbital).

Comedonal (noninflammatory) acne: Topical retinoids are the drugs of choice for comedonal acne. These include adapalene, tretinoin, and tazarotene. Retinoids (except adapalene) are deactivated by sunlight, so they should be applied at night.

Side effects are mainly skin irritation and photosensitivity. Start at a low concentration and apply 2–3×/week. Note: Topical retinoids are contraindicated in pregnancy! Other agents for comedonal acne include topical salicylic acid, benzoyl peroxide, azelaic acid, and glycolic acid; all 4 have comedonal activity. In addition, benzoyl peroxide has antibacterial properties.

Mild inflammatory acne (Figure 3-4): Use benzoyl peroxide in conjunction with topical erythromycin or clindamycin to treat the *C. acnes* of inflammatory acne.

The combination therapy decreases development of resistance; combination preparations are available commercially. Topical retinoids are also useful adjuncts. Topical dapsone (Aczone), an antimicrobial agent, is also used.



Figure 3-4: Mild inflammatory acne

Moderate-to-severe inflammatory acne (Figure 3-5) requires oral antibiotics, such as tetracycline, doxycycline, and minocycline. Topical and oral antibiotics should not be used together. Oral tetracyclines should be used for ≤ 6 months. The high prevalence of *C. acnes* resistance to erythromycin has led to decreased use of this agent. Trimethoprim/sulfamethoxazole (TMP/SMX) is recommended in selected refractory cases and should be used as short-term management.



Figure 3-5: Moderate-to-severe inflammatory acne

Source: James Heilman, MD

Oral isotretinoin (1 mg/kg/day) is highly effective in severe nodulocystic, scarring, or resistant cases but is also a powerful teratogen. The use of isotretinoin is restricted to physicians who have registered with the electronic FDA iPLEDGE program and requires multiple steps to prescribe. Some of the common birth defects it causes are hearing and visual impairment, facial dysmorphism, and intellectual disabilities. Because of these risks, female patients must have 2 negative pregnancy tests before beginning the medication and must use 2 forms of birth control while taking it. Additionally, women of childbearing potential are required to undergo monthly pregnancy tests prior to obtaining their next prescription.

Patients should be counseled on these risks and advised that conception is safe beginning 1 month after the last dose of isotretinoin.

Male patients are also advised not to impregnate a woman while taking isotretinoin, although there have been no reports of fetal abnormalities in this circumstance.

In addition to teratogenicity, there are serious side effects associated with the use of isotretinoin:

- Idiopathic intracranial hypertension (formerly known as pseudotumor cerebri), especially if used in conjunction with tetracyclines
- Depression and psychosis
- Pancreatitis
- Marked hypertriglyceridemia
- Hearing loss
- Night vision loss
- Skeletal abnormalities
- Myalgias
- Arthralgias
- Hair loss

There is a controversial association between isotretinoin and depression and inflammatory bowel disease as well. Anyone prescribing isotretinoin should be well versed in these side effects and take a careful history prior to prescribing it.

Hypertriglyceridemia, if severe, warrants discontinuation of isotretinoin and levels should reduce back to normal. Fenofibrate is used to treat hypertriglyceridemia.

Isotretinoin can cause palpitations, vascular thrombotic disease, and stroke, but aspirin is not routinely recommended.

If oral isotretinoin is used, all other acne treatments must be stopped.

Oral estrogen-based contraceptive therapy is used in PCOS to decrease androgen excess and to regulate menstrual cycles. Spironolactone, which has antiandrogen effects, is also used as hormonal therapy in combination with oral contraceptives. There is potential risk of feminization of a male fetus if pregnancy develops while on spironolactone. For more on acne during pregnancy, see the [Women's and Men's Health](#) section.

Rosacea

Rosacea (Figure 3-6) is a relapsing and remitting lifelong condition that primarily affects fair-skinned, middle-aged patients and presents with erythema, phymas, telangiectasias, papules, and pustules (acne-like lesions) on the central face. It occurs more frequently in women but is more severe in men.

According to the Global Rosacea Consensus (ROSCO) Panel, rosacea is defined according to diagnostic features and major and secondary symptoms and signs. **Diagnostic features** are central facial erythema and phymatous



Figure 3-6: Rosacea

changes. **Major features** (any 2 of which make a diagnosis) include pustules and papules, flushing, telangiectasias, and ocular changes. **Minor features** are burning, stinging, swelling, and dryness.

Ocular symptoms and signs occur in 50% but may predate or occur in the absence of rosacea. Symptoms include dryness, burning and stinging, light sensitivity, blurred vision, and foreign body sensation. Signs include lid margin and conjunctival telangiectases, blepharitis, plugging of the meibomian glands, chalazia, corneal inflammation, keratitis, iritis, scarring, and loss of visual acuity.

Know how to distinguish acne vulgaris from rosacea. Again, unlike acne vulgaris, rosacea can have telangiectasias and does **not** have comedones.

Rhinophyma is more common in elderly men and may require surgical therapy.

Patients with rosacea can have a **flushing reaction** to various stimuli (e.g., alcohol, stress, spicy foods) even before the lesions appear. Once the rosacea manifests, the flush can become **permanent**. Trigger avoidance is recommended. Sun protection is important.

Treatment depends on diagnostic features, symptoms, and signs but can be topical or oral and light therapy based.

Phymas can be treated topically with brimonidine, oxymetazoline, and retinoids. Oral therapies are carvedilol, doxycycline, minocycline, tetracycline, isotretinoin, azithromycin, and TMP/SMX. Intense pulsed light and laser therapies can be used. Papules respond to topical ivermectin, **metronidazole**, azelaic acid, ivermectin, retinoids, or sulfur/sulfacetamide preparations or oral antibiotics (e.g., tetracycline, doxycycline, azithromycin, minocycline, oral isotretinoin, TMP/SMX).

Treat ocular symptoms with topical azithromycin or cyclosporine or oral cyclosporine, azithromycin, doxycycline, and minocycline, but refer to an ophthalmologist.

Telangiectasias can be treated with laser therapy or retinol; persistent erythema and flushing can be treated with brimonidine topical gel (Mirvaso) and oxymetazoline.

Steroids should be avoided as they exacerbate the disease.

Periorificial dermatitis (Figure 3-7) is a rosacea-like rash that presents with grouped superficial papulovesicular or papulopustular lesions and erythema located around the mouth, chin, nasolabial, and periocular areas with vermilion sparing. It is also referred to as perioral dermatitis. Patients report intolerance to sunlight, cosmetics, topical moisturizers, water, and soaps. Steroids can worsen the condition. Treatment is generally the same as for rosacea.

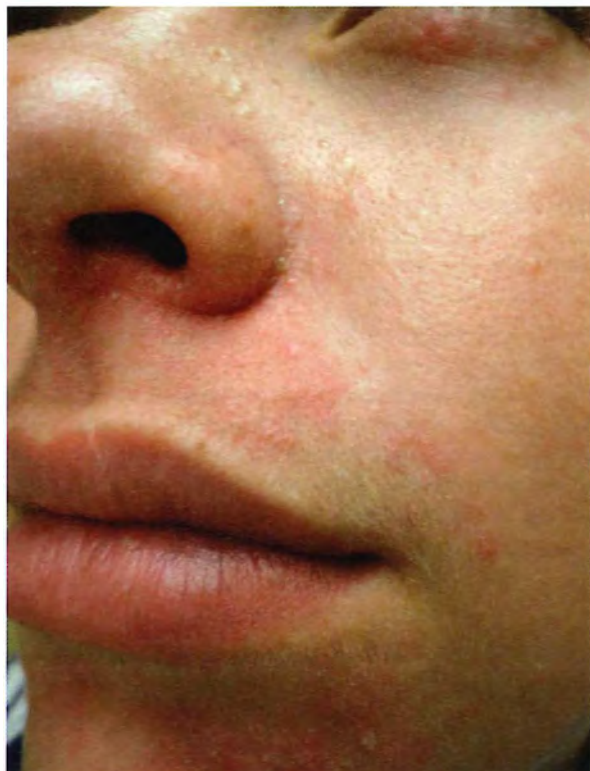


Figure 3-7: Periorificial dermatitis
Source: Jason Reichenberg, MD

HIDRADENITIS SUPPURATIVA

Hidradenitis suppurativa (a.k.a. acne inversa), which affects approximately 1% of the population, is a **chronic** inflammatory scarring process involving apocrine gland-bearing areas, such as the **groin/perianal** and the **axillary** regions (Figure 3-8). It typically develops after puberty and manifests as painful, deep-seated nodules, sinus tracts, and abscesses. The presentation is symmetric. The abscesses are usually sterile but can become secondarily superinfected. Although it occurs in both sexes (women > men, 4:1), axillary and vulvar involvement is more common in women and perianal involvement is more common in men. Smoking and obesity correlate with severity of disease.

The disease process begins with dilated, occluded follicles (comedones) that often have multiple openings. Subsequently, the disease can range from mild to severe (induration, scarring, pitting, and draining abscesses). There is often an association with severe acne, dissecting cellulitis of the scalp, and pilonidal cysts, known as the follicular occlusion tetrad.



Figure 3-8: Hidradenitis suppurativa; mild vs. severe
Source: Kimberly Salkey, MD

Treatment for hidradenitis suppurativa should be guided by disease severity and often is challenging. If applicable, recommend smoking cessation and weight loss. Patients should avoid deodorants (antiperspirants are okay), tight synthetic clothing, and prolonged exposure to hot, humid environments. Treat **early** disease with 1% topical clindamycin and intralesional steroids. Treat **acute** infections with incision, drainage, and packing. Treat **late** disease with either oral tetracycline or oral clindamycin + rifampin. Corticosteroids can be injected into the nodules or used orally for severe cases. Treat more **severe** disease with immunosuppressants, such as the anti-tumor necrosis factor (TNF)- α inhibitor adalimumab (Humira), which is FDA approved for treatment of moderate to severe hidradenitis suppurativa. Infliximab (Remicade) is also effective but not FDA approved; etanercept is not effective. Oral retinoids can improve severe cases (3rd line). Antiandrogens (cyproterone acetate, finasteride) and zinc gluconate can be beneficial nonsurgical alternatives. For severe refractory lesions, definitive therapy is complete surgical excision, but laser therapy is also increasingly being used.

For females, estrogen-containing birth control pills may help, as may spironolactone. Metformin can be beneficial depending on comorbid conditions.

MOUTH FINDINGS

PREVIEW | REVIEW

- What finding on the buccal mucosa can be seen with measles? Describe and name the finding.
- What viral infection causes oral hairy leukoplakia?
- A beefy red tongue is seen with what underlying disease states?
- What are the "4 Ds" that patients with glucagonomas develop?
- If you see macroglossia, what underlying diseases should you consider?

NOTE

Know all mouth findings outlined [here!](#)

ORAL BLISTERS AND ULCERS

Recurrent aphthous stomatitis is a common and multifactorial disorder with an unclear etiology, but it is thought to be secondary to a dysfunction of the immune system. Minor aphthae are the most common presentation and are round, shallow, and painful ulcerations that heal without scarring. Major aphthae are larger and deeper lesions that are more persistent and may heal with scarring. Herpetiform aphthae are uncommon and consist of groups of small, numerous, and painful ulcerations that are mostly limited to nonkeratinized surfaces (i.e., lining of mouth), a feature that helps to distinguish these lesions from herpes simplex virus (HSV).

Herpes simplex infections consist of painful, grouped vesicles on an erythematous base that are often preceded by tingling, burning, or pain. Outbreaks are often recurrent, and recurrent lesions are commonly on the vermillion border of the lips and less commonly on the nose, perioral skin, or cheek (Figure 3-9).



Figure 3-9: HSV-1 on lips and tongue
Source: CDC

Squamous cell carcinoma is the most common malignancy of the oral cavity and is associated with tobacco and alcohol use. It can manifest as an ulcer, an exophytic mass, or an endophytic, indurated lesion. These lesions are more aggressive than their counterparts on the skin.

Pemphigus vulgaris presents as painful oral erosions that may be scattered throughout the oral mucosa but are most typically found on the buccal and palatine mucosa. The presence of ulceration can lead to decreased oral intake, and patients presenting solely with oral lesions may experience a delay in diagnosis compared to those patients with cutaneous lesions. For more information on pemphigus vulgaris, see [Blistering Lesions](#) on page 3-29.

WHITE ORAL LESIONS

Koplik spots (Figure 3-10) are small, painless, white papules on an erythematous base that are found on the buccal mucosa in patients with measles. Even though the rash is not present yet, these patients



Figure 3-10: Koplik spots
Source: CDC

are highly contagious. The oral spots usually precede the skin lesions by several days.

Oral leukoplakia (Figure 3-11) is an adherent plaque found on the mucosal surface of the mouth. It is diagnosed only after ruling out other similar lesions with an identifiable cause, such as oral candidiasis, smoker's keratosis, and oral hairy leukoplakia. These are considered precancerous lesions.



Figure 3-11: Oral leukoplakia

Oral hairy leukoplakia (Figure 3-12) is a type of leukoplakia that most commonly occurs in patients with HIV/AIDS. It is due to opportunistic Epstein-Barr virus infection in the superficial layers of the tongue's squamous epithelium. It manifests as asymptomatic, white, corrugated (or "hairy") plaques along the sides of the tongue. In contrast to *Candida*, it cannot be scraped off!



Figure 3-12: Oral hairy leukoplakia
Source: CDC

Oral candidiasis, or thrush, causes white semiadherent plaques on the tongue and mucosa. Unlike hairy leukoplakia, these **can be scraped off**.

Lichen planus (LP) can have up to 7 presentations, including erosive, bullous, and atrophic, but the most common presentation is a lacelike pattern of white, raised lines, called Wickham striae. Oral LP, particularly the erosive type, has a reported association with hepatitis C.

TONGUE LESIONS

Beefy red tongue (glossitis) is seen in pernicious anemia and various vitamin B deficiencies. B₁₂ deficiency can present with glossitis but also shows anemia, fatigue, and neurologic symptoms. Beefy red tongue can also be associated with **glucagonomas**.

Glucagonomas (pancreatic α -cell tumors) secrete excessive amounts of glucagon and can cause a **beefy red tongue** (think **GL**ucagonoma = **GL**ossitis), angular cheilitis, and a **necrolytic** migratory erythematous rash. Patients with glucagonomas may develop the **4 Ds**: diabetes, deep venous thrombosis, depression, and dermatitis. Weight loss is characteristic. Erosions of the skin primarily affecting the groin, buttocks, and lower legs and sometimes affecting the face characterize the glucagonoma syndrome. When glucagonoma syndrome is diagnosed, it is important to rule out a zinc or magnesium deficiency because the presentations can be similar. The sooner the glucagonoma is found and treated, the better is the prognosis.

Macroglossia ("big tongue") is associated with multiple myeloma, primary amyloidosis, lymphoma, hemangioma, acromegaly, hypothyroidism, angioedema, and Down syndrome. Macroglossia associated with pinch purpura (i.e., purpura and ecchymoses that develop after mild trauma, such as pressure or rubbing), especially around the eyes, strongly suggests **amyloidosis**. Amyloid deposits present as waxy nodules around the face, neck, scalp, and hands.

"Geographic" tongue is an idiopathic inflammatory condition that results in the loss of filiform papillae. It has the appearance of **migratory**, denuded, erythematous patches with serpiginous, raised, white borders that resemble a map (**Figure 3-13**). It is asymptomatic and benign but is associated with psoriasis.



Figure 3-13:
Geographic tongue
Source: Kimberly Salkey, MD

"Strawberry" tongue is due to inflamed tongue papillae and is associated with scarlet fever, toxic shock syndrome, and Kawasaki disease (a mucocutaneous lymph node syndrome typically seen in children).

"Bald" tongue is **atrophy** of the lingual papillae associated with pellagra, iron deficiency anemia, pernicious anemia, and xerostomia (dry mouth; commonly seen in Sjögren syndrome, lymphoma, mumps, and sarcoidosis; occasionally idiopathic).

CUTANEOUS DRUG REACTIONS

PREVIEW | REVIEW

- What adverse cutaneous reactions are associated with phenytoin?
- What is gadolinium? What adverse reaction can it have?
- What drug class is the most common cause of isolated angioedema?

PRESENTATIONS

DRESS syndrome (drug reaction with eosinophilia and systemic symptoms) carries a mortality rate of about 10%. Patients typically present with a morbilliform rash, facial swelling, fever, lymphadenopathy, elevated liver enzymes, and hepatomegaly. The majority of cases have associated eosinophilia. Antiseizure medications and allopurinol are the most commonly implicated drugs. Treat by removing the offending medication. Of note, corticosteroids can improve the cutaneous and visceral (e.g., liver, lung, heart) manifestations of DRESS and can be lifesaving; however, relapses are often observed when the corticosteroids are tapered. In the months following DRESS resolution, monitor for long-term sequelae, which include autoimmune diseases such as Type 1 diabetes mellitus, hypothyroidism, and anemia.

Fixed drug eruption: This is a specific type of cutaneous drug reaction that recurs in the same location every time the offending drug is given. Most often, it will present in the mucosal sites of the vulva or penis, lips, hands, face, or feet and is a round or oval erythematous patch with some swelling and/or a blister. In time, it fades to purple/brown; the blister shrinks and peels off, but it can ulcerate. Treatment consists of discontinuing the offending drug.

SPECIFIC DRUGS

The following are the most frequently seen drug-associated skin changes. **Know all of them.**

Penicillin (PCN):

- **Immediate** hypersensitivity reaction; anaphylaxis (IgE)
- **Delayed** hypersensitivity reaction; immune complex reaction, such as vasculitis or morbilliform eruption

Tetracyclines: photosensitivity (demeclocycline > doxycycline > tetracycline > minocycline). Other drugs that commonly cause photosensitivity include fluoroquinolones (e.g., ofloxacin, ciprofloxacin), sulfonamides, furosemide, thiazides, phenothiazines, amiodarone, and retinoids.

Nonsteroidal antiinflammatory drugs (NSAIDs): urticaria/angioedema in 1% and asthma in 0.5% and can cause photosensitivity or toxic epidermal necrolysis (TEN).

Phenytoin:

- Hypersensitivity syndrome—rash, facial edema, lymphadenopathy, and hepatitis
- Various skin reactions, including erythema multiforme—an eruption of well-demarcated erythematous, targetoid papules (usually without scale) that commonly appear on palms and soles. It is often associated with drugs (e.g., NSAIDs, penicillin), as well as underlying infection such as herpes simplex virus (HSV) and *Mycoplasma*.

- Gingival hyperplasia is caused by 3 groups of drugs—immunosuppressants (e.g., cyclosporine), calcium channel blockers (e.g., nifedipine, verapamil, diltiazem, amlodipine), and anticonvulsants (e.g., phenytoin); also seen in M3 and M4 subtypes of acute myeloid leukemia.
- Hirsutism

Corticosteroids: skin changes, including striae, atrophy, telangiectasia, pigmentary changes, and acne-like lesions.

Warfarin: **necrotic** patches of skin appearing 3–10 days after starting warfarin, typically occurring in patients with previously undiagnosed **protein C deficiency**. Lesions classically affect areas with the highest fat deposition, such as the breasts, buttocks, thighs, and abdomen.

Radiocontrast media: This can cause urticaria/erythema (1:15 incidence) and, rarely, a severe anaphylactoid reaction (1:1,000 incidence; **not IgE mediated**). It is caused by the release of mast cells. With a prior reaction to contrast media, there is a 30% chance of a subsequent reaction; often, the recurrence is more severe. For the prevention of radiocontrast media cutaneous drug reaction, see the **Allergy & Immunology** section.

Gadolinium is a contrast material used for magnetic resonance imaging. It can cause nephrogenic systemic fibrosis, a fibrotic disease of the skin and internal organs similar to, but distinct from, systemic sclerosis (scleroderma) in that it typically spares the face. It is a disease exclusive to end-stage renal disease. There is no good treatment, so prevention is paramount. Do not give gadolinium to a patient with Stage 4 or higher chronic kidney disease!

ACE inhibitors (ACEIs): **Angioedema** occurs in only 0.5% of patients treated with an ACEI. However, because so many patients receive an ACEI, it is one of the most common causes of isolated angioedema (i.e., no concurrent urticaria [hives] or anaphylaxis). ACEI-associated angioedema usually involves the lips, tongue, mouth, and pharynx. Angioedema can occur at any time during treatment with ACEIs. Angiotensin receptor blockers (ARBs) **rarely** cause angioedema. However, use them cautiously in patients who have a previous history of angioedema with ACEI use. Make sure that the benefit outweighs the risk (e.g., systolic heart failure, significant proteinuria).

INFLAMMATORY SKIN DISORDERS

PREVIEW | REVIEW

- Nail pitting with onycholysis is a fairly specific finding for what dermatologic disorder?
- What drugs should be added to the regimen for patients with psoriatic arthritis?

- Characterize the malar rash of systemic lupus.
- What are the manifestations of limited systemic sclerosis?
- What skin findings are associated with sarcoidosis?
- What are the skin manifestations of dermatomyositis?
- Pyoderma gangrenosum is associated with which systemic illnesses?

NOTE

Many of the disorders described here are presented in more detail in the **Rheumatology** section.

PSORIASIS

Psoriasis is a response triggered by **T lymphocytes** in the skin. The epidermis becomes **hyperproliferative**, producing skin cells at a faster rate than normal. Trauma or irritation of normal skin commonly induces lesions of **psoriasis** at the site (Koebner phenomenon).

All types of psoriasis can be precipitated/exacerbated by **β-blockers**, stress, sunburn, lithium, and infection (e.g., virus, streptococcal pharyngitis). Obesity is associated with psoriasis, and significant weight loss may lead to clinical improvement.

Types of Psoriasis

Plaque psoriasis is the **most common** type of psoriasis (**Figure 3-14**). It presents with well-defined, stable, slow-growing, erythematous skin lesions with distinctive **mica-like** (silvery) scales. Pruritus is variable (absent to severe), with patients usually having mild itching. It is typically **symmetric** and occurs on **extensor** surfaces of the knees and elbows, the sacral area, and the scalp.



Figure 3-14: Plaque psoriasis
Source: Kimberly Salkey, MD

Guttate (eruptive) psoriasis is an **abrupt** eruption of **multiple** small salmon-pink or red lesions (3–10 mm in diameter) and typically occurs on the **trunk** of children or young adults with no previous history of psoriasis (**Figure 3-15 on page 3-10**). Streptococcal pharyngitis is a known trigger of guttate psoriasis.



Figure 3-15: Guttate psoriasis

Source: Jennifer Vickers, MD

Flexural (inverse) psoriasis affects **skin fold** areas. It is called inverse because it is **not** on the extensor surfaces.

There are 2 rare, especially **severe** types of psoriasis:

- 1) Erythrodermic psoriasis
- 2) Pustular psoriasis

Erythrodermic psoriasis is an exfoliative reaction in which the entire surface of the skin becomes red, warm, and scaly—and the patient is **unable to control body temperature** (hypo-/hyperthermia is typical). Dehydration, hypoalbuminemia, and anemia of chronic disease are common sequelae. Erythrodermic psoriasis is an uncommon psoriasis subset but can be life-threatening.

In patients with stable psoriasis, erythroderma (involvement of > 90% body surface area) can be precipitated by certain medications. Potential offenders exacerbating psoriasis include β -blockers, NSAIDs, antimalarials, TMP/SMX, gold, and lithium, as well as the rebound effect of topical and oral steroids. If possible, β -blocker use should be avoided in patients with psoriasis.

Pustular psoriasis has many small pustules, often coalescing to form “**psoriatic lakes of pus**.” There are 2 forms:

- 1) The **localized** form affects only the palms and soles. It is associated with distal interphalangeal joint (DIP) joint arthritis.
- 2) The rare, **generalized** form (von Zumbusch type) is the **most severe form** of psoriasis and can occur with the erythrodermic type. Sudden withdrawal of systemic corticosteroids is a well-described inciting event.

Exfoliative dermatitis (erythroderma) is not associated with herpes simplex or herpes zoster. It is frequently seen as an allergic reaction to drugs such as sulfonamides, antimalarials, penicillin, phenytoin, and barbiturates. It has also been associated with psoriasis, atopic dermatitis, or malignancy (especially cutaneous T-cell lymphoma). Up to 30% of cases are idiopathic. No matter what the etiology, skin biopsy is often nonspecific. The course and prognosis of exfoliative dermatitis are related to the

course of the underlying process. Drug-induced exfoliative dermatitis has the best prognosis, whereas cases associated with malignancy have the highest mortality.

Nail Changes in Psoriasis

50% of patients with plaque psoriasis and 80% of those with psoriatic arthritis have fingernail changes. These can cause significant functional impairment, pain, and distress.

Psoriatic changes of the nails differ in the fingernails and the toenails. The toenail changes seen in psoriasis can be difficult to distinguish from onychomycosis.

Know the following about these fingernail findings:

- The **most common** nail change in psoriasis is “ice-pick” pitting; these pits are usually in small irregular groups on the nail (in contrast to a gridlike pattern of pitting seen in alopecia areata). Pitting is an expression of disease activity; normal nails between the groups of pits indicate disease-free activity.
- The **most specific** psoriatic nail finding is a yellow or salmon-colored “oil spot” beneath the nail plate.
- Any of these fingernail changes in a psoriasis patient are a predictor of **psoriatic arthritis**; a strong predictor is pitted nails in association with onycholysis (separation of distal nail plate from the nail bed; [Figure 3-16](#)). For more on psoriatic arthritis, see the [Rheumatology](#) section.



Figure 3-16: Pitted nail with onycholysis

Source: Kimberly Salkey, MD

Drugs Used to Treat Psoriasis

Know all of these.

Topical corticosteroids are the primary treatment for plaques. To increase their effectiveness, topical steroids can be occluded with cellophane or plastic wrap. Long-term use of high-potency steroids causes striae and thinning of the skin, and their use is especially avoided on the face and intertriginous areas (i.e., skin-to-skin areas, such as the axillae, under the breasts, the anogenital area, and between digits). **Oral corticosteroids** are not used, because they cause “rebound flares.” (See pustular psoriasis under [Types of Psoriasis on page 3-9](#).)

Tar is a traditional treatment that is safe and moderately effective. It is often combined with a corticosteroid in a compounded preparation. Application is time consuming, odorous, and messy, but tar is well tolerated and reasonably priced.

Calcineurin inhibitors: **topical tacrolimus** and **topical pimecrolimus**. These are often used for facial and intertriginous areas where high-potency steroid use is avoided.

Be aware of the FDA black box warning for a potential increased risk of lymphoma and skin malignancy with calcineurin inhibitors.

Phosphodiesterase-4 inhibitor: Apremilast (Otezla; FDA approved in 2014) is a systemic medication that suppresses inflammatory cytokines and mediators.

Retinoids (vitamin A derivatives):

- Tazarotene gel decreases the hyperkeratosis or thick scales associated with psoriasis; the main side effect is skin irritation.
- Acitretin (Soriatane), a 2nd generation oral retinoid, is used for severe psoriasis of all types. Because of its potentially toxic effects, it must be monitored closely and used with caution. Acitretin has a side-effect profile similar to that of isotretinoin, although its potential for teratogenicity can last up to 3 years after discontinuing the medication; this is in contrast to isotretinoin, which has potential teratogenicity for 1 month following discontinuation of the medication. (See moderate-to-severe inflammatory acne under [Treatment of Acne Vulgaris on page 3-4.](#))

Do not use acitretin in women with childbearing potential who use unreliable contraceptive prevention. **Important:** The FDA has warned against the use of acitretin in women who are pregnant or who intend to become pregnant in the **3 years** following treatment.

Vitamin D₃ analogs: These agents are less effective than high-potency topical steroids but do not cause thin skin or striae.

Immunosuppressants: Both methotrexate (MTX) and cyclosporine are very effective for extensive severe psoriasis:

- MTX can cause severe liver and pulmonary toxicity, as well as bone marrow suppression. **Do not** give MTX to patients with a history of alcohol abuse, liver disease, or severe kidney impairment. (The drug is excreted renally.)
- Cyclosporine can cause renal toxicity and hypertension and is recommended only for short-term “rescue” use.

Biologic immunomodulators: These **effective** treatments for psoriasis have provided safe options for patients with moderate to severe psoriasis. The biologic immunomodulators include:

- TNF- α inhibitors: **etanercept**, **infliximab**, **adalimumab**, certolizumab
- IL-12 and IL-23 blockers—**ustekinumab** (Stelara)
- IL-17A blocker—secukinumab (Cosentyx), ixekizumab (Taltz), brodalumab
- IL-23 inhibitor—guselkumab (Tremfya), tildrakizumab (Ilumya)

Ultraviolet (UV) light can be added to the above treatments or used as monotherapy. UVB (290–320 nm) therapy is often used. Narrow-band UVB (NB-UVB; **311 nm**) is

possibly more effective than the broader-spectrum treatment and generally is the treatment of choice, but it requires more expensive equipment and a longer duration of therapy per session.

PUVA (psoralen + long-wave UVA [320–400 nm]) is also very effective and is usually given to those who fail UVB. UVA penetrates more deeply than UVB and is less likely to burn (hence, the photosensitizing psoralen), **but** it is associated with accelerated photoaging, an increased likelihood of skin cancer (squamous cell carcinoma), and possibly melanoma in fair-skinned Caucasians. Future treatment with cyclosporine increases this risk.

Any patient with psoriatic arthritis is at risk for permanent joint damage. Treat with a disease-modifying oral/injectable agent (cyclosporine, MTX, or the biologics). Classic presentation of psoriatic arthritis is symmetric DIP arthritis, but asymmetric arthritis can also be seen with a “sausage digit”; 1/3 of patients with psoriasis will get arthritis. See the [Rheumatology](#) section.

Treatment of Psoriasis

Recommended treatment for psoriasis depends on the severity of disease, percentage of body surface area (BSA) involved, and involvement of the hands, feet, or facial or genital regions. Involvement of these locations can interfere significantly with activities of daily living, irrespective of the amount of BSA involved.

Limited/mild disease (< 5% BSA): Use high-potency or ultra-high-potency topical corticosteroids. Taper to a mid-potency agent for maintenance. For scalp involvement, use topical steroid solutions, foams, or lotions.

For the face and intertriginous areas, use:

- low-potency corticosteroids,
- topical tacrolimus or pimecrolimus,
- calcitriol, or
- topical retinoids (tazarotene).

If the patient fails to respond, UV-based or short-term systemic therapy can be used.

Moderate disease (5–9% BSA): Treatment is the same as for limited disease except that UV light therapy (typically **NB-UVB**) is routinely used. PUVA can be used for those who fail UVB therapy. Depending on morbidity associated with the disease, consider treatment with systemic agents, such as MTX, acitretin, apremilast, or a biologic.

Widespread/severe disease ($\geq$ 10% BSA): NB-UVB is recommended, with consideration of PUVA for failures. Treat with MTX, cyclosporine, a biologic, or a combination of these therapies. The combination of UVB or PUVA with acitretin is especially effective for pustular psoriasis.

Guttate psoriasis: Treat with UVB +/- topical steroids. Treat any streptococcal infection.

Flexural psoriasis: Treat with low-potency topical corticosteroids or with topical tacrolimus or pimecrolimus.

LUPUS

Systemic lupus erythematosus (SLE): Malar (a.k.a. “butterfly”) rash occurs in about 1/2 of acute SLE patients and rarely occurs in patients without systemic symptoms. Classically, this rash involves both cheeks and extends across the bridge of the nose, sparing the nasolabial fold (Figure 3-17). The malar rash is erythematous and either flat or slightly edematous, and it often occurs after sunlight exposure (photosensitivity); there is no scarring.



Figure 3-17: Classic systemic lupus erythematosus rash

Rosacea can mimic a malar rash but can be distinguished by prominent telangiectasias, papules/pustules, and the lack of systemic symptoms. Likewise, seborrheic dermatitis can mimic a malar rash but can be distinguished by involvement of the nasolabial folds, which are spared with the malar rash of SLE.

SLE patients can get a red, scaly rash on the backs of the hands and fingers, often sparing the knuckles. This is in contrast to the Gottron papules of dermatomyositis, in which the rash occurs over the knuckles.

Patchy nonscarring alopecia is typical in SLE. See the Rheumatology section for more on SLE.

Subacute cutaneous lupus erythematosus (SCLE) is a distinct subset of lupus characterized by erythematous macules/papules that evolve into papulosquamous plaques on sun-exposed areas. Like the acute rash of SLE, but in contrast to discoid lupus, these lesions heal without scarring. Many patients are seropositive for SSA and/or SSB antibodies. Patients uncommonly have significant systemic manifestations.

Chronic cutaneous lupus erythematosus (discoid lupus): Discoid lesions are erythematous and raised with tightly adherent scales. They cause atrophic scarring. They typically occur on sun-exposed areas, including the face, scalp, neck, and ear canals. Only 5% of discoid lupus patients develop SLE. However, patients with SLE who develop discoid lupus lesions tend to have a very good prognosis, devoid of significant renal manifestations.

Intralesional corticosteroids are especially effective for discoid lupus. 1st line oral therapy includes antimalarials, such as hydroxychloroquine. More aggressive systemic therapy with immunosuppressants (e.g., MTX, azathioprine, mycophenolate mofetil) is used in severe cases or for treatment of SLE with significant systemic involvement.

SCLERODERMA — MORPHEA AND SYSTEMIC SCLEROSIS (SSc)

Scleroderma means “hard skin.” It is a connective tissue disorder that always involves the skin but may additionally

have systemic involvement. Skin (and subadjacent tissues) involvement is called **morphea** (a.k.a. localized scleroderma). Disease with systemic involvement is called **systemic sclerosis**.

Morphea is characterized by plaques that become sclerotic with a hypopigmented center and erythematous border. It usually occurs in children or young adults. It can be just a few lesions (localized morphea) or widespread with some confluence (generalized morphea).

SSc has systemic involvement, and patients commonly have associated fatigue, weakness, stiff joints, and pain. It has 2 major subtypes, depending on the extent of skin sclerosis:

- **Limited SSc** (previously CREST) is a grouping of symptoms that has limited systemic involvement, most commonly manifesting as skin thickening distal to the elbows and knees but sometimes affecting the face and neck. Patients classically present with several to all of the **CREST** features: calcinosis cutis (small tender nodules on the fingers), Raynaud syndrome, esophageal dysmotility, sclerodactyly of the fingers, and telangiectasias. Anticentromere antibody (ACA) is specific for limited SSc and is seen in about 50% of patients. Patients who are ACA+ tend to develop more severe digital ischemia and pulmonary hypertension.
- **Diffuse SSc** is the progressive form of SSc that leads to diffuse skin thickening and is more likely to have multiorgan involvement. Rapid skin involvement of the trunk, face (Figure 3-18), upper arms, and thighs characterizes this subset. It is frequently associated with antitopoisomerase I (anti-Scl-70) or anti-RNA polymerase III antibodies, and patients are more likely to develop interstitial lung disease and scleroderma renal crisis.



Figure 3-18: Diffuse systemic sclerosis
Source: Kimberly Salkey, MD

Raynaud phenomenon eventually develops in almost all patients with SSc. In **limited** SSc, Raynaud's usually occurs several years **before** other signs and symptoms become apparent, whereas in **diffuse** SSc, Raynaud's typically occurs simultaneously with the other manifestations.

Nail-fold capillary changes are commonly seen in both subtypes and correlate with severity of disease.

Immune modulation is the usual treatment.

SARCOIDOSIS

Sarcoidosis is a **noncaseating** granulomatous disease, of unknown etiology, that often affects the lungs, lymph nodes, eyes, and **skin**. It is most common in northern European countries (e.g., Sweden, Denmark). In the U.S., sarcoidosis affects African Americans 3–4× more often than Caucasians. Skin involvement is seen in about 25% of patients. Sarcoidosis is a great **mimicker** of other disorders, including many dermatologic diseases.

Lesions are divided into 2 categories:

- 1) Specific sarcoid skin lesions have noncaseating granulomas on biopsy and are most commonly found on the head, neck, and upper back. Specific lesions include:
 - Erythematous papules, mainly around the face (the most common presentation)
 - Scar sarcoidosis presenting as granulomatous changes in a healing skin wound or scar tissue (e.g., laceration, tattoo)
 - Plaquelike lesions
 - Micropapular lesions
- 2) Nonspecific skin lesions do not have granulomas and are considered reactive. They include:
 - Erythema nodosum is the most typical nonspecific skin lesion seen in sarcoidosis and is a marker of good prognosis. Sarcoidosis is one of the most common causes of erythema nodosum. **Do not** biopsy erythema nodosum in sarcoidosis for the diagnosis of sarcoidosis—the histopathology shows just a panniculitis (inflammation of the fat) and not granulomas. (See [Erythema Nodosum](#).)
 - Löfgren syndrome is an acute form of sarcoidosis that presents with erythema nodosum, bilateral hilar adenopathy, and arthritis and is frequently accompanied by fevers. It is usually self-limiting and requires only supportive care.

Lupus pernio is a type of sarcoidosis that has skin changes ranging from violaceous (purple) lesions on the tip of the **nose** and **earlobes** to large purple nodules/tumors on the **face** and **fingers**. It has a slow onset and almost **never** resolves! It is associated with chronic disease and extra-pulmonary involvement.

Treat cutaneous sarcoidosis with topical corticosteroids, intralesional steroid injections, antimalarials, and MTX. Lesions typically respond to treatment for pulmonary sarcoidosis.

For more information on sarcoidosis, see the [Pulmonary Medicine](#) section.

ERYTHEMA NODOSUM

Erythema nodosum ([Figure 3-19](#)) consists of red, warm, very tender nodules that are usually bilateral, symmetric, and classically located on the shins. It is more common in women than in men. **Know!** Erythema nodosum is associated with:

- Sarcoidosis (common)
- Inflammatory bowel disease
- Infection (e.g., tuberculosis, **streptococcal**, deep fungal, hepatitis B, *Coccidioides immitis*, *Histoplasma capsulatum*)
- Drugs (especially oral contraceptives, sulfas, and penicillins)
- Pregnancy
- Löfgren syndrome when arthralgia/arthritis and hilar adenopathy are also present
- Idiopathic



Figure 3-19: Erythema nodosum
Source: James Heilman, MD

Worldwide, **streptococcal infection** pharyngitis is probably the **most common cause** of erythema nodosum. Treatment consists of treatment of the underlying disorder and supportive therapy including NSAIDs.

DERMATOMYOSITIS

Buzzwords: **Gotttron papules** and **periorbital heliotropic** rash (a violaceous, sometimes scaly rash around the eyes; [Figure 3-20](#)) +/- periorbital edema.

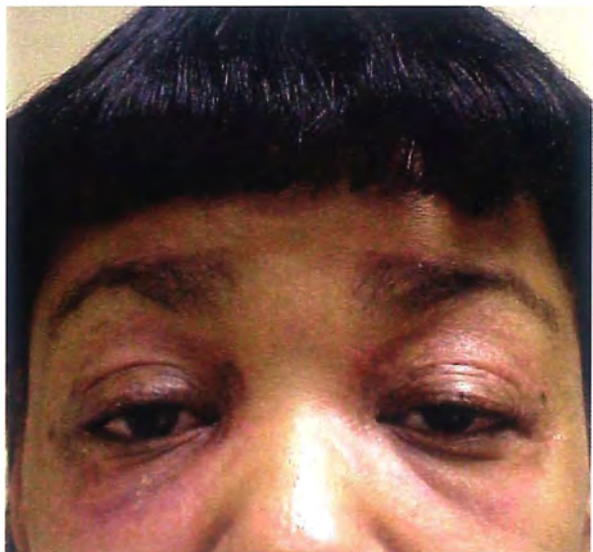


Figure 3-20: Periorbital heliotropic rash
Source: Kimberly Salkey, MD

Patients also manifest photodistributed, erythematous, scaly plaques—similar to psoriasis. Gottron sign is macular erythema over the dorsal aspects of the interphalangeal/metacarpophalangeal (MCP) joints or over the elbows and knees.

Gottron papules, an extension of Gottron sign, are flat-topped, reddish-to-violet, sometimes scaling papules; sometimes they just look like “cigarette paper” crinkling of the skin over the **knuckles** (MCP, proximal interphalangeal (PIP), and/or DIP). Gottron papules are the most specific finding with dermatomyositis. They may be described only as a “rash” or “eruption” over the knuckles (Figure 3-21). Again, this contrasts to the finger rash in SLE, which spares the knuckles. “Mechanic’s hands” are bilateral, symmetric areas of hyperkeratotic scale most typically on the lateral fingers or on the palm. This finding is associated with antisynthetase syndrome, anti-Jo-1 antibodies, and interstitial lung disease.



Figure 3-21: Gottron papules
Source: Kimberly Salkey, MD

Patients have symmetric proximal muscle weakness but may present solely with cutaneous disease, termed amyopathic dermatomyositis.

Remember: In **older** patients, dermatomyositis may be a **paraneoplastic** phenomenon. (Genitourinary [GU]/ovarian, gastrointestinal [GI], lung, and lymphoma are most common.) Offer all patients age-appropriate cancer screening. Patients who test positive for anti-p155/p140 are at particularly high risk of cancer.

Treatment of dermatomyositis is **corticosteroids**. This is usually given for 1 year in a slowly tapering dose. A steroid-sparing drug (azathioprine, MTX, or mycophenolate mofetil) is sometimes started with initial treatment; other clinicians start it when there is failure to respond to prednisone.

Antimalarials (hydroxychloroquine is 1st line) help with the skin disease but do **nothing for the muscle disease**. IV gamma globulin may be effective in patients who do not respond to the other medications. Rituximab is an effective 2nd line treatment for systemic disease and 3rd line treatment for cutaneous disease.

More information on dermatomyositis is given in the **Rheumatology** section.

REACTIVE ARTHRITIS

Reactive arthritis is an immunologic reaction to an infection elsewhere in the body and typically occurs 1–4 weeks after a GU or GI infection. The classic triad of urethritis, conjunctivitis, and asymmetric arthritis is seen in less than 1/3 of patients. Cutaneous manifestations are common

and include keratoderma blennorrhagicum and mucocutaneous genital lesions and/or mouth ulcers.

Keratoderma blennorrhagicum (Figure 3-22) classically presents as papules/pustules with central erosion and characteristic crusting on the palms and soles. It can be indistinguishable from pustular psoriasis.



Figure 3-22: Keratoderma blennorrhagicum
Source: CDC

Circinate balanitis presents as an erythematous pustular or plaquelike lesion on the glans or shaft of the penis.

For more information on reactive arthritis, see the **Rheumatology** section.

VASCULITIS

Vasculitis presents most classically as **palpable purpura**, usually starting on the legs. Palpable purpura is the extravasation of red blood cells into the skin and is commonly caused by a small vessel vasculitis. Skin biopsy typically displays leukocytoclastic vasculitis. There are many causes of cutaneous vasculitis, including infection (e.g., viral, bacterial), collagen vascular disease, and drug reactions. Up to 50% of self-limited cutaneous cases may be idiopathic. Always look for extracutaneous manifestations, especially kidney involvement. If a young patient presents with arthralgias, abdominal pain, renal disease, and palpable purpura, think IgA vasculitis.

For more information on small vessel vasculitides, see the **Rheumatology** section.

PETECHIAE / PURPURA / ECCHYMOSIS

Defined as hemorrhage into the skin or mucosal membranes, purpura has a vast and complicated differential diagnosis. Classifying the patient’s physical findings by morphology can facilitate the evaluation of a patient with primary purpura.

Petechiae (≤ 4 mm): The etiology of petechiae can be further broken down into 3 types of pathophysiology: hemostatically relevant thrombocytopenia (e.g., immune thrombocytopenia, thrombotic thrombocytopenia, disseminated intravascular coagulation), abnormal platelet function (congenital or acquired platelet dysfunction),

and nonplatelet etiologies (e.g., trauma, scurvy, benign pigmented purpura).

Macular purpura (5–9 mm): The differential diagnosis of macular purpura includes hypergammaglobulinemic purpura of Waldenström, infection or inflammation in patients with thrombocytopenia, scurvy, and small vessel vasculitis that is minimally inflamed.

Macular ecchymosis (≥ 1 cm): Like petechiae, ecchymosis can be further broken down into 3 types of pathophysiology: procoagulant defect (especially anticoagulant use, hepatic failure, and vitamin K deficiency), poor dermal support (as with solar purpura, systemic steroid therapy, Ehlers-Danlos, and scurvy), and platelet problems (usually thrombocytopenia or von Willebrand disease).

Palpable purpura: The potential etiologies of palpable, or inflammatory, purpura are vast. It may be triggered by the deposition of immune complexes, such as those caused by infection or drugs. It may be due to small or medium vessel vasculitis, such as that seen on biopsy in mixed cryoglobulinemias, rheumatic vasculitis, and antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis. Leukocytoclastic vasculitis (LCV) is a nonspecific inflammatory neutrophilic infiltration in the setting of a small vessel vasculitis. Non-LCV causes may include erythema multiforme and benign pigmented purpura.

PYODERMA GANGRENOSUM

Pyoderma gangrenosum is an inflammatory (not infectious and not a vasculitis) ulcer typically occurring on the legs (Figure 3-23). It is most commonly associated with inflammatory bowel disease but also can be seen with rheumatoid arthritis, ankylosing spondylitis, and hematologic malignancy. However, it is idiopathic in 25–50% of patients. Although a skin biopsy is **not** diagnostic (i.e., would reveal nonspecific neutrophilic infiltrate), it serves to exclude other causes of ulceration. The classic presentation is a deep ulceration with an inflamed and violaceous border that overhangs the ulcer. Treating the colonized bacteria usually does **not** help. Patients often complain of pain out of proportion to the clinical appearance of the lesion. **Pathergy**, the appearance of ulcers or lesions at sites of cutaneous trauma, is a common phenomenon; avoid wound debridement.

In idiopathic cases, 1st line treatment is corticosteroids. Otherwise, treat the underlying disorder. Patients may still require pulse dose steroids.



Figure 3-23: Pyoderma gangrenosum
Source: Kimberly Salkey, MD

SWEET SYNDROME

Sweet syndrome is an inflammatory disorder that is also referred to as acute febrile neutrophilic dermatosis. It can be:

- Idiopathic (50%)
- Drug induced
- Postinfectious
- Pregnancy related
- Seen with inflammatory or autoimmune disorders
- Seen with underlying hematologic malignancy (e.g., acute myeloid leukemia)

Patients have **high fever** and painful red plaques, ~ 1 inch in diameter, typically on the upper extremities, trunk, neck, and face. These plaques may be bullous in nature. A skin biopsy shows a dense but benign **neutrophilic** infiltrate. The lesions respond dramatically to corticosteroids. Potassium iodide, dapsone, and colchicine are also 1st line agents.

NAIL DISORDERS

PREVIEW | REVIEW

- What nutrient deficiency is associated with spooned nails?
- What do dark red lines on a nail bed in an IV drug abuser suggest?

Koilonychia is characterized by thin, concave (spoon-shaped) nails. It resolves spontaneously in children but often is secondary to occupational demands or severe iron deficiency in adults.

Psoriatic changes of the nails are covered in [Nail Changes in Psoriasis](#) on page 3-10.

Clubbing of the nails is common. See the [Pulmonary Medicine](#) section for more information.

Onychomycosis has varied clinical findings depending on its cause. The most commonly observed pattern is the distal or lateral subungual type with invasion of the hyponychium. This is characterized by nail thickening, subungual debris, and yellow or brown discoloration.

The superficial white type is caused by direct invasion into the nail plate and may have white patches or white linear striations. This pattern may be associated with immunosuppression such as that seen in AIDS.

The proximal subungual type may also be associated with immunosuppression and caused by invasion of the proximal nail fold.

Diagnosis of onychomycosis can be confirmed with KOH scraping, periodic acid-Schiff (PAS), and/or culture of a nail clipping and should be done before treating as 50% of suspected cases do not have a fungal infection and treatment with oral antifungals, although most efficacious,

can be toxic. Psoriasis and nail dystrophy can mimic fungal infection. Terbinafine is given for 12 weeks for toenail infections and 6 weeks for fingernail infections. Terbinafine is associated with hepatic failure, Stevens-Johnson syndrome (SJS)/TEN, and pancytopenia.

Onycholysis frequently involves the fingernails, and affected nails are detached from the nail bed. Idiopathic onycholysis may be due to exposure to irritants or water exposure. White or green discoloration may accompany changes. Onycholysis also can be secondary to trauma, psoriasis, tetracyclines, hypothyroidism, or fungal infections. As mentioned previously, onycholysis with pitting is a strong predictor of psoriatic arthritis. See [Nail Changes in Psoriasis on page 3-10](#).

Paronychia can be acute or chronic. Acute paronychia is characterized by swelling, redness, and pus of the proximal nail fold. It is most commonly caused by bacterial infection following trauma. If it is recurrent, consider HSV and perform culture or polymerase chain reaction (PCR). Treatment includes drainage of the abscess and appropriate antimicrobial treatment (antibiotics for bacterial etiology and antivirals for those cases due to HSV). Clinical features of chronic paronychia include erythema and edema of the proximal nail fold and absence of the cuticle ([Figure 3-24](#)). It is thought to be secondary to exposure to irritants or allergens and has a prolonged course. Treatment is avoidance of exacerbating factors, topical steroids, and antiseptics. Do not confuse a paronychia with a felon (which causes a painful infection involving the finger pad and nail bed) or a herpetic whitlow with an associated herpetic vesicular lesion (contagious).



Figure 3-24: Paronychia

Splinter hemorrhages are dark red, thin lines usually located to the distal portion of the nail ([Figure 3-25](#)). They are most commonly due to trauma, psoriasis, or onychomycosis. They may also indicate underlying systemic disease such as endocarditis, vasculitis, and antiphospholipid syndrome. Splinter hemorrhages can be seen in IV drug abusers, who are also at risk of endocarditis.



Figure 3-25: Splinter hemorrhage

Nail-fold telangiectasias are common in patients with connective tissue disorders. Patients with dermatomyositis and scleroderma may have reduced capillary density with avascular areas that alternate with dilated capillary loops. Patients with lupus may have normal capillary density with dilated capillary loops.

CUTANEOUS MANIFESTATIONS OF NUTRITIONAL DISORDERS

PREVIEW | REVIEW

- What vitamin deficiency causes a photosensitivity dermatitis?
- What are the dermatologic manifestations of zinc deficiency?
- What vitamin deficiency causes follicular hyperkeratosis?

Deficiency of B₁₂, folate, or niacin may cause diffuse hyperpigmentation, as well as hair and nail changes.

Niacin deficiency results in pellagra (remember the **3 Ds**: dermatitis [photosensitive areas], diarrhea, and dementia). **Isoniazid** and **carcinoid syndrome** (which is characterized by flushing of the skin) can also induce pellagra. Isoniazid is a competitive inhibitor of nicotinamide adenine dinucleotide (niacin precursor) and impairs pyridoxine functioning, which is essential for niacin synthesis from tryptophan.

Tryptophan can be metabolized to niacin or serotonin by 2 separate pathways. In carcinoid syndrome, most of the L-tryptophan is diverted to the production of serotonin, leaving the patient at risk for niacin deficiency.

Zinc deficiency causes an irritant eczematoid red rash that has a predilection for periorificial (e.g., perioral, periocular, anogenital) and acral (i.e., hands and feet) areas.

Iron deficiency is usually associated with hair loss, fragile longitudinal nail ridges, and koilonychia (spoon-shaped nails).

Vitamin C deficiency can result in follicular hyperkeratosis, especially on the posterolateral aspect of the arms, resembling keratosis pilaris. The hairs within these plugged follicles become curled, resulting in “corkscrew” hairs. Perifollicular purpura and petechiae develop as the disease advances.

ENVIRONMENTAL INJURY TO THE SKIN

Thermal burns are categorized by depth:

- **Superficial** (previously 1st degree): limited to epidermis; red, blanches with pressure, **dry**, minor swelling, and minor **pain**. Commonly resolves in 5–7 days.
- **Partial-thickness** (previously 2nd degree) is divided into superficial and deep:
 - Superficial partial-thickness: papillary dermis; blistering, pink, **moist**, much more painful. Typically heals in 2–3 weeks without scarring.
 - Deep partial-thickness: reticular dermis; blistering, red and/or white with poor blanching and capillary refill, moist or dry, typically **painful** with variable sensation to light touch. Can take 3–9 weeks to heal, often with scarring.
- **Full-thickness** (previously 3rd degree): entire epidermis and dermis; dry, leathery, waxy, and **painless**. Requires skin grafting unless small. When fully circumferential, a full-thickness burn can form a strangulating eschar that causes ischemia distally.
- **4th degree** involves skin, subcutaneous tissue, and underlying structures (i.e., fascia, muscle, bone).

General treatment of superficial or superficial partial-thickness burns includes cool compresses for pain relief and infection prevention with application of topical antimicrobial agents such as silver sulfadiazine. Deep partial-thickness, full-thickness, and 4th degree burns often require surgical debridement and skin flaps.

Frostbite (FB) occurs when skin temperature falls below 28.0°F (–2.0°C). It can be divided into 4 categories of severity:

- 1st degree FB is characterized by edema, erythema, and transient pain. Patients have full recovery.
- 2nd degree FB is characterized by severe erythema, edema, and blistering. Patients may have lasting neuropathy.
- 3rd degree FB is characterized by full-thickness loss of the dermis with hemorrhagic bullae and waxy, dull skin.

- 4th degree FB can result in loss of skin, as well as loss of underlying structures such as muscle and bone. Damage of this degree may require amputation.

Treatment includes rapid rewarming and reestablishment of circulation.

SKIN INFECTIONS

PREVIEW | REVIEW

- What is the significance of finding a lesion of ecthyma gangrenosum on physical exam?
- What 2 organisms can cause impetigo?
- Characterize the lesions of disseminated gonorrhea.
- How does staphylococcal scalded skin syndrome differ from toxic epidermal necrolysis?
- Characterize the rash of erythema migrans.
- What antibiotic is used to treat a cat bite?
- What tinea infections require oral therapy?
- Molluscum contagiosum, if seen in an adult, should raise your suspicion for what immunodeficiency?
- How does the dose of acyclovir differ when the drug is used to treat varicella and herpes simplex infections in the immunocompromised?
- What are the treatments for head lice? What topical treatment is not pesticide based? What drug is the most potent for head lice?
- What type of lice is sexually transmitted?
- How do the effects of the venoms of the brown recluse and black widow spiders differ?
- What spider bite has a longer recovery time?

BACTERIAL SKIN AND SOFT TISSUE INFECTIONS

Many of the following infections and treatments are covered more fully in the [Infectious Disease](#) section.

Cellulitis and Abscesses

Erythrasma is a well-defined, red lesion with some slight scaling. It is usually found in the axilla, groin, and toe webs. In the **obese**, it is seen **under the breasts**. Gram-positive *Corynebacterium minutissimum* is frequently isolated from the lesion (especially after it has become scaly or macerated). **Differential diagnosis**: tinea cruris, *Candida*, and intertrigo (an irritant dermatitis typically found in the skin folds of obese patients; see [Intertrigo on page 3-2](#)). Diagnosis: Erythrasma fluoresces **bright red** (attributed to coproporphyrin III) with a Wood lamp (UV light). Treat with benzoyl peroxide or topical erythromycin +/- an “-azole” antifungal cream. In severe cases, oral erythromycin or tetracycline may be used.

Folliculitis

Folliculitis inflammation of hair follicles usually caused by *S. aureus*. **Furuncles** (deep folliculitis or “boils”) are a folliculitis that extends deep into the dermis. **Carbuncles** are collections of furuncles that have coalesced under the skin, forming a networked, single mass. Treatment includes oral or parenteral antibiotics and moist heat; consider surgical drainage of fluctuant lesions.

Be aware that folliculitis associated with **hot tubs** is often caused by *Pseudomonas*, **not** *Staphylococcus*, and is acquired in hot tubs with inadequate chlorination. The resulting pustules usually occur around the buttocks and thighs or in occluded skin areas (e.g., in skinfolds; under a swimsuit). Pseudomonal folliculitis resolves **without** treatment in ~ 1 week. 5% acetic acid (i.e., vinegar) compresses can be used for symptomatic relief.

A much more serious infection is *Pseudomonas* septicemia with the initial dermatologic finding of small, dark-centered (necrotic) papules. In a very ill, **neutropenic** patient, this papule progresses and becomes the pathognomonic **ecthyma gangrenosum**, a necrotic ulcer with an erythematous rim (Figure 3-26).



Figure 3-26: Ecthyma gangrenosum
Source: Kimberly Salkey, MD

Impetigo

Staphylococcus aureus is by far the most common cause of impetigo, although it also may be caused by group A *Streptococcus*. It starts as an erythematous, vesicular lesion that quickly becomes pustular and crusty (a honey-colored crust). Impetigo is highly contagious, and patients generally do not appear systemically ill. The face and exposed areas are most commonly affected. Methicillin-resistant *S. aureus* (MRSA) causes many **community outbreaks**. When impetigo, an infection of the epidermis, extends into the dermis, it is called **ecthyma**.

Limited skin lesions can be treated with topical mupirocin for 5 days. Extensive lesions and ecthyma require oral treatment with antibiotics that cover both *S. aureus* and streptococci. These include dicloxacillin or cephalexin with erythromycin as an alternative for allergic patients. If MRSA is suspected by history or culture, use clindamycin, trimethoprim/sulfamethoxazole (TMP/SMX), or doxycycline. The usual course of treatment with oral agents is 7 days.

Note: Bullous impetigo usually occurs in young children < 2 years of age and presents with the acute onset of large, loose bullae (Figure 3-27). An exotoxin/exfoliatin toxin causes cleavage of the epidermis.

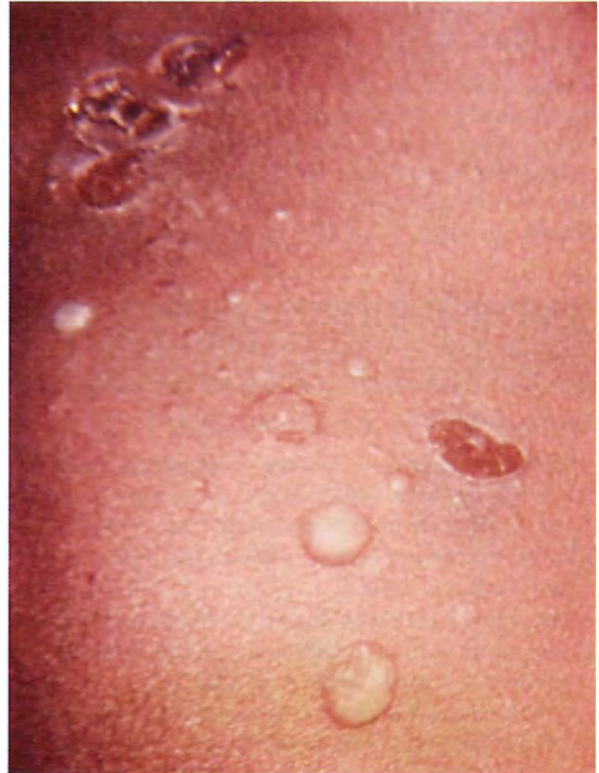


Figure 3-27: Bullous impetigo
Source: CDC

Erysipelas

Erysipelas is an explosive superficial infection (often caused by group A *Streptococcus*) that is confined to the dermis and spreads quickly through skin **lymphatics** (Figure 3-28). The area of infection is **clearly demarcated**, red, and palpable. It usually starts from a superficial abrasion, typically around the central face, with erythema and swelling. Lymphangitic spread with red **streaking** is seen. Initial treatment is IV antibiotics followed by oral therapy.



Figure 3-28: Erysipelas
Source: CDC

Necrotizing Fasciitis

Necrotizing fasciitis (NF) is a deep soft tissue infection involving planes of subcutaneous fat and fascia. This area contains the nerve bundles, which, when damaged, cause extreme pain followed by anesthesia. Blood supply can also be damaged, so antibiotic

response is poor and necrosis of the overlying tissue occurs. Unlike erysipelas, NF does not have a distinct border and can be difficult to diagnose early. NF can be hard to distinguish from cellulitis in the early stages, but in NF, the pain is usually out of context to the physical signs and there are septic symptoms. Enquire about any history of skin trauma. Cellulitis is characterized by erythema, swelling, and lymphangitis. Lymphadenopathy is absent in NF, and skin changes rapidly progress with violaceous discoloration and sometimes blisters (necrosis) and crepitus. Diagnosis of NF should lead to antibiotic therapy and urgent surgical exploration.

There are 2 types: **Type I**, the most common type, is a **polymicrobial infection** (including anaerobes) seen in **immunocompromised** patients, such as diabetics. **Type II** is generally caused by group A *Streptococcus* or MRSA and most commonly affects **healthy individuals**. If suspected, obtain cultures, start antibiotic therapy, and consult surgery immediately as this is a **surgical emergency** and there is a **high mortality rate** even with appropriate medical and surgical intervention. Avoid wasting time with computed tomography scans if diagnosis is suspected.

Gonococcus and Meningococcus

Disseminated gonococcal infection causes a few (commonly < 12) hemorrhagic pustules on the extremities, often around the joints. Culture of the skin lesions is typically negative. Swab for cultures from the initial site of infection (oral mucosa, cervix, urethra, or rectum) because there is a much higher yield.

Meningococcemic skin signs start as macular or petechial lesions and evolve to large purpura. Purpura fulminans consists of purpura, ecchymoses, and confluent maplike, gray-to-black, necrotic skin lesions. It is associated with severe infection and diffuse intravascular coagulation.

Staphylococcal Scalded Skin Syndrome (SSSS)

SSSS primarily affects newborns and children < 5 years of age, but, rarely, it affects immunocompromised adults. Patients with SSSS present with **tender, red, peeling skin**—due to circulating toxins from localized *Staphylococcus* infection or colonization that generally is initiated at a **nonskin site** (e.g., sinuses, umbilicus in infants). Skin changes are similar to those seen in toxic epidermal necrolysis (TEN), which is noninfectious (i.e., a side effect of drugs), so consider it during the workup. The skin in SSSS separates **much more superficially** than in TEN. The peeling skin is caused by a similar exotoxin or exfoliatin toxin, as seen in bullous impetigo (a localized form of SSSS); however, it **circulates systemically in SSSS**. Treatment includes debridement of necrotic superficial epidermis, topical antibiotics for bullous impetigo lesions, and systemic antibiotics for more severe and/or widespread disease.

Toxic Shock Syndrome (TSS)

TSS is caused by *Staphylococcus aureus* and *Streptococcus pyogenes*. First described in 1978 in association with the use of highly absorbent tampons in menstruating women, today > 50% of cases are not associated with menstruation.

Staphylococcal TSS presents with abrupt development of fever, shock, and **multiorgan** system failure. In the acute phase, patients develop a diffuse, painless, macular erythrodermic rash (“sunburn”) followed by desquamation of the palms and soles during the convalescent phase. Patients are commonly < 30 years of age, and mucosal involvement is typical. Treatment includes supportive care and systemic antibiotics.

Streptococcal TSS causes symptoms similar to those of staphylococcal TSS. Treatment is with IV penicillin (PCN) + clindamycin +/- intravenous immunoglobulin (IVIG). In contrast to staphylococcal TSS, blood cultures are **usually positive** in streptococcal TSS.

See the **Infectious Disease** section for more information on TSS.

Scarlet Fever

Scarlet fever primarily presents in children with streptococcal pharyngitis and a rash known as “**scarlatina**”—a fine, red, sandpaper-like rash that is more prominent in skin folds (Pastia lines) and involves the trunk and extremities but spares the palms and soles. “**Strawberry tongue**” also commonly presents in the acute phase. During the convalescent stage, desquamation of the palms and soles occurs.

Strep Throat

PCN is by far the best treatment for group A *Streptococcus* throat infection. Give oral PCN (× 10 days) or intramuscular (IM) benzathine PCN. Give **erythromycin** for PCN-allergic patients. **Clindamycin** is often added to PCN when there is serious infection (to decrease toxin production), such as necrotizing fasciitis or toxic shock.

Rocky Mountain Spotted Fever (RMSF)

RMSF is usually heralded by several days of fever. Then, small lesions develop that progress from peripheral to central (centripetal) distribution and from macular to petechial to purpuric type. As you can see from **Figure 3-29**, the skin findings can be deceptively nondescript. Treat with **doxycycline** or chloramphenicol.



Figure 3-29: Rocky Mountain spotted fever

Spirochetal Skin Infections

Lyme disease: The first stage of Lyme disease is often associated with erythema migrans (Figure 3-30). Typically, this is a slowly enlarging (over about 1 week), annular, erythematous rash with a clear center (looks like a bull's-eye). Occasionally, the center is not clear. Treat early Lyme disease with oral antibiotics—including doxycycline, amoxicillin, or cefuroxime axetil—to reduce the signs and symptoms and decrease the risk of late Lyme disease development.



Figure 3-30: Erythema migrans
Source: CDC

Syphilis: A chancre (painless ulcer at site of inoculation) indicates primary syphilis. This is commonly on the penis or vagina but can present on the pharynx or anus depending on sexual practices. A few weeks after the chancre appears, a diffuse scaling nonitchy macular papular rash is seen on the palms and soles. This rash is a hallmark of secondary syphilis but it also can be found on the trunk, head and neck, genitals, and mucosal surfaces. White, thickened plaques (condylomata) are additional secondary syphilis signs. There is lymphadenopathy. Gummas occur in tertiary syphilis; these are painless, indurated, nodular, or ulcerative lesions.

Animal Bites

Both *S. aureus* and *Pasteurella multocida* infections are caused by dog and cat bites, but cat bites more commonly cause *P. multocida* infection. Human bite infections are caused by multiple bacteria (e.g., *Eikenella*) and can be severe.

Clean and lavage well and give amoxicillin/clavulanate as prophylaxis and treatment. Doxycycline can be given alone if allergic to penicillin. Trimethoprim/sulfamethoxazole or cefuroxime or ciprofloxacin does have coverage against *Pasteurella*, but they need to be combined with clindamycin or metronidazole to provide adequate full anaerobic coverage.

Macrolides (erythromycin), clindamycin, and antistaphylococcal penicillins (dicloxacillin) lack activity against *P. multocida*.

Use antibiotic prophylaxis in the following situations:

- Immunocompromised host
- Facial bites
- Significant tissue destruction
- Presenting edema
- Clear crush injury

- Near a bone or joint
- On the hand

Bites on the hand are prone to deep infection due to the relative paucity of soft tissue above bones and joints.

Assess the tetanus immunization status with all bites. Give a tetanus vaccine:

- If patient has received fewer than 3 doses of vaccine in lifetime
- If the wound is clean and it has been longer than 10 years since the last dose of tetanus
- If the wound is dirty and it has been longer than 5 years since the last dose of tetanus

In addition, if the wound is contaminated, tetanus immune globulin may be recommended if the person has had fewer than three tetanus vaccines in lifetime or does not know status.

The animal should be observed for 10 days if possible; rabies postexposure immunization is necessary only if the animal shows signs of illness or if the animal cannot be quarantined.

FUNGAL INFECTIONS OF THE SKIN

Superficial Fungal Infections

Dermatophytes (*Microsporum*, *Epidermophyton*, and *Trichophyton*) cause superficial fungal infections (outer layer of skin) and are named according to the site involved:

- Tinea capitis (scalp ringworm)
- Tinea corporis (common ringworm on torso or extremities; Figure 3-31)
- Tinea cruris (jock itch)
- Tinea unguium/onychomycosis (nails; Figure 3-32)
- Tinea pedis (athlete's foot; Figure 3-33)



Figure 3-31: Tinea corporis



Figure 3-32: Tinea unguium
Source: CDC



Figure 3-33: Tinea pedis
Source: Kimberly Salkey, MD

The diagnosis is often made **clinically** but can be confirmed with potassium hydroxide (KOH) test on skin scrapings, which reveals **branching filamentous hyphae**.

Topical antifungal creams, such as ketoconazole, miconazole, clotrimazole, and terbinafine (Lamisil), control most fungal skin infections. Systemic therapy (the same as is used for tinea capitis; see below) is required for those who fail topical therapy or who have extensive skin involvement. Due to the potential for liver toxicity with terbinafine, liver function tests should be done at baseline and periodically throughout therapy.

Tinea unguium (onychomycosis) can be treated with either **topical** or **oral** antifungal agents.

Use topical treatments when < 1/2 of the distal nail plate is affected. Topical options include ciclopirox (e.g., Penlac, Loprox) 8% and efinaconazole (Jublia) 1% nail solutions, as well as tavaborole (Kerydin) 5% solution. Duration of topical treatment is 48 weeks.

Oral therapy may be needed for topical therapy failures and generally is more efficacious. Oral treatment for tinea unguium is terbinafine, itraconazole, or fluconazole.

Obtain a nail clipping sample and send it to the lab. Up to 50% of patients with suspected onychomycosis do not have a fungal nail infection. Common conditions, such as psoriasis or a nail dystrophy, can mimic onychomycosis. Given the potentially severe toxicity of terbinafine, confirmation of a fungal infection is recommended prior to initiation of therapy. Terbinafine is rarely associated with hepatic failure, Stevens-Johnson syndrome (SJS)/TEN, and pancytopenia. The diagnosis can be confirmed with a nail clipping with KOH scraping, periodic acid-Schiff (PAS), and/or culture.

Oral terbinafine is prescribed for 12 weeks when toenails are involved; it is prescribed for 6 weeks for fingernails. Check transaminases at baseline and consider repeating at 6 weeks.

Tinea capitis must **always** be treated with **oral** antifungals: griseofulvin, terbinafine, fluconazole, or itraconazole for 8 weeks. Tinea capitis is a superficial fungal infection caused by dermatophytes: *Microsporum*, *Epidermophyton*, and *Trichophyton*. This is an infection of the scalp and causes

erythema, scale, pruritus, and localized alopecia. KOH scraping shows branching (filamentous hyphae).

Tinea corporis is spread primarily by direct skin-to-skin contact or secondarily from other sites of fungal infection. Classic presentation is an annular, scaly rash with raised, advancing erythematous margin and scale that is clear toward the center with a history of pet contact. A differential diagnosis includes the herald patch of pityriasis rosea and granuloma annulare (GA). Itch is a differentiating factor (present in tinea), and GA lacks scales. Nummular eczema is similar. Microscopically, these demonstrate long, narrow hyphae; spores are not seen. Tinea corporis can be treated with topical antifungals or oral antifungals. Oral treatment is the same as for tinea capitis.

Tinea versicolor (pityriasis versicolor) is caused by *Malassezia globosa* or *M. furfur*. Skin infection results in hypopigmented or hyperpigmented (depending on the patient's skin tone/color) spreading macules, usually on the upper torso and upper arms, but the infection can spread over the body. Microscopic KOH skin scraping reveals **"spaghetti and meatballs"** (Figure 3-34). Treatment is topical: imidazole creams, selenium sulfide, or ketoconazole shampoo and/or oral: itraconazole or fluconazole. Always consider secondary syphilis when evaluating disseminated rashes on the body, although the hallmark sign for syphilis is on the palms and soles.

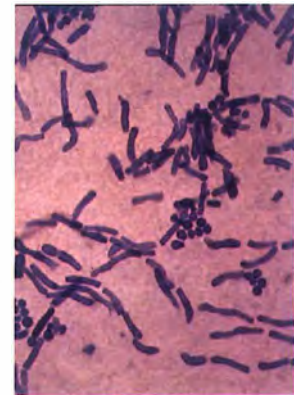


Figure 3-34: Tinea versicolor (KOH prep)
Source: Kimberly Salkey, MD

Deeper Fungal Infections

Candidiasis intertrigo is a **deeper** skin fungal infection that causes red patches in intertriginous areas. These sites are often chronically moist with lack of circulation. A variant occurs in the interdigital spaces of the hands, especially for persons in occupations where hands are frequently in water such as dishwashers or nurses. Candidiasis of the mouth (thrush) causes white semiadherent plaques on the tongue and mucosa. Unlike hairy leukoplakia, these **can be scraped off**. Vaginal candidiasis has similar plaques with cheesy discharge. Other presentations are perleche and diaper dermatitis. Treatment can be with topical formulations or systemic agents, depending on the area affected and patient's comorbidities. Visualization demonstrates pseudohyphae and yeast cells. Treatment is topical imidazoles (e.g., clotrimazole).

Cutaneous mucormycosis is a rare infection caused by extremely common fungus of the class *Mucorales*. Infection can occur after inoculation of the fungal spores, usually by trauma, into the dermis of an

immunocompromised person, most commonly a poorly controlled diabetic. It first appears as a single tender and painful indurated area that quickly spreads, causing tissue necrosis. Cutaneous mucormycosis usually remains cutaneous and does **not** spread to the deeper dermis tissues or become systemic.

VIRAL SKIN INFECTIONS

Human Papillomavirus (HPV)

Warts are caused by any 1 of > 100 types of HPV. They often **resolve spontaneously**, but this can take up to **2 years**. However, because of their appearance, patients may request treatment, which typically involves some form of tissue destruction:

- Verruca vulgaris is the common wart. Treatments include liquid nitrogen, topical acids, and CO₂ laser.
- Verruca plana is the flat wart. Treatment is the same as that for verruca vulgaris, but note that these lesions **do** exhibit koebnerization (i.e., spread) with trauma to the skin.
- Verruca plantaris is the plantar wart (Figure 3-35). Initial treatment may consist of a strong acid (trichloroacetic acid), concentrated (40%) salicylic acid plaster, liquid nitrogen, or laser.
- Condylomata acuminata are anogenital warts. 90% are caused by HPV-6 or -11. They are sometimes coinfecting by HPV-16, -18, or -31—the **oncogenic HPV** types (associated with cancer of the cervix and anus). If unsure of diagnosis, do a shave biopsy. Treat with topical podophyllin, trichloroacetic acid, imiquimod (e.g., Aldara, Zyclara), liquid nitrogen, or CO₂ laser. Podophyllin is teratogenic, so do **not** give it to **pregnant** patients.



Figure 3-35: Plantar wart
Source: Kimberly Salkey, MD

Molluscum Contagiosum

Know: Molluscum contagiosum is caused by a poxvirus. It consists of smooth, umbilicated, pearly papules (Figure 3-36). It usually occurs in children (anywhere on the body except the palms and soles), but you may also see it in the pelvic area of sexually active young adults—and it is **common in AIDS patients** (can be sexually transmitted). Although molluscum contagiosum often resolves spontaneously, except in immunosuppressed patients (e.g., AIDS), treatment options include cryotherapy with liquid nitrogen, surgical curettage, and cantharidin application. Antiretroviral treatment imiquimod is used to treat molluscum associated with HIV infection.



Figure 3-36: Molluscum contagiosum

Measles and Rubella

Know: Measles (rubeola) has several stages. The prodromal stage lasts 3–4 days with fever, malaise, sinus discharge, and a hacking cough. Koplik spots (Figure 3-10 on page 3-7; pathognomonic) often appear on the palate from 1 to several days before the onset of rash. As the Koplik spots begin to disappear, a red maculopapular rash starts on the face and behind the ears and quickly spreads downward and outward, with the densest concentration of lesions from the face to the shoulders. The palms and soles are affected last. Lesions gradually fade in order of appearance and may have some desquamation.

Rubella (a.k.a. German measles and 3-day measles) is benign **except** when it occurs in pregnant women. The rash is similar to measles but lasts only 3 days. Rubella has been eradicated in the Americas, but there are still ~ 120,000 cases/year worldwide. Congenital rubella results in a variety of serious birth defects:

- Heart malformations
- Ocular defects
- Microcephaly
- Intellectual disability
- Deafness
- Thrombotic thrombocytopenic purpura (TTP)
- Bone problems

Varicella-Zoster Virus (VZV)

VZV causes 2 diseases: chickenpox and herpes zoster (shingles). **Both** diseases present with vesicles on an erythematous base. Herpes zoster is reactivation of VZV in a person who has had chickenpox.

Chickenpox (Figure 3-37) has decreased in incidence with routine childhood vaccination. Rash is initially maculopapular and rapidly progresses to vesicles and then to scabbed lesions. These tend to come in “crops” over 2–4 days.



Figure 3-37: Chickenpox

Herpes zoster (shingles; [Figure 3-38](#)) manifests as grouped vesicles along a dermatome with focal pain and is unilateral. Affected dermatomes can include the regions of the eye (herpes zoster ophthalmicus; [Figure 3-39](#)) and ear (herpes zoster oticus). Older age and immunosuppression (e.g., HIV) are risk factors. Zoster occurring along the 1st branch of the trigeminal nerve (V1) affecting the **nasal tip** is known as Hutchinson sign. Zoster in this pattern runs the risk of zoster ophthalmicus, a **sight-threatening** condition, and requires an ophthalmology evaluation. Treatment of herpes zoster is 800 mg oral acyclovir 5×/day for 7–10 days, but if the patient has an immunocompromised status, such as an HIV-infected patient, then intravenous acyclovir is needed at 10 mg/kg 5×/day for 7 days (adjust dose for chronic kidney disease).



Figure 3-38: Herpes zoster (shingles)

If started within 72 hours of onset, antiviral therapy with acyclovir, famciclovir, or valacyclovir decreases disease duration. Systemic steroids can help reduce acute pain, but its use is controversial, whereas gabapentin can reduce the likelihood of progression to postherpetic neuralgia.

More information on the VZV and herpes zoster vaccine is in the [Infectious Disease](#) section.

Herpes Simplex Virus

See herpes simplex infections under [Oral Blisters and Ulcers](#) on page 3-7.

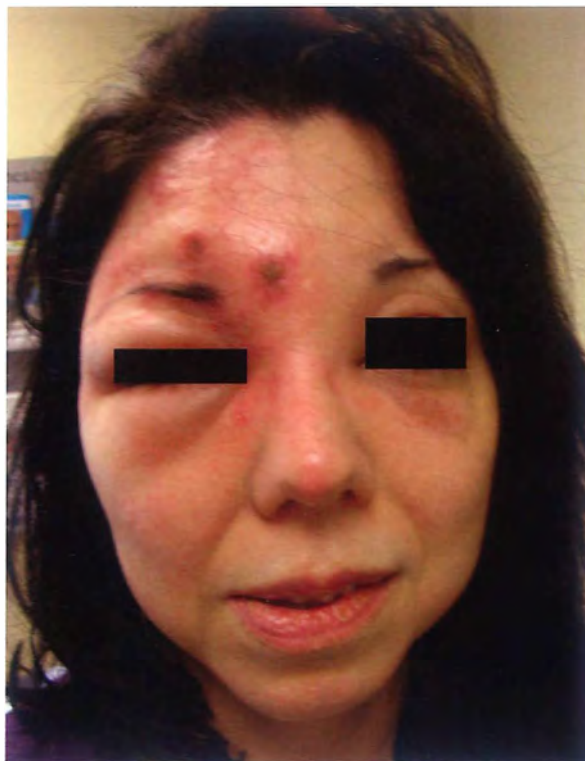


Figure 3-39: Herpes zoster ophthalmicus

Source: Jason Reichenberg, MD

INFESTATIONS AND BITES

Note: Parasitic skin infection outbreaks typically occur in schools, nursing home communities, and camps.

Lice

Head lice (*Pediculus humanus capitis*) have a 1-month life span, during which the females lay ~ 10 eggs per day and firmly attach them to the base of hair strands. Transmission is through direct contact with the head of an infected person. Diagnosis is made by direct visualization of lice and/or nits (eggs) in the hair. A Wood lamp examination can be performed in difficult cases: Live nits are fluorescent white when illuminated with a Wood lamp, but empty nits are fluorescent gray.

Treatment is pesticide based or uses asphyxiation, followed by nit removal. Chemical treatments:

- Topical ivermectin is the strongest drug. It requires a single application and has an effectiveness of ~ 95%. Oral ivermectin can also be effective but is not FDA approved.
- Malathion is a pesticide-based treatment that kills both lice and eggs. Effectiveness of malathion is ≥ 90%, but it is expensive and flammable (!) and must be left on for 8 hours.
- Spinosad is derived from a soil bacterium, *Saccharopolyspora spinosa*. It overexcites the central nervous system (CNS) of the lice, interacting with their acetylcholine (ACh) receptors. Second application is done only if live lice are seen 7 days later. It has an effectiveness of ~ 85%.

- Benzyl alcohol lotion 5% (Ulesfia) contains **no** neurotoxic pesticides. It kills by suffocating the lice. It is safe in children older than 6 months. Retreatment after 7 days is required. It has an effectiveness of ~ 75%.
- Over-the-counter treatments include permethrin cream 1% and a lotion with permethrin + piperonyl butoxide. Unfortunately, in the U.S., resistance is growing against permethrin preparations and malathion. Effectiveness of permethrin treatments is not very high (< 50% overall and even worse in areas of high resistance).
- 1% lindane shampoo is a 2nd line treatment because of neurotoxicity.

Removal of nits with a fine-toothed comb is done following application of all medications and is a necessary step for eradication of the lice. There are professional services that for a fee will remove lice in their clinics or in the patient's home. Treat infested close contacts and bed mates at the same time and disinfect brushes, combs, and hats.

Body lice (*Pediculus humanus corporis*; **Figure 3-40**)

live in clothes and are on the body only when feeding. Treatment is bathing and discarding or carefully **laundering** clothes and bed linens, using hot water. Clothes can also be ironed with focus on the seams. If the patient has a few nits on body hair, additionally treat with permethrin 5% cream.



Figure 3-40: Body louse
Source: CDC

Pubic lice (*Phthirus pubis*): The crab louse is sexually transmitted and can also infect the eyelashes. Fomites **rarely** transmit crab lice. Itching in the groin area is the most common manifestation of infection. The bluish macules (maculae ceruleae) are not always present, but examination may reveal them in the groin area, usually in patients who have been infested for a prolonged period. Treatment is similar to that of head lice. Use topical permethrin or pyrethrin + piperonyl butoxide. Wash bedding and clothing in hot water and use a hot dryer.

Scabies

Scabies is caused by a the tiny (0.2–0.4 mm) (*Sarcoptes scabiei*) mite that **tunnels** into the skin to lay eggs (**Figure 3-41**). It is spread by **skin-to-skin contact**—the mites do not live > 48 hours without a host! Consider it in anyone with unexplained, intense itching in areas of erythematous papules that is worse at night and after a hot shower, particularly in hospitalized or institutionalized patients. Classically, scabies is associated with itching of the flexor aspects of wrists, axilla, and interdigital spaces. Diagnosis is made by microscopic visualization of the mite, feces, or eggs from skin scrapings that are prepped with mineral oil.



Figure 3-41: Scabies burrow

Treat with 5% permethrin applied to **all** areas of the body from the head down and washed off after 8–14 hours. A 2nd dose in 7 days is recommended. Treat all household contacts simultaneously. Alternatives: crotamiton lotion 10% and crotamiton cream 10% (crotamiton is for scabies in adults only and is not very effective), sulfur (5–10%) ointment, or lindane lotion 1% (not 1st line). Use oral ivermectin for severe or recalcitrant cases, with a repeat dose in 1 week, although it is not FDA approved for this use. In nursing homes and for cases of crusted scabies (Norwegian scabies), a combination therapy of topical permethrin and oral ivermectin, 2 doses given 7 days apart, may be used. Oral therapy alone is also used in institutions, when a patient is mentally impaired, or when permethrin is inappropriate. Lindane has CNS toxicity, so do not use during pregnancy, in infants, or in young children. Permethrin can be used in pregnancy. Precipitated sulfur is also considered safe to use during pregnancy but may be less effective. Wash all linens and clothing in hot water.

Bedbugs

Bedbugs (*Cimex lectularius*;

Figure 3-42) are blood-sucking ectoparasites that hide in cracks and crevices during the day and feed at night. They cause edematous pink papules that may have a central punctum. Bites are often found in groups of 3 in a linear array (breakfast, lunch, and dinner) but can be scattered (**Figure 3-43**). Reactions to bites can take days to develop. Symptoms can be treated with topical corticosteroids, but insects need to be eradicated from the home, which can be difficult and can require professional extermination.



Figure 3-42: Bedbug



Figure 3-43: Bedbug bites

Spiders

In the U.S., the spider whose bite can cause a necrotic reaction is the **recluse** spider (genus *Loxosceles*). The brown recluse (*Loxosceles reclusa*) is found in the south-central U.S.; other recluse species are found along the southwestern border of the U.S. See Figure 3-44 for their distribution in the U.S.



Figure 3-44: Geographic distribution of *Loxosceles* species spiders in 2018

Brown recluse spiders (Figure 3-45) tend to hide in wood-piles, attics, closets, and seldom-worn clothing. Adults have a leg span of ~ 25 mm, 6 eyes, and a dark **violin** pattern on the dorsal front portion of the body (cephalothorax); thus, they are also called “fiddleback” or “violin” spiders. Their venom contains sphingomyelinase and other substances that lyse cell walls, activate complement, and cause local necrosis.



Figure 3-45: Brown recluse spider. Note the violin pattern on the dorsal cephalothorax.

The reaction to the bite of all the recluse spiders is similar. Initially, the bite is painless; pain develops at the site 2–8 hours later. Over the next 1–2 days, a hemorrhagic blister develops that eventually progresses to a necrotic ulceration. Patients rarely have systemic symptoms, such as fever, chills, nausea, or vomiting. Cutaneous

loxoscelism is the term given for the ulcerative effect of the recluse bite (genus *Loxosceles*). It is the only spider that affects humans this way.

Treatment is supportive with local wound care, because these bites are seldom infected but can take a week to heal. (If there is obvious infection, think **MRSA** instead.) The lesions may continue to expand for as long as 10 days, but most eventually heal spontaneously without surgical or other intervention. Other treatments (e.g., dapsone, steroids) are controversial because data on effectiveness is lacking. Dapsone is commonly used to prevent the wound from necrosing. Glucose-6-phosphate dehydrogenase (G6PD) deficiency is a contraindication.

Black widow spiders (Figure 3-46) are found throughout the U.S. (except Alaska); the southern black widow and western black widow spiders are most commonly responsible for serious symptoms. Widow spiders hide in dimly lit, warm, dry outhouses and sheds. They are large, with leg spans of up to 40 mm. Patients usually have a recent history of outdoor activity, such as cleaning out a garage. Female spiders are twice the size of males and cause the most severe bites; a mature black widow female has a **red or orange hourglass** marking on the **ventral** surface of the abdomen.



Figure 3-46: Black widow spider. Note the red/orange hourglass on the ventral abdomen.

Black widow spider venom is a neurotoxin that causes very little local reaction, although cutaneous reactions can include erythema, edema, and piloerection. Initial signs and symptoms include pain at the site, diaphoresis, muscle cramping, chest tightness, vomiting, malaise, sweating, abdominal pain (can mimic appendicitis), agitation, and hypertension.

Treatment includes local wound care, analgesia, and tetanus prophylaxis. Usually, all symptoms resolve within 24–48 hours. More severe cases can be treated with widow antivenin. Be aware that widow antivenin, like snakebite antivenin, can cause anaphylaxis.

Wounds from the painless bite of the brown recluse can take a week or longer to heal as a result of the enzymatic tissue breakdown, whereas the wound from the painful bite of a black widow releasing a neurotoxin heals more rapidly and with no tissue destruction.

CUTANEOUS ULCERS

PREVIEW | REVIEW

- Where is the preferred biopsy site of a cutaneous lesion?
- Venous ulcers are usually related to what underlying disorders?

Ulcers, defined by loss of both epidermis and dermis, can be quite challenging to diagnose and treat. They are most commonly found on the lower legs and have a vast range of causes. Biopsy and culture of ulcers can aid in ruling out neoplastic or infectious etiologies, respectively. The biopsy should be performed at the edge or margin of the ulcer rather than the center to allow for better healing and control of bleeding and to avoid a biopsy of nondiagnostic necrotic debris. The 3 most common causes are venous, arterial, and neuropathic etiologies.

Venous ulcers are commonly located on the medial malleolus and are related to venous hypertension or venous insufficiency. They typically have irregular, shallow borders and a yellow fibrinous base and may be accompanied by clinical findings of stasis dermatitis, lymphedema, varicosities, and edema. Hemosiderin deposition and/or petechiae may also be observed.

Arterial ulcers are often located on distal sites and bony prominences. The base of these ulcers may be yellow and fibrinous or dry and necrotic. Lesions are described as punched out. Surrounding skin can be shiny and devoid of hair. Peripheral pulses may be weakened or absent.

Neuropathic ulcers, like arterial ulcers, are located at pressure sites and may be described as punched out; however, they may also be surrounded by thick callus. Accompanying clinical findings include peripheral neuropathy and foot deformities.

Pyoderma gangrenosum (PG) (Figure 3-23 on page 3-15) is a neutrophilic, ulcerating disorder. Lesions start as tender nodules, papules, or pustules that progress to necrotic ulcerations with violaceous, rolled borders and a rim of erythema. PG is a diagnosis of exclusion, and other causes must be worked up and ruled out. Patients can have a history of underlying disease, or it can be idiopathic. It occurs often in inflammatory bowel disease, ulcerative colitis, rheumatoid arthritis, and multiple myeloma. Other associations with PG include Sweet's, Behçet's, and Sjögren's. It may be idiopathic in up to 50% of cases. Treatment includes topical steroids, systemic corticosteroids, dapsone, immunosuppressive medications, and TNF- α inhibitors. PG is worsened by trauma (pathergy), so debridement or other procedures should be avoided.

There is a wide range of less common causes of cutaneous ulcers, including infection, vasculitis, physical trauma (e.g., prolonged pressure, burns, factitial), hematologic disease (e.g., sickle cell disease, α - and β -thalassemias, hereditary spherocytosis), hypercoagulable states, and vaso-occlusive disease.

HAIR DISORDERS

PREVIEW | REVIEW

- What form of alopecia is from an autoimmune state?
- What is the origin of excessive hair growth that is located centrally?
- What causes excessive facial hair in women?

NONSCARRING HAIR LOSS (ALOPECIA)

Androgenic alopecia results from the genetic sensitivity of hair follicles to androgens. This leads to miniaturization of the follicles and subsequent hair thinning and loss. Thinning occurs in the frontotemporal regions and vertex in men and on the central crown in women. Treatment includes topical minoxidil and oral antiandrogens, such as finasteride.

Alopecia areata is an autoimmune disease specific to hair and presents with discrete round patches of hair loss without scarring. It can progress to alopecia totalis (loss of scalp hair) and alopecia universalis (loss of scalp and body hair). Nails in patients with alopecia areata may have pitting in a regular or geometric pattern.

Treatment for limited disease includes topical and intralesional steroids. For more extensive disease, treatment with systemic steroids has been successful but temporary, and while topical irritant therapy (e.g., with squaric acid) may be helpful, results are not consistent. Immunosuppressives may also be helpful, but, again, results are not consistent. There is no FDA-approved Janus kinase treatment for alopecia, although research is promising.

Trichotillomania is a self-inflicted hair disorder and often associated with psychological stress or a personality disorder. Clinical features include irregular patches of hair loss with hair of varying lengths. Patients may also pluck hairs from other areas, such as the eyebrows, eyelashes, and body.

Traction alopecia is most commonly seen in African American female patients in their 30s to 40s. It typically involves the frontotemporal regions. It results from consistent traction of the hair over years. In early stages, it may be reversible, but over time, it becomes permanent as the hair follicles become scarred.

Telogen effluvium occurs when large numbers of hairs simultaneously enter the telogen phase and shed. This can be triggered by a pathological or physiological change in the patient's health status, such as pregnancy, extreme dieting, thyroid disorder, surgery, medications, and severe stress. Hair loss occurs 4–6 months after the precipitating event and is diffuse. Eventual complete hair regrowth is possible, particularly if the underlying cause is eliminated.

EXCESSIVE HAIR

Hirsutism is defined as excessive body hair in areas where it is usually absent or scarce. It may be caused by increased androgens or an increased sensitivity to androgens. It may be associated with seborrhea, acne, or androgenic alopecia. It is useful to determine the source of the affecting androgens, such as an ovarian source or adrenal source. The patient's pattern of hair growth can be useful. If it is centrally located, then it is likely adrenal in origin. If the hair is mostly located on the areolae and lateral neck and face, then it is likely ovarian in origin. Polycystic ovarian syndrome is the most common cause of hirsutism in women. Other etiologies include Cushing syndrome, anabolic steroids, and androgen-secreting tumors. For more information on hirsutism, see the [Endocrinology](#) section.

SKIN CANCER AND PRECANCEROUS LESIONS

PREVIEW | REVIEW

- What is the metastatic potential for basal cell carcinoma?
- Squamous cell carcinoma has the highest rates of metastasis on what body areas?
- What measurement is most important when determining melanoma prognosis?
- What are the main forms of cutaneous T-cell lymphoma? Which has the worse prognosis?

DYSPLASTIC NEVI

Dysplastic nevi are “odd-looking” moles and may even look like melanomas (Figure 3-47). However, **most** melanomas **arise de novo**—**not** in a preexisting nevus. Therefore, removing all moles does **not** prevent melanoma development. Closely monitor patients with these lesions, using photographic documentation. If a patient with a dysplastic nevus has 2 relatives with malignant melanoma, the patient has a 300× chance of getting malignant melanoma!



Figure 3-47: Dysplastic nevus

PREMALIGNANT SKIN CONDITIONS

Actinic keratoses are **precancerous** lesions that can develop into squamous cell carcinoma (SCC). Like SCC, these lesions are found on sun-exposed areas, more often in those with fair skin. These types of lesions can be treated with cryotherapy, photodynamic therapy, topical 5-fluorouracil, and topical imiquimod.

MALIGNANT CONDITIONS

Basal cell carcinoma (BCC) arises from epidermal basal cells and is the most common form of skin cancer, especially in **Caucasians** (Figure 3-48). The usual type of BCC is characterized by translucent pearly papules, often with arborizing vessels. It often has raised borders. It spreads by **local extension** and, when large enough, gets a “rodent-eaten” appearance.



Figure 3-48: Basal cell carcinoma

Source: Charles Crutchfield, III, MD

BCC is caused by UV radiation from sun exposure. It is typically found on **sun-exposed areas**, such as the head and neck, but it may appear elsewhere. Diagnose on clinical presentation with skin biopsy to confirm pathology.

Know that the **metastatic** potential of BCC is **< 0.1%**. BCCs are usually surgically removed. Treatment is most often excision, Mohs surgery, cryo- or radiation therapy, and/or topical immunomodulation (e.g., 5-fluorouracil, imiquimod). Intralesional 5-fluorouracil and interferon, photodynamic therapy, and laser therapy have also been used.

Squamous cell carcinoma (SCC): SCC develops from keratinizing epidermal cells, occurring especially in **fair-skinned** persons and on sun-exposed areas, such as the forearms, ears, lower lip, and dorsal surfaces of hands (Figure 3-49). In contrast to the low metastatic potential of BCC, SCC has a 0.3–5.0% metastatic potential—and even higher when it appears on the head and neck: **ear** (11%) and **lower lip** (13%)! The metastatic rate of **recurring tumors** is 30%, and the rate in SCC originating from **scars** approaches 40%.



Figure 3-49: Squamous cell carcinoma

Other risk factors associated with a higher metastatic rate include size > 2 cm, depth > 4 mm, poorly differentiated lesions, and immunocompromised hosts (e.g., transplant patient). Histopathology obtained from a shave biopsy confirms the diagnosis.

SCCs are generally removed with wide local excision or Mohs surgery, depending on location and size.

SCC in situ (a.k.a. Bowen disease) is a noninvasive form of SCC that presents as small, red, scaly patches that grow slowly. These tumors are associated with sun exposure, especially on the face, scalp, hands, and lower legs, or with HPV infection in the genital area. They are also caused by arsenic exposure. These lesions tend to grow slowly, with gradual asymptomatic enlargement over many years. SCC in situ can be treated with topical 5-fluorouracil, topical imiquimod, and surgical excision. In addition, the FDA has approved photodynamic therapy.

Melanoma: This also tends to occur more commonly in fair-skinned, light-haired, and freckled people with sunlight exposure, especially those who had severe sunburns in childhood (Figure 3-50). There has been a 300% increase in incidence of melanoma in the past 40 years. Other risk factors are numerous dysplastic nevi, a family history of melanoma, a high number of ordinary nevi, a congenital nevus, previous personal history, and immunosuppression.



Figure 3-50: Malignant melanoma

Melanoma is more common in women < 50 years of age and in men > 50. It commonly presents on the lower legs of women and the backs of men.

There are 4 types of melanoma: superficial spreading, lentigo maligna, acral lentiginous (palms, soles, nails, and mucosa), and nodular. Nodular is the only 1 of the 4 types that does not exhibit radial growth; instead, it grows deeply vertical, with an increased incidence of early metastasis.

Think **ABCDE** when assessing a lesion that might be malignant melanoma:

- Asymmetry
- Borders are irregular.
- Color variation
- Diameter > 6 mm is suspicious.
- Evolving lesions are more suspicious.

General prognostic factors include **age** and sex of the patient (better prognosis for patients who are < 50 years of age and female), **location** of the lesion (improved outcomes: extremities > trunk > head and neck), and, most importantly, the **depth** of the lesion (deeper lesions have a poorer outcome). Specific prognosis factors are depth of the lesion, mitotic index, ulceration, number of regional lymph nodes, and systemic metastases. Early diagnosis of this lesion **does** affect prognosis. Excisional biopsy should be done promptly, because early diagnosis and excision reduce mortality.

Refer for an **excisional biopsy** of any suspicious lesion with a 1- to 3-mm rim of normal skin and contiguous subdermal fat on the bottom; a saucerization of the lesion can also be done, with a 1- to 3-mm rim of normal skin. Punch biopsy is not recommended.

A partial biopsy may result in an inaccurate diagnosis as size, symmetry, and circumscription are important histologic criteria when evaluating melanocytic lesions.

Staging is based on the American Joint Committee on Cancer's *AJCC Cancer Staging Manual, Eighth Edition* and refers to the TNM (tumor size, lymph node involvement, and metastases), which corresponds to different stages. Previously, the Breslow thickness (i.e., the depth of the lesion found on biopsy) alone was used.

If melanoma is found and the lesion depth is < 1 mm, the lesion is excised with a 1-cm, tumor-free margin. If the lesion is 1–2 mm, then excision is with a 1- to 2-cm margin. If the lesion is > 2 mm, then excision is with a 2-cm margin. If the lesion is < 0.8 mm but with ulceration, in a young person, has lymphovascular invasion, or has a high mitotic rate, sentinel lymph node biopsy (SLNB) should be discussed. In addition, if the lesion is between 0.8 and 1 mm, discuss the option of a sentinel lymph node procedure with the patient and the surgeon, according to 2017 National Comprehensive Cancer Network guidelines.

Always recommend an **SLNB** for patients with lesions > 1 mm in depth.

Survival rates for melanoma Stages 0, I, and II are 99%; that for Stage III is 65%; and that for Stage IV is 25%.

Treatments depend on stage at diagnosis:

- Stage 0: excision
- Stages I and II: excision +/- SLNB
- Stage 3 resectable: excision, SLNB, adjuvant therapy, and immunotherapy
- Stage 3 unresectable, Stage 4, and recurrent: intralesional immunotherapy and signal transduction inhibitors, chemotherapy and palliative care
- Adjuvant therapy is based on whether **BRAF** positive (combination therapy) or **BRAF** negative (programmed cell death-1 inhibitor).

Know: Dark-skinned individuals also get melanoma. The lesions tend to be in acral areas (palms, soles, and nail beds). **Hutchinson** nail sign is an important clinical clue to subungual melanoma, which is typified by extension of brown or black pigment from the nail bed, matrix, and nail plate to the adjoining cuticle and proximal or lateral nail folds.

Mycosis fungoides and **Sézary syndrome** are the main forms of cutaneous T-cell lymphoma. Mycosis fungoides (Figure 3-51) can be mistaken for psoriasis or eczema. Sézary syndrome has peripheral blood involvement in addition to the skin manifestations and is associated with a poorer prognosis. Patients with Sézary syndrome are often erythrodermic (erythema affecting ≤ 90% BSA).



Figure 3-51: Mycosis fungoides
Source: Jason Reichenberg, MD

Paget disease of the nipple is a **rare** form of breast cancer and is something to consider anytime there is a **persistent** unilateral oozing from the nipple and/or from eczematous plaques on the **areola**. It is usually due to underlying intraductal breast cancer and is due to retrograde extension of the tumor. By far, the **most common** causes of an acute eczema-type rash on an areola are **contact dermatitis** or **skin irritation**; consider Paget disease if there is **no** response to treatment.

Nevoid basal cell carcinoma syndrome (NBCCS; a.k.a. Gorlin syndrome) is an **autosomal dominant** disorder caused by mutations in the *PTCH1* tumor suppressor gene. Bifid ribs, calcification of the falx cerebri, and hyper-telorism are found in addition to numerous BCCs, palmar and plantar pits, and bone cysts, especially of the mandible (Figure 3-52). There is a small chance for children with

NBCCS to develop medulloblastoma. Management consists of regular surveillance by a dermatologist, treatment of BCCs, and surgical excision of bone cysts. Prognosis is generally good.

Peutz-Jeghers syndrome is an autosomal dominant syndrome consisting of multiple hamartomatous polyps in the GI tract and melanotic pigmentation (lentigines) on the lips and buccal mucosa. These patients are at **higher risk** for **GI malignancy**. Note that healthy, darkly pigmented individuals and those with Addison disease may have similar intraoral dark spots.

Metastases to the skin: The 5 cancers with the most **cutaneous metastases** are lung cancer, GI cancer, melanoma, renal cancer, and breast cancer.

BLISTERING LESIONS

PREVIEW | REVIEW

- Characterize the skin findings associated with porphyria cutanea tarda (PCT).
- What type of hepatitis is associated with PCT?
- Dermatitis herpetiformis is associated with what gastrointestinal disorder?

Porphyria cutanea tarda (PCT; Figure 3-53 on page 3-30 and Figure 3-54 on page 3-30) is the most common type of porphyria. PCT causes **hyperpigmentation, tense blisters, scaly macules, vesicles, or hemorrhagic bullae** in **sun-exposed** areas; milia; skin fragility; and increased **facial hair**. PCT is caused by a congenital or acquired **decreased** activity of uroporphyrinogen decarboxylase (UROD), which allows a buildup of phototoxic porphyrins in the skin. Symptoms can be induced by **estrogens, alcohol, hepatitis C virus infection, HIV infection, and smoking**. Check for hepatitis C virus, HIV, and hereditary hemochromatosis. Whenever a patient with HCV presents with a photosensitive rash isolated to the hands, think of PCT. Lab results usually show increased serum iron, ALT, and AST. To screen, check for increased urinary **coproporphyrins** and **uroporphyrins**. Patients may have **dark or pink urine**.



Figure 3-52: Signs of nevoid basal cell carcinoma syndrome: (A) bifid ribs; (B) intracranial calcification (falx cerebri); (C) nevoid basal cell carcinoma; (D) palmar pits (plantar pits may occur); (E) keratocystic odontogenic tumor (mandible)



Figure 3-53: Porphyria cutanea tarda
Source: Kimberly Salkey, MD



Figure 3-54: Porphyria cutanea tarda with blisters

Treatment is the same as for hemochromatosis: regular phlebotomy. Iron can inhibit the activity of UROD. By decreasing iron stores with phlebotomy, the activity of UROD increases, resulting in porphyrins being metabolized quickly, thus preventing them from building up in the skin. Antimalarials (e.g., hydroxychloroquine, chloroquine) are also effective, helping to mobilize porphyrins. They are typically used when phlebotomy is contraindicated. PCT due to hepatitis C virus infection resolves with treatment of hepatitis. Protecting skin from the sun and discontinuing aggravating agents, including alcohol and estrogen, are also indicated.

Porphyria variegata (variegate porphyria) is also known as South African porphyria. It is called variegate because patients can present in a variety of ways. They can have acute episodes (e.g., acute intermittent porphyria [AIP]), chronic skin manifestations (e.g., PCT), or both. Patients may get blisters on sun-exposed areas and have mechanical fragility of the skin. These patients may also have abdominal pain, polyneuropathies, and mental disturbances. The symptoms are due to a deficiency of protoporphyrinogen oxidase, which leads to the build-up of excess porphyrins.

Treatment of acute attacks is the same as for AIP: glucose and heme. Glucose and heme theoretically work by inhibiting aminolevulinic acid (ALA) synthase and preventing the accumulation of toxic precursors. Differential diagnosis: Note that AIP presents similarly to variegata

porphyria, except without the skin changes. PCT presents with the skin changes but without the neurologic/mental changes!

Epidermolysis bullosa: Congenital structural defects of the skin cause blistering after minor skin trauma such that the skin splits at the junction of the epidermis and the dermis. There are many different classifications, all of which are genetically transmitted, and each is due to a specific gene mutation. The major classifications include epidermolysis bullosa simplex (EBA), which affects the keratin genes *KRT5* and *KRT14*; junctional epidermolysis bullosa (JEB), which affects the laminin and collagen genes; and dystrophic epidermolysis bullosa (DEB), which affects the collagen 7 gene.

Nikolsky sign: Slight lateral pressure on the skin causes sloughing of the epidermis. It is positive in pemphigus vulgaris, pemphigus foliaceus, TEN, and staphylococcal scalded skin syndrome (SSSS). It is negative in bullous pemphigoid.

Bullous pemphigoid causes recurrent crops of tense, deep, intact blisters with negative Nikolsky sign (do not spread laterally with pressure). It usually starts on the legs and can remain there for years before spreading (Figure 3-55). Elderly individuals are usually affected. The disease process is classified as a Type 2 hypersensitivity reaction and can appear similar to urticaria when it starts. It is intensely pruritic and does not involve the mucosa. It has an autoimmune



Figure 3-55: Bullous pemphigoid
Source: Kimberly Salkey, MD

etiology with formation of antiepithelial basement membrane antibodies. Precipitating events include exposure to UV light, radiation therapy, and certain drugs, including furosemide, ibuprofen, captopril, and penicillamine. Therapy includes topical (mild disease) and systemic corticosteroids and immunosuppressants.

Pemphigus vulgaris (Figure 3-56) is an autoimmune disease with intraepidermal antibodies against the desmosome desmoglein 3. This causes acantholysis (i.e., the separation of epidermal cells from each other due to decreased cohesion), which results in the formation of large, superficial, loose bullae that peel off and leave denuded skin. Nikolsky sign, which is the production of blistering through mechanical pressure at the edge of a blister, is often present. Oral mucosal involvement is common, and any cutaneous area can be affected. Lesions tend to be quite painful. Treatment of pemphigus vulgaris is similar to that of bullous pemphigoid but rituximab was FDA approved in 2018 for pemphigus vulgaris. Rituximab is used as 1st line treatment both to control disease severity and induce remission.

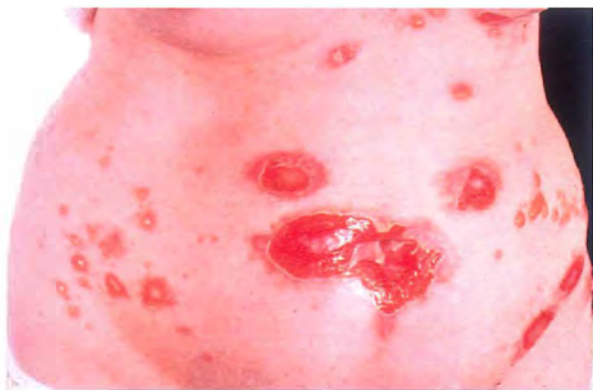


Figure 3-56: Pemphigus vulgaris

Source: Kimberly Salkey, MD

Table 3-1 summarizes key differences between pemphigus vulgaris and bullous pemphigoid.

Table 3-1: Comparison of Pemphigus Vulgaris and Bullous Pemphigoid

	Pemphigus Vulgaris	Bullous Pemphigoid
Age	30–60 years	Elderly
Rash	Flaccid bullae with mostly erosions (+ Nikolsky sign)	Tense blisters
Autoantibodies	Intraepidermal junctions	Basement membrane

Pemphigus foliaceus is caused by antibodies against the desmosome desmoglein 1 and is characterized by superficial erosions that favor the face, upper trunk, and scalp. Due to their superficial nature, vesicles are not often visualized, and clinical presentation is more consistent with crusts and scale that may be confused with impetigo. In contrast to pemphigus vulgaris, mucosal involvement is rare. Treatment is similar to that of pemphigus vulgaris, although systemic treatments are not usually necessary and the condition may be controlled with potent topical steroids only.

SJS is a severe mucocutaneous reaction considered to be on the milder end of the spectrum of TEN. SJS is usually caused by medications including a variety of antibiotics, allopurinol, antiseizure medications (especially phenytoin and carbamazepine), and NSAIDs. Less commonly, SJS is associated with infections. In SJS, sloughing affects < 10% of the BSA. Treatment requires removal of the offending drug and supportive care. Corticosteroids are controversial; use for only a very short time and prior to skin sloughing, if at all. Diagnosis is clinical + biopsy (shave or punch). For treatment, discontinue offending drug and provide supportive care in a burn unit. For more information on SJS, see the [Allergy & Immunology](#) section.

TEN is considered a variant or more severe form of SJS. It is caused by a hypersensitivity reaction to a drug (especially allopurinol, antiseizure medications, NSAIDs, sulfas, and antibiotics). Early symptoms include fever and skin pain and tenderness out of

proportion to physical findings. Like SSSS, it results in a peeling or exfoliation of large areas of skin, but it occurs at a deeper level than SSSS. By definition, sloughing affects > 30% of the BSA. Treatment requires removal of the implicated drug, aggressive skin care, and supportive care in an intensive care burn unit. Prognosis is poor with a mortality rate of up to 40%. See more on TEN in the [Allergy & Immunology](#) section.

Dermatitis herpetiformis (DH) is a skin disease where pruritic vesicular lesions appear on the extensor surfaces and the mid-to-lower back (Figure 3-57). Lesions are caused by IgA deposition in the dermal papillary tips. Given the extreme pruritus, intact vesicles are often not apparent. DH is associated with celiac disease (gluten-sensitive enteropathy). DH and celiac disease can both be treated with a gluten-free diet. Alternatively, oral dapsone can be used to treat DH but is not effective for celiac disease.



Figure 3-57: Dermatitis herpetiformis

Source: Kimberly Salkey, MD

ROUND LESIONS

PREVIEW | REVIEW

- In what age group does nummular eczema occur? How is it treated?
- What skin disorder is characterized by a “Christmas tree” pattern and a herald patch?
- What is the pathognomonic lesion for erythema multiforme? What virus is often the cause?

Granuloma annulare is an idiopathic, annular, ringworm-like lesion without scaling, commonly appearing on the distal portion of the extremities (Figure 3-58). It often occurs in children and young women. It usually is self-limited, disappearing in months to a few years. Other treatment options include topical or intralesional corticosteroids.



Figure 3-58: Granuloma annulare

Source: CDC

Nummular eczema consists of small, circular (nummular = coin-shaped), pruritic lesions that are more typical on the extremities and often are associated with dry skin and atopy. The lesions are very common in the **elderly** and have **no** pathologic significance. Rule out fungal infection. Treat with mid- to high-potency topical steroids.

Pityriasis rosea (PR) is a pruritic rash that is common in children and young adults. Its etiology is unknown, but it may be infectious in origin (possibly human herpesvirus 6 or 7). The disease is **self-limited** and asymptomatic (occasionally mildly pruritic), usually lasting 4–8 weeks. Prodromal symptoms of sore throat or runny nose may be present before the rash appears.

A **herald patch** presents as a single, pink, oval patch, often on the trunk, and precedes subsequent pityriasis rosea lesions by 1–2 weeks (**Figure 3-59**). This patch is sometimes confused with tinea corporis (**Figure 3-31 on page 3-20**), but the 2 are **not** related. Subsequently, small, scaly, pruritic, papulosquamous, oval lesions with the long axis parallel to skin folds and rib lines develop in a “**Christmas tree**” pattern, usually on the trunk



Figure 3-59: Herald patch
Source: CDC

(**Figure 3-60**). The scale is at the periphery of the lesion and appears as a collarette (or trailing scale), unlike psoriasis, which has confluent scale over the entire plaque. Treatment is reassurance. However, topical corticosteroids, phototherapy, and/or sunlight may help. Acyclovir reduces symptoms and reduces length of disease. Pityriasis in pregnancy can cause spontaneous abortion.

Urticaria (hives) are raised pruritic papules and plaques on the skin that result from a Type 1 hypersensitivity reaction. The mast cell is the main effector cell. Mast cells have high affinity to IgE and therefore may trigger IgE-dependent allergic responses. Individual lesions of urticaria, by definition, do not last longer than 24 hours and can have **smooth or irregular borders or may be annular**. They are accompanied by pruritus, which often is severe. Common causes of acute urticarial (episodes occurring ≤ 6 weeks) include upper respiratory infections, drugs, and foods. 50% of patients have idiopathic acute urticaria. Chronic urticaria (episodes occurring more often than twice a week for > 6 weeks) may be associated with autoimmune disease or infection or can be idiopathic. Dermatographism is a type of urticaria due to mechanical stimuli and is characterized by whealing of the skin in response to moderate stroking. Simple dermatographism occurs in $\sim 5\%$ of the general population and is considered an exaggerated physiological response. Symptomatic dermatographism is characterized by pruritus and whealing at sites of friction and scratching. Treatment of urticaria



Figure 3-60: Pityriasis rosea with “Christmas tree” distribution

includes avoiding triggers and aggravating factors, such as NSAIDs, aspirin, codeine, and morphine. Cooling and antiitch creams, such as those containing pramoxine, may be helpful. Antihistamines are 1st line therapy, followed by 2nd line therapies, such as systemic corticosteroids. Chronic urticaria may require immunotherapy.

Dermatofibromas are dome-shaped papules resulting from benign dermal proliferation. They are quite common and are most often idiopathic, but they can also be caused by trauma or bites. A “dimple sign” with central depression is often displayed secondary to lateral pressure and is specific to diagnosis. Treatment is observation only, although biopsy can be indicated if the diagnosis is in question. Multiple dermatofibromas may suggest underlying systemic disease such as immune disorders, autoimmune disease, or HIV infection, and previous and current medications should be reviewed.

Erythema multiforme consists of well-defined asymptomatic lesions varying from annular to targetoid (**Figure 3-61**). Palms and soles are frequently involved, and mucous membranes may be affected. These immune-mediated “target” lesions (those with 3 defined zones) are pathognomonic for erythema multiforme. Erythema multiforme is associated with HSV, *Mycoplasma*, and, much less frequently, drugs (e.g., NSAIDs, PCNs). Treatment involves antimicrobial therapy (if a causative organism, such as *Mycoplasma*, is found) or removal of an offending medication. Patients with a history of cold sores and recurrent erythema multiforme may benefit from suppressive antiviral therapy (i.e., valacyclovir, acyclovir, or famciclovir taken daily for ~ 6 months).



Figure 3-61: Erythema multiforme

Source: Kimberly Salkey, MD

PIGMENT CHANGES

PREVIEW | REVIEW

- Hyperpigmented areas of the axilla are associated with what underlying disease states?
- What diseases are on the short list of causes of black lesions?
- What skin discoloration occurs rarely with a polyglandular autoimmune deficiency syndrome?

HYPERPIGMENTATION

Diffuse hyperpigmentation may occur in primary biliary cholangitis (previously known as primary biliary cirrhosis), scleroderma, Addison disease, and hemochromatosis (patients have a grayish/bronze coloration) and with use of the cancer drug busulfan. Other causes include PCT, malabsorption and/or Whipple disease, pellagra (niacin deficiency), B₁₂ deficiency, and folate deficiency. Check for metastatic melanoma in “slate-blue” patients!

Hyperpigmentation in sun-exposed areas can be caused by amiodarone, PCT, and phenothiazines. Hyperpigmentation is diffuse but darker in sun-exposed areas in pellagra, biliary cholangitis, and scleroderma. MTX can cause reactivation of sunburn.

Melasma is an acquired hyperpigmentation often seen in pregnancy or with oral contraceptive use. Diagnose based on history and clinical appearance. Hyperpigmentation occurs in sun-exposed areas of the face and is treated with varying degrees of success using skin protection from the sun and skin-lightening modalities.

Pigmented growths, such as acquired melanocytic nevi, seborrheic keratoses, and solar lentigines, are usually benign and common in the general population:

- **Nevi**—Commonly encountered nevi include:
 - **Common acquired** nevi are round to ovoid lesions typically measuring 2–6 mm. They are generally orderly and symmetrical.

- **Junctional** nevi are macular and often darker in color, compared to compound nevi, which vary in elevation and are slightly lighter in color.
- **Dermal** nevi are even more raised, often dome shaped, and lighter or more evenly pigmented. Over time, the number of nevi seen in a given patient increases and peaks by the 3rd decade of life. Indications for removing a nevus include a lesion that is changing, cosmetic concerns, irritation, and an atypical clinical appearance.

- **Seborrheic keratoses** are light brown, yellow, or dark brown macules, papules, or plaques that are waxy and “stuck-on” in appearance. They are commonly found on the face, head, neck, and back but can be located on any hair-bearing area of the body. They exhibit a familial predisposition, but sun exposure has also been implicated in their development and they are common with increasing age. Conditions associated with abrupt onset of multiple lesions followed by regression include pregnancy, erythroderma, and HIV infection. Rarely, this abrupt onset of seborrheic keratoses is associated with internal malignancy and is called the Leser-Trélat sign. Such onset should lead to investigation for a neoplasm.

- **Solar lentigines** are most commonly found in sun-exposed areas of older individuals but may also be found in younger patients after sun exposure. They are well-circumscribed, round or irregularly shaped brown macules that range from light to dark brown or black. These should be distinguished from pigmented actinic keratoses, which tend to have a rough surface, and lentigo maligna, which tends to be larger and have more pigment variation and irregularity of borders than a solar lentigo.

Peutz-Jeghers syndrome (multiple intestinal hamartomatous polyps) should be ruled out in patients with melanotic pigmentation (**lentigines**) on the lips and buccal mucosa.

Café au lait spots

(Figure 3-62) are brown macules that occur in association with neurofibromatosis Type 1 (a.k.a. von Recklinghausen disease) and McCune-Albright disease. Café au lait spots occur in people with no disease (1 or 2 spots are normal and typical). In neurofibromatosis, 78% of patients have > 6 spots—and 95% have at least 1 spot > 1.5 cm. In McCune-Albright disease, the spots have a more irregular outline and can be rather large.



Figure 3-62: Café au lait spots
Source: Jennifer Vickers, MD

Acanthosis nigricans is hyperpigmented skin with a thickened, velvety appearance, noticed mostly in the skin folds. Involvement of the axilla is commonly shown as an example (Figure 3-63). It is rarely familial. Acanthosis nigricans is associated with:

- Obesity
- Gastrointestinal malignancies
- Endocrinopathies such as diabetes mellitus, Cushing disease, hyper-/hypothyroidism, acromegaly
- Autoimmune problems

Malignant acanthosis nigricans is severe and progressive and is usually associated with gastric adenocarcinoma. It is more commonly seen on the lips, oral mucosa, and palms.

Black lesions—The etiology for black lesions is somewhat extensive, but especially consider the following:

- Rhinocerebral mucormycosis
- Anthrax
- Ecthyma gangrenosum
- Emboli to distal extremities
- Melanoma/Lentigo/Pigmented BCC
- Warfarin skin necrosis
- Necrotic spider bite
- Kaposi sarcoma

WHITE AND HYPOPIGMENTED LESIONS

Pityriasis alba is frequently seen in children and teens with atopic dermatitis. Ill-defined white macules and patches with overlying fine scale are located on the face and, occasionally, the arms. Postinflammatory hypopigmented skin changes can appear similarly after resolution of atopic dermatitis. Pityriasis alba generally improves with age, and its appearance can be minimized with use of sunscreen and sun protection.

Tinea (pityriasis) versicolor is characterized by well-defined, hypopigmented spreading macules, usually on the upper torso and upper arms. The associated fine scale may not be observed unless the skin is stretched. It can be confirmed with use of KOH prep (Figure 3-34 on page 3-21). The associated hypomelanosis may persist for several months after eradication of the organism, but the lesions do not have scale.

Vitiligo is an autoimmune disease that causes destruction of melanocytes, resulting in depigmentation (Figure 3-64). It usually occurs in otherwise healthy persons but can



Figure 3-63: Acanthosis nigricans

Source: Kimberly Salkey, MD

rarely occur as part of a polyglandular autoimmune (PGA) syndrome. Any of the following may be seen with a PGA: diabetes mellitus, autoimmune thyroid disease (hyper- or hypo-), Addison disease/adrenal insufficiency, hypoparathyroidism, and pernicious anemia. Any time you see a patient with vitiligo, think of these possibilities and screen appropriately!



Figure 3-64: Vitiligo

Tuberous sclerosis is uncommon and autosomal dominant. It is associated with seizures, intellectual disabilities, periungual fibromas, and hypopigmented (ash-leaf) macules (Figure 3-65). You see these macules best with a Wood lamp. **Adenoma sebaceum** manifests in these patients as numerous midfacial papules, which are actually angiofibromas (Figure 3-66).



Figure 3-65: Hypopigmented (ash-leaf) macules



Figure 3-66: Angiofibromas

PRURITUS

Pruritus is severe itching as an effect of various conditions. It may be localized or generalized. The most common

cause of pruritus in elderly patients is **dry skin**. Other causes seen across the age spectrum include:

- Hyper- or hypothyroidism
- Malignancy (Think lymphoma—especially Hodgkin's, but also breast cancer.)
- Iron deficiency (even if patient is not anemic)
- Polycythemia vera
- Aquagenic pruritus
- Chronic kidney disease (but not acute kidney injury)
- Cholestatic liver disease
- Diabetes mellitus
- HIV/AIDS

Treat pruritus first by attempting to reverse the cause. With severe systemic disorders, this often is not possible.

Treatment of the itching itself starts with general measures:

- Skin moisturization
- Covering the itchy areas to decrease trauma from scratching
- Making the environment cool and humid
- Education and psychological support to decrease stress and give the patient more control of the situation

Try topical agents if more relief is needed:

- Corticosteroid creams
- Capsaicin cream (yes, the stuff in chili peppers!). Initial burning, which occurs in the first 2–3 weeks of use, is followed by decreased pruritus. Treatment is especially effective in neuropathic disorders and with chronic kidney disease.
- Anesthetic creams
- Antihistamine creams
- Phosphodiesterase 4 inhibitors

Phototherapy is often effective for localized and systemic pruritus.

Systemic therapy is reserved for generalized pruritus not controlled by topical solutions:

- Oral antihistamines are usually the first therapy tried, but they decrease the pruritus only when it is due to histamine release, such as with urticaria or mastocytosis. Antihistamines also cause drowsiness, which can help by decreasing the perceived intensity of itching.
- Opioid receptor antagonists (naltrexone, naloxone, and nalmefene) may help in certain cases.
- Gabapentin and pregabalin are GABA (γ-aminobutyric acid) analog antiseizure medications. They appear to help with neuropathic pruritus caused by nerve entrapment.
- Thalidomide is effective, but it has a lot of side effects and is very teratogenic.
- Aprepitant is a newer, expensive drug that is being used in refractory cases.

HIV- AND AIDS-RELATED SKIN LESIONS

PREVIEW | REVIEW

- What gram-negative infection in AIDS can resemble Kaposi sarcoma?
- What cutaneous neuroendocrine tumor is more common in HIV?

Many common and uncommon skin conditions become more prevalent in HIV/AIDS:

- Infection
 - Bacterial
 - Bacillary angiomatosis (*Bartonella henselae*, the same organism that causes cat scratch disease) lesions appear as vascular purple lesions that bleed easily and can be confused with Kaposi sarcoma. Treatment is with antibiotics for several months.
 - Folliculitis usually occurs in uncontrolled HIV infection and may be caused by *S. aureus*; it improves with antiviral therapy and antibiotics. Of note, people who are HIV positive may also have eosinophilic folliculitis, which is **not** associated with an infectious organism.
 - Viral
 - Herpes simplex
 - Herpes zoster (shingles) is often refractory to treatment in patients with HIV/AIDS. Treat with acyclovir or famciclovir. Valacyclovir is not recommended due to its association with thrombotic thrombocytopenic purpura (TTP) in the immunocompromised. For more on herpes zoster, see [Varicella-Zoster Virus \(VZV\) on page 3-22](#).
 - Condyloma acuminatum (HPV)
 - Molluscum contagiosum (poxvirus)
 - Oral hairy leukoplakia (Epstein-Barr virus; [Figure 3-12 on page 3-7](#)) is corrugated (“hairy”) white lesions along the lateral surface of the tongue that cannot be scraped off. It improves with antiviral therapy.
 - Kaposi sarcoma in HIV is frequently associated with HHV-8.
 - Merkel cell skin cancer (associated with Merkel cell polyoma virus)
 - Fungal/Yeast
 - Oral candidiasis can be scraped off the tongue and mucosal surfaces.
 - Folliculitis usually occurs in uncontrolled HIV infection and may be caused by *Pityrosporum orbiculare*; it improves with antiviral therapy and antibiotics.

- Disseminated *Cryptococcus* infection (Figure 3-67) is an AIDS-defining condition and may imitate molluscum contagiosum. *Cryptococcus neoformans* is a life-threatening fungal infection seen in immunocompromised patients. Cutaneous lesions may present as umbilicated papules similar to molluscum in patients with HIV infection. Other lesions may be papules, pustules, nodules, ulcers, or draining sinuses. Yeast can be seen with India ink stain of the capsule or with tissue slides with mucicarmine stain. Treatment is systemic antifungals.



Figure 3-67: Disseminated *Cryptococcus* infection
Source: CDC

- Neoplastic
 - Kaposi sarcoma, a vascular soft tissue malignancy, usually presents as < 0.5-cm, purple/red/violet/black, maculopapular lesions, which are generally concentrated on the head, neck, and lower extremities (Figure 3-68) but can also occur in the GI tract and the lung. It is common in patients with advanced HIV and improves with antiviral therapy. The CDC considers it an AIDS-defining condition.
 - Basal cell carcinoma risk is 2–3× greater than in the HIV-negative population and occurs in regions of the body not exposed to sunlight.
 - Merkel cell carcinoma, a neuroendocrine tumor, has a 10-fold increased incidence in HIV patients. It is associated with Merkel cell polyoma virus and is a fast-growing, painless, vascular-appearing, intracutaneous, firm nodule on sun-exposed areas. Treatment involves wide surgical excision.
- Other
 - Xerosis (dry skin)
 - Atopic dermatitis
 - Eosinophilic folliculitis
 - Seborrheic dermatitis (occurs in virtually all patients!) improves with antiviral therapy. For more information on this topic, see [Seborrheic Dermatitis on page 3-2](#).
 - Telangiectasias



Figure 3-68: Kaposi sarcoma

SKIN SIGNS OF SYSTEMIC DISEASES

PREVIEW | REVIEW

- What is the significance of eruptive xanthomas?
- What is the significance of dark atrophic macules in a diabetic?

DIABETES MELLITUS

Necrobiosis lipoidica diabetorum (Figure 3-69) can be associated with diabetes in approximately 10–20% of cases. This thin, atrophic, hyperpigmented plaque, appearing on the **shins**, is subject to trauma and ulceration and is thought to be due to microangiopathy.



Figure 3-69: Necrobiosis lipoidica diabetorum
Source: Kimberly Salkey, MD

Eruptive xanthomas are caused by severe hypertriglyceridemia. They are often seen in diabetic ketoacidosis, appearing abruptly as yellowish-red papules over the extensor surfaces and buttocks (Figure 3-70). These lesions resolve when the hyperglycemia is controlled.



Figure 3-70: Eruptive xanthomas in a patient with diabetes

Diabetic dermopathy (“shin spots”) are dark atrophic macules; they are common and often appear on the shins. They have no clinical significance.

Acanthosis nigricans is characterized by velvety hyperpigmented patches commonly seen in intertriginous areas such as the neck, axillae, and groin. It is associated with diabetes and insulin resistance. If seen on the lips, oral mucosa, and palms, it may be malignancy related. For more on acanthosis nigricans, see [Hyperpigmentation on page 3-33](#).

KIDNEY DISEASE

Calciophylaxis occurs in patients with end-stage renal disease, particularly diabetic, Caucasian, obese women on long-term hemodialysis. Ischemic necrosis results from the calcification of dermal arterioles. Early lesions can manifest as painful erythematous nodules or livedo reticularis. Older lesions appear as indurated subcutaneous nodules with overlying retiform purpura and necrosis. They are exquisitely painful and carry a poor prognosis, especially when located proximally, such as on the trunk, thighs, and buttocks. Treatment includes sodium thiosulfate, control of pain, and wound care, including debridement.

ENDOCRINE DISORDERS

Cushing syndrome: Patients with Cushing syndrome may exhibit a rounded face (moon facies), a buffalo hump, and global atrophy that may manifest as purpura, striae, cutaneous fragility, and poor wound healing.

Hereditary hemochromatosis: Patients with hereditary hemochromatosis can have diffuse bronzing of the skin (sparing the mucous membranes) that is secondary to increased melanin.

Addison disease: Patients with Addison disease can experience diffuse hyperpigmentation, particularly in sun-exposed areas, hair and nails, palmar creases, mucous membranes, and the axillae, perineum, and nipples. They may also note loss of pubic and axillary hair (in postpubertal women) and fibrosis of the cartilage of the ear.

RHEUMATOLOGIC DISORDERS

Gout: Patients with tophaceous gout may have deposits of monosodium urate that manifest as skin-colored to yellow-hued dermal or subcutaneous nodules or papules. They may be smooth or lobulated. The most common location for these lesions is the helix of the ear or overlying joints. They may be ulcerated or drain a chalky material.

Lupus erythematosus can have varied cutaneous findings. Acute cutaneous lupus erythematosus (ACLE) is characterized by pink, scaly, and/or edematous lesions in sun-exposed areas. A malar rash on the cheeks and nasal bridge that spares the nasolabial folds exemplifies these lesions ([Figure 3-17 on page 3-12](#)). They heal

without scarring. Erythematous scaling plaques occur on the dorsal hands and spare the knuckles.

Subacute cutaneous lupus erythematosus (SCLE) is characterized by annular lesions with raised red borders and central clearing in sun-exposed areas. These lesions also do not typically scar and can be seen in association with Sjögren syndrome. They are often caused by sunlight exposure and drugs, such as antihypertensive medications. The face is spared.

Lesions of discoid lupus erythematosus (DLE) are commonly found on the head and neck. They are initially erythematous and indurated plaques. Chronic lesions may exhibit hypopigmentation centrally with peripheral hyperpigmentation and often leave disfiguring scarring.

Rheumatoid arthritis (RA): Patients with RA may have numerous cutaneous manifestations of their disease. More common findings include rheumatoid nodules, vasculitic lesions, pyoderma gangrenosum, and Sweet syndrome.

Sweet syndrome (acute febrile neutrophilic dermatosis) can resemble RA and presents with leukocytosis, fever, and tender, erythematous papules and plaques, with painful joints and nodules on the skin (see [Sweet Syndrome on page 3-15](#)).

Rheumatoid nodules are found in 20% of patients with RA and are firm, somewhat mobile papules and nodules that occur over extensor surfaces and areas of pressure or trauma. They can be asymptomatic or tender.

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Infectious Disease

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DISEASE-BASED REVIEW

URINARY TRACT INFECTIONS (UTIs)

PREVIEW | REVIEW

- In which 3 settings would you treat asymptomatic bacteriuria?
- What are the standard treatments for uncomplicated cystitis, complicated cystitis, uncomplicated pyelonephritis, and complicated pyelonephritis?
- What 2 types of prostatitis require antibiotic therapy, and which drugs should be given?

CYSTITIS AND PYELONEPHRITIS

Microbiology

A wide variety of organisms cause UTIs, but *Escherichia coli* and other gram-negative aerobic enterics are the most common causes. Among gram-positive organisms, *Enterococcus* is the most common genus. In the absence of a urinary catheter, *Staphylococcus aureus* is an uncommon cause of a UTI, and its presence in the urine should raise the concern that it seeded the kidney via a bacteremia from another source. Coagulase-negative staphylococci are rarely true pathogens and suggest contamination of the urine from skin flora. The one exception is *Staphylococcus saprophyticus*, which is a definite cause of cystitis but rarely a cause of pyelonephritis.

Epidemiology

Risk factors for UTIs in women include sexual activity, diaphragm use, vaginal atrophy, and diabetes mellitus. UTIs are less common in men, and sexual activity is not a risk factor **except** in men who have sex with men. In heterosexual men, UTIs are usually the result of a structural abnormality in the urinary tract, such as vesicoureteral reflux or obstruction from prostatic hyperplasia. UTIs are the most common nosocomial infections. In either sex, UTIs are increased in the presence of diabetes mellitus, sickle cell disease, or renal stones. *Proteus* infections are specifically associated with urinary stones, so if *Proteus* is identified in the urine, order imaging tests to look for stones. Group B *Streptococcus agalactiae* infections are more commonly seen in pregnancy (see the [Women's and Men's Health](#) section).

Presentation

The classic symptoms of UTIs include dysuria, frequency, and urgency. Flank pain and fever are seen in ~ 50% of patients with pyelonephritis but are not common with uncomplicated cystitis.

Diagnosis

Confirm the diagnosis by culture growth of $\geq 10^5$ gram-negative organisms/mL of urine. Yeast or gram-positive organisms can cause infection with lower colony counts. A positive urine culture in the absence of symptoms is **not** considered a UTI; it is called asymptomatic bacteriuria. In a nonneutropenic patient, the absence of pyuria has good negative predictive value and essentially rules out a UTI. The presence of pyuria alone, however, is not sufficient to diagnose a UTI.

Treatment

The 1st step in determining treatment for a positive urine culture is to determine if the patient has signs or symptoms of infection. If signs or symptoms are present, it is a UTI; if not, it is asymptomatic bacteriuria. **Treat asymptomatic bacteriuria under only 3 circumstances:**

- 1) Treat pregnant women to prevent progression to pyelonephritis and to decrease maternal and fetal morbidity and mortality. Safe regimens in pregnancy include a 3-day course of trimethoprim/sulfamethoxazole (TMP/SMX; during weeks 12–36 only), nitrofurantoin (not at term), or cephalexin.
- 2) Treat patients about to undergo an invasive urologic procedure.
- 3) Treat renal transplant recipients within the first month after transplantation to decrease the risk of a symptomatic UTI, which increases the risk of rejection.

With **symptomatic** UTIs, the 2nd step is to determine whether the infection is in the lower tract (cystitis) or upper tract (pyelonephritis). Cystitis usually has no systemic signs of infection or flank tenderness, and fever is usually low grade if present. Pyelonephritis typically has high-grade fever (often $> 102.0^\circ\text{F}$ [38.9°C]) and flank pain. Sepsis may be present, and blood cultures are positive in ~ 10% of patients.

The 3rd step is to determine whether the UTI is complicated or not. **Complicated** UTIs occur with structural anomalies, foreign bodies, or prior resistant organisms and in patients who are immunocompromised, have diabetes, or are male.

Uncomplicated cystitis can be treated based on symptoms alone and does not require a urine culture. Do a urine culture for all other UTIs. In cystitis, do not perform imaging of the urinary tract (ultrasound [U/S] or computed tomography [CT]). In **uncomplicated pyelonephritis**, perform imaging of the urinary tract only if symptoms persist after 72 hours of culture-guided therapy.

Antibiotic therapy:

- **Uncomplicated cystitis:** The treatment of choice is either nitrofurantoin monohydrate/macrocrystals or a 3-day course of TMP/SMX depending on local resistance patterns (do **not** use TMP/SMX if there is $\geq 20\%$ resistance in the community), the patient's allergy history, and whether prior antibiotics have been used. A single dose of fosfomycin is a 2nd line treatment due to slightly lower cure rates. Avoid the use of fluoroquinolones for uncomplicated cystitis because of resistance and toxicity issues (discussed in [Fluoroquinolones on page 4-82](#)).
- **Complicated cystitis or uncomplicated pyelonephritis:** Treat with a fluoroquinolone, TMP/SMX, or a β -lactam depending on the culture and sensitivity (C&S) data.
- **Complicated pyelonephritis and/or hospitalized patients:** Treat with a fluoroquinolone, ceftriaxone, a β -lactam + a β -lactamase inhibitor, or ampicillin + aminoglycoside for 7–10 days. Adjust the antibiotic regimen based on the C&S results.

Change a urinary catheter only if the UTI is symptomatic.

Differentiate **recurrent** UTIs into 2 types: **relapses** (the same strain within 2 weeks of the end of prior therapy) or **reinfection** (a different strain than the initial infection). Relapses are commonly due to a persistent nidus of infection (e.g., stones, abscess, urethral/ureteral/bladder diverticula, obstruction) in the urinary tract. So, to evaluate relapses, perform a renal U/S and/or CT of the abdomen and pelvis with contrast. Reinfection is sometimes related to diaphragm use, spermicides, and sexual activity. If this is the case, consider alternative contraception, but if the reinfection is correlated with sexual intercourse, give low-dose prophylaxis (e.g., TMP/SMX 1/2 single-strength tablet, nitrofurantoin 50 mg) before or after sexual activity. If there is no sexual activity and the patient has < 3 episodes a year, treat the UTIs as they occur. If the patient has ≥ 3 episodes a year, consider chronic low-dose suppression for 6 months.

Complications

A perinephric abscess can occur as a complication of pyelonephritis, usually from infection with gram-negative organisms, by the direct spread of the renal infection. The diagnosis can be difficult since the symptoms are nonspecific and insidious. These include fever, chills, abdominal pain, fatigue, and weight loss. Dysuria and increased frequency are uncommon because the infection is often completely **outside** of the urinary tract and organisms are not entering the bladder. The patient typically has unilateral costovertebral flank pain on physical examination. Occasionally, a flank mass is palpated if the abscess is large enough.

Lab work reveals leukocytosis and elevated inflammatory markers (erythrocyte sedimentation rate [ESR] and C-reactive protein [CRP]). Pyuria may be present if the

abscess communicates with the collecting system. Obtain blood and urine cultures. U/S may be the initial imaging, but a CT scan has a higher sensitivity and may show renal enlargement and inflammation with extrarenal fluid and gas collections. Perform CT- or U/S-guided percutaneous drainage for C&S testing and to therapeutically drain the abscess.

The treatment consists of empiric antibiotics directed toward Enterobacteriaceae, such as the regimens recommended for pyelonephritis (refer to [Treatment on page 4-1](#)), until the culture results are known, at which time the therapy is tailored to the culture results. If the abscess occurs in the setting of staphylococcal bacteremia, modify the selection of antibiotics and complete the entire course with intravenous (IV) antibiotics. The inflammatory markers help monitor the clinical status.

PROSTATITIS

Prostatitis has 4 subtypes based on symptoms, the presence or absence of bacteria, and the presence or absence of inflammation.

Type I prostatitis is **acute** bacterial prostatitis. The causative organisms are the same as for cystitis. Acute bacterial prostatitis typically has a very dramatic presentation, with frequency, dysuria, hesitancy, perineal pain, and referred penile tip pain and associated high-grade fevers and chills. Bacteremia is common. All antibiotics penetrate well into prostatic tissue during acute infection. Severely ill patients with **Type I** prostatitis require hospital admission and IV antibiotics (e.g., ceftriaxone). Once stable, treat patients with 6 weeks of antibiotics based on the susceptibility of the organism cultured.

Type II prostatitis is **chronic** bacterial prostatitis. Patients with this type of prostatitis present with recurrent UTIs with the same organism (relapsing UTIs). The symptoms are less dramatic than for Type I disease; Type II presents as cystitis or persistent/recurrent bacteriuria. Penetration of antibiotics into the chronically, more mildly inflamed gland varies among antibiotic classes. Prostatic secretions are acidic, so drugs with alkaline pharmacokinetics (i.e., fluoroquinolones, TMP/SMX) penetrate best. Give a fluoroquinolone as the 1st line treatment for Type II prostatitis and TMP/SMX as an alternative. Antibiotics are given for at least 6 weeks, but recurrences are common. If there is a recurrence, retreat the infection with 6 more weeks of a fluoroquinolone. Consider atypical organisms such as *Ureaplasma* or *Chlamydia* in sexually active men, and treat empirically with a tetracycline if prior antibiotic failure has occurred.

Type III chronic prostatitis/chronic pelvic pain has 2 forms, Type IIIA and Type IIIB, neither of which is an infectious disease. Both forms present like Type II. Type IIIA has evidence of prostatic inflammation (white blood cells [WBCs] in expressed prostatic secretions or

post-prostatic massage urine specimens) but **no bacterial** infection on culture. Type IIIB has neither signs of prostatic inflammation nor bacterial infection. Use α -blockers as the initial treatment, and if symptoms persist, refer to a urologist.

Type IV prostatitis is asymptomatic inflammatory prostatitis. Prostate inflammation is found incidentally when tissue is removed for another reason, such as prostate biopsy or resection. Patients do not require antibiotics.

CATHETER-ASSOCIATED UTIs (CAUTIs)

Indwelling urinary catheters are a common cause of UTIs, especially in hospitalized patients. Studies show that 23% of patients in U.S. hospitals, up to 70% of patients in critical care units, and up to 10% of patients in long-term care facilities have an indwelling urinary catheter. Consider indwelling catheters that are in place for ≤ 30 days as short term and those that are in place for > 30 days as long term. It is important (and often difficult) to distinguish between catheter-associated asymptomatic bacteriuria (CA-ASB) and a CAUTI, because the former does not warrant antibiotic treatment.

Catheter-Associated Asymptomatic Bacteriuria (CA-ASB)

CA-ASB develops quickly in patients with an indwelling urinary catheter. The daily risk of acquiring CA-ASB is 3–10%, and CA-ASB is present in almost all patients after 2 weeks. In addition to catheterization, other risk factors for CA-ASB are older age, female sex, diabetes mellitus, and errors in catheter care. Up to 80% of hospitalized patients with urinary catheters get antibiotics for a variety of infections, and this may lead to acquisition of organisms with antibiotic resistance.

Symptomatic UTIs

Anywhere from 10% to 25% of patients with CA-ASB will develop symptoms and thus have a CAUTI. CAUTIs account for 20% of all health care-associated bacteremias, and patients with CAUTIs have a mortality rate of $\sim 10\%$.

Pathogens

E. coli infection is the most common infection. Other pathogens include *Klebsiella*, *Enterococcus*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, and *Candida*.

P. mirabilis infection becomes more prevalent in patients with long-term indwelling catheters. *P. mirabilis* produces urease, which alkalinizes the urine. This increases the risk of urolithiasis from struvite stones.

Diagnosis

Establish the diagnosis of CA-ASB in a patient with $> 100,000$ CFU/mL of an organism with no symptoms of a CAUTI. Catheters in place for > 2 weeks have an established biofilm, so samples collected from the catheter may reflect organisms in the biofilm but not in the bladder. The suggestion is to replace the catheter and send a sample from the new catheter to be sure the organism is present in the bladder and not just in the biofilm.

The diagnosis of a CAUTI can be made if there is no other explanation for fever, malaise, altered mental status, hematuria, or costovertebral angle tenderness. Suprapubic tenderness may also be present. If a catheter is no longer present, the patient may have dysuria, frequency, or urgency.

Finding the same organism in urine and blood cultures is useful to diagnose a CAUTI.

Pyuria in itself does not establish the diagnosis of a CAUTI because it may reflect inflammation from either the indwelling catheter or other diseases such as interstitial nephritis. By itself, pyuria is not a reason for treatment.

Treatment of CAUTIs

For CAUTIs:

- Consider empiric therapy that accounts for local common isolates and antibiotic resistance patterns.
- Data exists that suggests empiric antibiotics do not lead to a better outcome.
- Consider changing the catheter prior to administering antibiotics.
- Since CAUTIs are considered to be a complicated UTI, treatment is generally longer than for uncomplicated UTIs. There is no consensus as to the duration of treatment, but it is generally 5–21 days.

Prevention of CAUTIs

Avoiding the use of urinary catheters is clearly the most effective way to prevent CAUTIs. Along those lines, when a catheter is in use, providers should remove the catheter as soon as possible. Automatic stop orders (orders for catheter removal) can reduce the occurrence of CAUTIs. Smaller catheters may be safer because they cause less trauma. There is no proven benefit with the use of antimicrobial-coated catheters or the administration of prophylactic antibiotics after catheter insertion. Avoid treatment of CA-ASB.

Some accepted indications for urinary catheters are:

- Tracking urine output in critically ill patients or during surgery
- Urinary obstruction or retention
- Perioperative use for certain surgeries

- Urologic surgery or surgery in the adjacent areas
- When giving large amounts of fluids or diuretics during surgery
- To facilitate skin healing with pressure sores or grafts in a patient who is not continent of urine (consider condom catheters instead for men)
- Patient comfort, such as hospice care

UPPER RESPIRATORY TRACT INFECTIONS

PREVIEW | REVIEW

- Otitis externa is usually due to which organism?
- How many days of symptoms are required to diagnose a patient with bacterial sinusitis and prescribe antibiotics?
- What are the usual causative organisms of bacterial sinusitis?
- What are some symptoms of rhinocerebral mucormycosis, and what is the best treatment?
- How can you differentiate allergic rhinitis from bacterial rhinosinusitis?
- What antibiotics should be given for sinusitis?
- What clinical findings eliminate the need to test for group A β -hemolytic streptococcal pharyngitis?

ACUTE OTITIS MEDIA (AOM)

AOM is very uncommon in adults, and its presence suggests structural anomalies or immunocompromise. It presents with ear pain and hearing loss +/- fever. Diagnose AOM by visualizing both inflammation of the tympanic membrane (erythema or purulent drainage) and fluid in the middle ear. *Streptococcus pneumoniae* is the most common infecting bacterium. Nontypeable *Haemophilus influenzae* and *Moraxella catarrhalis* are also causative agents.

Treat with amoxicillin alone if the patient has not taken antibiotics recently. Treat with amoxicillin/clavulanate, cefuroxime, ceftriaxone, or quinolones if the patient has recently taken other antibiotics or if initial treatment failed. If patients do not respond, perform tympanocentesis to obtain culture data.

OTITIS EXTERNA (SWIMMER'S EAR)

Otitis externa is also predominantly a pediatric infection. Only 5% of cases are in adults > 20 years of age. It is predisposed by trauma, foreign bodies, dermatitis, and moisture, especially from swimming (hence the term "swimmer's ear"). Otitis externa presents with pain and itching in the external auditory canal. The causative organism is usually *Pseudomonas aeruginosa*. Note that

Staphylococcus epidermidis and *Staphylococcus aureus*, even when combined, are still a distant 2nd. Treat otitis externa with a topical fluoroquinolone.

Malignant (necrotizing) otitis externa is potentially fatal. Over 90% of patients are diabetic, and immunosuppression is another risk factor. Malignant otitis externa presents the same as otitis externa but progresses to an invasive and destructive infection of the soft tissue and bone. *P. aeruginosa* is the cause in > 95% of cases. Treat the infection with IV antibiotics directed against *P. aeruginosa* (e.g., a fluoroquinolone, an antipseudomonal β -lactam), and adjust the treatment based on the culture results. Therapy is usually required for 6–8 weeks.

SINUSITIS

Sinusitis is inflammation of the paranasal sinuses.

The classification is based on the duration:

- Acute sinusitis: persists $\leq$ 4 weeks
- Subacute sinusitis: persists 4–12 weeks
- Chronic sinusitis: persists > 12 weeks
- Recurrent sinusitis: > 3 episodes of acute sinusitis per year

Most sinusitis stems from viral infections. Use clinical criteria (see below) to decide whether there is a likelihood of bacterial infection and thus a benefit to giving antibacterials. The pathogenesis of bacterial sinusitis is obstruction of the sinus ostia that allows bacteria that are usually transient colonizers to persist in the sinus cavity.

There are 2 clinical findings predictive of bacterial sinusitis:

- 1) Duration of symptoms $\geq$ 10 days or
- 2) Worsening of symptoms after an initial improvement (double sickness) that occurs after $\geq$ 3 days

Unless these criteria are met, most infectious sinusitis is viral, and should be treated symptomatically with nasal saline. There is no role for decongestants and antihistamines.

Fever > 102.0°F (38.9°C) with purulent drainage or facial pain for $\geq$ 3 days at the beginning of the illness supports the diagnosis of acute bacterial sinusitis.

The most common causative bacterial organisms are *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* (the same 3 as for AOM). **Chronic sinusitis** can also be caused by *Staphylococcus aureus*, group A *Streptococcus*, enteric gram-negative bacilli (GNBs), *Pseudomonas aeruginosa* (especially with cystic fibrosis), and anaerobes, such as *Fusobacterium* and *Bacteroides*. Cultures are difficult to interpret in this setting, because patients often have received multiple courses of antibiotics, and the cultures usually represent colonization.

Fungal sinusitis (specifically mucormycosis) is seen in patients with diabetes, cancer, iron overload, and hematologic malignancies and in those receiving corticosteroid therapy. A patient with rhinocerebral mucormycosis

may present with symptoms of only a sinus infection or with unilateral nasal congestion. Tissue necrosis occurs as infection spreads outside of the sinuses, with the resulting distinctive **black eschar** sometimes visible on the palate and/or nasal mucosa. (See the discussion on **Mucormycosis** on page 4-57.) This is not the same as for asymptomatic patients who have had multiple courses of antibiotics and are colonized with fungi.

Symptoms can assist in localizing which sinus is involved. Frontal sinusitis can include headache that is worse when leaning forward (known as bowler's headache). Maxillary sinusitis sometimes presents with maxillary tooth pain, which is a very specific finding. Sphenoid sinusitis can include headache at the vertex of the skull.

Patients with chronic sinusitis commonly have > 1 symptom, including nasal congestion, alteration in smell, facial pressure or headache, and purulent rhinorrhea.

It is important to differentiate bacterial rhinosinusitis from allergic rhinitis, especially if seasonal. Both allergic rhinitis and nonallergic rhinitis with eosinophilia syndrome show a high number of eosinophils on a nasal smear. Bacterial rhinosinusitis, however, shows large numbers of neutrophils and bacteria.

Bacterial sinusitis is treated empirically, but failure to respond or frequent relapses warrant sinus cultures, which can be obtained endoscopically. Consider cystic fibrosis if *Pseudomonas* grows from a sinus culture (especially in a young adult with a history of recurrent respiratory issues).

Radiography: Sinusitis is generally a clinical diagnosis; imaging is not typically required and does not help differentiate a viral from a bacterial infection. Only perform imaging (CT or magnetic resonance imaging [MRI]) for patients who fail to respond to empiric therapy or who have frequent relapses to look for a structural abnormality.

Treatment of sinusitis: If you suspect acute bacterial sinusitis based on the above criteria, start amoxicillin/clavulanate. 2nd line drugs are the fluoroquinolones and doxycycline. The recommended duration of therapy is 5–7 days for amoxicillin/clavulanate and 7–10 days for the 2nd line agents. Intranasal corticosteroids and saline irrigation can be used as adjunctive treatment. Intranasal decongestants and antihistamines are not useful.

Chronic sinusitis rarely responds to antibacterial therapy. An ear, nose, and throat (ENT) consultation is helpful to obtain cultures, provide surgical drainage, and correct any anatomical causes.

Treatment of rhinocerebral mucormycosis requires emergent measures, including the correction of any underlying diseases (e.g., diabetic ketoacidosis), radical surgical debridement, and lipid amphotericin B to decrease the high mortality rate. (The lipid formulation is used so that you can give higher amphotericin B doses with less toxicity.) Posaconazole or isavuconazole is used after patients begin to improve on amphotericin B or in patients who cannot tolerate amphotericin B.

DEEP INFECTIONS OF HEAD AND NECK

Deep infections of the head and neck are named by their location and include submandibular space infections (which include infections of the sublingual and submylohyoid spaces), lateral pharyngeal space infections, and retropharyngeal space infections. An infection can spread from one space to another.

All of these infections are caused by a mixed oral flora that includes oral anaerobic bacteria. They develop from an extension of the normal oral flora into deeper locations from more superficial infections (e.g., tonsillitis leading to a peritonsillar abscess) and/or from the invasion of a high inoculum of bacteria due to poor dental hygiene. The presentation depends on which space is infected, and more than one infection can occur at the same time. Treatment is with antibiotics directed at normal flora and surgical drainage if abscess forms.

Submandibular space infection (a.k.a. Ludwig angina):

- Cellulitis of the floor of the mouth and submandibular neck
- If it extends posteriorly, it can obstruct the airway.

Lateral pharyngeal space infection:

- Anterior to the sternocleidomastoid muscle
- Contains carotid artery, jugular vein, cranial nerves 9 through 12
- Carotid infection can lead to infected cerebral emboli.
- Jugular infection can lead to infected pulmonary emboli.
- Can be caused by *Fusobacterium necrophorum*, an anaerobic GNB. This is known as **Lemierre syndrome**.

Retropharyngeal space infection:

- Contiguous spread from pharyngitis, tonsillitis, or other neck space
- Descends to C7–T1
- Presents with dysphagia and neck pain increased with hyperextension and possibly stridor
- Posterior to this is the **danger space**, so called because it tracks to the mediastinum.
- Posterior to this is the **prevertebral space**, which is a space that travels down to the pelvis.

In an otherwise healthy patient without comorbidities, ampicillin-sulbactam or a similar antibiotic is appropriate. In a patient with extensive surgery, neoplasm, or prior antibiotic therapy, use broad-spectrum antibiotics pending the surgical culture data.

PHARYNGITIS

The majority of pathogens that cause a sore throat are viruses and are self-limited. The most common of these are rhinoviruses, coronaviruses, and enteroviruses. *Streptococcus pyogenes* (group A β -hemolytic *Streptococcus* [GABHS]) is the bacterial pathogen that causes adult pharyngitis with enough frequency to consider routine testing.

The only other bacteria that cause pharyngitis amenable to treatment are *Neisseria gonorrhoeae* (pharyngeal gonorrhea) and *Corynebacterium diphtheriae* (diphtheria).

The 2012 Infectious Diseases Society of America (IDSA) guidelines for the management of group A streptococcal pharyngitis delineate which adults to test for GABHS, which diagnostic tests to perform, and who to treat based on this testing.

Use associated symptoms to assess the likelihood of GABHS vs. a viral infection. GABHS rarely infects below the pharynx, so having an associated cough and hoarseness are not typical. It does not inflame the nasopharynx; therefore, coryza is not seen, and it does not cause ulcerative lesions. It rarely causes conjunctivitis. Respiratory viruses can cause all of these symptoms, so the presence of these symptoms makes it unnecessary to test for or treat GABHS. Conversely, do test an adult with pharyngitis who has none of these symptoms and has a fever or swollen lymph nodes.

Initially test for GABHS via a rapid antigen-detection test (RADT). This test has a sensitivity of ~ 80% but a specificity of > 95%. Because of its high specificity, a positive test is sufficient evidence for GABHS infection to begin treatment.

Adults generally are not at high risk for streptococcal pharyngitis; therefore, a negative RADT result has a sufficient negative predictive value, and no further testing or treatment is required; however, do obtain cultures for all adults with high exposure to children and adolescents (e.g., school teachers, day care center workers) even with a negative RADT result. Regardless of which test is performed, treat only patients with a positive test result.

Treatment of GABHS infection decreases the risk of local complications (e.g., peritonsillar abscess) and rheumatic fever as long as it is given within the first 72 hours. If the RADT result is negative and clinical suspicion is low, it is appropriate to wait for a positive culture prior to treatment to avoid overtreatment of viral pharyngitis. It is also not clear whether treatment decreases the occurrence of poststreptococcal glomerulonephritis. Treat for 10 days with oral penicillin (PCN) or amoxicillin. Treat PCN-allergic patients with clindamycin for 10 days or azithromycin for 5 days.

Only a few infectious diseases cause pharyngitis with a rash. These are limited to scarlet fever caused by GABHS (which presents with diffuse erythema with fine, sandpaper-like papules), acute human immunodeficiency virus (HIV, which presents with a maculopapular rash), *Arcanobacterium haemolyticum* (which presents with diffuse erythema), *Mycoplasma pneumoniae* (which presents with erythema multiforme), Epstein-Barr virus (which presents with a maculopapular rash in 30% of patients and up to 90% of patients given ampicillin), and coxsackieviruses (which present with a vesicular rash).

EPIGLOTTITIS

Infection of the epiglottitis is a potentially life-threatening disease due to the possibility of airway compromise. It presents as sore throat and odynophagia but can be differentiated from pharyngitis if patients also have drooling or stridor. The base of the tongue inserts next to the epiglottis, so 50% of patients have pain with movement of the tongue and speak as if they have hot food in their mouth (referred to as the “hot potato” voice). They also may be more comfortable with neck flexion rather than extension. The most common infecting organism is *Haemophilus influenzae*, but there are myriad other bacterial pathogens (including *Streptococcus pneumoniae* and *Staphylococcus aureus*) and viral pathogens, and in most cases the blood and throat cultures are negative.

Diagnose epiglottitis by demonstrating inflammation of the epiglottis with the gold standard, direct laryngoscopy (the oropharyngeal examination is often normal), or with imaging showing a swollen epiglottis on a lateral neck film (indicated by a thumb sign) or neck CT scan.

Paramount treatment consists of protecting the airway immediately if there are any signs or symptoms suggestive of airway compromise and administering empiric antibiotics. Throat cultures are only obtained after airway safety is secure. Empiric antibiotics to use are ceftriaxone or cefotaxime plus an agent with methicillin-resistant *S. aureus* (MRSA) coverage (e.g., vancomycin).

SKIN / SOFT TISSUE, JOINTS, BONES

PREVIEW | REVIEW

- What factors determine the approach to therapy of common skin and soft tissue infections?
- What is the clinical presentation of *Mycobacterium marinum*?
- How is a prosthetic joint infection diagnosed?
- Which organism besides *Staphylococcus aureus* causes osteomyelitis in a patient with sickle cell disease?

COMMON SKIN AND SOFT TISSUE INFECTIONS

As of 2014, the IDSA recommends that skin and soft tissue infections (cellulitis affecting the deeper dermis and subcutaneous tissues) be separated into purulent and nonpurulent categories that are predictive of their microbiologic cause and best empiric treatment. Purulent cellulitis is most commonly caused by *Staphylococcus aureus*, and nonpurulent cellulitis is most commonly caused by *Streptococcus pyogenes*. The approach to management is based on the presence or absence of purulence and the severity of illness.

Patients with mild cellulitis have no associated systemic signs or symptoms. Patients with moderate cellulitis have systemic signs (e.g., fever, chills, myalgias). Patients with severe cellulitis have associated sepsis, have skin bullae or sloughing, or are immunocompromised.

Purulent Cellulitis

Incise and drain purulent cellulitis.

A **mild purulent** soft tissue infection does not require culture. Studies from 2016 show a benefit in giving a 7-day course of TMP/SMX with respect to cure, the need for repeat incision and drainage, and the spread of infection to household contacts. Doxycycline is an alternative in the sulfa-allergic patient.

Culture **moderate purulent** soft tissue infections and then give empiric therapy that targets MRSA, which is the pathogen in ~ 50% of these cases. Treat moderate infections with oral TMP/SMX or doxycycline. These inexpensive antibiotics remain active against ~ 90% of *S. aureus* strains regardless of methicillin sensitivity. Alter the treatment if needed based on the C&S report.

Culture **severe purulent** cellulitis and begin IV agents active against MRSA (e.g., vancomycin, daptomycin, linezolid) empirically.

Nonpurulent Cellulitis

The absence of pus makes obtaining cultures difficult. Treat **mild nonpurulent** cellulitis with oral agents that target *Streptococcus pyogenes*, such as penicillin, a 1st generation cephalosporin, cephalexin, or clindamycin. Because of the rapidly progressive nature of *S. pyogenes* infections, give IV therapy with the same agents or ceftriaxone to patients with **moderate** disease and obtain blood cultures.

Severe disease, especially if there is bullae formation or slough, requires immediate surgical debridement to rule out necrotizing fasciitis (see [Necrotizing Fasciitis](#)) and to obtain tissue cultures along with blood cultures. Because organisms other than *S. pyogenes* can cause necrotizing fasciitis, treat empirically with vancomycin and piperacillin/tazobactam while awaiting these culture results.

Rapidly Progressive Cellulitis

A few soft tissue infections are rapidly progressive and can spread up to 1 cm/hour through infected tissue.

Necrotizing Fasciitis

Necrotizing fasciitis is a life- and limb-threatening infection that only a handful of organisms can cause. These infections can progress as rapidly as 1 cm/hour. Solitary organisms capable of doing this include group A or B *Streptococcus*, *Vibrio vulnificus*, *Staphylococcus aureus*, and *Clostridium* species. A mixed infection with

gram-negative aerobic and anaerobic organisms can also cause necrotizing fasciitis. This can occur if stool flora contaminate a pressure ulcer near the anus or as a post-delivery obstetrical complication. Patients with microvascular disease from diabetes are at increased risk. When these organisms gain entrance to the fascial plane, there is little physical resistance to their spread. In addition, neurovascular bundles run along the fascia, and destruction of these bundles leads to the classic symptoms that occur.

The destruction of the arterial supply of the skin causes necrosis with resultant bleb formation (often black) and sloughing. The inflammation of cutaneous nerves leads to initial extreme pain, often disproportionate to the skin appearance, that paradoxically improves as the disease progresses due to nerve destruction. If gas-forming organisms (e.g., *Clostridia* GNBs, enteric GNBs) are the cause, there can be crepitus on examination. Imaging may show fascial inflammation and/or gas, but the definitive diagnosis is made by surgical exploration, which should be done emergently to debride dead tissue and obtain cultures. Empiric broad-spectrum antibiotics are important but are only adjunctive to surgery because they do not reach the infected devascularized tissue. Repeated surgical intervention is often needed.

Erysipelas

Erysipelas is the name given to streptococcal lymphangitis characterized by well-demarcated, raised borders affecting the superficial dermis and lymphatics. Lymphatic involvement with streaks in infected limbs is common and is predisposed by lymphedema or trauma to the lymphatic system (e.g., postmastectomy in the arms, post-saphenous vein harvesting in the legs, liposuction).

Pasteurella multocida

Pasteurella multocida is a GNB that causes infection in many animals and colonizes their mouths. Transmission to humans is typically via a dog or cat bite. Initially there may be little inflammation, but a rapidly progressive, nonnecrotizing cellulitis can ensue. The overall management of bite wounds is discussed in more detail under [Animal Bites on page 4-9](#). *P. multocida* is susceptible to most antibiotics. Amoxicillin/clavulanic acid is the treatment of choice. Alternative drugs include 3rd generation cephalosporins, doxycycline, and the fluoroquinolones.

UNIQUE SOFT TISSUE INFECTIONS

Vibrio vulnificus is a GNB that causes a necrotizing soft tissue infection after ingestion or inoculation of salt water into nonintact skin (e.g., skin penetrated by a fishing hook, fish spines, or oyster shucking knife). It is common in coastal, warm, salt, or brackish water. Particularly susceptible to sepsis are those who are immunocompromised or have chronic liver disease

or hemochromatosis. It can also cause fever, shaking chills, and bullous lesions. Diagnose *V. vulnificus* infection by culture, and treat with ceftriaxone and doxycycline.

Mycobacterium marinum is an acid-fast organism often called the fish tank bacillus. It causes nonhealing ulceronodular skin lesions when inoculated into the skin in people exposed to freshwater or saltwater via swimming or fish tanks. Infection can present as a single granuloma, but the organism often invades the lymphatics and can cause a series of nodular lesions along the lymphatic drainage similar to the lesions seen in sporotrichosis. It can also penetrate to joints or bones. The lesions tend to localize in the distal extremities because the organism does not grow well at core body temperature. Diagnose *M. marinum* infection by biopsy and acid-fast bacilli (AFB) stain and culture. (It needs to be incubated in lower temperatures for growth.) Mild disease can be treated with a single agent (clarithromycin, doxycycline, or TMP/SMX), but treat severe or progressive disease with a combination of clarithromycin and ethambutol or rifampin. The duration of treatment is at least 1–2 months after the lesions have resolved.

Erysipelothrix rhusiopathiae is a gram-positive rod that infects a large number of domestic and marine animals and causes a zoonotic skin infection in fish and meat handlers. The lesions are usually localized nodules, with lymphangitis occurring in ~ 25% of affected patients. Systemic disease with bacteremia is uncommon and more likely in those with alcohol use disorder. The major complication is endocarditis. Treat this infection with PCN. If the patient is allergic to PCN, use a quinolone or 3rd generation cephalosporin—oral for localized lesions and parenteral for bacteremia.

SEPTIC ARTHRITIS

Joints become infected by 2 routes: direct inoculation (e.g., adjacent cellulitis, trauma, surgery) or hematogenously from another focus. Risk factors for joint infection are injection drug abuse, diabetes mellitus, and prior joint disease or injury (e.g., rheumatoid arthritis, trauma, surgery). By far the most common infecting organism in native joints is *Staphylococcus aureus*. It presents with the acute onset of monoarticular joint pain, swelling, and redness.

Perform joint aspiration urgently (and prior to antibiotics to increase the yield) and send for a WBC count, Gram stain, and culture. Crystal disease (e.g., gout, pseudogout) can mimic and/or accompany septic arthritis, so send joint fluid for crystal analysis. Gonococcal arthritis is discussed separately under [Disseminated Gonorrhea on page 4-20](#). Nongonococcal septic arthritis shows organisms ~ 50% of the time on Gram stain and > 95% of the time on culture if no prior antibiotics have been given. Synovial fluid usually has a WBC count > 40,000/μL ($40 \times 10^9/L$).

Initial therapy can be based on the Gram stain: vancomycin for gram-positive cocci (GPC) or a 3rd generation cephalosporin for GNBs. The definitive therapy is based on the culture results. Treat septic arthritis typically for 3 weeks with IV antibiotics or 2 weeks with IV antibiotics followed by oral therapy. To decrease joint damage from the organisms and the inflammatory reaction to them, perform repeat joint aspirations if fluid reaccumulates while the patient is on treatment. Endemic fungi and Lyme disease from *Borrelia burgdorferi* cause a chronic monoarticular septic arthritis (see [Endemic Fungi on page 4-55](#) and [Lyme Disease on page 4-51](#)).

Prosthetic joint infection: Having a joint prosthesis is a major risk factor for septic arthritis. Joint infection occurs in 1–5% of prosthetic joint recipients. Manifestations are wound drainage, cutaneous erythema and warmth, prosthetic joint pain, and/or abnormal motion of the joint. Plain x-rays are helpful if they show a widening of the bone-cement interface, changes in the position of the prosthesis, cement fractures, a periosteal reaction, or motion of the components on stress views. Other imaging, such as bone scans, CT, MRI, and positron emission tomography (PET), are not useful in most cases. The diagnosis is definitively made by a joint aspiration; *S. aureus* and coagulase-negative staphylococci are the most commonly recovered bacteria.

There are 3 approaches to combined surgical and antibiotic therapy that attempt to preserve the joint. Incision and drainage with retention of hardware can be considered if the infection occurs within 30 days of surgery, the prosthesis is well fixed, and there is no sinus tract. In this setting, give 2–6 weeks of pathogen-specific IV antibiotics with oral rifampin if you have identified *Staphylococcus*. This can be followed by up to 6 months of oral therapy. A 1-stage procedure (incision and drainage with the exchange of prosthetic components) can be considered, especially in patients who may not tolerate 2 surgical interventions due to comorbidities. This decision is usually left to the discretion of the orthopedist at surgery. For most cases, consider a 2-stage procedure (prosthesis removal, 4–6 weeks of pathogen-specific IV antibiotics, and prosthesis reinsertion). Patients with comorbidities that place them at high risk of not tolerating surgical procedures can be tried on lifetime suppressive therapy if the organism is susceptible to oral antibiotics with high bioavailability.

OSTEOMYELITIS

Osteomyelitis is either acute or chronic, the distinction being that the latter has **necrotic bone**. Acute osteomyelitis is most commonly caused by *Staphylococcus aureus*. Some organisms have certain epidemiologic niches. In IV drug abusers, *Pseudomonas aeruginosa* and *Serratia* may be causative and have a predilection for the sternoclavicular joint, symphysis pubis, and vertebrae. In the U.S., the most common etiologic agent causing osteomyelitis in patients with sickle cell disease is *Salmonella*.

Diagnosis of diabetic foot osteomyelitis has high accuracy if a solid probe is able to reach the bone on examination. Otherwise, image in order to demonstrate osteomyelitis prior to recommending bone biopsies for culture. Initial plain x-rays can be done with the understanding that radiolucency requires > 50% demineralization of the bone, and this takes weeks to occur. MRI is the most sensitive and the study of choice. Do not use bone scans because they are very nonspecific and have a very high false-positive rate.

If probing to bone or MRI is suggestive of osteomyelitis, perform cultures of the bone to confirm the diagnosis and guide antibiotic therapy. Superficial cultures are not reliable predictors of infecting organisms. Evidence of osteomyelitis on imaging and a positive blood culture are presumptive evidence of microbiologic causation.

Except for small bone disease and early prosthetic joint infection (< 30 days from insertion of the prosthesis), all necrotic bone and prosthetic material must be removed before chronic osteomyelitis can be cured with antibiotics. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) assays can be used to help follow the course of the disease.

ANIMAL BITES

Animal bites create 3 specific problems:

- 1) Bacterial infections
- 2) Tetanus
- 3) Rabies

Bacterial infection: The risk of infection is highest from human bites, followed by cat bites and then dog bites. Causative agents can be from the animal's mouth (e.g., *Pasteurella*, streptococci, anaerobes) or inoculated from colonized skin at the bite site (e.g., *Staphylococcus aureus*). Wash and debride wounds immediately and take images if there is suspicion of joint or bone injury. Empiric antibiotic treatment is recommended for all human bites. Other bites can be observed without antibiotics unless the patient is immunocompromised, the bite is to the face or hand or is near a joint or bone, there is obvious crush injury, or there is edema (suggesting deep involvement or crush injury). Amoxicillin/clavulanate covers most of the causative organisms and is the empiric drug of choice.

Tetanus: All bites are considered tetanus-prone injuries; decide when to give prophylaxis with tetanus toxoid +/- tetanus immunoglobulin based on the patient's prior immunization history. See [Approach to Tetanus Prevention on page 4-88](#).

Rabies: The risk of rabies from a bite and the need for the rabies vaccine +/- rabies immunoglobulin is based on the type of animal involved. This is discussed further under [Rabies on page 4-24](#).

FEVER AND RASH

OVERVIEW

The febrile patient with skin lesions can run the gamut from a benign infection to a medical emergency. Not all patients have an infectious disease as the etiology of this combination, but the approach to patients with infectious causes of fever and rash is outlined in the following topics.

LIFE-THREATENING ETIOLOGIES

A few etiologies of fever and rash constitute potentially life-threatening infectious diseases. These require urgent diagnosis and treatment and are recognized by the specific dermatologic manifestations they cause. Neutropenic patients with fever require immediate empiric antibiotics even without rash (see [Febrile Neutropenia on page 4-38](#)). Neutropenic patients with *Pseudomonas aeruginosa* bacteremia can have characteristic skin lesions known as **ecthyma gangrenosum**, which are black, necrotic, ulcerative lesions ([Figure 4-1](#)). Neutropenic patients with candidemia may have a symmetric maculopapular rash as a tip-off.



Figure 4-1: Ecthyma gangrenosum

Petechial rash with fever can be seen from disseminated intravascular coagulation (DIC) from any cause. It also occurs without DIC from the viral hemorrhagic fevers, meningococcemia, and Rocky Mountain spotted fever.

Disseminated varicella-zoster virus or herpes simplex virus (HSV) infection causes fever and **vesicular lesions**.

Toxic shock syndrome associated with *Staphylococcus aureus* manifests as fever, hypotension, and a diffuse, erythematous, **sunburn-like rash**.

NON-LIFE-THREATENING ETIOLOGIES

Nodular or ulcerated nodular lesions with fever can be seen with disseminated infection from any of the endemic fungi, *Mycobacterium marinum*, other nontuberculous mycobacteria, sporotrichosis, *Erysipelothrix*, or *Leishmania*.

Vesicular lesions can result from infection with the enterovirus family of viruses (e.g., enterovirus, coxsackievirus, echovirus).

Pustules are seen in disseminated gonococcemia.

Secondary syphilis can produce any form of rash, with the exception of vesicles and bullae.

GASTROINTESTINAL (GI) INFECTIONS

PREVIEW | REVIEW

- What is the incubation period for the toxin-induced syndromes causing nausea and vomiting?
- Which findings on stool evaluation suggest invasive diarrhea?
- Know the recommendations for the prophylaxis and treatment of traveler's diarrhea.
- *Salmonella* infection is spread by which animals?
- What is a possible adverse consequence of treating infectious diarrhea due to *E. coli* O157:H7 with antibiotics?
- What is the treatment for *Shigella* infection?
- *Vibrio vulnificus* can cause severe disease in which groups of patients?
- What is the treatment of choice for patients with severe *Clostridioides* (formerly *Clostridium*) *difficile* diarrhea?
- What is the treatment recommendation for the 1st recurrence of *C. difficile* infection?
- Which infection control precautions must be used on patients with *C. difficile* diarrhea?

FOOD POISONING

Food poisoning is the common term for GI diseases resulting from bacterial toxins, although it is sometimes extended to include all foodborne illnesses. The 3 organisms that produce illness from ingestion of toxins are *Staphylococcus aureus*, *Bacillus cereus*, and *Clostridium perfringens*.

S. aureus produces disease due to ingestion of preformed enterotoxin. Food handlers can contaminate food through improper handling and inadequate temperature controls, allowing for an increased quantity of emetogenic toxins to be ingested. The incubation period is 1–6 hours, so the causative meal is usually evident. Mayonnaise and cream pies are frequent culprits, although meat, eggs, and produce can be contaminated as well. The predominant symptom is vomiting that lasts < 24 hours. Vomiting with concomitant cramps and diarrhea is characteristic. Disease is self-limited and treatment is supportive.

B. cereus grows best in starchy foods such as rice, and its spores are very heat resistant. It, too, causes vomiting

within 1–6 hours but can also cause a diarrheal illness within 8–16 hours depending on which toxin it has produced. Disease is self-limited and treatment is supportive.

C. perfringens is a bowel colonizer of almost all animals that humans ingest and has an incubation period of 8–16 hours prior to causing a watery diarrhea of 1–2 days' duration. Disease is self-limited and treatment is supportive.

VIRAL GASTROENTERITIS

There are many viral causes of diarrhea. **Rotavirus** is the most common cause of severe diarrhea in infants; it infrequently infects older children but can infect adults. It is easily found in the stool via an enzyme-linked immunosorbent assay (ELISA) or polymerase chain reaction (PCR) assay. **Noroviruses** (formerly known as Norwalk-like viruses) are the most common viral cause of gastroenteritis in adults. They are highly contagious (with low inoculum needed) and spread via person-to-person transmission, fomites, and food (e.g., salads, shellfish, fruit). Often called the “winter vomiting disease,” noroviruses can cause outbreaks on **cruise ships**, in schools, and on athletic teams. Noroviruses can be detected via reverse transcriptase polymerase chain reaction (RT-PCR) in stool samples. The treatment is supportive. There are no antivirals active against these viruses.

BACTERIAL DIARRHEA

Bacteria cause diarrhea after ingestion only if they are ingested in sufficient quantities to survive the hostile environment of the stomach and competition for nutrients with our normal microbiome, allowing them to invade the small bowel and/or colon or to produce inflammatory toxins. Detection of WBCs in the stool is a quick but variably sensitive indicator of an **invasive** bacterial diarrhea, with a sensitivity of 50–70% and a specificity of 50–80%. Detection of the WBC protein lactoferrin has a higher sensitivity and specificity: > 90% and > 80%, respectively.

In the U.S., *Salmonella* is the most common cause of non-toxin-related bacterial diarrhea, with *Campylobacter* being a close second, each causing ~ 1 million cases a year. Shiga toxin-producing *Escherichia coli* (enterohemorrhagic *E. coli* [EHEC]) causes ~ 200,000 cases a year, and *Shigella* causes ~ 150,000 cases a year. Since many patients are empirically treated and do not get cultures, these incidences represent significant underreporting.

Traveler's Diarrhea

This is the most common infection to occur in travelers and affects 50 million U.S. travelers to all destinations except northern Europe, Canada, Australia, and New Zealand. For those traveling to less developed regions, the risk can approach 60%. Almost 50% of those infected are forced to change their itinerary, 20% spend 1 day in bed, and 1% are hospitalized.

The majority of infections are due to strains of *E. coli*, followed by *Salmonella*, *Campylobacter*, and *Shigella*.

Educate patients on how to prevent traveler's diarrhea by suggesting the following:

- Avoid consumption of local, untreated water or ice, including in mixed alcoholic drinks.
- Boil or filter any water before ingesting.
- Avoid fresh fruits that cannot be peeled.
- Even at luxury resorts, avoid uncooked vegetables, meat salads (e.g., tuna), and condiments (e.g., salsas).

Carbonated drinks without ice are okay. A good general rule: Boil it, peel it, cook it, or forget it.

Prophylactic antibiotics are **not** routinely indicated, but they are justified for those with immunodeficiencies or a history of cardiac, kidney, or inflammatory bowel disease. They are also appropriate for persons conducting important business who cannot afford to be ill. Prophylactic regimens include:

- Ciprofloxacin 500 mg daily
- Rifaximin 200 mg daily or twice a day (bid)

Often a fluoroquinolone (e.g., ciprofloxacin), rifaximin, or azithromycin is given as a pretrip prescription to be taken should diarrhea occur.

For self-treatment, the patient should determine the severity of diarrhea and treat it accordingly. Mild diarrhea should be treated with aggressive oral hydration. Bismuth subsalicylate can be of benefit. Antibiotics are only required for severe disease (i.e., > 4 stools/day, high fever, or blood/pus/mucus in stools). For severe disease, prescribe one of the following:

- Ciprofloxacin 500 mg bid $\times$ 1–2 days
- Azithromycin 1,000 mg $\times$ 1 dose
- Rifaximin 200 mg 3 times a day (tid) $\times$ 3 days

Antidiarrheals (e.g., loperamide) can be used cautiously along with the antibiotics, but an antidiarrheal should **not** be the only treatment in severe disease because of the risk of causing toxic megacolon.

Salmonella

S. enterica is found in the stool of many different host animals and is the only *Salmonella* species that infects humans. *Salmonella* can be spread by frozen foods (especially chicken), milk, and eggs. Baby chicks, iguanas, turtles, and other exotic pets also can be sources of infection.

An inoculum of $> 10^5$ organisms is typically required to produce disease, but fewer organisms are needed in patients on acid-suppressive drugs. After an incubation period of 1–3 days, a usually nonbloody diarrhea with fever occurs. Untreated, the fever resolves by day 3 and the diarrhea by day 7.

Do not give antibiotic treatment routinely because it prolongs the shedding of the organism in the stool, increases antibacterial resistance, and does not shorten the course of disease. Because a small percentage of patients can

have severe disease, however, treat patients > 50 years of age, with significant comorbid illnesses, or who are immunosuppressed. Also, severe exacerbations of pre-existent inflammatory bowel disease can occur, so treat these patients as well. Treatment, if required, is with a quinolone, TMP/SMX, or amoxicillin if susceptibilities are known. If intravenous therapy is required, use ceftriaxone.

***S. enterica* serotype Typhi** (a.k.a. ***Salmonella* Typhi**; formerly *S. typhi*) causes typhoid fever after ingestion of contaminated food, milk, or water. This organism is found in humans only. Infection commonly begins with fever, chills, initial constipation followed by diarrhea, leukopenia, and the appearance of classic **rose spots** on the trunk (Figure 4-2), which appear ~ 1 week after the fever starts. These look like little, 2–3 mm angiomias. There may be relative bradycardia as a clue. Blood cultures are usually positive during the 1st week, followed by stool cultures and then urine cultures



Figure 4-2: Typhoid fever with classic 2–3 mm “rose spots”
Source: CDC

Treat typhoid fever with quinolones, 3rd generation cephalosporins, ampicillin, trimethoprim/sulfamethoxazole (TMP/SMX), or chloramphenicol depending on the sensitivities. Carriers (those excreting the organism for > 12 months) without gallbladder disease or stones can typically be cleared with 4 weeks of fluoroquinolone administration. Chronic carriers with gallstones are at increased risk of biliary cancer.

There are moderately effective live attenuated and polysaccharide vaccines that can be given to travelers (> 2 years of age) who go outside of the usual tourist areas of Latin America, Asia, and Africa.

Campylobacter

C. jejuni and *C. coli* cause human disease usually from ingestion of undercooked meat—most notably poultry, as these bacteria often inhabit the lining of their intestinal tracts. Diarrhea, with cramping and often a high fever, occurs after 1–7 days. The disease is self-limited, and antibiotic therapy only decreases the duration of illness by an average of 1 day. Treat those with severe disease or who are immunocompromised. Although resistance has been reported, most strains are susceptible to fluoroquinolones and macrolides.

Escherichia coli

E. coli is the most common cause of bacterial diarrhea worldwide. Depending on which strain is responsible, *E. coli* produces diarrhea via one of the following mechanisms:

- Production of a secretory toxin (enterotoxigenic *E. coli* [ETEC]), which causes a noninflammatory watery diarrhea
- Production of a Shiga toxin (enterohemorrhagic *E. coli* [EHEC]), which causes mucosal injury and bloody diarrhea
- Invasion (enteroinvasive *E. coli* [EIEC]), which causes a watery or bloody stool. EIEC's mechanism of infection is similar to that of *Shigella* and causes a similar presentation.

ETEC is the most common cause of traveler's diarrhea. Refer to [Traveler's Diarrhea on page 4-10](#) for information on prophylaxis and treatment.

EHEC, which is usually from serotype O157:H7, causes localized outbreaks of hemorrhagic colitis, thrombotic thrombocytopenic purpura (TTP), and hemolytic uremic syndrome (HUS), typically after eating undercooked beef or unpasteurized milk. Fever is conspicuously absent, but nausea and vomiting are common. Do **not** treat diarrhea caused by *E. coli* O157:H7 with antibiotics because killing large numbers of organisms can release large amounts of Shiga-like toxin, resulting in an increased risk of HUS development.

Shigella

Shigella species (*S. sonnei* and *S. flexneri* being the most common) produce Shiga toxin, causing fevers, bloody diarrhea, cramping, and tenesmus. It is the most contagious bacterial diarrhea, with an inoculum of 10 organisms being sufficient to cause disease in 50% of individuals; thus, it is easily spread from person to person (men who have sex with men are at especially high risk), via contaminated food, or even via flies that have had contact with infected feces. Because of increasing resistance to quinolones, as of 2017, the CDC no longer recommends treating all patients with *Shigella*. Only treat patients if they are immunocompromised or have severe disease. Treatment may also be directed by local health departments to quell outbreaks. Fluoroquinolones can be used if the minimum inhibitory concentrations (MICs) show sensitivity; otherwise, use other agents based on lab-reported susceptibilities.

Yersinia

Y. enterocolitica causes diarrhea (sometimes bloody), fever, right lower quadrant (RLQ) abdominal pain (mimicking appendicitis), and often **sore throat**. Pigs are the major reservoir, and disease can occur after ingesting undercooked pork. This pathogen is siderophilic; therefore, conditions with iron overload, such as hemochromatosis

and those requiring frequent transfusions (such as some patients with sickle cell disease), increase its pathogenicity. The use of deferoxamine also increases risk. Treatment is typically supportive, but antibiotic therapy is warranted for invasive disease. Options include 3rd generation cephalosporins, TMP/SMX, and tetracyclines.

Vibrio

Vibrio species grow in salt water and are transmitted via raw or undercooked seafood and shellfish, which, as filter feeders, concentrate the organism. *V. cholerae* O1 (which causes cholera) is occasionally seen in Gulf Coast crabs but is more common in the endemic regions of Africa and Asia from contaminated water sources. The diagnosis is made clinically with the presentation of profuse watery diarrhea and significant, life-threatening volume loss. **Rice-water stool** is the classic descriptor; it looks like the soaking water from rice. The treatment is aggressive rehydration; without it, mortality approaches 70%. The addition of antibiotics (e.g., a fluoroquinolone, a macrolide, doxycycline) can decrease shedding in the stool and should be selected based on known regional susceptibilities or culture results.

The non-O1 *V. cholerae*, *V. parahaemolyticus*, and other *Vibrio* species are even more frequent causes of shellfish-associated diarrhea. They cause abdominal pain and diarrhea that is often bloody. Treatment is supportive and antibiotics (doxycycline, macrolides or fluoroquinolones) are given when the disease is severe. *V. vulnificus* causes skin infections and sepsis, especially in immunocompromised patients and those with chronic liver disease. See [Unique Soft Tissue Infections on page 4-7](#) for additional information.

Vibrio parahaemolyticus is acquired from ingestion of saltwater fish or crustaceans and presents with abdominal pain and bloody diarrhea.

Summary of Bacterial Diarrhea

The initial presentation of infectious diarrhea is often not sufficient to determine a specific etiologic organism. Send a stool sample for a WBC count or for lactoferrin testing to determine if it is likely to be an infectious bacterial diarrhea. If bacteria are detected, send the sample for bacterial cultures. For patients with mild disease, give hydration but no empiric antibiotics. Avoid antimotility drugs. Treat severe disease or patients at risk for severe disease (e.g., immunocompromised patients) with a fluoroquinolone unless EHEC is suspected or cultured.

DIARRHEA DUE TO CLOSTRIDIODES DIFFICILE

Background and Presentation

Clostridia has been a catch-all basket for bacteria that have similar findings—strictly anaerobic, spore-forming,

gram-positive rods. Recent findings place *C. difficile* with bacteria that are far removed phylogenetically from other clostridia. Its name has been changed from *Clostridium difficile* to *Clostridioides* (clostridia-like) *difficile* to minimize potential confusion from a more radical name change.

Diarrhea due to *C. difficile* infection (CDI) is discussed apart from the other bacterial diarrheas due to several unique characteristics. Diarrhea during or after the administration of antibiotics is usually caused by an alteration of fecal flora (resulting in the decreased breakdown of small molecules and an osmotic diarrhea) or the promotility action of some antibiotics (e.g., macrolides); however, if the fecal flora is altered and acquisition of *C. difficile* occurs, CDI ensues. Clindamycin, cephalosporins and quinolones are the most common precipitants of CDI. Most cases occur in health care settings, but an increasing number of cases are occurring in the outpatient setting. The use of proton pump inhibitors increases the risk.

Symptoms can develop up to **10 weeks** after the antibiotics are stopped. The diarrhea is typically a watery diarrhea but may be bloody in 15% of patients. An ileus without diarrhea is common. Fever and very high peripheral WBCs can be seen.

Diagnosis

A PCR assay using a stool sample (or perirectal swab in cases of ileus) to detect the cytotoxin-producing genes of *C. difficile* is superior to enzyme immunoassay (EIA) used to detect the toxins themselves. Although the organism can also be cultured from the stool, this has no utility because it takes several days to grow the bacteria and many strains do not produce toxins or disease.

Treatment

The Infectious Diseases Society of America (IDSA) clinical practice guideline for the treatment of CDI, updated in 2017, recommends stopping the offending antibiotics if possible and treating disease based on its severity.

Treat **nonsevere** disease (a WBC count < 15,000/ μ L [15×10^9 /L] **and** a serum creatinine < 1.5 mg/dL [132.6 μ mol/L]) with vancomycin or fidaxomicin (FDX) given by mouth (PO). Use metronidazole **only** if these drugs are not available or are too expensive.

Treat **severe** disease (a WBC count > 15,000/ μ L [15×10^9 /L] **or** a serum creatinine > 1.5 mg/dL [132.6 μ mol/L]) with PO vancomycin or PO FDX. Metronidazole is **not** a recommended option.

Fulminant disease is present when patients have ileus, megacolon, or hypotension. Give these patients high-dose PO vancomycin and IV metronidazole. Give vancomycin by enema if the PO route is not an option or if there is severe ileus. Consider colectomy in patients with rising lactate levels, peritoneal signs, or sepsis.

Relapse

Relapses occur in ~ 25% of patients. **Treatment for the 1st relapse depends on the initial therapy:**

- If a standard vancomycin regimen was used initially, use FDX or a pulsed, tapered vancomycin regimen.
- If a standard FDX regimen was used initially, use a pulsed, tapered vancomycin regimen.
- If metronidazole was used initially, use a standard vancomycin regimen.

There are several options for **treating > 1 relapse:**

- A standard or pulsed, tapered vancomycin regimen
- FDX
- Fecal microbiota transplantation (FMT)

FDX has a 50% lower relapse rate than vancomycin and thus can be given to patients with multiple relapses or in whom a relapse would be devastating due to comorbid disease (e.g., an ICU patient). FMT is a highly successful procedure for treating severe, recurrent CDIs.

Prevention

Sanitizing hand gels do **not** prevent transmission because they do not kill the spores of *C. difficile*. Only handwashing with soap and water prevents spread. Isolate patients with *C. difficile* diarrhea in a private room and place them on contact precautions. Because the organism is found on various surfaces throughout the infected patient's room, even those who do not examine the patient should use precautions.

PROTOZOAL DIARRHEAS

Protozoal diarrheas include amebiasis, giardiasis, and several acid-fast organism infections that are discussed under [Protozoa on page 4-57](#).

LIVER AND BILIARY INFECTIONS

PREVIEW | REVIEW

- What is the treatment for bacterial liver abscesses?
- To which 3 groups of patients should you give antibiotic prophylaxis for primary peritonitis?
- How is secondary peritonitis treated?

LIVER ABSCESS

Liver abscesses are most commonly bacterial or amebic. Amebic abscesses are discussed under [Entamoeba on page 4-58](#). Patients with prolonged neutropenia can develop hepatosplenic candidiasis, in which there are numerous fungal (candidal) abscesses throughout the liver and spleen.

Bacterial liver abscesses are either due to direct bacterial spread from infection in the biliary tree (e.g., cholecystitis, cholangitis) or from transmission of gut flora to the liver from the venous drainage of the mesenteric veins through the portal vein. Many liver abscesses have no clear cause and are called cryptogenic. The microbiology is mixed fecal flora (e.g., GNBs, enterococci, anaerobes).

The presentation may initially be overshadowed by the primary infectious process. Symptoms are fever and right upper quadrant (RUQ) pain. The liver can be enlarged and tender on examination, and there may be a positive Murphy sign (pain with inspiration while patient in supine position and examiner palpating the right subcostal area).

Confirm the diagnosis by imaging, and perform aspiration to discern the microbiologic cause and guide antibiotic therapy.

The treatment includes drainage and culture-guided antibiotics. Drain abscesses < 5 cm by aspiration. For larger abscesses, place and maintain a catheter until the drainage becomes minimal. Surgical intervention is required if complete drainage cannot be obtained by other means.

CHOLANGITIS

Cholangitis is a bacterial infection of the biliary tree. Entry of bacteria into bile occurs on a regular basis because the sphincter of Oddi is not a one-way valve and the duodenum is not sterile. Despite this, cholangitis does not typically ensue because biliary pressures flush organisms back into the duodenum and bile salts are bacteriostatic. Thus, a prerequisite in the vast majority of cases of cholangitis is biliary obstruction, typically from stones, benign strictures, or cancer.

The bacteriology usually shows enteric GNBs (or enterococci for acute cases), but if there is a chronic process such as tumor obstruction or stents, then anaerobes can be part of the polymicrobial flora.

Many patients have the **Charcot triad** of fever, RUQ pain, and jaundice. Confirm the diagnosis by imaging, which shows biliary dilation and/or obstruction.

No antibiotics reliably enter an obstructed biliary tree, so treatment includes urgent biliary drainage by endoscopic retrograde cholangiopancreatography (ERCP), performed either percutaneously or surgically. Antibiotics are guided by the culture results of the drainage.

PERITONITIS

Infection of the peritoneal cavity can be primary or secondary. Primary peritonitis has no evident intraabdominal, surgically treatable source. Other cases are secondary, meaning they are caused by a surgically treatable source (e.g., bowel perforation).

It is critical to differentiate primary from secondary bacterial peritonitis because:

- the mortality rate is ~ 80% for patients with primary peritonitis who undergo an exploratory laparotomy and
- the mortality rate is ~ 100% for patients with secondary bacterial peritonitis who do not go to surgery.

Primary peritonitis occurs in the presence of ascites and hypoalbuminemia. The low albumin, in addition to creating the ascites, causes bowel edema, which allows the aerobic bowel flora to transmigrate (i.e., swim across) from the mucosal to the serosal surface of the bowel and enter the peritoneum. When the ascites is due to cirrhosis or nephrotic syndrome, patients have a markedly decreased ability to opsonize these organisms due to decreased complement production (cirrhosis) or loss of complement and antibodies in the urine (nephrotic syndrome). The most common causative organisms of primary peritonitis are GNBs, with *Escherichia coli* and *Klebsiella* causing the majority of cases. *Streptococcus pneumoniae* is seen as well. Anaerobes are not found.

Because of the decreased amount of opsonins, inflammation is blunted and many patients are asymptomatic. If symptoms occur, they include fever, abdominal pain, abdominal tenderness, and altered mental status, but not necessarily simultaneously. Suspect primary peritonitis in a cirrhotic patient with worsening portosystemic encephalopathy, even in the absence of symptoms. The diagnosis of primary peritonitis is made if the paracentesis fluid shows > 250 polymorphonuclear leukocytes (PMNs), the Gram stain is positive, or the culture is positive and no other cause of peritonitis is evident. This is usually a monomicrobial infection. Treat primary peritonitis empirically with a 3rd generation cephalosporin. Give antibiotic prophylaxis for primary peritonitis to 3 groups of patients who are at high risk for this disease:

- Patients with cirrhosis and ascites if the ascitic fluid protein is < 1,000 mg/dL
- Patients with cirrhosis and a GI bleed
- Patients with a prior episode of primary peritonitis

Use ciprofloxacin or TMP/SMX.

Secondary bacterial peritonitis is an infection of the peritoneal cavity due to the direct entry of bacterial flora from disruption of the integrity of the bowel. Unlike with primary peritonitis, patients with secondary peritonitis almost always have abdominal pain, fever, and peritoneal signs. The ascitic fluid has a markedly elevated WBC count (often > 5,000/ μ L [5×10^9 /L]) and can be grossly purulent. Cultures are usually polymicrobial. Imaging typically reveals the source, necessitating emergency surgical intervention while administering antibiotics to cover gram-negative aerobes and anaerobes. Acceptable regimens include piperacillin/tazobactam or a carbapenem.

Peritonitis from peritoneal dialysis can also occur; this is discussed in the [Nephrology](#) section.

INTRAABDOMINAL ABSCESS

Intraabdominal abscesses are walled-off pockets of infection that occur after peritonitis. Anaerobic flora are major participants in the process, and abscesses commonly do not occur after primary peritonitis. Instead, they usually occur after bowel perforation or appendicitis (secondary peritonitis). Abscess formation takes several days to occur and often presents itself after initial surgical and antibiotic treatment of the underlying process. Signs and symptoms include the new onset and/or recurrence of fever, abdominal pain, abdominal tenderness, and leukocytosis. The bacteriology is similar to that of secondary peritonitis, which is often a precursor, and includes gram-negative aerobic rods and anaerobes. If an abscess is recurrent or occurs after a course of antibiotics, *Candida* and coagulase-negative staphylococci are common. Diagnose an intraabdominal abscess by imaging, and treat it with percutaneous or surgical drainage with antimicrobial therapy. Antibiotic therapy is similar to that for secondary peritonitis (i.e., piperacillin/tazobactam or a carbapenem) but is directed at cultured organisms from the abdomen. Empiric treatment for enterococci and *Candida* species is not recommended unless these are present on prior or subsequent cultures from drainage. Multiple abscesses or abscesses due to gross fecal soiling often require repeated surgical drainage.

SEXUALLY TRANSMITTED INFECTIONS (STIs)

PREVIEW | REVIEW

- Who and how do you test for gonorrhea? For chlamydia? For syphilis?
- What are the stages of syphilis, and how are they treated?
- What drugs are used to treat syphilis in pregnancy? What if the woman has an anaphylactic penicillin allergy?
- How do primary syphilis and chancroid differ?
- Discuss the clinical manifestations of lymphogranuloma venereum and granuloma inguinale.
- What are the outpatient and inpatient regimens for the treatment of pelvic inflammatory disease?
- What is the empiric treatment for cervicitis?
- What are the clinical presentations of disseminated gonorrhea?

- Which 3 tests are useful to determine the etiology of vaginitis? In what way are the tests useful?
- Women with recurrent or recalcitrant vulvovaginal candidiasis should be tested for which 2 associated illnesses?

OVERVIEW

Most STIs are categorized into those that cause urethritis, cervicitis, and pelvic inflammatory disease (PID; i.e., gonorrhea and chlamydia) and those that cause genital ulcers (i.e., syphilis, chancroid, herpes simplex virus [HSV], lymphogranuloma venereum [LGV], and granuloma inguinale). The following discussions reflect the diagnostic and treatment guidelines recommended by the CDC in its 2015 Sexually Transmitted Diseases Treatment Guidelines.

SCREENING

General

Populations that are at increased risk for STIs include the following:

- Persons 15–24 years of age
- African Americans
- Individuals with a new partner in the past 2 months
- Individuals with multiple partners
- Persons with a history of previous STIs
- Drug users
- Persons with recent exposure to a jail or detention facility
- Individuals who find sex partners from the internet
- Persons who have contact with sex workers
- Men who have sex with men

Gonorrhea Screening

Since most men with gonorrhea are symptomatic, there is no recommended screening for them. Screen sexually active women annually if they are < 25 years of age or if they are older and in one of the general risk groups. Screen for gonorrhea in women using nucleic acid amplification testing (NAAT) of a vaginal swab.

Chlamydia Screening

The CDC's 2015 recommendations for chlamydia are similar to those for gonorrhea, with no recommended screening in men and screening of women in the same risk groups. NAAT of a vaginal swab is the test of choice.

Syphilis Screening

Screen for syphilis in all the general risk groups and in women during each pregnancy. See [Syphilis on page 4-16](#) and the [Women's and Men's Health](#) section for additional information.

Hepatitis Screening

Screen for hepatitis B virus (HBV) and hepatitis C virus (HCV) in patients with risk factors (e.g., sexual contacts, injection drug users) and for each pregnancy (see the [Women's and Men's Health](#) section). Screen for HBV by sending serum for hepatitis B virus surface antigen (HBsAg) and hepatitis B core antibody (anti-HBc) detection. Screen for HCV by sending serum for anti-HCV antibody detection.

Human Immunodeficiency Virus (HIV) Screening

Screen for HIV in women during each pregnancy (see the [Women's and Men's Health](#) section). The CDC also recommends HIV screening in all persons 13–64 years of age at least once. Test those outside of this age range who are in a high-risk group. High-risk individuals are considered those who use IV drugs, men who have sex with men, and those presenting for STI testing or who have a history of STIs or a new diagnosis of tuberculosis (TB). Test **high-risk groups annually**. Otherwise, repeat screening based on clinical circumstances.

Herpes Simplex Virus (HSV) Screening

No general screening is recommended for HSV infections.

INFECTIOUS GENITAL ULCERS

Genital ulcer diseases include syphilis, HSV, chancroid, LGV, and granuloma inguinale. See [Table 4-1](#).

Syphilis

Treponema pallidum, a motile spirochete, causes syphilis, which is a reportable disease in the U.S. Syphilis has 3 stages. The 3rd stage has 3 forms, and one of the 3 forms, neurosyphilis, has 3 manifestations. (Thus, it is $3 \times 3 \times 3$.)

Primary syphilis presents with a **painless** chancre at the site of inoculation—usually genital, anal, or oral—within 3–40 days depending on the number of inoculated organisms. This may be followed by painless regional lymphadenopathy. In women, if the infection is cervical, it is often unnoticed. Even without treatment, it lasts 2–6 weeks and then resolves.

Secondary syphilis occurs ~ 2 months later as spirochetes disseminate throughout the body. Symptoms include generalized lymphadenopathy, fever, malaise, and mucosal and/or cutaneous lesions that can mimic many other lesions (“the great imitator”). The skin lesions are macular or papular but **never** vesicular. They can occur on the palms and soles and are described as “nickel and dime” lesions ([Figure 4-3](#)). Condylomata lata are cauliflower-like wet lesions in the genital areas or mouth that teem with treponemes. Meningovascular disease can also occur in secondary syphilis and presents as strokes or blindness in a young person. Nonneurologic signs and symptoms resolve in 3–12 weeks, after which the disease goes into a latency period. Untreated, 1/3 of secondary syphilis cases eventually proceed to tertiary syphilis.



Figure 4-3: Secondary syphilis “nickel and dime” lesions
Source: CDC

Table 4-1: STIs with Genital Ulcers

Disease	Organism/ Virus	Characteristic Ulcer	Treatment
Syphilis	<i>T. pallidum</i>	Painless 1- to 2-cm ulcer; “punched out,” clean-appearing ulcer with nonexudative base; sharp, firm, slightly elevated indurated borders	Penicillin G
Herpes genitalis	Herpes simplex	Painful grouped vesicles that rupture to form shallow, painful ulcers	Acyclovir or famciclovir or valacyclovir
Chancroid	<i>H. ducreyi</i>	Painful , shallow, soft, friable ulcer with ragged margins and a foul-smelling necrotic purulent exudate	Preferred: azithromycin or ceftriaxone Alternative: ciprofloxacin or erythromycin
Lymphogranuloma venereum	<i>C. trachomatis</i> L1, L2, or L3	Painless general ulcer	Preferred: doxycycline Alternative: erythromycin or azithromycin
Granuloma inguinale	<i>K. granulomatis</i>	Painless, friable, progressive, beefy-red ulcerative lesion with raised, rolled margin	Azithromycin or doxycycline or ciprofloxacin

Tertiary syphilis occurs in 15–30% of untreated patients and manifests 1–15 years or more after initial infection. There are 3 forms:

- 1) **Gummatous** syphilis presents with ≥ 1 gumma, which is a noncaseating granulomatous lesion that is locally destructive.
- 2) **Cardiovascular** syphilis is obliterative endarteritis of the aortic vasa vasorum, which results in ascending aortic aneurysms and aortic insufficiency.
- 3) **Neurosyphilis** has several manifestations:
 - **Chronic meningovascular syphilis** can present with brain and/or spinal cord strokes similar to meningovascular disease in secondary syphilis.
 - **Tabes dorsalis** is due to destruction of the posterior spinal cord columns, leading to the loss of position sense, an abnormal foot-slapping gait, and a positive Romberg sign.
 - **General paresis** is the name given to diffuse cortical disease seen in neurosyphilis. Its numerous manifestations can be remembered with the following mnemonic:
 - **P** = defects in personality
 - **A** = reduced affect
 - **R** = abnormal reflexes
 - **E** = eye problems (Argyll Robertson pupil, which is miotic and irregular; it accommodates but does not react to light)
 - **S** = defects in sensorium
 - **I** = defects in intellect
 - **S** = defects in speech
 - **Ocular syphilis** can involve any structure of the eye including keratitis, uveitis, retinitis, and optic neuritis.
 - **Otosyphilis** presents with hearing loss from involvement of the cochlea and/or the auditory nerve.

Latent syphilis is defined as a serology diagnostic of syphilis with **no** active manifestations of infection. It can occur in the 4–10 weeks between primary and secondary syphilis but is most commonly diagnosed in the much longer asymptomatic period after secondary syphilis. Latent syphilis is divided into early latent and late latent depending on whether the last manifestations of syphilis or seroconversion to syphilis occurred within 1 year or after 1 year, respectively. This distinction arose from observational studies that showed that 90% of patients become symptomatic within the 1st year of infection.

The diagnosis of syphilis was historically based on direct visualization of the organism via dark-field microscopy of chancre exudate or cutaneous lesions of secondary syphilis; however, this is unavailable in most laboratories. Serology is otherwise required to confirm the diagnosis of syphilis. There are 2 types of serologic tests:

- 1) **Nontreponemal tests** (Venereal Disease Research Laboratory [VDRL] and rapid plasma reagin [RPR] tests)

detect antibodies directed against the cardiolipin-cholesterol-lecithin antigen (a.k.a. reagin). These are predominantly immunoglobulin M (IgM) antibodies and are absent in $\sim 1/3$ of patients with primary syphilis because the disease has not been present long enough to have produced an IgM response. These antibodies are present in essentially all patients with secondary syphilis. A third of patients with tertiary syphilis are seronegative because the IgM response has burnt out. Expect these antibodies to decline with appropriate treatment in primary or secondary disease. In late latent disease, some patients are serofast and titers do not decline with treatment.

- 2) **Treponemal tests** (the microhemagglutination assay for antibodies to *Treponema pallidum* [MHA-TP] and the fluorescent treponemal antibody absorption [FTA-ABS] test) detect antibodies that directly react with *T. pallidum*. These are predominantly immunoglobulin G (IgG) antibodies. The tests turn positive after 2–4 weeks and remain positive for life, even with treatment.

Perform a treponemal test to confirm a nontreponemal test because false-positive nontreponemal test results can occur with a variety of other inflammatory and infectious illnesses. If this sequence is followed, patients with a positive RPR test result and a confirmatory positive FTA-ABS test result are considered to have past or present syphilis.

A lumbar puncture (LP) is indicated in patients who have neurologic or ophthalmic manifestations consistent with neurosyphilis, other signs of tertiary syphilis, or serum RPR titers $\geq 1:32$ or who have failed prior appropriate therapy for syphilis. The diagnosis of neurosyphilis should be made if any of the following are found in the CSF: VDRL (+), protein > 45 , or WBC > 5 . RPR testing should not be done on CSF because it has a lower sensitivity than the VDRL test.

RPR and VDRL titers typically decrease with treatment. Expect titers to be positive only in an undiluted specimen, or entirely negative, 1 year after treatment of primary disease, 2 years after treatment of secondary disease, and 5 years after treatment of latent disease. Most treated patients will become seronegative, but some remain seropositive despite cure.

Test all pregnant women with a nontreponemal test in the 1st trimester. If a pregnant patient is at high risk, repeat testing in the 3rd trimester and at delivery. Pregnant patients are treated with the same regimen as nonpregnant patients based on the stage of infection.

The treatment of syphilis is as follows:

- For primary, secondary, and early latent syphilis, give benzathine PCN G 2.4 MU intramuscularly (IM) $\times 1$.
- For late latent syphilis, latency of unknown duration, and nonneurologic tertiary syphilis, give benzathine PCN G 2.4 MU IM every week $\times 3$.

- For neurosyphilis, benzathine PCN G does not reliably cross the blood-brain barrier, so the following must be used:
 - PCN G 18–24 MU IV divided every 4 hours or continuous infusion for 10–14 days
 - Ceftriaxone 2 g/day × 10–14 days (an alternative for PCN-allergic patients; however, cross-reactive allergies may occur)

Doxycycline is an alternative for PCN-allergic patients, except for those with neurosyphilis or who are pregnant. If a patient with neurosyphilis or a pregnant patient is allergic, that patient should undergo desensitization.

Herpes Simplex Virus (HSV)

HSV presents with tender, grouped vesicles on a red base (Figure 4-4) with or without regional adenopathy. Although the appearance is diagnostic, it should be confirmed with PCR serotyping. Treatment is only of benefit for initial infection if given within 72 hours and for recurrent infection if given within 48 hours. Effective agents are acyclovir, valacyclovir, or famciclovir. Patients with frequent recurrences may benefit from chronic suppressive therapy.



Figure 4-4: Herpes simplex
Source: CDC

Other Infectious Genital Ulcers

Chancroid is caused by *Haemophilus ducreyi*, a small gram-negative coccobacillus. Although a much less common ulcerative STI than syphilis in the U.S., it is the most common ulcerative STI in Africa. The initial chancroid lesion transforms from a papule to a pustule to a ragged ulcer, all of which are **painful**, unlike the syphilis chancre. It can progress to secondary chancroid with tender inguinal lymphadenopathy (buboes), which can spontaneously drain. Spread from there (tertiary chancroid) is rare. Diagnose chancroid by the clinical appearance, and confirm the diagnosis by culture. Treat it with a single dose of azithromycin (1,000 mg) or ceftriaxone (125 mg) or give the patient ciprofloxacin 500 mg bid × 3 days.

Lymphogranuloma venereum (LGV) is due to 3 specific serogroups of *Chlamydia trachomatis*: LGV-1, -2, and -3. It is extremely rare in the U.S. (< 500 cases/year) but is endemic in many parts of Asia, Africa, and South America. In the 1st stage, LGV presents with a painless papule and vesicle that eventually form a clean, **painless** ulcer. This stage is present in only 1/3 of infected patients. Most patients present in the 2nd stage with tender inguinal masses on both sides of the inguinal ligament (a.k.a. a groove sign). Diagnose LGV by the clinical appearance and via culture and NAAT. Treatment is with doxycycline for 21 days.

Granuloma inguinale (a.k.a. donovanosis) is very rare. *Klebsiella granulomatis* (formerly called *Calymmatobacterium granulomatis*) is the causative gram-negative organism that produces beefy, oozing, and paradoxically painless genital ulcers (Figure 4-5). Spread to the inguinal area produces bilateral soft tissue granulomas that look like lymphadenopathy (pseudobuboes). Diagnose the infection by its clinical appearance. Culture has a low yield, but a crushed biopsy specimen may show intracellular bacilli (**Donovan bodies**). Treat granuloma inguinale with azithromycin or doxycycline for at least 21 days, until all the ulcers are gone.

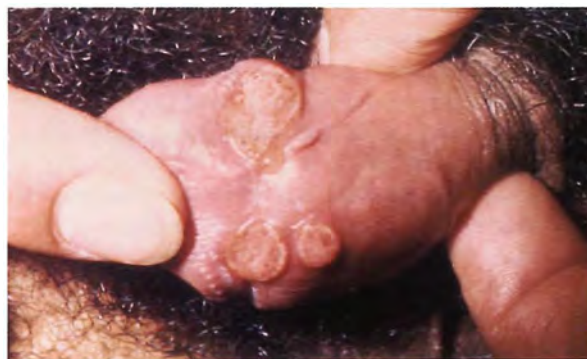


Figure 4-5: Genital lesions in granuloma inguinale
Source: CDC

PELVIC INFLAMMATORY DISEASE (PID)

PID can be caused by *Neisseria gonorrhoeae*, *Chlamydia*, or mixed genitourinary flora (aerobes and anaerobes).

Patients present with bilateral lower quadrant pain and fever +/- vaginal discharge. Physical examination commonly reveals bilateral adnexal tenderness, lower quadrant tenderness, and acute cervical motion tenderness. The clinical diagnosis has a positive predictive value (PPV) of < 90%, so use laparoscopy when the diagnosis is uncertain.

If there is no cervical discharge and cervical swabs fail to show WBCs, PID is unlikely. Test these patients for gonorrhea and chlamydia (refer to [Gonorrhea Screening on page 4-15](#) and [Chlamydia Screening on page 4-15](#)). Patients may get an associated perihepatitis (**Fitz-Hugh-Curtis syndrome**) with mild transaminase elevations and RUQ pain.

The CDC recommends empiric therapy for PID if a sexually active woman presents with one of the following findings and no other cause is identified:

- Uterine tenderness
- Adnexal tenderness
- Cervical motion tenderness

Treatment depends on whether the patient requires hospital admission or not. Admit patients if:

- prior oral antimicrobial therapy failed,
- they are unable to follow or tolerate an outpatient oral regimen,
- they have a high-grade fever with abdominal pain or vomiting,

- you suspect or find a tuboovarian abscess, or
- they are pregnant.

If a patient is admitted, the CDC recommends either of the following **inpatient** regimens:

- Cefoxitin or cefotetan IV and doxycycline PO or IV (Substitute azithromycin for doxycycline if the patient is pregnant.)
- Clindamycin and gentamicin IV

Most treatment regimens are designed to ensure treatment of both gonorrhea and chlamydia.

If admission is not indicated, the CDC recommends either of the following **outpatient** regimens:

- Ceftriaxone IM $\times 1$, then doxycycline $\times 14$ days $\pm$ metronidazole $\times 14$ days
- Cefoxitin IM $\times 1$ and probenecid plus doxycycline $\times 14$ days $\pm$ metronidazole

If you suspect the infection is **not** due to *Chlamydia* or *N. gonorrhoeae* based on the lack of STI risk factors, add metronidazole to cover bowel anaerobes.

Follow up with patients treated for chlamydial infections with a test for cure at 3 weeks. The PCR test can remain positive for many weeks.

CERVICITIS

Cervicitis is usually caused by *Chlamydia* (especially if the discharge is mucopurulent) but can also be from *Neisseria gonorrhoeae*, HSV, and *Trichomonas*. Because *Chlamydia* is intracellular, you must have cervical cells for a valid smear/culture (so scrape or use a brush). A Gram stain of cervical secretions is not sensitive or specific in the diagnosis of gonococcal cervicitis (in contrast to male gonococcal urethritis). Empiric treatment for mucopurulent cervicitis is ceftriaxone 250 mg IM $\times 1$ **plus** azithromycin 1 g PO $\times 1$. Dual therapy with ceftriaxone and azithromycin is also recommended in documented gonococcal infection. For patients with uncomplicated genital chlamydial infections, oral azithromycin as a 1 g single dose is preferred; doxycycline (100 mg PO 2 $\times$ /day for 7 days) is an alternative. Treat sexual partners as well.

Because of high rates of reinfection, retest all individuals diagnosed with *C. trachomatis* or *N. gonorrhoeae* for repeat infection 3 months after treatment, but not as a “test of cure” (unless the patient is pregnant).

URETHRITIS

Presentation

Urethritis can be divided into gonococcal and nongonococcal infection. Endocervical, vaginal, urethral (men only), or urine specimens can be tested to detect *Neisseria gonorrhoeae*. Genitourinary infections with *N. gonorrhoeae* can be detected using culture, nucleic acid hybridization testing, and NAAT. With gonococcal urethritis, the patient virtually always has a very painful, **purulent** discharge. The diagnosis is confirmed by either positive

culture results or the finding of gram-negative intracellular diplococci on Gram stain (within PMNs; **Figure 4-6**). Otherwise, consider the infection nongonococcal urethritis, which is generally due to *Chlamydia trachomatis* or, less frequently, *Ureaplasma urealyticum*, *Trichomonas vaginalis*, or HSV. For 35% of cases, the cause is unknown.

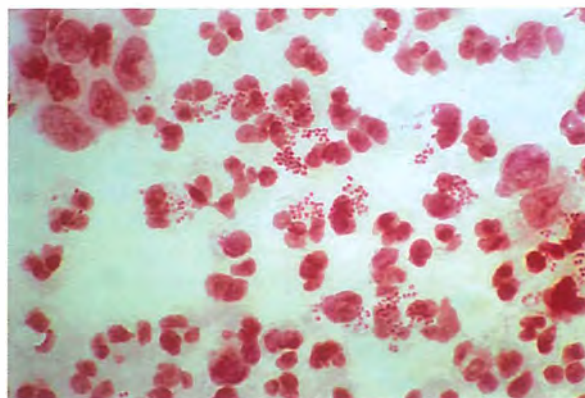


Figure 4-6: Gonorrhea (Gram stain)

Patients with nongonococcal urethritis typically have a **clear** urethral discharge, and a Gram stain shows WBCs and **no** bacteria. Gonococcal urethritis has a shorter incubation period (2–6 days vs. 1–2 weeks for chlamydia) and produces a more purulent and more productive discharge.

In all patients, perform a VDRL or RPR test and, if the result is negative, repeat it in 2 months (to allow for possible seroconversion from when blood for the 1st test was drawn). Do HIV testing for all patients with urethritis.

Consider gonococcal disease in sexually active adolescents with acute exudative pharyngitis, especially if the test results for *Streptococcus pyogenes* are negative.

Treatment

Nongonococcal urethritis: Treat with a directly observed single dose of azithromycin 1 g PO. A less desirable option due to compliance concerns is doxycycline 100 mg bid $\times 7$ days. Levofloxacin is also effective, but avoid its use in pregnant patients. Routine cotreatment for gonorrhea is no longer recommended.

Gonococcal urethritis: Resistance to PCNs, tetracyclines, and fluoroquinolones is commonly found. As a result, the CDC recommends **dual** therapy with ceftriaxone + azithromycin for gonorrhea infections of the cervix, urethra, and rectum, hoping that routine cotreatment might hinder the development of further antimicrobial-resistant *N. gonorrhoeae*.

Treat uncomplicated gonococcal infections of the cervix, urethra, rectum, and pharynx with a single dose of ceftriaxone and azithromycin.

For **pregnant women**, do **not** use quinolones or tetracyclines. Use a cephalosporin for gonorrhea and either erythromycin or azithromycin for *C. trachomatis* infection. If the pregnant patient is allergic to cephalosporins, the CDC recommends azithromycin 2 g PO $\times 1$. Perform test of cure for pregnant women 3–4 weeks after treatment.

In addition, as with all patients with documented chlamydia or gonococcal infection, pregnant women should also undergo repeat testing to evaluate for reinfection 3 months following treatment.

Always treat sexual partners of patients with either type of urethritis, even if they are not symptomatic, and always treat suspected cases immediately without waiting for culture results.

DISSEMINATED GONORRHEA

Disseminated gonococcal infection is more predominant in females and typically occurs during menses because this allows the organisms on the cervix to enter the blood stream. The clinical manifestations can consist of a sparse pustular dermatitis, tenosynovitis, as well as a septic arthritis.

Gram stains and cultures of skin lesions have a very low yield (25%), but if specimens are taken from genital, mucosal, and rectal sources, they have an 85% yield.

Treat patients diagnosed with disseminated gonorrhea with a 3rd generation cephalosporin. Include a single dose of azithromycin or levofloxacin or 14 days of doxycycline to treat possible chlamydia coinfection. After 1–2 days, patients can be switched to oral antibiotics based on susceptibilities to complete a 7-day course.

EPIDIDYMITIS

Epididymitis typically presents as unilateral testicular pain and a palpably swollen epididymis. STI pathogens are the most likely cause in sexually active men < 35 years of age. Other pathogens are usually enteric GNBs, most commonly *Escherichia coli*. If *Neisseria gonorrhoeae* is the etiology, urethritis is usually present with the typical findings; otherwise, perform NAAT of urine for *N. gonorrhoeae* and *Chlamydia trachomatis*. Treatment of epididymitis is the same as for gonorrhea in patients at high risk for STIs. For suspected enteric rod infections, use a 10-day course of a fluoroquinolone.

HUMAN PAPILLOMAVIRUS (HPV)

HPV is transmitted by direct contact and causes warts.

Genital warts result in an increased risk of cervical, vaginal, vulvar, penile, and anal cancer. There are many variants, but 15 of these variants found worldwide are designated as being high risk for cancer. HPV-16 and HPV-18 are the most common causes of cervical cancer (with an incidence of 60% and 10%, respectively). The strains that cause cervical cancer are usually subclinical. There's much more information on cervical cancer in the [Oncology](#) section.

HPV-6 and HPV-11 are the most common causes of exophytic, grossly visible genital warts. HPV-6 and HPV-11 carry **little risk** for cervical cancer.

HPV-1, HPV-2, and HPV-5 are common causes of plantar warts.

HPV vaccines contain the most oncogenic serotypes and are recommended for **all** males and females 9–26 years of age.

VAGINITIS

Vaginitis presents with a change or increase in vaginal discharge. There are 3 major causes (in descending order of frequency): bacterial vaginosis, candidiasis, and trichomoniasis. Use a systematic approach to diagnose the etiology. See [Table 4-2](#).

Table 4-2: Vaginitis Diagnostic Tests

	Vaginal pH	Wet Prep	KOH Prep
Bacterial Vaginosis	> 5.0	Clue cells	Fishy odor
Candidiasis	< 5.0	Fungal elements	Fungal elements
Trichomoniasis	> 5.0	Trichomonads	Fishy odor

KOH = potassium hydroxide

Systematic Approach to Vaginitis

Three tests on vaginal secretions/discharge can determine the etiologic agent on initial examination: pH, wet prep, and potassium hydroxide (KOH) prep.

pH: The normal vaginal pH is < 5.0 and remains so with vaginal candidiasis. A pH > 5.0 is seen in bacterial vaginosis and trichomoniasis.

Wet prep (secretions placed in normal saline under microscopy): This reveals epithelial cells studded with causative organisms (i.e., clue cells) in bacterial vaginosis and trichomonads in trichomoniasis. It shows fungal elements in candidiasis.

KOH prep (secretions placed in KOH under microscopy): This yields an amine (fishy) odor in bacterial vaginosis and trichomoniasis. KOH dissolves cellular membranes and debris but not the cellulose in fungi, so it increases the yield of finding yeast forms and pseudohyphae in candidiasis.

Bacterial Vaginosis

Bacterial vaginosis results from the replacement of the normal *Lactobacillus* in the vagina with high concentrations of anaerobic bacteria (e.g., *Mobiluncus*, *Gardnerella vaginalis*). There is a thin, “skim milk,” scanty, foul-smelling, **nonirritating** discharge that has 2 identifying features on testing:

- 1) Clue cells (epithelial cells with many adherent bacteria; [Figure 4-7](#))
- 2) An amine (fishy) odor when mixed with KOH (+whiff/sniff test)

There is no **cervical** discharge.

Treatment is with metronidazole PO × 7 days or vaginal cream × 5 days. Alternately, give tinidazole or 2%

clindamycin orally or as a cream intravaginally $\times 7$ days. Unlike with other vaginal infectious diseases, there is no single-dose therapy.

Oral metronidazole is safe in pregnancy; give this formulation instead of the gel. Bacterial vaginosis increases the risk of preterm labor if not treated orally.

Male sexual partners do **not** require treatment, because bacterial vaginosis is not an STI.

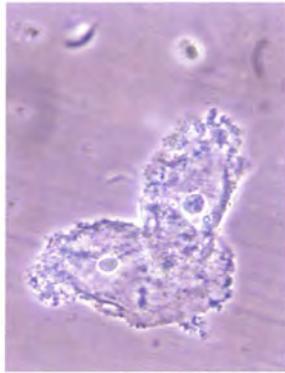


Figure 4-7: Clue cells. Stippled appearance from being covered with bacteria
Source: CDC

Vulvovaginal Candidiasis (VVC)

VVC is almost always caused by the species *Candida albicans*. It presents with adherent white plaques on an erythematous base and is usually pruritic. Remember that this can be a sign of undiagnosed diabetes or HIV, especially if recurrent.

The treatment is as follows:

- For uncomplicated VVC in a nonpregnant patient, give any azole vaginal cream. Oral azoles are equally effective, especially oral fluconazole 150 mg $\times 1$.
- For **recurrent** VVC, weekly topical azole and oral fluconazole 150 mg 1-time doses are equally effective.
- Although systemic or topical fluconazole was previously considered safe in pregnancy, a 2016 study showed that women treated with systemic or topical fluconazole had an increased risk of spontaneous abortion and stillbirth. This does not occur with topical clotrimazole or miconazole, which are the drugs of choice for pregnant women.

Trichomoniasis

Trichomonas vaginalis, a flagellated protozoan, causes vaginitis in women. (Men can also be infected but are typically asymptomatic.) Trichomoniasis presents with a profuse, thin, **frothy**, yellow-green, foul-smelling discharge (which, like bacterial vaginosis, has a +whiff test), vaginal erythema, and a **strawberry cervix**.

Treat trichomoniasis with a single dose of either metronidazole 2 g or tinidazole 2 g. Even though these are the best treatments, they are only moderately effective. Metronidazole is safe in pregnancy. Treat sexual partners as well.

CENTRAL NERVOUS SYSTEM (CNS) INFECTIONS

PREVIEW | REVIEW

- What is the clinical presentation of bacterial meningitis?
- Which organisms are the most common cause of bacterial meningitis in adults?
- What is the standard empiric treatment for bacterial meningitis in adults < 50 years of age?
- To which contacts should you give prophylaxis for meningococcal meningitis?
- Empiric coverage for a patient with a spinal epidural abscess should cover which organism, specifically?
- What are acceptable empiric regimens for a brain abscess?
- Which animals are at high risk for the transmission of rabies?

BACTERIAL MENINGITIS

Untreated bacterial meningitis is a routinely fatal disease. In the U.S., there are 3 main causes of bacterial meningitis in adults:

- *Streptococcus pneumoniae* causes the majority of bacterial meningitis in **all** adult age groups.
- *Neisseria meningitidis* (meningococcus) is more common in young adults until ~ 25 years of age and in adults > 60 years of age.
- *Listeria monocytogenes* meningitis starts at ~ 50 years of age.

Neisseria meningitidis has been declining since the 1990s. It is currently at historic lows (0.1 per 100,000).

Approach to the Patient with Suspected Bacterial Meningitis

Time is of the essence in bacterial meningitis, and an organized approach to diagnosis and treatment is essential to decrease morbidity and mortality. Suspect bacterial meningitis in anyone with a fever, headache, and stiff neck.

The Kernig and Brudzinski signs are very insensitive but highly specific ($> 95\%$). First obtain stat blood cultures, and then perform a lumbar puncture (LP) as soon as possible, but take caution to avoid precipitating herniation in patients who may have a space-occupying CNS lesion. The following parameters are predictive of finding such lesions on a CT scan, and the CT scan should

be performed prior to the LP in these circumstances; however, do not delay the administration of antibiotics while waiting on imaging results for patients with any of the following:

- An immunocompromised state
- Prior CNS disease
- Seizures in the last week
- Altered consciousness
- Papilledema
- A focal neurologic deficit

If a CT is performed and shows no contraindication (e.g., abscess), proceed with the LP. In patients who do not warrant a CT scan, obtain stat blood cultures, give IV dexamethasone and empiric IV antibiotics, and then perform the LP. Doing the LP first is ideal, but **never delay** the administration of antibiotics while waiting on an LP kit delivery or the results.

With the obtained cerebrospinal fluid (CSF), perform a Gram stain, C&S, and cell count with differential and obtain the protein and glucose levels. Rapid antigen testing is not routinely recommended because it uncommonly alters treatment. Typical findings in normal CSF vs. bacterial and viral (aseptic) meningitis are shown in Table 4-3.

Culture results are the gold standard and are positive in the majority of cases.

Antibiotics Used for Bacterial Meningitis

Because the CNS is an immune sanctuary with a decreased ability for complement and immunoglobulin to reach the site of infection, the antibiotics chosen must be **bactericidal**. Classes of antibiotics that are bactericidal are the β -lactams, glycopeptides, fluoroquinolones, and aminoglycosides. In addition, the drugs must be able to cross through the inflamed meninges. This presents a problem for the aminoglycosides, which, if used, may need to be given intrathecally. Selected 3rd generation cephalosporins with vancomycin should be the primary 1st line agents.

Chloramphenicol and TMP/SMX are bactericidal against certain organisms but are 2nd line drugs. Tetracyclines and macrolides are **not** bactericidal; do not use these.

Selecting Empiric Therapy

Age is the most useful predictor of the bacterial etiology of meningitis.

In adolescents and adults < 50 years of age, *S. pneumoniae* and *N. meningitidis* are the predominant organisms. Empiric therapy for this age group is ceftriaxone (which treats > 90% of *S. pneumoniae* strains and 100% of *N. meningitidis* strains) and vancomycin (which treats 100% of *S. pneumoniae* strains).

In adults > 50 years of age, *L. monocytogenes* becomes more common. This bacterium is not routinely susceptible to vancomycin and is resistant to cephalosporins, so add ampicillin empirically until the culture results are known. The CSF WBC count is lower with *Listeria* infection than with other bacterial infections, and the Gram stain is more commonly negative.

Patients with bacterial meningitis after neurosurgical procedures are at risk for staphylococcal and gram-negative aerobic infections; treat these patients with vancomycin and a 3rd generation cephalosporin.

Therapy Based on Gram Stain

Gram stain results allow for the reassessment of therapy within hours. If the CSF Gram stain results show an organism (as in the majority of bacterial meningitis cases), change the empiric therapy based on those results (Table 4-4).

Definitive Therapy

Cultures grow organisms from the CSF in the majority of patients with bacterial meningitis. Use the results to adjust the therapy.

Dexamethasone

Dexamethasone decreases the morbidity and mortality in adults with pneumococcal meningitis. Because > 50% of meningitis is caused by pneumococcus, start dexamethasone empirically 15–20 minutes before antibiotic administration, and continue dexamethasone treatment for 4 days if pneumococci are cultured. Discontinue dexamethasone if another causative agent is found.

Table 4-3: Normal CSF vs. Bacterial and Viral (Aseptic) Meningitis

	Normal CSF	Bacterial Meningitis	Viral Meningitis
WBC Count	< 5 cells/ μ L (0.01×10^9 /L) No PMNs	> 1,000 cells/ μ L (1×10^9 /L) High PMNs	< 1,000 cells/ μ L (1×10^9 /L) PMNs then monocytes
Glucose Level	50–75 mg/dL (2.77–4.16 mmol/L)	Low	Normal
Protein Level	< 45 mg/dL	> 100 mg/dL	< 100 mg/dL

CSF = cerebrospinal fluid PMN = polymorphonuclear leukocyte WBC = white blood cell

Table 4-4: Therapy Based on Cerebrospinal Fluid Gram Stain Results

Gram Stain	Likely Organism	Antibiotics	Comment
Gram-positive cocci	<i>Streptococcus pneumoniae</i>	Vancomycin + ceftriaxone	Until ceftriaxone sensitivity is known
Gram-negative cocci	<i>Neisseria meningitidis</i>	Ceftriaxone or penicillin	
Gram-positive bacilli	<i>Listeria monocytogenes</i>	Ampicillin +/- gentamicin Trimethoprim/sulfamethoxazole if penicillin allergic	
Gram-negative bacilli	Enteric aerobe	3 rd generation cephalosporin or meropenem	Cover for <i>Pseudomonas aeruginosa</i> if postneurosurgical

PREVENTION OF MENINGOCOCCAL MENINGITIS

Give prophylaxis to close contacts of patients with meningococcal bacteremia and/or meningitis to eradicate any possible nasopharyngeal colonization, which increases the risk of subsequent development of invasive disease. Close contacts are defined as:

- persons who have spent > 8 hours within 3 feet of the index case from 7 days prior to 1 day after presentation (e.g., those who live in the patient's household, contacts at day care centers) and
- persons exposed to the patient's oral secretions (e.g., a health care worker who has intubated the patient).

Usual clinical encounters do not merit prophylaxis for health care workers.

To eradicate the carrier state, use **one** of the following:

- Ciprofloxacin 500 mg PO × 1 (for nonpregnant adults)
- Rifampin 600 mg PO bid × 2 days (for children and nonpregnant adults)
- Ceftriaxone 250 mg IM × 1 (for pregnant adults and children < 15 years of age)

Patients with meningococcal disease who are treated with penicillin still need to be given one of these prophylactic drugs prior to discharge because penicillin does not eradicate the carrier state. See [Vaccine Schedules on page 4-86](#) for additional information.

Of the many serotypes of meningococcus, serotypes A, B, C, W, and Y are the main cause of meningitis. As of 2005 there has been a conjugate vaccine against serotypes A, C, W, and Y. In 2014, the FDA approved MenB vaccine against serotype B. Serotype B has been the main cause in the U.S. Recently, serotype Y has increased. Because there is no overlap between the vaccines, decisions on vaccination should be informed by results of serotyping meningococcal meningitis cases in the region.

SETTINGS TO CONSIDER NONBACTERIAL MENINGITIS

Suspect **Cryptococcus** in patients with acquired immunodeficiency syndrome (AIDS), acute lymphocytic

leukemia, or lymphoma or who use corticosteroids, and look for cryptococcal antigen in the blood and CSF.

Consider **amebic meningitis** when the patient has been swimming in freshwater lakes, ponds, or irrigation canals.

ASEPTIC MENINGITIS

The diagnosis of aseptic meningitis is based on clinical and CSF signs of meningeal inflammation (mild CSF pleocytosis and mildly elevated protein) without a clear infectious cause. The vast majority of these cases are due to viral infection. Patient complaints are similar to those for bacterial meningitis, although the symptoms are less acute and severe.

The viruses that cause aseptic meningitis are:

- Enteroviruses (e.g., coxsackievirus, echovirus, enterovirus)
- Arboviruses (e.g., West Nile virus)
- HSV
- Acute HIV infection

Fungal and bacterial causes of aseptic meningitis include:

- Endemic fungi
- Cryptococcal meningitis (seen in AIDS, acute lymphocytic leukemia, and lymphomas)
- *Nocardia*
- *Mycobacterium tuberculosis*
- *Borrelia burgdorferi* (Lyme disease)

TUBERCULOUS MENINGITIS

Tuberculous meningitis causes a thick, basilar meningitis that often causes cranial nerve injury and presents with cranial neuropathy, such as a 6th nerve palsy, and CSF with a lymphocytic pleocytosis, high protein level, and very low glucose level.

LYME MENINGITIS

Lyme meningitis can cause peripheral and cranial nerve palsies, especially of the 7th cranial nerve (Bell's palsy), so think of Lyme disease or HSV infection when a patient presents with an isolated facial nerve palsy. For treatment information, see [Lyme Disease on page 4-51](#).

SPINAL EPIDURAL ABSCESS

Spinal epidural abscesses (pus between the dura and vertebrae) are caused by either hematogenous spread or local extension (e.g., from vertebral osteomyelitis). *Staphylococcus aureus* is the most common cause. Patients can present with the classic triad of fever, back pain, and radiculopathy.

On CSF analysis, a spinal epidural abscess resembles aseptic meningitis, with a moderate pleocytosis, modest protein elevation, normal glucose level, and negative result on Gram stain and culture. If an LP is performed, take care not to go through the area of infection. Obtain an MRI if any 2 of the 3 previously mentioned symptoms occur. CT is not as good as MRI because it is susceptible to bony artifacts. Obtain blood cultures. Drainage is required if technically feasible. Empiric coverage includes drugs effective against staphylococci. Definitive therapy is based on the blood or surgical cultures.

NEUROSYPHILIS

See the prior discussion of neurosyphilis under [Syphilis on page 4-16](#).

BRAIN ABSCESS

Bacteriology of a brain abscess reflects organisms found in sinusitis, dental infections, and otitis media. Postsurgical abscesses can show *Staphylococcus aureus* or GNBs. *Cutibacterium* is a common organism for postneurosurgical abscesses. Common locations from hematogenous sources are the frontal, temporal, and parietal lobes via the middle cerebral artery.

The symptoms are a subacute onset of fever, focal neurologic deficit, and sometimes seizures. Diagnose a brain abscess using a CT scan with contrast or MRI. If accessible, aspirate the abscess and give antibiotic treatment based on the results. An LP is contraindicated if signs of increased intracranial pressure are present, such as papilledema or focal neurologic signs. An LP rarely helps identify the infectious bacteria because the organisms are seldom in the subarachnoid space.

Treatment is initially empiric, followed by definitive therapy for 4–8 weeks if cultures are obtained by drainage. Give ceftriaxone + metronidazole to cover aerobes and anaerobes. Penicillin has been used for anaerobic coverage in the past but there is increasing resistance to this. If you suspect GNBs (e.g., if there is an ear focus), consider an agent with *Pseudomonas* coverage + metronidazole. If there was a history of bacteremia/endocarditis, a neurosurgical procedure, or penetrating head trauma, add vancomycin for MRSA. For postoperative neurosurgical patients, use ceftazidime, cefepime, or meropenem to cover hospital-related gram-negative organisms, including *Pseudomonas*.

VIRAL ENCEPHALITIS

Herpes Simplex Virus Type 1 (HSV-1)

The most common sporadic viral encephalitis is due to HSV-1. The virus enters the CNS via the trigeminal or olfactory tract following an episode of primary or recurrent HSV-1 of the oropharynx or reactivation of latent virus in the CNS without evident oropharyngeal herpes. Disease is usually frontotemporal, and the symptoms range from alterations in behavior, seizures, cranial nerve dysfunction, and hemiparesis to alterations of consciousness, all over a period of < 1 week. Brain imaging is usually abnormal, showing unilateral, sometimes bilateral focal cerebral inflammation. The CSF shows a lymphocytic, aseptic meningitis that is sometimes hemorrhagic. In HSV meningoencephalitis, the CSF glucose is sometimes mildly decreased. The CSF can be normal initially in encephalitis; HSV PCR of the CSF is positive > 95% of the time. Treatment is with high-dose IV acyclovir for ≥ 14 days.

Arboviral Encephalitis

The arboviruses are the most common seasonal viral encephalitides and are named after the geographic location from which they originally came (e.g., West Nile, St. Louis). They are discussed under [Arboviruses on page 4-75](#).

Rabies

Rabies is a preventable but almost always fatal illness that is very rare in the U.S. (< 5 cases a year) but causes ~ 30,000 deaths a year worldwide. Fewer than 20 patients worldwide have survived rabies without treatment. Rabies virus is found in bats, raccoons, skunks, foxes, dogs, cats, and ferrets but not in squirrels, rats, or any other rodents. Worldwide, rabies is primarily transmitted to humans by dogs, but in the U.S., bats are the most common cause. Rabies typically presents within 1–3 months after exposure with a viral prodrome followed by encephalitis, ascending paralysis, neuropathic pain +/- sensorimotor deficits, and eventually hydrophobia, aerophobia, and delirium.

Diagnose rabies by:

- virus-specific immunofluorescent staining of a skin biopsy sample of hair follicles at the nape of the neck,
- detection of the virus from the saliva by reverse transcriptase polymerase chain reaction (RT-PCR), or
- detection of antirabies antibodies in the serum or CSF.

Preexposure prophylaxis is recommended for cave explorers, veterinarians, animal control workers in endemic areas, and anybody who handles bats—but **not** for hunters, mail carriers, or other persons.

Determine the need for postexposure prophylaxis based on the suspected animal source. Bites from bats, raccoons, foxes, and skunks are considered high risk and warrant prophylaxis. Have pet dogs, cats, and ferrets observed for 10 days, and if there are no signs of rabies,

there is no need for prophylaxis. Bites from small rodents never need prophylaxis. Prophylaxis consists of human rabies immunoglobulin (HRIG)—with ~ 50% injected in the tissue around the wound and the remainder administered IM—and vaccination with the rabies human diploid cell vaccine. Give each in a separate site. If a person has been vaccinated previously, administer only a booster vaccine after a bite, not HRIG.

PRION DISEASE

Prions are proteinaceous infectious particles that lack nucleic acid and are destructive to neural tissue.

The most important prion diseases are Creutzfeldt-Jakob disease (CJD) and variant CJD (vCJD). In animals, prions cause mad cow disease (bovine spongiform encephalopathy), which is vCJD if transmitted to humans.

CJD is almost always sporadic, but ~ 5% of cases are transmitted from person to person (via, e.g., corneal transplants, cadaveric human growth hormone), and very few cases are genetic. The incubation period is ~ 18 months. Patients with CJD get myoclonus and severe, rapidly progressive dementia. MRI shows diffuse cerebral disease, and electroencephalography (EEG) classically shows periodic synchronous biphasic or triphasic sharp wave complexes. An abnormal amount of 14-3-3 protein may be present in the CSF. The clinical course is one of progressive rapid deterioration, with the majority of patients dying within 6 months of diagnosis. There is no effective therapy.

vCJD is transmitted from eating meat from cattle with bovine spongiform encephalopathy (a.k.a. mad cow disease). No endemic human cases of vCJD have been reported in the U.S., although some veterinary cases have been reported. Patients with vCJD have initial psychiatric symptoms and paresthesias and then ataxia and cognitive impairment. Paresis of upward gaze occurs in ~ 50% of patients. Death occurs in ~ 1 year.

INFECTIVE ENDOCARDITIS (IE)

PREVIEW | REVIEW

- What is the most common organism causing native valve endocarditis?
- What is the usual cause of prosthetic valve endocarditis > 2 months after surgery?
- What are some specific physical examination signs of endocarditis?
- How many sets of blood cultures should be drawn on a patient with suspected endocarditis?
- Which organisms cause culture-negative endocarditis?
- What 2 types of tests make up the major criteria for the diagnosis of endocarditis?

- Know the various regimens to treat endocarditis based on resistance patterns and the type of valve (native vs. prosthetic).
- List the indications for the early surgical treatment of bacterial endocarditis.

OVERVIEW

IE occurs on prosthetic and native valves or other endocardial surfaces. We will specifically discuss culture-negative IE and IE seen in injection drug users. These categorizations are predictive of the microbiology and hence the treatment of the disease. The previous designations of acute and subacute are no longer used.

NATIVE VALVE ENDOCARDITIS (NVE)

NVE is more common on the **left** side of the heart and usually occurs on defective or damaged valves. It can also occur in the path of abnormal flow across a ventricular septal defect (VSD) or patent ductus arteriosus. Over the last half century, the median age of onset has increased and is now around 60 years of age.

The most common organism infecting native valves is *Staphylococcus aureus*, followed by viridans streptococci and then enterococci. Patients with *S. aureus* endocarditis have a higher incidence of embolic phenomena and death. There is a group of organisms that causes a small percentage of IE cases. This group was previously called HACEK but is now called **AACEK**, which stands for the following:

- *Aggregatibacter aphrophilus* (formerly *Haemophilus aphrophilus*)
- *Aggregatibacter actinomycetemcomitans* (formerly *Actinobacillus actinomycetemcomitans*)
- *Cardiobacterium hominis*
- *Eikenella corrodens*
- *Kingella kingae*

These organisms share several commonalities: They take longer to show growth in vitro, cause large vegetations with a high risk of embolization, and are susceptible to PCNs.

Fungal endocarditis is seen in IV drug abusers and patients with central IV catheters.

PROSTHETIC VALVE ENDOCARDITIS (PVE)

Early PVE (occurring within 2 months of valve insertion) is usually due to inoculation during surgery, and staphylococcal species are the most common infecting organisms. PVE is harder to cure than NVE; if there is no response to the 1st round of (adequate) antibiotics, replace the valve. If acute cardiac decompensation occurs, patients need emergent surgical intervention regardless of the duration of prior antibiotics and have a mortality rate of ~ 40%.

Late PVE (occurring > 2 months after valve insertion) is caused by organisms similar to those causing NVE; however, coagulase-negative staphylococci are much more common (~ 15%). If the infecting organisms are viridans streptococci or enterococci, the likelihood of cure with antibiotics is higher than with staphylococci. Better antibiotic treatment success is seen with porcine bioprosthesis than with metal valves.

The valve must be replaced if there is evidence of a valve ring infection, myocardial penetration, or an unstable prosthesis. If you see new heart block or a new bundle branch block, think of this.

HISTORY AND PHYSICAL EXAMINATION

Occasionally IE presents only with signs of embolic events, such as black toes or septic emboli to organs (e.g., embolic stroke, brain abscess, splenic infarct). It can also present as a lingering illness with nonspecific symptoms (e.g., weight loss, fevers, chills, night sweats) or heart failure due to valvular insufficiency.

Focus the history on recent potential exposures to typical organisms:

- Skin infections (staphylococci)
- Dental work (viridans streptococci)
- Genitourinary manipulation or obstruction (enterococci)
- IV catheters (staphylococci)
- Injection drug use (*S. aureus*, GNBs, or yeast)

Also look for clues to uncommon organisms, especially if the blood cultures are negative. Animal exposures predispose patients to *Coxiella*, *Bartonella*, and *Tropheryma whippelii*.

Physical examination may show the following classic stigmata, many of which are part of the Duke criteria used to diagnose the disease:

- Conjunctival hemorrhages
- Petechiae (conjunctival and cutaneous; this is the most common skin finding)
- Splinter hemorrhages (of the fingernails and toenails)
- Janeway lesions (nonblanching, painless, reddish lesions on the hands or feet)
- Osler nodes (painful, purplish lesions on the fingers or toes)
- Roth spots (retinal hemorrhages)

These signs are seen in < 25% of cases. When found, however, they are highly specific for endocarditis. 85% of patients will have a murmur and ~ 20% a changing murmur, but these are less-specific findings.

Systemic involvement commonly includes neurologic deficits (the most common cause of death), infarctions of the spleen and kidneys, immune complex glomerulonephritis, and septic pulmonary infarction in right-sided disease.

LABORATORY EVALUATION

Blood cultures are routinely positive (>95% of the time) for patients with IE. This is because the infection is in contact with the bloodstream.

Blood cultures are vital in diagnosing endocarditis of any type; draw **3 sets before** starting empiric antibiotics.

Additional nonspecific laboratory abnormalities commonly seen in endocarditis include:

- Elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)
- Anemia of chronic inflammation
- Leukocytosis or leukopenia
- Thrombocytopenia
- Proteinuria, hematuria, and pyuria
- Evidence of immune activation (low complement levels, cryoglobulinemia, rheumatoid factor [RF], and a +RPR test)

CULTURE-NEGATIVE ENDOCARDITIS

If all 3 blood cultures are negative, there is no history of preculture antibiotic treatment, and the patient meets the clinical criteria for endocarditis, this is called culture-negative endocarditis. Consider the following causative agents:

- Fungi
- Q fever (*Coxiella burnetii*)
- *Bartonella* species
- *Tropheryma whippelii*
- *Chlamydia psittaci*
- *Abiotrophia* species (previously known as nutritionally deficient streptococci)

The following are the appropriate tests/procedures for each cause listed above:

- Fungal blood cultures and urinary antigen testing for *Histoplasma* and *Blastomyces*
- Serologies for *Coxiella*, *Bartonella*, and *C. psittaci*
- Alerting the lab to use special culture techniques to look for *Abiotrophia*

T. whippelii endocarditis is commonly diagnosed in removed valves by using special culture techniques or 16S ribosomal ribonucleic acid (rRNA) testing. If you alert the microbiology lab, it will hold blood cultures longer when culture-negative endocarditis is suspected.

ECHOCARDIOGRAPHY

In NVE, transthoracic echocardiography (TTE) has a sensitivity of up to 75% and a specificity of > 90% for the detection of vegetations. In PVE, the sensitivity drops to 17-36%. Transesophageal echocardiography (TEE) has a sensitivity and specificity of > 90% in NVE and a sensitivity of 86-92% in PVE. The 2015 AHA/ACC Infective Endocarditis in Adults: Diagnosis, Antimicrobial

Therapy, and Management of Complications guidelines recommend the following indications for the use of TTE and TEE in diagnosing endocarditis:

- Use TTE as the initial test to detect vegetations.
- If the TTE is nondiagnostic and there is a moderate to high suspicion of endocarditis, perform TEE. Also use TEE to detect suspected complications (such as abscess) or when intracardiac leads are present.

DIAGNOSIS

The diagnosis is based on fulfillment of the **modified Duke criteria**, which include clinical, laboratory, and echocardiographic characteristics, regardless of whether a patient has native or prosthetic valves.

Definite endocarditis is diagnosed when the patient has any of the following:

- Pathologic evidence of disease
- 2 major criteria (see below)
- 1 major criterion + 3 minor criteria (see below)
- 5 minor criteria

Pathologic evidence is either visible organisms from a vegetation or valve lesion or a positive culture from the same tissue.

Possible endocarditis is diagnosed with either:

- 1 major criterion + 1 minor criterion or
- 3 minor criteria.

The 2 major criteria are:

- 1) **Positive blood cultures.** There are 3 ways that this criterion can be met:
 - The organism is one that typically causes endocarditis and is found in ≥ 2 blood cultures 12 hours apart. These organisms are *S. aureus*, viridans streptococci, *Streptococcus bovis*, enterococci, or the AACEK organisms.
 - If the organism is **not** one that typically causes endocarditis, there must be ≥ 3 positive cultures or the majority of ≥ 5 cultures drawn at least an hour apart from first to last.
 - There is a single positive blood culture for *C. burnetii* (or seropositivity for *C. burnetii*). This is the only organism that meets the criterion with a single positive blood culture.
- 2) **Abnormal echocardiogram** with any of the following:
 - An oscillating mass on a valve or on supporting structures
 - An oscillating mass in the path of a regurgitant jet
 - An oscillating mass on an implanted device
 - An abscess
 - Prosthetic valve dehiscence
 - A new regurgitant valve by echocardiography or auscultation

The 5 minor criteria are:

- 1) A predisposing condition (i.e., valve disease, injection drug use)
- 2) Fever $> 100.4^{\circ}\text{F}$ (38.0°C)
- 3) Vascular phenomena (e.g., arterial emboli, pulmonary infarcts, mycotic aneurysms, stroke, conjunctival hemorrhages, Janeway lesions)
- 4) Immunologic phenomena (e.g., acute glomerulonephritis, Osler nodes, Roth spots, +RF)
- 5) A positive blood culture that does not meet a major criterion

Of note, *S. bovis* has recently been reclassified into 4 species: *S. gallolyticus*, *S. lutetiensis*, *S. infantarius*, and *S. pasteurianus*.

ANTIBIOTIC TREATMENT OF BACTERIAL ENDOCARDITIS

While therapy is based on specific organisms, remember these 5 general concepts:

- 1) Endocarditis requires bactericidal antibiotics because white cells and opsonins have difficulty penetrating to the center of vegetations, so the antibiotic must do the killing.
- 2) With rare exceptions, give antibiotics IV for the duration of treatment.
- 3) Give antibiotics at the appropriate dose to ensure bactericidal levels.
- 4) There are only 3 scenarios in which a 2-week duration is sufficient:
 - For viridans streptococci if an aminoglycoside is added to the regimen
 - For *S. bovis*
 - For uncomplicated right-sided *S. aureus* endocarditis
- 5) Treat all other organisms for a minimum of 4 weeks (Table 4-5 on page 4-28).

Viridans Streptococci and *Streptococcus bovis*

If the organism is susceptible to PCN, give 4 weeks of PCN G, ampicillin, or ceftriaxone (2 g/day). Adding gentamicin can reduce the duration to 2 weeks; however, keep it at 4 weeks if there is an abscess. Gentamicin is not recommended for patients with chronic kidney disease (CKD). Vancomycin can be used for 4 weeks in patients unable to tolerate the β -lactam, but it is **not** preferred for initial treatment.

If there is intermediate resistance to PCN, the regimen is the same except that the dose of PCN G is increased or ceftriaxone is substituted.

Prosthetic valve treatment is generally the same regimen, but the duration of treatment is lengthened.

Table 4-5: Treatment of Bacterial Endocarditis

Organisms	Susceptibility Testing	Drug Regimen	Duration
Viridans streptococci, <i>Streptococcus bovis</i> (See reclassification of this species under <i>Viridans Streptococci</i> and <i>Streptococcus bovis</i> on page 4-27.)	PCN-sensitive	PCN G, ampicillin, or ceftriaxone	4 weeks Prosthetic valve = > 4 weeks
		(PCN G, ampicillin, or ceftriaxone) + gentamicin	2 weeks
		Vancomycin (alternative)	4 weeks
<i>Staphylococcus aureus</i> or coagulase-negative staphylococci	PCN-intermediate	Increased dose of PCN G or ceftriaxone	4 weeks
	Methicillin-susceptible	Nafcillin	6 weeks Prosthetic valve = add rifampin + gentamicin
	Methicillin-resistant	Vancomycin	6 weeks Prosthetic valve = add rifampin + gentamicin
Uncomplicated right-sided staphylococci	Methicillin-susceptible	Nafcillin; if PCN allergic, daptomycin or vancomycin	2 weeks
Enterococci	PCN-sensitive (depending on ampicillin and vancomycin susceptibilities)	(PCN G or ampicillin or vancomycin) + gentamicin	4–6 weeks Prosthetic valve = 6 weeks
	Resistant to ampicillin, PCN G, and vancomycin	Very specialized	Very specialized
AACEK (<i>Aggregatibacter aphrophilus</i> , <i>Aggregatibacter actinomycetemcomitans</i> , <i>Cardiobacterium hominis</i> , <i>Eikenella corrodens</i> , <i>Kingella kingae</i>)		Ceftriaxone	4 weeks Prosthetic valve = 6 weeks

PCN = penicillin

Perform a colonoscopy if endocarditis is caused by what was formerly known as *S. bovis*, given the high prevalence of colon cancer in these patients. (*S. bovis* has been reclassified and consists of 4 species: *S. gallolyticus*, *S. lutetiensis*, *S. infantarius*, and *S. pasteurianus*.)

Staphylococcus aureus without Prosthetics

Methicillin-susceptible *S. aureus* (MSSA) left-sided or right-sided disease with emboli requires nafcillin × 6 weeks. The addition of an aminoglycoside is not recommended, because it does not improve cure rates and it increases nephrotoxicity.

Treat methicillin-resistant *S. aureus* (MRSA) endocarditis with vancomycin × 6 weeks. Alternatively, use daptomycin, especially if the vancomycin MIC is > 1 mcg/mL.

For MSSA uncomplicated right-sided disease, give nafcillin or oxacillin × 2 weeks. For patients with hypersensitivities to the nafcillin or oxacillin, cefazolin × 2 weeks can be used. Daptomycin or vancomycin × 4 weeks are acceptable alternatives for patients with anaphylactic penicillin allergy.

Treat MRSA isolates × 6 weeks with vancomycin or daptomycin only.

Staphylococcus aureus with Prosthetic Valves

For MSSA prosthetic valve disease, give nafcillin + rifampin + gentamicin for ≥ 6 weeks. For MRSA prosthetic valve disease, give vancomycin + rifampin + gentamicin for ≥ 6 weeks. Surgery is almost always indicated.

Enterococci

For native valve endocarditis, based on susceptibilities, if the organism is sensitive to PCN, give gentamicin + PCN or ampicillin or vancomycin × 4–6 weeks.

Prosthetic valve treatment is the same regimen, but the duration of treatment is lengthened to 6–8 weeks.

If the organism is resistant to PCN, ampicillin, and vancomycin, treatment is difficult and specialized, utilizing variations of linezolid or daptomycin (if sensitive) +/- imipenem/cilastatin with either ampicillin or ceftriaxone.

AACEK Organisms

Treat AACEK organisms with ceftriaxone × 4 weeks. Alternatives include ampicillin-sulbactam and ciprofloxacin. If a prosthetic valve is involved, the duration of treatment is 6 weeks.

SURGICAL TREATMENT OF BACTERIAL ENDOCARDITIS

Early surgery (defined as surgery during the initial hospitalization prior to the completion of antibiotic therapy) is indicated in the following situations:

- Heart failure refractory to medical therapy
- Resistant organisms with no available bactericidal therapy
- Development of heart block
- Development of an abscess
- Persistence of positive blood cultures or fever for > 5–7 days into therapy
- A relapse of PVE

A less well-established indication for early surgery is a vegetation > 10 mm.

PREVENTION OF ENDOCARDITIS

Administration of antibiotics to prevent endocarditis is only done under specific circumstances depending on whether the patient is in a high-risk group for endocarditis and if the procedure has a high risk of causing bacteremia.

The only adult patients considered to be at high risk for acquiring endocarditis are those with prosthetic cardiac material (e.g., valves, unrepaired or repaired cyanotic congenital heart disease) or a prior history of endocarditis.

The only procedures requiring prophylaxis are the following:

- Dental procedures that cause bleeding because of manipulation of the gingiva or periapical areas or perforation of the oral mucosa
- Respiratory tract procedures that cut through the mucosa, such as tonsillectomy or bronchoscopy with biopsy

For dental procedures:

- Most patients receive a single 2 g dose of amoxicillin 30–60 minutes prior to the procedure.
- PCN-allergic patients can receive cephalexin, clindamycin, clarithromycin, or azithromycin.
- Those unable to take an oral medication should receive parenteral ampicillin, cefazolin, or ceftriaxone.

For respiratory tract procedures that cut through the mucosa, use the above regimens. If an active respiratory tract infection is the reason for the procedure (e.g., drainage of an abscess or empyema), use one of these antibiotics as part of the treatment regimen. If the patient is known or suspected to be colonized or infected with *S. aureus*, add antistaphylococcal antibiotics.

CARDIAC IMPLANTABLE ELECTRONIC DEVICE (CIED) INFECTIONS

CIED (i.e., pacemaker, implantable cardioverter-defibrillator) infections occur at a rate of ~ 1%. The infection can be limited to the tissue in which the device is placed (i.e., a pocket infection) or involve the leads within the heart, and it can occur as a result of contamination at the time of placement or from bacteremia. *Staphylococcus aureus* and coagulase-negative staphylococci are the main culprits. Risk factors include early device reoperation (posing the highest risk), a longer procedure duration, a device battery change, chronic kidney disease, and immunosuppression (either from an underlying condition or from a medication).

A pocket infection typically presents with pain, erythema, swelling, and sometimes systemic symptoms. A deeper infection presents with systemic symptoms, namely fever, chills, and right-sided endocarditis (refer to [Infective Endocarditis \(IE\)](#) on page 4-25).

Obtain 3 sets of blood cultures separated by at least 1 hour unless the patient is septic, in which case the cultures must be obtained sooner. Perform a TEE (not TTE) as the initial imaging modality.

Treatment of a pocket infection consists of device removal (including leads) and initiation of empiric antibiotics to cover MRSA (e.g., vancomycin). The therapy is tailored to the causative organism once the culture results are known, and the total duration of therapy is 10–14 days. Treat a deeper device infection as you would treat endocarditis (refer to [Infective Endocarditis \(IE\)](#) on page 4-25).

HUMAN IMMUNODEFICIENCY VIRUS (HIV) AND ACQUIRED IMMUNODEFICIENCY SYNDROME (AIDS)

PREVIEW | REVIEW

- What is the viral set point, and what is its significance?
- Patients with immunosuppression from autoimmune deficiency syndrome (AIDS) are at risk for developing infections with which organisms?
- How is human immunodeficiency virus (HIV) infection diagnosed in the acute and chronic stages? What is the utility of measuring HIV ribonucleic acid?
- What is the significance of the CD4 count?
- Which new HIV+ patients should receive resistance testing?
- Which nucleoside reverse transcriptase inhibitor can cause the development of kidney disease?
- Which antiretroviral is teratogenic?

- What is the primary toxicity of nevirapine?
- Jaundice can occur with which antiretroviral drug?
- Which protease inhibitor (PI) is used to boost the drug concentrations of other PIs?
- What is the serious side effect of abacavir, and how can it be screened for?
- Which exposures should receive postexposure prophylaxis for HIV?
- Which pregnant women should be treated for HIV, and with what? What is the treatment goal?
- What are the symptoms of early HIV infection?
- How is *Pneumocystis jiroveci* pneumonia (PJP) best diagnosed?
- Which ancillary treatment should you give to patients who develop severe hypoxemia due to PJP?
- When should you give patients primary prophylaxis for PJP?
- What is the treatment duration for latent tuberculosis in patients with HIV/AIDS?
- How is cryptococcal meningitis diagnosed?
- What is the typical presentation of central nervous system toxoplasmosis?
- Name some of the organisms that can cause chronic diarrhea in patients with AIDS.

OVERVIEW

Changes in the treatment and management of HIV infection are evolving rapidly. The following information covers the basics. Antiretroviral drugs are listed in the contents specifications for the exams, so this information is presented here. Realize, however, that exam questions are more likely to focus on the diagnosis and complications of disease and on side effects of medications than on having you start or change antiretroviral therapy (ART) regimens.

EPIDEMIOLOGY

According to the CDC, as of 2016 in the U.S.:

- There were 1.2 million people living with HIV (~ 15% are unaware).
- There were ~ 38,500 new HIV infections that year.
- Men who have sex with men made up a disproportionate number of the cases, at 63%, as did Blacks, at 44%.
- Heterosexual contact was the transmission category in 25% of cases, and injection drug use was the transmission category in 14% of cases.
- Men represented 80% of cases.
- The most common decile was 20–29 years of age.

HIV PATHOGENESIS

The HIV pathogenesis is relevant to the mechanism of the antiretroviral drugs.

The HIV particle is composed of a dense, single-stranded ribonucleic acid (RNA) core surrounded by a lipoprotein envelope. The RNA contains reverse transcriptase, which allows the RNA to be transcribed into deoxyribonucleic acid (DNA), which is then integrated into the host's genome. The cell then becomes an HIV-producing machine.

The HIV envelope glycoprotein (gp120) binds to the cluster of differentiation 4 (CD4) receptors and coreceptors (such as C-C chemokine receptor Type 5 [CCR5]) on the helper T cells, macrophages, and monocytes. The virus must bind to both the CD4 and CCR5 molecules to fuse with the cell. After fusion, the viral core material enters the cell and is reverse transcribed into DNA that integrates into the human genome and codes for the production of more virion RNA and structural proteins. These proteins, after being cleaved by a protease, then combine with the viral RNA and bud off of the cell using the CD4 cell membrane as a new envelope. This eventually causes destruction of the CD4 cells. The CD4 cells are the major regulator cells in the body; they suppress B lymphocytes and regulate the CD8 suppressor cells.

After initial infection, the virus replicates quickly and robustly until the body controls the infection with cell-mediated immunity. The body establishes a kind of homeostasis with the virus in which the virus is contained to some degree. Some people contain their virus better than others.

The **viral set point** is the viral load that is established after a patient's immune system controls the primary infection; it varies from person to person. When a patient stops ART, the virus typically rebounds to a level that is at the patient's baseline. The higher the viral set point, the faster the CD4 cells are killed and the faster the HIV progresses and the patient becomes ill if not treated.

Continued HIV replication is lytic for CD4+ cells, and B cells also become dysregulated and dysfunctional and are no longer suppressed, causing a polyclonal increase in total serum immunoglobulins but with a decreased ability to create new antibodies. For this reason, infectious diseases in patients with AIDS include not only those occurring from cell-mediated immunodeficiency (e.g., *Pneumocystis* pneumonia, viruses, mycobacteria, fungi), but also those seen with humoral deficiency (e.g., pneumococcus, meningococcus, *Giardia*).

PRESENTATION

Untreated HIV has a long latent period prior to its clinical manifestations unless diagnosed in the acute stage. The acute stage is called symptomatic acute HIV infection, acute retroviral syndrome, or primary retroviral infection. The most common symptoms are rash, sore throat, headache, fever, lymphadenopathy, myalgias, and arthralgias.

The subsequent immunologic decline occurs over several years, and unless screened prior to this, the HIV infection is commonly diagnosed only when the patient presents with symptomatic disease.

SCREENING

Test all persons at least once when they are 13–64 years of age or if they have at-risk behavior outside of this age range. Repeat testing is based on their risk group:

- For high-risk populations (e.g., persons who use IV drugs, men who have sex with men, patients with prior STIs), screen at least annually.
- Screen other populations as the clinical situation warrants. New-onset TB or an STI should trigger screening. Recurrent *Candida* infections or herpes zoster are also examples of situations in which screening is appropriate.

DIAGNOSIS

In the acute and chronic stages, HIV infection is diagnosed by demonstrating the presence of the virus or antibody to the virus. Antibody in acute infection may take up to 3–7 weeks after infection to be detectable.

The presence of HIV can also be detected with tests that measure the actual levels of HIV RNA (the viral load) by amplifying its RNA. These tests are used for initial diagnosis, to assess prognosis, and to monitor the response to ART. Current PCR assays can detect the virus as early as 5 days after infection.

The CDC 2015 Sexually Transmitted Diseases Treatment Guidelines recommend testing with a 4th generation assay, which tests to see if any of the following are present:

- HIV-1 antibody
- HIV-2 antibody
- HIV-1 antigen
- HIV-2 antigen

If any of these are positive, do further testing to see which specific assays are positive to detect chronic infection (antibody present) or acute infection (antigen present).

TREATMENT

Give **all** patients with HIV infection ART with a combination of agents. Adherence to the ART regimen is a key determinant in the degree and duration of viral suppression. The CD4 count is an indication of how immunosuppressed the patient is at the commencement of therapy. The viral load is an indicator of how rapidly the CD4 count will continue to decline if the HIV is left untreated. Therapy is monitored by following the CD4 count and viral load with the goal of getting the viral load to an undetectable level, after which the CD4 count usually increases. Clinical treatment guidelines are released annually by the National Institutes of Health. Prior to treatment, test **all** patients for HIV genotype or phenotype for resistance to antiviral drugs. Repeat testing

if a patient is failing therapy, as indicated by a failure to suppress the viral load below detection when that patient is taking medications reliably.

When the viral load is high and the CD4 count is < 100 cells/ μL ($0.1 \times 10^9/\text{L}$) and decreases rapidly with ART, an **immune reconstitution inflammatory syndrome (IRIS)** can occur. There can be an exacerbation of other preexisting infections that are now unmasked, such as TB, HSV, cytomegalovirus (CMV), and cryptococcal meningitis, because the body now has the ability to mount a response. The overall risk of developing an IRIS is 7–10%. The benefit of starting ART generally outweighs the IRIS risk. If an IRIS develops, the recommendations are to continue with ART and treat the underlying opportunistic infections. In severe situations, corticosteroids can be given for a brief time.

Antiretroviral Drugs

Summary

The classes of anti-HIV drugs are:

- Nucleoside reverse transcriptase inhibitors (NRTIs) and nucleotide reverse transcriptase inhibitors (NtRTIs)
- Nonnucleoside reverse transcriptase inhibitors (NNRTIs)
- Protease inhibitors (PIs)
- Fusion inhibitors (FIs)
- Integrase strand transfer inhibitors (INSTIs)
- CCR5 antagonists
- Postattachment inhibitors

A review of these classes follows, with individual agents highlighted in [Table 4-6 on page 4-32](#).

Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

NRTIs are drug analogs of the deoxynucleotides needed to synthesize viral DNA. They inhibit the replication of HIV by competing with the normal deoxynucleotides. When an NRTI is incorporated into the growing viral DNA, the growing chain terminates, and that DNA cannot be incorporated into the cell's DNA or produce more HIV.

Nonnucleoside Reverse Transcriptase Inhibitors (NNRTIs)

NNRTIs work very differently from NRTIs. These make the reverse transcriptase ineffective by binding to a different site on the enzyme.

Protease Inhibitors (PIs)

PIs inhibit the HIV protease enzyme that is involved with processing the final assembly of the virion. PIs are typically given with low-dose ritonavir (another PI) because ritonavir interferes with the catabolism of the drug and thus boosts the drug levels of the coadministered PI (which is known as ritonavir boosting). This allows for less frequent dosing.

Table 4-6: Antiretrovirals Used in the Management of Human Immunodeficiency Virus

Drug Class	Drug	Use	Toxicity	Comment
Nucleoside/nucleotide reverse transcriptase inhibitors	Abacavir	1 st line with lamivudine	Severe hypersensitivity reaction if HLA-B*57:01+	Test for HLA-B*57:01 gene prior to administration; once-daily dosing
	Emtricitabine	1 st line with tenofovir	Rare	Cross-resistance with lamivudine; once-daily dosing
	Lamivudine	1 st line with abacavir	Rare	Cross-resistance with emtricitabine; once-daily dosing
	Tenofovir (TDF; newer formulation is TAF)	1 st line	Renal injury and bone density loss with TDF; not seen with the newer TAF formulation; mild gastrointestinal upset	Once-daily dosing
	Zidovudine	Uncommon	Marrow suppression, myopathy	Used only in those who initially responded years ago and in IV form in the perinatal care of HIV-positive mothers
Nonnucleoside reverse transcriptase inhibitors	Doravirine	2 nd line	Rare	P450 interactions
	Efavirenz	2 nd line	Rash, central nervous system toxicity	P450 interactions; once-daily dosing
	Etravirine	2 nd line	Rash	P450 interactions
	Nevirapine	2 nd line	Rash, hepatotoxicity	Initial lead-in phase with lower dose required; once-daily dosing; P450 interactions
	Rilpivirine	2 nd line	Rare	Needs to be taken with food; do not use with viral load > 100,000 copies/mL
Protease inhibitors	Atazanavir	1 st line	Jaundice	Once-daily dosing; P450 interactions
	Darunavir	1 st line	Rare	No cross-resistance with other protease inhibitors; once-daily dosing; P450 interactions
	Lopinavir	2 nd line	Diarrhea	Ritonavir-boosted tablet; P450 interactions
	Ritonavir	1 st line as a booster of another protease inhibitor	Diarrhea, nausea, vomiting	Used only to boost other protease inhibitors; P450 interactions
Fusion inhibitors	Enfuvirtide	Salvage	Local reactions	Subcutaneous administration
Integrase strand transfer inhibitors	Bictegravir	1 st line	Rare	Only available in combination with emtricitabine and tenofovir alafenamide
	Dolutegravir	1 st line	Rare	Blocks creatinine secretion, so can give artifactually elevated creatinine level
	Elvitegravir	1 st line	Rare	Needs to be boosted; needs to be taken with food
	Raltegravir	1 st line	Rare	Twice-daily dosing, but new once-daily form approved in 2016
CCR5 antagonists	Maraviroc	Most commonly 2 nd line	Rare	P450 interactions; twice-daily dosing
Postattachment inhibitors	Ibalizumab-uiyk	Salvage	Rare	IV injection every 14 days
CCR5 = C-C chemokine receptor Type 5		HIV = human immunodeficiency virus	HLA = human leukocyte antigen	IV = intravenous

Fusion Inhibitors (FIs)

FIs bind to and alter the structure of the gp41 glycoprotein on the HIV envelope, which is required for fusion of the virus with the CD4+ cell. FIs have been used infrequently since the introduction of INSTIs.

Integrase Strand Transfer Inhibitors (INSTIs)

INSTIs prevent the HIV integrase enzyme from inserting HIV's reverse-transcribed DNA into an infected cell's own DNA, halting this critical step in the life cycle of HIV. They cause the most rapid decline in viral loads of any agent.

C-C Chemokine Receptor Type 5 (CCR5) Antagonists

CCR5 antagonists prevent the binding of HIV to the CCR5 coreceptor. Not all HIV strains use this coreceptor, so test for this prior to treatment.

Postattachment Inhibitors

Postattachment inhibitors are monoclonal antibodies that bind to the CD4 receptor. They do not prevent HIV from binding to this receptor, but they do prevent subsequent binding to CCR5 and C-X-C chemokine receptor Type 4 (CXCR4) and thus prevent HIV from entering the cell.

Recommended Combination Regimens

According to the 2019 Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV from the National Institutes of Health, there are 4 preferred initial treatment regimens that all use an INSTI (either bictegravir or dolutegravir) and an NRTI:

- Bictegravir + tenofovir + emtricitabine
- Dolutegravir + abacavir + lamivudine
- Dolutegravir + (emtricitabine or lamivudine) + tenofovir
- Dolutegravir + lamivudine

For the first time, this list includes a 2-drug regimen. Do not use dolutegravir + lamivudine with viral loads > 500,000 copies/mL or in patients with HBV infection.

You must conduct genotypic resistance testing prior to treatment. Many of these drugs are available as combination drugs to facilitate adherence to therapy.

Prior to giving abacavir, test all patients for the HLA-B*5701 allele; if positive, do not give patients abacavir. Such patients are at high risk for a severe hypersensitivity reaction.

When to Change HIV Therapy

It's time to change therapy when:

- the current regimen fails to completely suppress the viral load to an undetectable level on > 1 occasion (assuming the patient is reliably taking the medications),

- the patient becomes intolerant to ≥ 1 of the drugs, or
- there is a rebound in the viral load after it has been suppressed.

Base any changes to therapy on resistance testing done while the patient is still taking the current regimen. Start the patient on a regimen of 3 drugs to which the virus is susceptible and that will not cross-react with side effects from prior medications. If a patient is not taking a medication reliably, the resistance testing may not show any mutations.

Preexposure Prophylaxis to Prevent Sexual Acquisition of HIV

Several studies have shown that once-daily administration of tenofovir-emtricitabine is very effective for decreasing rates of HIV transmission in high-risk populations such as men who have sex with men, heterosexuals with frequent/multiple partners, and HIV-discordant heterosexual couples. In 2012, FDA approved this combination for HIV-negative persons in such risk groups.

Postexposure Prophylaxis for Health Care Workers

Transmission of HIV from patients to health care workers is rare, with the risk from needlestick being 0.33% (1 in 300) and the risk from mucous membrane contact with bloody secretions being 0.09% (1 in 1,100). Transmission has only been documented to occur from bloody fluids and only when these fluids are injected or come into contact with nonintact skin or mucous membranes. If both of these conditions are met, vigorously wash the area with soap and water (flush the mucous membranes with saline) and give postexposure prophylaxis immediately with a 3-drug-combination of 2 NRTIs plus an INSTI. This can be altered based on the index patient's HIV resistance pattern. Treatment is for 4 weeks; test the health care worker for HIV at baseline, 6 weeks, 12 weeks, and 6 months. If the index patient has an undetectable viral load, the risk of transmission is much lower than that stated above.

Pregnancy and Antiretroviral Therapy (ART)

An additional benefit of treating all pregnant women with HIV infection is reducing the risk of vertical transmission from 25% to < 1%. Although initial studies with dolutegravir suggested an increase in neural tube defects, further analysis did not reveal any association. Initial studies of efavirenz also suggested it could cause neural tube defects but sufficient numbers of women have received it in the 1st trimester and this has not been confirmed. Although it is not a 1st line drug for treatment, if a woman is already on efavirenz and becomes pregnant, it is not recommended to discontinue it. For more information, see the [Women's and Men's Health](#) section.

Treat all HIV-infected pregnant women with ART regardless of their CD4 level or viral load. The goal is to make their viral load undetectable. Always do initial resistance testing.

With respect to labor and delivery, give all HIV-infected pregnant women whose viral load is $> 1,000$ copies/mL zidovudine as a continuous infusion during labor in addition to their current ART therapy, and deliver the baby by C-section.

EARLY HIV INFECTION

Early HIV infection is the term used for the first 6 months of infection. The majority of individuals will become ill with a flu-like or mononucleosis-like syndrome that occurs 2-4 weeks after initial infection and lasts 1-2 weeks. Patients with early HIV infection present with some or all of the following:

- Fever
- Lymphadenopathy
- Pharyngitis
- Rash (usually erythematous and maculopapular with lesions on the face, trunk, or extremities; can include the palms and soles)
- Painful, mucocutaneous ulcerations involving the mouth, esophagus, or genitals
- Myalgias or arthralgias
- Aseptic meningitis

The HIV enzyme immunoassay (EIA) antibody test becomes positive at 3-7 weeks after exposure, so it is typically not positive during primary HIV infection. The diagnosis is made by assaying plasma for HIV antigen, which, with current assays, can detect infection as early as 5 days after the patient has acquired the virus. Give all patients with primary HIV infection ART.

HIV / AIDS OPPORTUNISTIC INFECTIONS (OIs) AND OPPORTUNISTIC MALIGNANCIES

Introduction

OIs are caused by microorganisms that do not usually cause disease unless the host is immunocompromised. In the setting of immunosuppression, such as in HIV/AIDS, these microorganisms are able to take advantage of the weakened host. The OIs a patient is at risk for depend on the patient's CD4 cell count. Opportunistic malignancies are those that occur with a markedly higher frequency in HIV-infected persons.

Opportunistic infections in HIV-infected persons typically present in 1 of 4 ways:

- 1) **Pulmonary symptoms:** dyspnea, cough, fever—think of:
 - Bacterial pneumonia
 - Pneumocystosis
 - TB
 - Endemic fungi
- 2) **Systemic symptoms:** fever and wasting—think of:
 - *Mycobacterium avium* complex (MAC) / *Mycobacterium avium* infection
 - CMV

- 3) **CNS symptoms:** altered mental status, focal defects, seizures—think of:

- Cryptococcosis
- Toxoplasmosis
- Progressive multifocal leukoencephalopathy
- Neurosyphilis

- 4) **GI symptoms:**

- Odynophagia—think of:
 - Candidiasis
 - Viral infections (CMV, HSV)
- Chronic diarrhea—think of:
 - Parasitic infections (e.g., *Cystoisospora*, *Cyclospora*, *Cryptosporidium*, *Microsporidium*)
 - Bacterial infections (*Salmonella*, *Shigella*, *Campylobacter*)
 - CMV

Common infections and skin findings in HIV disease include:

- Persistent or recurrent seborrheic dermatitis
- Tinea infections
- Psoriasis
- Molluscum contagiosum
- Folliculitis
- Recurrent HSV and varicella-zoster virus
- Recurrent vaginal and oral candidiasis
- Oral hairy leukoplakia

HIV and Pulmonary Infections

Bacterial Pneumonia

With the successful implementation of primary and secondary prophylaxis against *Pneumocystis*, bacterial pneumonia has become the most common pulmonary infection in HIV-infected persons. The presentation and bacteriology of these infections are similar to those in non-HIV-infected persons and are discussed in the [Pulmonary Medicine](#) section.

Pneumocystis jiroveci Pneumonia (PJP)

PJP (a.k.a. PCP and *Pneumocystis* pneumonia) is a fungal infection acquired via the respiratory route. This pneumonia is the 2nd most common pulmonary infection in patients with HIV and is the presenting illness in 50% of patients with AIDS. 90% of patients with PJP have a CD4 count of < 200 cells/ μ L (0.2×10^9 /L).

Unlike bacterial pneumonia, PJP has an insidious onset of fever, shortness of breath, and dry cough that usually worsens over weeks, not days. There is minimal inflammatory response, which accounts for the lack of sputum production and the rarity of pleuritic pain.

Arterial blood gases typically show a primary respiratory alkalosis. An increased A-a gradient is common along with hypoxia. Lactate dehydrogenase (LDH) is elevated (> 400 U/L [6.68μ kat/L]), and liver enzymes are normal.

The chest x-ray (CXR) usually shows a diffuse, bilateral “batwing” infiltrate, although it is sometimes lobar or unilateral. In 10–15% of patients, the CXR is **normal**, but a CT scan of the chest typically reveals infiltrates.

The best method of diagnosis is by methenamine silver stain (Figure 4-8) or immunostain of pulmonary secretions, either from induced sputum or bronchoalveolar lavage (BAL). Because of the high inoculum of the organism present during active disease, BAL is highly sensitive. PCR assays are also available with similar sensitivity; however, they are less specific in that they may detect colonization instead of infection with the organism.

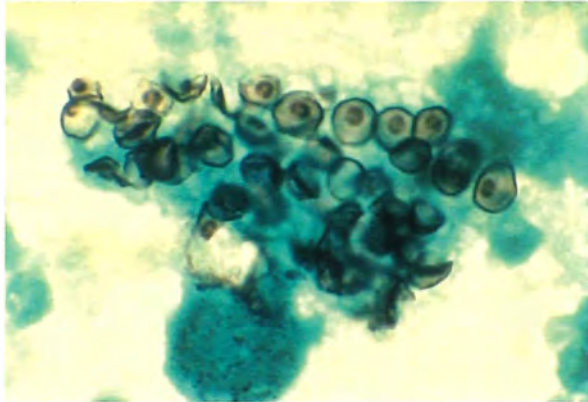


Figure 4-8: *Pneumocystis pneumonia* methenamine silver stains cyst walls black
Source: CDC

Base treatment on disease severity. Patients with mild to moderate disease have a partial pressure of oxygen (pO_2) > 60 mmHg. Those with severe disease have a $pO_2 < 60$ mmHg.

Treat PJP with high-dose TMP/SMX for 3 weeks. Use oral regimens for mild to moderate disease and the IV form for severe disease. Patients with AIDS have a 15% incidence of sulfa allergy, so 2nd line drugs are often needed. Treat mild to moderate PJP with clindamycin + primaquine or atovaquone. Treat severe disease with IV pentamidine.

Give all patients with an A-a gradient ≥ 35 mmHg or a $pO_2 < 70$ mmHg glucocorticoids concurrently with antibiotics to prevent worsening respiratory failure due to the increased inflammation incited by the killing of the fungal organisms.

TMP/SMX side effects include neutropenia/leukopenia, skin rash, nausea/vomiting, and occasionally fever. TMP/SMX blocks tubular K^+ secretion and can cause severe hyperkalemia, especially at the high doses used to treat PJP.

Possible side effects of pentamidine use include neutropenia/leukopenia, nausea, arrhythmias, renal failure, hypoglycemia, pancreatitis, and hypotension. Long courses of pentamidine may destroy the β cells of the pancreas, causing diabetes mellitus.

Primary prophylaxis is the term used when prophylaxis is given to a patient with no prior history of the OI.

Secondary prophylaxis is what is given when a patient has a history of previous treatment for that OI.

Double-strength (DS) TMP/SMX 1 $\times$ /day or 3 $\times$ /week is the drug of choice. Start primary prophylaxis when the CD4 count is < 200 cells/ μ L ($0.2 \times 10^9/L$). Give secondary prophylaxis after a full course of treatment for PJP. Stop PJP prophylaxis when the CD4 count is > 200 cells/ μ L ($0.2 \times 10^9/L$) for ≥ 3 months in response to ART.

If a patient cannot tolerate TMP/SMX, dapsone or atovaquone are alternative prophylactic agents. Atovaquone is more efficacious than dapsone and has a lower incidence of side effects than TMP/SMX, but it is much more expensive than the other agents. TMP/SMX also provides prophylaxis against toxoplasmosis (see *Toxoplasma gondii* on page 4-59).

Tuberculosis (TB)

Most cases of TB in HIV-infected patients are the reactivation of a prior asymptomatic infection and thus occur in those with the usual risk factors for TB (e.g., homelessness, institutionalization, IV drug abuse, birth in an endemic country). Reactivation occurs at the rate of 3–16% per year in patients coinfecting with HIV and TB.

TB typically presents as a chronic pneumonia but with a presentation different from that in patients without HIV. Specifically, infiltrates can be absent or diffuse, and cavitation is uncommon. Patients can also present with an acute pneumonia, clinically similar to bacterial community-acquired pneumonia. It may also present as cervical lymph node infection, known as scrofula. Disseminated disease is more common in HIV-infected persons.

Diagnose TB in the usual fashion by demonstrating acid-fast bacilli (AFB) by smear or culture of the sputum, of a BAL specimen, a bronchial biopsy specimen, or lymph node biopsy.

Treat patients with a 4-drug regimen of isoniazid, rifampin, ethambutol, and pyrazinamide $\times 2$ months, and then narrow the regimen to isoniazid + rifampin (or rifabutin) $\times 4$ months unless resistance is suspected or proven.

Rifampin may have to be replaced by rifabutin or other drugs in patients with HIV and TB coinfection because of extensive drug interactions with antiretroviral drugs. Rifabutin dosing also needs adjustments because of these drug interactions.

See the **Pulmonary Medicine** section for more information on treatment.

Prevention of active TB in HIV-infected persons is facilitated by annual screening for latent infection with either a TB skin test (purified protein derivative [PPD] test) or an interferon- γ release assay (IGRA). Both can be negative in highly immunocompromised patients.

Give **all** patients with a +PPD (> 5 mm) or +IGRA result without signs of active disease isoniazid for 9 months.

Endemic Fungi

Histoplasma, *Blastomyces*, and *Coccidioides* are the endemic fungi that cause pulmonary infections in HIV-infected individuals. These infections are more likely to be severe as well as to disseminate (in which case they constitute an AIDS-defining illness). These fungi are discussed individually under [Fungal Infections](#) on page 4-53.

Systemic Infections

Mycobacterium avium Complex (MAC) Infection

MAC consists of 10 species, by far the most common of which are *M. avium* and *M. intracellulare*. MAC causes a chronic pulmonary infection in immunocompetent patients. It is ubiquitous in the environment. The infection is acquired by the respiratory or GI route, and when the CD4 count drops to < 50 cells/ μL ($0.05 \times 10^9/\text{L}$), symptoms can occur.

In patients with HIV, MAC usually presents as a disseminated infection, causing a wasting syndrome with fever, weight loss, night sweats, lymphadenopathy, hepatosplenomegaly, diarrhea, and abdominal pain.

Confirm the diagnosis by culturing MAC from blood or body fluids or from biopsies of involved organs, such as the lung, bowel, and lymph nodes.

Treat MAC infection with clarithromycin or azithromycin + ethambutol + rifampin.

Although it was previously recommended to give primary prophylaxis for MAC infection if the CD4 count was < 100 cells/ μL , primary prophylaxis is no longer recommended since the 2018 CDC Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV. This is because ART can usually produce a rise in CD4 counts above this level in a matter of weeks.

Cytomegalovirus (CMV) Infection

CMV infection can present as diarrhea and/or a wasting syndrome and is by far the most common cause of retinitis in HIV-infected persons (see [Cytomegalovirus \(CMV\)](#) on page 4-71). Most patients with these manifestations have a CD4 count < 50 cells/ μL ($0.05 \times 10^9/\text{L}$). Treatment is with ganciclovir or valganciclovir. Primary prophylaxis is not recommended. Secondary prophylaxis is with valganciclovir.

Central Nervous System (CNS) Infections

Cryptococcus

C. neoformans is endemic worldwide. Although it causes disease in both immunocompetent and immunosuppressed individuals, most HIV-infected patients have a CD4 count of < 100 cells/ μL ($0.1 \times 10^9/\text{L}$) at the time of diagnosis, and the fungus commonly presents as a subacute meningitis with or without disseminated disease.

The most common presentation is a subacute meningitis or meningoencephalitis that is very different than bacterial meningitis. Subtle signs of decreased mental status, personality changes, and memory loss may be the only manifestations and are due to increased intracranial pressure, not invasion of the organism.

Detection of cryptococcal antigen in the CSF or serum is diagnostic and is seen in the vast majority of infected patients.

Treat cryptococcal meningitis in 3 stages:

- 1) Induction with amphotericin B + flucytosine $\times 2$ weeks
- 2) Consolidation with fluconazole 400 mg/day for ≥ 8 weeks
- 3) Maintenance with fluconazole 200 mg/day for ≥ 1 year

Repeat the LP and remove CSF on a daily basis as necessary to obtain normal CSF pressures. If this is not possible or effective, insert CSF shunts.

If the patient presents with a cryptococcal lung infection, you must still perform an LP to investigate for meningitis, even if the patient is asymptomatic.

There is no primary prophylaxis used for this infection. Give secondary prophylaxis as part of the maintenance stage of treatment.

Toxoplasma

T. gondii is the most common cause of focal lesions in the CNS in HIV-infected persons. Typical symptoms of toxoplasmosis are new-onset seizures, focal neurologic deficit, and/or altered consciousness. MRI (which is more sensitive) and CT show multiple ring-enhancing lesions. The main differential diagnoses are primary B-cell lymphoma and brain abscesses that produce focal lesions.

Diagnose toxoplasmosis using imaging that shows multiple bilateral ring-enhancing lesions (often with a predilection for the basal ganglia) in a patient with demonstrable IgG antibody to *T. gondii*. Confirmation is by demonstrating radiographic improvement with empiric treatment. A biopsy is not initially needed if imaging is typical and there is a response to therapy.

Treat toxoplasmosis with pyrimethamine and sulfadiazine. Also give folinic acid (a.k.a. leucovorin) to prevent megaloblastic anemia from the pyrimethamine. Use clindamycin in sulfa-allergic patients. Failure to respond warrants a brain biopsy.

Primary prophylaxis is indicated in patients with a CD4 count < 100 cells/ μL ($0.1 \times 10^9/\text{L}$) and a positive *T. gondii* IgG result. It is accomplished with the same regimen used for PJP prophylaxis (i.e., DS TMP/SMX 1 $\times$ /day or 3 $\times$ /week). Use dapsone in sulfa-allergic patients. In addition, as with primary prophylaxis against PJP, primary prophylaxis for *Toxoplasma* encephalitis can be stopped when the CD4 count is > 200 cells/ μL ($0.2 \times 10^9/\text{L}$) for 3 months.

John Cunningham (JC) Polyomavirus

JC polyomavirus (a.k.a. JC virus) is a commonly acquired asymptomatic infection. If the CD4 count drops to < 100 cells/ μ L (0.1×10^9 /L), JC virus can reactivate and cause a lytic infection in oligodendroglial cells that make myelin. This results in **progressive multifocal leukoencephalopathy (PML)**. PML, because it is multifocal, has varied and widespread presentations. Patients experience altered mental status, motor and sensory changes, and specifically decreased visual acuity.

The diagnosis is suggested by an MRI showing multifocal demyelinating lesions in the white matter and can be confirmed by CSF PCR testing for JC virus, which has a sensitivity of 70–90%.

No specific antiviral therapy is available; however, reconstitution of CD4 cells after ART can reverse some (but not all) symptoms.

Neurosyphilis

Syphilis, even if previously treated, can reactivate in patients with AIDS and cause neurosyphilis. Syphilis and neurosyphilis are treated the same, with or without HIV infection (refer to [Syphilis on page 4-16](#)).

Gastrointestinal (GI) Infections

Esophagitis

Candida albicans is the most common cause of infectious esophagitis in patients with HIV. Viral causes include CMV and HSV. Patients can be infected with more than one of these at the same time. Consider a coexistent viral infection if the symptoms do not improve after empirically treating the *Candida* infection. Because the response to therapy is usually dramatic, no prophylaxis for candidal esophagitis is recommended.

Diarrhea

Chronic diarrhea in patients with AIDS is commonly caused by protozoa: *Cryptosporidium*, microsporidia (includes *Enterocytozoon bienersi* and *Encephalitozoon intestinalis*), *Cyclospora cayentanensis*, and *Cystoisospora belli* (previously known as *Isospora belli*). All of these can also infect the gallbladder and cause acalculous cholecystitis. Bacterial pathogens (e.g., *Salmonella*, *Shigella*, *Campylobacter*) cause an acute diarrhea that may persist and become chronic.

CMV is the only common viral cause of diarrhea.

Stool or bowel biopsy specimens are diagnostic and require modified acid-fast staining to detect *Cryptosporidium*, *Cyclospora*, and *Cystoisospora*. Microsporidia are seen with a modified trichrome stain. PCR assays are now available to detect these organisms in stool.

CMV can be diagnosed by biopsy of the ulcers or erosions during endoscopy. (Remember, if the patient has CMV colitis, check for ocular involvement.)

Treat *Cyclospora* and *Cystoisospora* infections with TMP/SMX. *Cryptosporidium* has a variable response to nitazoxanide. Microsporidia respond to albendazole. Treat *Salmonella*, *Shigella*, and *Campylobacter* infections with ciprofloxacin. Treat CMV with ganciclovir or foscarnet.

Miscellaneous Infections

Hepatitis C Virus (HCV)

Test all HIV-infected patients for HCV. Treat hepatitis C with the current well-tolerated, short-term regimens. HIV is generally treated first. Hepatitis C treatment is covered in the [Gastroenterology](#) section.

AIDS-Defining Malignancies

Although there is evidence that there is a higher frequency of many malignancies in HIV-infected persons, 4 are considered AIDS defining. These are Kaposi sarcoma, cervical cancer, high-grade non-Hodgkin lymphoma, and primary B-cell lymphoma of the brain. These are discussed in the [Oncology](#) section.

FEVER OF UNKNOWN ORIGIN (FUO)

FUO was initially defined as documented fever on several occasions for ≥ 3 weeks with no etiology identified on routine evaluation after 1 week in the hospital. Over the last 50 years, the definition has changed, and a hospital stay is no longer necessary, nor is a several-week course of investigation. Causes vary geographically due to regional exposures, diagnostic tools, and health care availability. They also differ based on the host, especially in HIV-infected persons, and in the elderly. Overall, the most common identifiable causes of FUO are rheumatic diseases (e.g., rheumatoid arthritis, SLE), infections, and malignancies.

Routine evaluation must be unrevealing to diagnose FUO. This includes a history, physical, CBC with differential, comprehensive metabolic panel, blood culture, urinalysis, urine culture, and CXR.

Once FUO is established, further workup may include:

- ESR or CRP
- Serum protein electrophoresis (SPEP)
- RF
- LDH
- Creatine kinase (CK)
- Antinuclear antibody
- HIV
- TB screening
- Heterophile antibody test
- Echocardiogram
- CT scan of the abdomen
- CT scan of the chest
- Gallium or indium WBC scan

Unless a patient is clinically unstable, do not use empiric therapy in cases of FUO; patients are usually stable. Treatment is directed toward the underlying etiology once discovered. The diagnostic evaluation in up to 25% of patients with FUO fails to identify a cause; however, these patients have a good prognosis. If the initial workup is negative and the fever persists, repeat the same workup in several months.

FEBRILE NEUTROPENIA

PREVIEW | REVIEW

- What is the definition of febrile neutropenia?
- What are the empiric treatment options for the febrile neutropenic? When is vancomycin included?
- In the empiric treatment of febrile neutropenia, when would you choose voriconazole over an echinocandin?

EPIDEMIOLOGY AND RISK FACTORS

Neutropenia occurs in the setting of leukemia, bone marrow transplantation, chemotherapy, exposure to drugs or toxins, and bone marrow metastasis. If infection ensues, it is usually caused by colonizing flora that enter the bloodstream across disrupted gut mucosa, via an IV catheter, or through the oropharynx into the lungs and/or sinuses.

Neutropenic sepsis can be caused by both gram-negative and gram-positive bacteria. Of the gram-positives, the most common are *Staphylococcus aureus*, *Staphylococcus epidermidis*, and streptococcal species. Less common are *Corynebacterium* species, *Cutibacterium acnes* (previously known as *Propionibacterium acnes*), *Bacillus* species, and *Leuconostoc* species. These less-common gram-positives are important to remember because they may not be effectively treated with vancomycin. Common gram-negative organisms include *Pseudomonas* species and Enterobacteriaceae, including *Escherichia coli*, *Klebsiella* species, and *Enterobacter* species. Anaerobic bacteria are not commonly seen in neutropenic sepsis.

Fungi, such as *Candida* and *Aspergillus* species, are important pathogens in patients with prolonged neutropenia. Infections with *Fusarium* species and agents of mucormycosis can also occur.

The risk for infection in the patient with neutropenia is directly proportional to the degree and duration of neutropenia.

For an additional discussion of febrile neutropenia, see the [Oncology](#) section.

PRESENTATION

It is important to recognize febrile neutropenia and begin emergent evaluation and empiric antibiotics. The definition of febrile neutropenia is a temperature of $> 101.0^{\circ}\text{F}$ (38.3°C) $\times$ 1 occurrence or 100.4°F (38.0°C) for 1 hour and severe neutropenia, defined as an absolute neutrophil count (ANC) $< 500/\mu\text{L}$ ($0.5 \times 10^9/\text{L}$) or expected to be $< 500/\mu\text{L}$ ($0.5 \times 10^9/\text{L}$) in the next 48 hours.

The decrease in neutrophils creates a blunted inflammatory response, so clinical signs and symptoms that localize the source of infection may be absent. Any localizing symptoms (e.g., sore throat, cough, dysuria, perirectal pain), however, are helpful in determining the source. For the physical examination, concentrate on the upper airway mucosa (looking for mucositis), teeth and periodontal tissues, eyes, and rectum. Any rash or skin ulceration/swelling is potentially significant. Portals that allow infections to enter include catheters and implants.

DIAGNOSIS

Send blood cultures immediately and obtain a CXR. Perform a urine culture if there are UTI symptoms or a bladder catheter is in place. Obtain a sputum culture if there are pulmonary signs or symptoms or if the CXR shows infiltrates. If the CXR is normal in a patient with pulmonary symptoms, obtain a CT scan of the chest. If diarrhea is present, send a stool sample for *Clostridioides difficile* toxin gene PCR testing.

Reserve LP for patients with altered mental status without an identifiable cause or other signs of meningitis. Remember that these patients are usually thrombocytopenic. There should be a low threshold for bronchoscopy for pathology, Gram stains, and bacterial/viral/fungal cultures in patients with undiagnosed pulmonary infiltrates. Open lung biopsy may be needed. Perform skin biopsies for pathology and bacterial and fungal smears and cultures when lesions are present.

TREATMENT

Empiric Treatment

According to the 2011 Infectious Diseases Society of America (IDSA) guidelines, when a neutropenic patient presents with fever, the initial treatment is directed against gram-negative aerobic bacilli, including *Pseudomonas*. The 2018 IDSA clinical practice guideline update adds that oral empiric treatment can be used in patients at low risk of complications, and the regimen of choice is a combination of amoxicillin/clavulanic acid and ciprofloxacin.

Treat patients with fever and neutropenia with one of the following:

- 1) Piperacillin/tazobactam
- 2) A carbapenem (imipenem or meropenem)
- 3) Cefepime

Do **not** include vancomycin as part of the initial regimen **unless** any of the following are present:

- Hypotension or other evidence of severe sepsis
- A positive blood culture for gram-positive bacteria (before the organism or susceptibility is determined)
- Pneumonia documented radiographically
- Persistent fever while on empiric antibiotics
- Obvious skin infection or erythema at the site of an indwelling catheter
- A history of MRSA infection or known colonization
- Severe mucositis

If vancomycin is started, discontinue it after 2 days if there is no evidence of a gram-positive infection.

Persistent Febrile Neutropenia

If the fever and neutropenia persist after 4–7 days on empiric antibiotics (including vancomycin), begin adding empiric antifungal therapy with:

- an echinocandin (caspofungin is the only one approved by the FDA for this indication, but other echinocandins are equally effective) **or**
- voriconazole.

Use voriconazole instead of an echinocandin if there are pulmonary infiltrates, because voriconazole more predictably covers *Aspergillus* infection.

Prophylaxis

Prophylactic antibiotics are given to those at high risk of infection, particularly those with an expected neutropenia duration > 7 days and an ANC $\leq 100/\mu\text{L}$ ($0.1 \times 10^9/\text{L}$) during this time period.

Septic Shock

The management of septic shock is covered in the [Pulmonary Medicine](#) section. The infectious disease workup and treatment are the same for each specific entity that can cause sepsis (e.g., bacteremia, UTI, pneumonia, cholangitis). Sepsis intensifies the urgency of the workup and critical care management.

NOSOCOMIAL INFECTIONS

PREVIEW | REVIEW

- Differentiate the 2 types of nosocomial pneumonias.
- Which organisms usually cause a central line-associated bloodstream infection?

OVERVIEW

Important nosocomial infections include pneumonia (e.g., hospital-acquired, ventilator-associated) and central line-associated bloodstream infections (CLABSIs). UTIs and *Clostridioides difficile* infections were discussed under [Urinary Tract Infections \(UTIs\)](#) on page 4-1 and [Diarrhea due to *Clostridioides difficile*](#) on page 4-12. Standard precautions begin with hand hygiene but may also include gowns, gloves, and respiratory protective equipment.

PNEUMONIA

Hospital-acquired pneumonia is defined as pneumonia occurring > 48 hours after hospital admission (and that was not incubating at the time of admission). **Ventilator-associated pneumonia** is defined as pneumonia occurring > 48–72 hours after intubation. **Health care-associated pneumonia** is no longer recognized as an entity.

These pneumonias are almost always **bacterial** and have the highest mortality rate of all the nosocomial infections. They are most commonly due to gram-negative organisms. The next most common organism is *Staphylococcus aureus*.

The diagnosis is based on a combination of findings, including a new infiltrate on chest imaging, fever, increased and purulent sputum, leukocytosis or leukopenia, and increased oxygenation requirements. Obtain sputum and blood cultures; however, note that the former can be nonspecific, especially if prior antibiotics were administered.

For empiric therapy, include a drug that is active against MRSA (e.g., vancomycin) and a broad-spectrum gram-negative antibiotic (e.g., piperacillin/tazobactam, cefepime, a carbapenem). Adjust the antibiotics if an organism cultured from the sputum or blood is resistant to the empiric therapy.

CENTRAL LINE-ASSOCIATED BLOODSTREAM INFECTIONS (CLABSIs)

Central line infections are usually due to *Staphylococcus epidermidis* and *Staphylococcus aureus*, but almost any organism can cause infection, including GNBs, *Candida* species, and *Corynebacterium jeikeium*. An IV-catheter-related infection presents as sepsis without symptoms localizing to the line or as a localized infection of the subcutaneous tunnel and/or of the exit site with purulence and erythema at the site. Septic thrombophlebitis of the catheterized vein and/or right-sided endocarditis can also occur and result in septic pulmonary emboli.

When a CLABSI is suspected, obtain 2 blood cultures from 2 sites, with at least one of these sites being peripheral. Remove the infected line when possible, and culture the catheter tip. The diagnosis of a CLABSI is confirmed if both the catheter tip **and** the blood cultures grow the same organism.

If the catheter is retained (and you are therefore unable to culture the tip), the hub can be cultured, and this culture can be compared with the peripheral blood culture(s). A CLABSI is then diagnosed if the hub and peripheral blood cultures show the same organism **and** if quantitative cultures of the hub:

- are ≥ 3 -fold that of the blood cultures or
- turn positive ≥ 2 hours prior to the blood cultures.

If the hub culture is positive but the blood cultures are sterile, this is consistent with catheter colonization only. If the hub culture is negative but the blood cultures are positive, the bacteremia may be unrelated to the line.

In addition to antibiotics, a key decision in treating CLABSIs is whether or not to remove the line. Remove the catheter if a CLABSI occurs with any of the following conditions:

- Severe sepsis
- Hemodynamic instability
- Metastatic infection (e.g., meningitis, osteomyelitis, endocarditis)
- Suppurative thrombophlebitis
- Blood cultures remaining positive > 72 hours after appropriate antibiotic therapy

In addition, remove lines for infections with *S. aureus*, *Pseudomonas aeruginosa*, fungi, or mycobacteria. In the case of enterococci, GNBs, or coagulase-negative staphylococci, remove short-term catheters; salvage of long-term catheters can be attempted.

Empiric antibiotic treatment is with vancomycin alone, with the following 2 exceptions:

- 1) Give gram-negative coverage (that includes *P. aeruginosa*) if there is neutropenia or severe sepsis, the patient is known to be colonized with a resistant GNB, or the patient has a femoral line, which predisposes that patient to a fecal flora infection.
- 2) Give antifungal therapy with an echinocandin if the patient has previously been on broad-spectrum antibacterials, has more than one site colonized with *Candida* species, has a hematologic malignancy, is on total parenteral nutrition, or has a femoral line.

Treat infections for 14 days after line removal. In cases of *S. aureus* infections of long-term catheters, give antibiotics for 4–6 weeks.

INFECTION CONTROL AND ISOLATION

Health care workers are a risk for acquisition of pathogens from patients and the environment. This topic deals with a review of the types of precautions.

Needlesticks and HIV were discussed under [Human Immunodeficiency Virus \(HIV\) and Acquired Immunodeficiency Syndrome \(AIDS\) on page 4-29](#).

For other needlesticks, obtain hepatitis B and C and HIV serologies from the index patient. The health care worker should have been vaccinated against hepatitis B; if not, administer vaccination. If the index case is positive, give hepatitis B immunoglobulin as well. Obtain the same serologies from the health care worker, and follow up with laboratory studies based on the serologic test results from the index patient and health care worker. There is no prophylaxis for hepatitis C.

Standard precautions: All health care workers must wash their hands with soap and water or gel before **and** after entering a patient's room. Use soap and water for *Clostridioides difficile*, norovirus, and rotavirus.

In addition to the standard precautions, take the following precautions depending on the scenario:

- **Contact precautions** (gloves and gown): *C. difficile*, scabies, norovirus, MRSA colonization
- **Droplet precautions** (mask): influenza, *Neisseria meningitidis*, pertussis, coronavirus
- **Airborne precautions** (private room, negative pressure, and N95-type mask): TB, varicella, measles
- **Contact and droplet precautions:** parainfluenza
- **Contact and airborne precautions:** disseminated zoster

Isolation for *C. difficile* was discussed under [Diarrhea due to *Clostridioides difficile* on page 4-12](#). In general, isolate patients with multiple antibiotic-resistant bacteria as appropriate for the site of infection (e.g., contact isolation, droplet isolation).

ORGANISM-BASED REVIEW

BACTERIA

PREVIEW | REVIEW

- What is the clinical presentation of toxic shock syndrome?
- Which antibiotics are recommended to treat skin and soft tissue staphylococcal infections?
- How do blood culture results differ between staphylococcal and streptococcal toxic shock?
- When should you use 2 antibiotics to treat enterococcal infections? Which drugs would you choose?
- Which patient populations are at risk for *Listeria*, and how do you treat *Listeria*?
- If a pathology report describes beaded, branching, mildly acid-fast, filamentous organisms, which organism is likely?
- When should you suspect *Pseudomonas* as a cause of infection?
- Which form of plague is transmitted person to person?
- Which associated symptoms are often observed with *Legionella* pneumonia?
- Which geographic locations have the most cases of tularemia?
- What are the manifestations of bartonellosis?
- Name the clinical signs and symptoms of Rocky Mountain spotted fever. Which drugs are used for treatment?
- What is Q fever? How is it treated?
- How does *Mycobacterium marinum* infection present?
- Which associated symptoms are often seen in respiratory infections due to *Chlamydia pneumoniae*?

GRAM-POSITIVE BACTERIA

Staphylococci

Staphylococcus aureus, which on Gram stain shows cocci in grapelike clusters, colonizes the anterior nares of ~ 20% of humans, and coagulase-negative staphylococci are ubiquitous on human skin. *S. aureus* is the most common cause of soft tissue infections and causes purulent infections that manifest as folliculitis, furuncles (boils) and carbuncles (Figure 4-9), and impetigo. Patients often inaccurately report a spider bite when in fact they have a staphylococcal abscess. Treatment is based on the clinical presentation (see [Common Skin and Soft Tissue Infections](#) on page 4-6).

S. aureus is also an important cause of bacteremia, especially among those exposed to needles, such as IV drug abusers, insulin-using diabetics, hospitalized patients, and hemodialysis patients. *S. aureus* is never considered a skin contaminant when it is seen in blood cultures. In addition, it is a leading cause of central line-associated bloodstream infection (CLABSI). Infection with *S. aureus* can also result in toxic shock syndrome and staphylococcal scalded skin syndrome (Figure 4-10). The latter



Figure 4-9: Carbuncle on buttock



Figure 4-10: Staphylococcal scalded skin syndrome

does not occur in adults unless they have chronic kidney disease because the toxin is otherwise easily excreted through the kidneys. Remember that with influenza, there can be a bacterial superinfection with *S. aureus*.

S. aureus also commonly causes osteomyelitis. The ABCs of diabetic foot ulcer infections is a way to remember their management: antibiotics, bone imaging (e.g., MRI, nuclear scan), cultures (blood, wound), Doppler scan of leg arteries, erythrocyte sedimentation rate/C-reactive protein, and foot doctor/podiatry.

Pathogenicity of *S. aureus* results from a variety of toxins. Only rare isolates are susceptible to PCN, and ~ 50% of isolates are methicillin-resistant *S. aureus* (MRSA) regardless of whether they are acquired from the community or in a health care setting. Methicillin resistance connotes resistance to all other β -lactam antibiotics, with the exception of ceftaroline.

Toxic Shock Syndrome (TSS)

An important complication of *S. aureus* infection is TSS. Staphylococcal TSS presents with red skin (sunburn-like rash), hypotension, and fever along with ≥ 3 signs of organ system involvement: GI (e.g., vomiting, diarrhea), muscle (myalgia or elevated creatine kinase), acute kidney injury, liver (transaminase or bilirubin elevation), thrombocytopenia, or altered consciousness. Hypocalcemia can also occur. Bacteremia is uncommon. A strawberry tongue may be seen on exam, which can also be seen in scarlet fever and Kawasaki disease. The classic association is with retained tampon use during menses; however, currently the majority of cases are not related to menstruation. Tampon use is still a risk factor, albeit a small one, as there is a decrease in cases associated with tampon use. The

majority of cases are caused by colonization of other foreign bodies (e.g., nasal packing) or *S. aureus* infection (e.g., cellulitis, pneumonia). Treatment is with fluids and pressors, source control, and antistaphylococcal antibiotics with consideration of clindamycin to inhibit toxin production.

Streptococcal TSS is the other classic form of TSS. See [Streptococcus pyogenes \(Group A\)](#) for more on that topic.

Treatment

Bacteremia and other serious *S. aureus* infections are initially treated with vancomycin until sensitivity results are available. If isolates are methicillin susceptible, then change therapy to an antistaphylococcal PCN (e.g., nafcillin) or a 1st generation cephalosporin. Otherwise, continue vancomycin. Very few cases of vancomycin-resistant *S. aureus* are reported worldwide. Additional drugs with predictable activity against MRSA include linezolid, tedizolid, tigecycline, ceftaroline, daptomycin, telavancin, dalbavancin, and oritavancin. Be aware that most of the additional drugs have no approved indication for bacteremia or serious disease.

Treat milder infections, including skin and soft tissue infections, with TMP/SMX or doxycycline, to which ~ 90% of strains remain susceptible, especially if known to be MRSA. Clindamycin has higher resistance rates so is a limited option for empiric treatment, but if susceptibilities are known, then it would be an option. Additionally, there can be inducible resistance with clindamycin. The erythromycin-clindamycin D-zone test evaluates for the capacity for the isolate to express inducible resistance genes in the presence of clindamycin; therefore, clindamycin would not be an option if there is a positive D-zone test. If MSSA, can use PCN or cephalosporin.

Avoid quinolones due to increasing resistance and the ability of the organism to acquire resistance while the patient is on therapy plus additional recognized toxicities. Delafloxacin was approved in 2017 with an indication for treating MRSA skin infections and is the only quinolone with reliable MRSA activity.

Staphylococcus epidermidis and *S. saprophyticus*

S. epidermidis and *S. saprophyticus* are 2 species of coagulase-negative staphylococci that on Gram stain are seen in irregular clusters. *S. epidermidis* is usually methicillin resistant. It is the most common cause of both catheter-related bacteremia and bacteremia occurring post-op when a foreign body (e.g., prosthetics [including heart valves and joints], pacemakers, shunts) is placed. Treat with vancomycin. Add rifampin and gentamicin for prosthetic valve endocarditis.

S. saprophyticus causes cystitis in young women and, unlike other coagulase-negative staphylococci, is usually susceptible to antistaphylococcal PCNs and ampicillin.

Streptococcus pneumoniae

S. pneumoniae (pneumococcus) is the most common cause of bacterial meningitis and community-acquired bacterial pneumonia in adults. The former is discussed under [Bacterial Meningitis on page 4-21](#), and the latter is discussed in the [Pulmonary Medicine](#) section. On Gram stain, *S. pneumoniae* appears as lancet-shaped diplococci. A history of splenectomy is a risk factor for infections due to encapsulated bacteria (e.g., *S. pneumoniae*). Remember that with influenza, there can be bacterial superinfection with *S. pneumoniae*.

Resistance to PCN occurs in ~ 5% of *S. pneumoniae* isolates, but all isolates are susceptible to vancomycin. Ceftriaxone sensitivity is > 95%. Do not use vancomycin for bacteremia unless resistance to other agents is present. Pneumonia is commonly treated with ceftriaxone or levofloxacin.

Streptococcus pyogenes (Group A)

S. pyogenes is the **only** group A β -hemolytic *Streptococcus* species. On Gram stain, it appears in chains. It causes:

- **Pharyngitis** ([Figure 4-11](#); Centor criteria: fever, sore throat, exudative pharyngitis, anterior cervical lymphadenopathy, absence of cough; see [Pharyngitis on page 4-5](#).)
- **Scarlet fever** (may have strawberry tongue as seen with TSS and may see circumoral pallor, Pastia lines, and desquamation)
- **Toxic shock syndrome (TSS)**
 - This rapidly invasive infection can occur following minor trauma, recent surgery, or pharyngitis. Fever and pain can occur at the inoculation site, followed by hypotension.



Figure 4-11: Streptococcal pharyngitis
Source: James Heilman, MD

- In contrast to TSS related to *S. aureus*, **bacteremia** occurs in ~ 60% of cases of streptococcal TSS.
- The most common entry sites are mucous membranes and skin. Chickenpox lesions can become superinfected with group A strep with bacteremia and, less commonly, toxemia. Since use of the vaccine (released in 1995), the incidence has dropped significantly.
- Streptococcal TSS is rapidly progressive with shock and multiorgan failure. The mortality rate is 30–60%. Empiric therapy is clindamycin plus either a carbapenem or a PCN plus β -lactamase inhibitor until the etiology is confirmed.
- Rapidly progressive cellulitis that spreads through superficial cutaneous lymphatics (i.e., **erysipelas**; [Figure 4-12](#)) or along fascial planes (i.e., **necrotizing fasciitis**; discussed under [Rapidly Progressive Cellulitis on page 4-7](#)). *S. pyogenes* necrotizing fasciitis may develop after trauma and present with pain out of proportion to exam and may have crepitus or bullous lesions.



Figure 4-12: Erysipelas
Source: CDC

Immune reaction to a cell surface protein called the **M protein** can lead to rheumatic fever or poststreptococcal glomerulonephritis. This organism has yet to acquire PCN resistance.

Streptococcus agalactiae (Group B)

S. agalactiae (group B) is more common in the elderly, **especially** if they are alcoholic or diabetic. It appears on Gram stain in long chains. In pregnant women, *S. agalactiae* causes UTIs and is a cause of postpartum endometritis and bacteremia. It originates from a GU reservoir, although many cases of bacteremia have an unclear source. Treat with PCN or ampicillin; in PCN-allergic patients, treat with clindamycin or vancomycin.

Streptococcus dysgalactiae Subspecies *equisimilis* (Groups C and G)

Streptococci that react to groups C and G Lancefield typing sera are considered to be a single species and subspecies: *Streptococcus dysgalactiae* subspecies *equisimilis* (SDSE). This is part of the normal flora of the upper airway, skin, GI tract, and female GU tract. It can cause pharyngitis, soft tissue infection, septic arthritis, and endocarditis. It is universally susceptible to PCNs and cephalosporins. Diabetes and malignancy are risk factors.

Group D Streptococci

Group D streptococci includes 4 species previously grouped as *S. bovis* (*S. gallolyticus*, *S. lutetiensis*, *S. infantarius*, and *S. pasteurianus*) that are inhabitants of the GI tract and cause bacteremia and endocarditis. Group D *Streptococcus* bacteremia is seen in conjunction with colon cancer in 20–30% of cases; therefore, positive blood cultures from this organism warrant a colonoscopy.

Enterococci

Enterococci are gram-positive cocci that are difficult to distinguish from streptococci under the microscope. Like streptococci, they occur in pairs and short chains. Two species normally inhabit the intestines, with a higher amount of *Enterococcus faecalis* (95%) than *Enterococcus faecium* (5%). Thus, *E. faecalis* causes the vast majority of enterococcal infections (which include UTIs, bacteremia from lines, endocarditis, and intraabdominal polymicrobial infections). Asymptomatic enterococcal bacteriuria is managed similar to other cases of asymptomatic bacteriuria, which is generally treated only in the setting of pregnancy, those about to undergo urological procedures, and in the first 3 months after a kidney transplant.

All enterococci are resistant to cephalosporins and penicillinase-resistant PCNs. They are moderately resistant to the aminoglycosides, such as gentamicin, but these drugs are often used for synergy in the treatment of endocarditis.

E. faecium is resistant to imipenem and commonly exhibits high-level resistance to vancomycin (vancomycin-resistant *Enterococcus* [VRE]).

Single antibiotics are used to treat mild to moderate infections (UTIs and uncomplicated bacteremia) and include PCN G, ampicillin, or vancomycin, depending on sensitivities. If VRE, then additional antibiotic options include linezolid, daptomycin, and tigecycline depending on location of the infection.

Combination treatment must be used for complicated bacteremia and endocarditis because single drugs are not bactericidal. In these cases, check the isolate for gentamicin susceptibility and, if susceptible, add low-dose gentamicin. According to 2015 Infectious Diseases Society of America endocarditis guidelines, use ampicillin combined with ceftriaxone as a treatment that is less nephrotoxic than using ampicillin combined with gentamicin.

Listeria monocytogenes

Listeria monocytogenes, an aerobic gram-positive rod, causes infection in patients with decreased **cellular** immunity, such as from AIDS, lymphoma, or leukemia, and in the elderly, alcoholics, and pregnant women.

Drugs that depress cellular immunity (e.g., glucocorticoids, transplant drugs) increase the risk for infection.

Listeria is one of the most virulent foodborne pathogens, with a mortality rate of ~ 15%. It can be found in deli meats, hot dogs, milk, soft cheeses, poultry, and even fruit.

Listeria can cause neonatal meningitis via transvaginal inoculation and can affect the fetus. For this reason, pregnant women are cautioned against eating soft cheeses, unpasteurized milk, and other high-risk foods.

Like enterococci, *Listeria* is resistant to all cephalosporins, so you must include ampicillin in the empiric treatment of meningitis in the elderly, the immunosuppressed, or neonates. Treat mild to moderate cases of listeriosis with PCN or ampicillin. Give PCN-allergic patients TMP/SMX. Vancomycin and chloramphenicol are 3rd line drugs. Although no randomized trials have been conducted, an aminoglycoside is often added to treat meningitis.

Corynebacterium diphtheriae* and *C. jeikeium

Corynebacterium diphtheriae (Figure 4-13) cause diphtheria. They are pleomorphic gram-positive rods that, on microscopy, may group together in patterns that somewhat resemble Chinese characters. Diphtheria is an upper respiratory infection with a gray-white **pharyngeal pseudomembrane** (Figure 4-14) that occurs along with hoarseness, sore throat, and a **low-grade fever** (< 101.0°F [38.3°C]). Toxin production causes myocarditis with heart failure and polyneuritis. Treat with erythromycin; 2nd choice is PCN. Diphtheria equine antitoxin is **always** given with the antibiotic.

Corynebacterium jeikeium (JK) is a multidrug-resistant strain that colonizes and infects neutropenic patients and/or bone marrow transplant patients, where it causes IV catheter-related infections. Vancomycin is the only reliably effective antibiotic.



Figure 4-13: *Corynebacterium diphtheriae*
Source: CDC



Figure 4-14: Pharyngeal pseudomembrane

Arcanobacterium haemolyticum

Arcanobacterium haemolyticum causes pharyngitis in adolescents with a desquamative scarlatiniform rash and lymphadenitis. Treat with PCN, erythromycin, or tetracycline.

Bacillus anthracis* and *B. cereus

Bacillus anthracis is a large, gram-positive rod that causes anthrax, a potential agent of bioterrorism.

There are 3 main clinical manifestations:

- 1) Cutaneous (95%)
- 2) Inhalation (e.g., wool hides, terrorism)
- 3) GI

Inoculation occurs from handling naturally contaminated hides/wool, ingestion, or maliciously contaminated sources (e.g., mail, aerosol). Unlike plague (discussed under *Yersinia* on page 4-12), anthrax is **not** transmitted from person to person. All forms can lead to a hemorrhagic meningitis, but this is more common with inhalation type.

Cutaneous anthrax starts as a painless papule that vesiculates and forms an ulcer (Figure 4-15), then becomes a painless black eschar, often with nonpitting, painless induration (Figure 4-16). Treat with an oral fluoroquinolone for 60 days.



Figure 4-15: Anthrax ulcer (painless)



Figure 4-16: Anthrax later-stage eschar

Inhalation anthrax presents similarly to influenza with malaise, fever, cough, and myalgias. After 2–3 days, there is a dramatic worsening of symptoms with hypoxia, hypotension, and death. Rather than causing a pneumonia, it causes a necrotizing mediastinitis that appears as mediastinal widening on imaging.

GI anthrax is acquired by eating undercooked, contaminated meat. Patients get pharyngeal eschars and/or GI ulcerations.

Until susceptibilities are known, treat systemic disease with 3 drugs: ciprofloxacin, meropenem, and linezolid. There are 2 FDA-approved monoclonal antibodies (oblitoximab and bezlotoxumab). One of these should be given for inhalation or disseminated disease.

Bacillus cereus is a close relative of *B. anthracis*. Found in the normal flora of the skin, *B. cereus* causes a benign food poisoning if its toxins are ingested. This is further discussed under [Food Poisoning on page 4-10](#). The majority of the time when it is found in a blood culture, it is a contaminant, but on rare occasions, it is the culprit in line sepsis. It can also cause endophthalmitis if inoculated into the eye by trauma, especially in contact lens wearers. It is universally susceptible to vancomycin.

Clostridioides difficile

Clostridioides difficile (*C. difficile*; formerly known as *Clostridium difficile*) is a cause of toxin-producing diarrheal illness usually precipitated by antibiotic exposure and/or health care exposures. Any antibiotic can precipitate *C. difficile* colitis, but fluoroquinolones, clindamycin, and β -lactams have a higher propensity than others. Diagnosis is made with stool polymerase chain reaction (PCR)/toxin (see [Diarrhea due to *Clostridioides difficile* on page 4-12](#)).

Clostridium

Clostridium species (there are > 100) are anaerobic, gram-positive rods that cause a wide variety of human illnesses:

- *C. difficile*, now classified as *Clostridioides difficile*, is discussed under [Clostridioides difficile](#).
- *C. botulinum* produces the most potent human toxin known. It works by blocking presynaptic acetylcholine release, causing a descending motor paralysis and parasympathetic cranial nerve dysfunction that results in dilated pupils, dry tongue, and dysphagia with death from respiratory arrest if untreated. It does not enter the CNS, and thus there is no alteration of consciousness. The toxin is usually acquired via the ingestion of contaminated food (typically from people who do their own canning) but can be from a wound source. It is the only disease other than diphtheria for which we still use an equine antitoxin. PCN is given to eradicate a wound source. Honey is a source of infant botulism.
- *C. perfringens* is one of the most common causes of food poisoning in the U.S. and presents as a diarrheal illness similar to the enteric form of *B. cereus*. It manifests as watery diarrhea and crampy abdominal pain. It also causes a rapidly progressive cellulitis. See [Necrotizing Fasciitis on page 4-7](#).
- *C. septicum* is a gut organism, and the majority of persons with infection from this organism have an associated GI malignancy. Thus, persons with bacteremia should undergo upper and lower GI endoscopy.
- *C. tetani* causes tetanus. There are < 50 cases/year in the U.S. See [Approach to Tetanus Prevention on page 4-88](#).

Clostridium species are susceptible to PCNs, cephalosporins, and clindamycin. The latter is useful when treating *C. perfringens* cellulitis to inhibit the organism's ability to produce its numerous toxins. Again, remember the antitoxin properties of clindamycin.

Nocardia

Nocardia species: *Nocardia asteroides* and *Nocardia brasiliensis* are 2 examples of pathogenic species. These are aerobic, weakly acid-fast, beaded, branching, filamentous, gram-positive rods.

N. asteroides usually starts as a lung infection, commonly causing a thin-walled cavitory lesion. It can cause focal brain abscesses and chronic **neutrophilic** meningitis—most chronic meningitides are lymphocytic. Nodular skin lesions are common. *Nocardia* are slow growers on culture medium. The usual setting is in patients with impaired cell-mediated immunity.

Usual treatment is high-dose sulfonamides or TMP/SMX. In severely ill patients, imipenem or amikacin is added. Minocycline can be used for sulfa-allergic patients. Treat for at least 3 months; 6–12 months may be required. Resistance testing is important for *Nocardia* species.

N. brasiliensis is in the soil. Like *M. marinum* and *Sporothrix schenckii*, if inoculated into the skin, it causes nodular lesions that spread along lymphatic channels. Treat with sulfonamides or TMP/SMX.

Actinomyces israelii

Actinomyces israelii is an anaerobic, gram-positive, beaded rod that causes an infection in which yellow sulfur-like granules can be visualized, which are actually clusters of organisms. The usual presentation of actinomycosis is cervicofacial involvement (“lumpy jaw”; Figure 4-17). *A. israelii* is part of the normal bowel flora and thus can be a participating organism in intraabdominal abscesses and pelvic inflammatory disease. Treatment is PCN or ampicillin; 2nd choice is tetracycline.



Figure 4-17: Cervicofacial involvement in actinomycosis
Source: CDC

GRAM-NEGATIVE BACTERIA

Neisseria

Neisseria meningitidis (meningococcus) is a gram-negative diplococcus that is carried in the human nasopharynx in 5–10% of healthy persons. It typically does not cause disease because specific antibodies and complement lyse the organisms as they enter the bloodstream.

Thus, patients with complement deficiency or asplenia are especially prone to meningococcal sepsis (a.k.a. meningococcemia), which presents with fever, hypotension, and skin signs that vary from petechiae (early disease) to diffuse purpuric lesions and DIC (later disease). Bloodstream infection can occur with meningococcal meningitis.

The diagnosis and treatment of bacterial meningitis are discussed under [Bacterial Meningitis on page 4-21](#).

Prophylaxis to prevent meningococcal disease is discussed under [Prevention of Meningococcal Meningitis on page 4-23](#).

Neisseria gonorrhoeae is a gram-negative diplococcus that causes gonorrhea, which is discussed under [Sexually Transmitted Infections \(STIs\) on page 4-15](#).

Moraxella catarrhalis

Moraxella catarrhalis is a gram-negative coccobacillus that causes otitis, sinusitis, and respiratory illness including exacerbations of COPD and pneumonia. All strains produce penicillinases but are usually susceptible to amoxicillin/clavulanate, a 2nd or 3rd generation cephalosporin, TMP/SMX, macrolides, and quinolones.

Pseudomonas aeruginosa

Pseudomonas aeruginosa is a gram-negative rod (GNR) that is a ubiquitous water organism and a common cause of hospital-acquired infections. There are several clinical presentations suggestive of infection with this organism:

- **Tennis shoe cellulitis and/or osteomyelitis**—*P. aeruginosa* survives in the moisture-absorbing middle layer of tennis shoes and can be inoculated into soft tissue or bone after the wearer steps on a nail.
- **Otitis externa**—both benign and malignant; discussed under [Otitis Externa \(Swimmer's Ear\) on page 4-4](#)
- **Ecthyma gangrenosum**—a round, indurated, necrotic lesion with central ulceration (Figure 4-18) seen in neutropenic patients with *Pseudomonas*
- **Hot tub folliculitis** (hot tub rash)—from improperly chlorinated hot tubs. This is a self-limited inflammation from *P. aeruginosa* entering the base of hair follicles in the submerged areas.



Figure 4-18: Ecthyma gangrenosum
Source: Kimberly Salkey, MD

There is no single antibiotic to which all *P. aeruginosa* are universally susceptible. Therefore, it is reasonable to treat invasive infections with 2 antipseudomonal antibiotics from different classes (i.e., piperacillin/tazobactam plus a fluoroquinolone or an aminoglycoside) until you know the susceptibility pattern.

The most active drugs include:

- Carbapenems (except ertapenem)
- Aztreonam
- Fluoroquinolones
- Aminoglycosides
- Ceftazidime
- Cefepime
- Ceftolozane/tazobactam
- Ceftazidime/avibactam
- Piperacillin/tazobactam
- Colistin

Enterobacteriaceae

Enterobacteriaceae is a family of aerobic GNRs that includes *Escherichia coli*, *Klebsiella*, *Proteus*, *Salmonella*, *Shigella*, *Yersinia*, *Citrobacter*, *Serratia*, and *Enterobacter*. *Salmonella* and *Shigella* are discussed under [Bacterial Diarrhea on page 4-10](#).

Yersinia

Yersinia pestis is a gram-negative, rod-shaped coccobacillus that causes plague. Wild rodents are the reservoir. *Y. pestis* is transmitted by fleas or direct contact with an infected animal, and mortality is high if not properly treated.

The **bubonic** type causes large, localized lymphadenopathy (buboes) that suppurates at the site of the inoculation. If not treated, it can lead to sepsis and death. The **pneumonic** form occurs after inhalation of the organism via aerosols from infected animals or from other humans with pneumonic plague. Only a small inoculum is required, which can lead to epidemics and makes it a potential agent of bioterrorism.

Plague and tularemia present similarly (adenopathy after hunting), except that the geographic locations are different—Desert Southwest for plague vs. Arkansas, Missouri, and Oklahoma for tularemia. There is more on tularemia under [Francisella tularensis on page 4-48](#).

Diagnose plague by aspirating lymph nodes or obtaining sputum specimens that reveal bipolar-staining GNRs (safety pin shape) and growth of *Y. pestis*.

Plague is 1 of 2 infectious diseases for which an aminoglycoside is the drug of choice; the other is tularemia. Streptomycin is the aminoglycoside of choice, but if it is not available, gentamicin is an acceptable alternative. 2nd line choices are tetracycline, doxycycline, or quinolones.

Citrobacter

Citrobacter species (especially *C. freundii*, *C. koseri*, and *C. amalonaticus*) are GNRs that colonize the human gut and cause UTIs as their most common disease manifestation. They can be part of a polymicrobial intraabdominal abscess after bowel perforation or bowel necrosis but rarely cause other illnesses. They

are universally resistant to ampicillin and 1st generation cephalosporins but are usually killed by other generations of cephalosporins, carbapenems, fluoroquinolones, and TMP/SMX.

Escherichia

E. coli is the most common GNR aerobe in the bowel. It is the most common cause of community- and health care-associated UTIs. It causes diarrheal disease via several mechanisms (see [Bacterial Diarrhea on page 4-10](#)): intraabdominal infection, primary peritonitis, a minority of bacterial pneumonias (typically nosocomial or aspiration), a minority of endocarditis (usually on a prosthetic valve), and, rarely, osteomyelitis. Resistance to ampicillin, TMP/SMX, and quinolone is commonly > 25%, and extended-spectrum β -lactamase (ESBL)-containing organisms are becoming prevalent. These are sensitive to carbapenems.

Klebsiella

Klebsiella pneumoniae and *K. oxytoca* are GNRs and normal flora of the bowel that can cause UTI, intraabdominal infection, primary peritonitis, and nosocomial pneumonia. All strains are resistant to ampicillin, but almost all strains are killed by carbapenems. Susceptibility to cephalosporins and quinolones is variable.

Some strains of *Klebsiella*, known as *Klebsiella pneumoniae* carbapenemases (KPCs), are carbapenemase-producing strains. These are frequently encountered in residents of nursing homes or long-term care facilities. KPCs are resistant to carbapenems and all other β -lactams. They are frequently resistant to other antibiotic classes as well. Options for therapy can include colistin, tigecycline, or aminoglycosides, depending on the susceptibility of each strain.

Proteus

Proteus mirabilis and *P. vulgaris* are normal flora of the bowel and cause urinary tract and intraabdominal infections. They are GNRs. They produce urease, which splits urea in the urine, releasing ammonium. This creates an alkaline environment that facilitates stone formation. These stones can be a nidus for recurrent UTI. *P. mirabilis* is usually susceptible to ampicillin-sulbactam, piperacillin/tazobactam, and all cephalosporin generations. Resistance to TMP/SMX is common. *P. vulgaris* is often resistant to multiple β -lactams and fluoroquinolones.

Serratia

Serratia marcescens is a GNR found in the environment but does not often colonize the human microbiome. When it does, it can cause UTIs and nosocomial pneumonia. It can also cause septic arthritis and bacteremia in drug abusers. All isolates are resistant to ampicillin

and 1st generation cephalosporins but are usually susceptible to 3rd generation cephalosporins, aminoglycosides, and piperacillin/tazobactam.

Enterobacter

Enterobacter cloacae and *E. aerogenes* are GNRs and the 2 most common species infecting humans. They are part of normal gut flora, and due to their resistance to commonly used antibiotics (e.g., ampicillin-sulbactam and cefazolin), they can become predominant species in patients receiving these drugs and cause nosocomial UTIs, pneumonia, and complicated intraabdominal infection. Both species are almost always susceptible to cefepime and aminoglycosides, and most are susceptible to TMP/SMX and fluoroquinolones.

Legionella

Legionella species are aerobic GNRs (but show up poorly on Gram stain) and require special media for culture (charcoal yeast extract). Obtaining a urine *Legionella* antigen is a good rapid test. *Legionella* has > 19 known pathogenic species, but *Legionella pneumophila* causes 80–90% of human infections. *Legionella* species easily colonize standing water and enter the lungs via inhalation, causing pneumonia.

L. pneumophila causes **legions** of problems with multisystem manifestations as the rule. Patients often present with diarrhea, hyponatremia, hypophosphatemia, and CNS symptoms (headache, delirium, and confusion) in addition to the pneumonia.

Treat with a fluoroquinolone or a macrolide. Tetracyclines also have activity. Add rifampin for severe disease.

Brucella

Brucella is an aerobic gram-negative bacillus. *B. melitensis* causes brucellosis in goats, sheep, and camels. Other strains are *B. abortus* (cattle), *B. suis* (pigs), and *B. canis* (dogs). These are transmitted to humans via unpasteurized milk or cheese or by inhalation (work related).

Acute **brucellosis** is a nonspecific febrile disease—with night sweats (often with a foul, moldy odor), diarrhea, myalgias, arthralgias, and fatigue—that is difficult to pinpoint unless there is an occupational or travel exposure history to assist. Think “BruSmella” to help remember the association of *Brucella* with smelly sweat. If inhaled, *Brucella* pneumonia occurs. A small percentage of patients have diffuse rash, orchitis, or uveitis.

Localized infection can ensue and manifest as osteomyelitis, tissue abscesses, or endocarditis (that can initially be culture negative because the organism takes weeks to grow).

Because cultures can take up to 6 weeks to grow, confirming the diagnosis is difficult. Diagnosis can also be made via acute and convalescent serum titers, as well as PCR.

Treatment requires 1 of the following regimens:

- 1) Doxycycline + aminoglycoside (streptomycin or gentamicin) × 4 weeks
- 2) Doxycycline + rifampin × 6–8 weeks
- 3) Avoid doxycycline in pregnant women; treat with rifampin 900 mg daily for 8 weeks.

Francisella tularensis

Francisella tularensis is a small, gram-negative, pleomorphic bacillus that causes **tularemia**. It is found in many animals, particularly rabbits (“rabbit fever”). *Francisella* is transmitted by ticks and bloodsucking flies, but the organism can also be ingested, transmitted by contact with animal skins, or inhaled. It is seen most often in Arkansas, Missouri, and Oklahoma. It has 6 distinct forms: ulceroglandular (the most common type), glandular, oropharyngeal, oculoglandular, typhoidal, and pneumonic.

Patients with the ulceroglandular form of tularemia present with a history of sudden onset of fever, chills, myalgias, and arthralgias, as well as a single, red papuloulcerative lesion with a central eschar at the site of the tick bite. Additional symptoms can develop, based on portal of entry. Regional lymphadenopathy can develop, and these nodes can necrose and suppurate. If pneumonia occurs, it demonstrates hilar adenopathy, nodular infiltrates, and pleural effusion similar to pneumonic plague.

The diagnosis is based on the clinical and epidemiological presentation. Serologic testing for *F. tularensis* is confirmatory, but it usually takes > 2 weeks to turn positive. Culture apparently infected tissue, but know that these cultures have a very low yield.

Treat with streptomycin or gentamicin. Doxycycline or ciprofloxacin can be used if the patient is not severely ill.

Bartonella henselae

Bartonella henselae (cats are the natural reservoir, especially kittens) causes **cat scratch disease** or, in the immunocompromised patient, **bacillary angiomatosis**. Cat scratch disease has a macule → papule → pustule at the site of the infection (**Figure 4-19**) with painful regional lymphadenopathy. Often the site of inoculation is no longer visible when the patient presents with lymphadenopathy. Rarely it can cause encephalitis or endocarditis. It is a very slow-growing GNR. Treatment with azithromycin decreases the duration of illness and is recommended, although it may be a self-limited process.



Figure 4-19: Catscratch disease primary lesion
Source: CDC

Helicobacter pylori

Helicobacter pylori is a gram-negative, spiral, flagellated bacillus. It causes gastritis and peptic ulcer disease (PUD) and is a risk factor for adenocarcinoma of the stomach and GI lymphoma. Further discussion about *H. pylori* is in the [Gastroenterology](#) section.

RICKETTSIA

Rocky Mountain Spotted Fever (RMSF)

Rickettsia rickettsii is a poorly staining gram-negative coccobacillus that causes RMSF. This tickborne disease has a 5–10% mortality rate. Classic signs and symptoms include a rash, fever, severe headache, arthralgias (but not overt arthritis), and history of recent exposure to ticks in endemic areas (predominantly southeastern United States). The rash ([Figure 4-20](#)) occurs on the distal extremities. It progresses from maculopapular to petechial. Patients sometimes also present with diarrhea and abdominal pain.



Figure 4-20: Rash in Rocky Mountain spotted fever

Labs show leukopenia or leukocytosis, thrombocytopenia, hyponatremia, and increased transaminases. PT, aPTT, and fibrin split products are often increased, although the condition does not often result in true DIC. The increase in these parameters is thought to be due to organism-induced local injury in the blood vessels.

It is important to diagnose this infection presumptively on clinical grounds (especially the distinct rash) to allow emergent treatment. The **quickest** confirmation of the diagnosis is via immunofluorescent staining of a biopsy sample of a petechial lesion. Serology eventually turns positive but is often negative on presentation.

Treat with doxycycline or chloramphenicol.

Endemic Typhus

Rickettsia typhi causes endemic typhus, which presents with fever, headache, myalgia, a faint rash, and transaminase elevation. In the U.S., the opossum is the reservoir, and it is transmitted by the cat flea. A history of cat ownership with opossums in the neighborhood is helpful. The diagnosis is made serologically, and the treatment is doxycycline. The disease will eventually resolve, but doxycycline shortens the course of the illness.

Q Fever

Q fever (*Coxiella burnetii* infection) is a zoonosis transmitted mainly by inhalation of the aerosol released from the infected animal. Q fever is seen in abattoir (**slaughterhouse**) workers and people exposed to an infected animal's products of conception during **birthing**. It usually presents as a flu-like febrile illness, with or without pneumonia and/or hepatitis. Headache is common. ~ 5% of infections become chronic and manifest as a fever of unknown origin or culture-negative endocarditis.

Diagnose with serology, particularly Phase II IgG (acute Q fever) and Phase I IgG (chronic Q fever). Treat chronic Q fever or endocarditis with doxycycline and hydroxychloroquine.

Ehrlichia and *Anaplasma*

Ehrlichia and *Anaplasma* are small, obligate, intracellular gram-negative organisms that cause ehrlichiosis and anaplasmosis, respectively. Ehrlichiosis is called "**spot-less**" Rocky Mountain fever even though ~ 30% have a rash. Like RMSF, ticks are the transmission vectors, and also like RMSF, ehrlichiosis and anaplasmosis predominantly occur in the eastern half of the U.S. ([Figure 4-21](#) and [Figure 4-22 on page 4-50](#)).

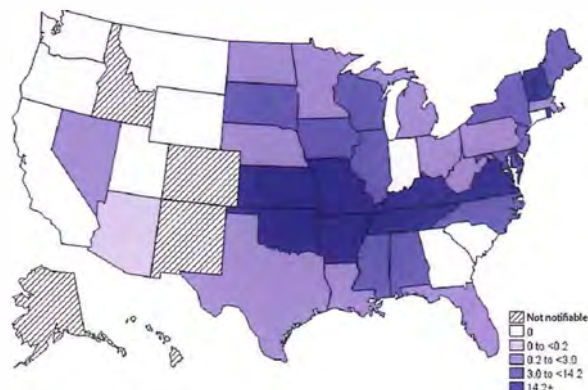


Figure 4-21: Annual reported incidence (per million population) for *Ehrlichia chaffeensis*, 2018
Source: CDC

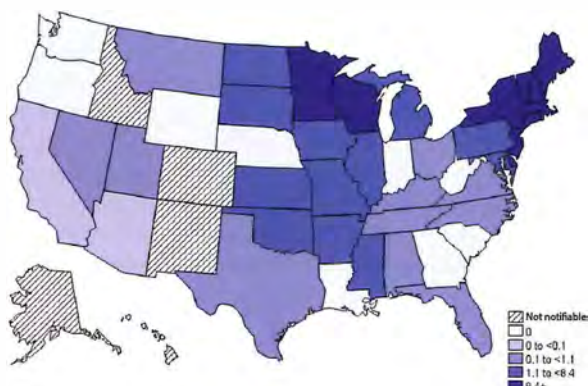


Figure 4-22: Annual reported incidence (per million population) for anaplasmosis, 2018

Source: CDC

The 2 species of *Ehrlichia*, *E. chaffeensis* and *E. ewingii*, cause **human monocytic ehrlichiosis** (HME), mainly in Missouri and Arkansas.

Anaplasma phagocytophilum causes **human granulocytic anaplasmosis** (HGA), mainly in the Northeast and upper Midwest U.S.

Patients with either illness present similarly with fever and severe headache. Both HME and HGA can cause thrombocytopenia, leukopenia, and pancytopenia. Rash is present in ~30% of HME patients but rare in HGA patients. Definitive diagnosis is established by finding intracytoplasmic inclusions (**morulae**) in white blood cells (Figure 4-23 and Figure 4-24).

These inclusions are found within PMNs in HGA and within monocyte cells in HME. Serologies are available but require a 4-fold change in titer and thus are not useful at presentation.

Treat all patients suspected or proven to have ehrlichiosis or anaplasmosis with doxycycline just like with RMSF.

Because the same ticks are vectors for all 3 illnesses, coinfection with *Ehrlichia/Anaplasma* and *Babesia microti* (an intra-RBC protozoan parasite) or *Borrelia burgdorferi* (Lyme disease) can occur in endemic northeast areas.

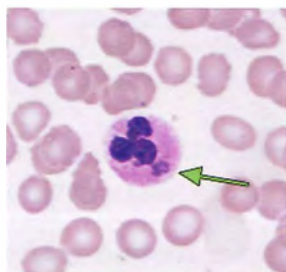


Figure 4-23: Ehrlichia morula

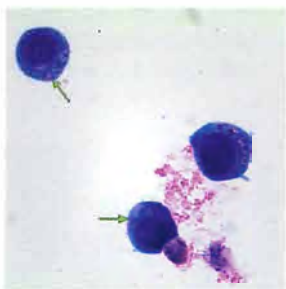


Figure 4-24: Anaplasma morula
Source: CDC

MYCOBACTERIA

All mycobacteria are **acid-fast**—they do not lose their stained color when exposed to acids (red on a green background). As a rule, treat mycobacterial infections with a **prolonged multidrug regimen**.

M. tuberculosis is a prominent global cause of pulmonary infection and death. In addition, it can cause myriad extrapulmonary infections in any organ. See more on TB in the **Pulmonary Medicine** section.

Mycobacterium avium complex (MAC; a.k.a. *M. avium-intracellulare* [MAI]) causes a chronic pulmonary infection with either *M. avium* or *M. intracellulare*. Immunocompromised (especially HIV) patients are at risk for disseminated disease. Older women and patients with COPD can also present with an indolent pneumonia (Lady Windermere syndrome). Treatment includes a macrolide (clarithromycin or azithromycin) plus ethambutol and rifampin. For severe or refractory disease, aminoglycosides may be necessary. Remember that for **MAC**, you need a **MACrolide** antibiotic.

M. leprae causes leprosy. Transmission is primarily via respiratory droplets from person to person, although it can also occur from direct contact on open wounds. The majority of the population is genetically not susceptible to infection. Armadillos serve as a reservoir of *M. leprae* in the southern U.S. Presentation is with nodular, hypopigmented, and anesthetic skin lesions and sometimes palpable peripheral nerves. Biopsy of affected areas can demonstrate the organism with Fite stains. PCR can also be used.

M. marinum is the so-called fish-tank bacillus. It causes nonhealing skin ulceration in people working around fish tanks, in addition to being associated with aquatic trauma involving saltwater. It causes strings of lesions or nodules along the lymphatic channels. (Similar lesions occur with *Nocardia brasiliensis* and *Sporothrix schenckii*.) If mild, treat with doxycycline, TMP/SMX, or clarithromycin. Treat more serious disease with clarithromycin + either rifampin or ethambutol for 1–2 months after symptoms resolve.

Other nontuberculous mycobacteria (NTM) include *M. kansasii* (pneumonia in patients with COPD) and *M. abscessus* (chronic pulmonary infections in patients with underlying lung disease).

CHLAMYDIA AND CHLAMYDOPHILA

Chlamydia and *Chlamydophila* are obligate, intracellular bacteria. *Chlamydia psittaci*, *Chlamydia trachomatis*, and *Chlamydophila pneumoniae* (formerly TWAR) are pathogenic in humans.

C. psittaci is found in psittacine (e.g., parrots, parakeets, macaws, cockatoos) and other birds and causes psittacosis: pneumonia and **splenomegaly**. Any pneumonia associated with poultry contact, especially with splenomegaly, strongly suggests *C. psittaci*. (Differential diagnosis: *Histoplasma* also causes pneumonia and

splenomegaly; it is found in patients with contact with bird and bat droppings; difficult to distinguish based on presentation while awaiting evaluation, but psittacosis may be more severe with onset over a shorter period of time.) Onset of psittacosis presents with myalgias, rigors, headache, and high fever—to 105.0°F (40.6°C).

C. trachomatis causes GU infections and **trachoma** (chronic, anterior eye infection causing cataracts but **not** glaucoma; found especially in Asia and Africa). ~ 5% of pregnant women have *C. trachomatis* in their genital tracts. The same *C. trachomatis* also causes neonatal pneumonia. Lymphogranuloma venereum is an STI caused by the same *C. trachomatis* but a different immunotype. See [Sexually Transmitted Infections \(STIs\)](#) on page 4-15.

Chlamydomydia pneumoniae (formerly *Chlamydia* but found to have different DNA and antigen) causes community-acquired pneumonia in adults who typically have **not** been exposed to birds; i.e., person-to-person spread. Bronchospasm is particularly prominent, as is an association with early pharyngitis and laryngitis.

Treatment is with doxycycline, macrolides, or fluoroquinolones.

SPIROCHETES

PREVIEW | REVIEW

- What are the clinical presentations of leptospirosis?
- Which symptoms manifest in the various stages of Lyme disease?
- What are the treatments for Lyme disease?

SYPHILIS

Syphilis is discussed under [Infectious Genital Ulcers](#) on page 4-16.

LEPTOSPIROSIS

Leptospirosis is a spirochetal disease caused by *Leptospira interrogans* and transferred by contact with infected animals or contaminated water. It is seen in association with exposure to rodent urine. Leptospirosis is considered the most widespread zoonosis in the world. It is common in Hawaii (~ 50% of all U.S. cases) and can be seen after recreational water exposures (e.g., in whitewater rafters, adventure racers, surfers, swimmers, triathletes).

Leptospirosis has a wide range of signs and symptoms, from myalgias, fever, and headache (with or without aseptic meningitis) to Weil disease (severe hepatitis with renal failure, pneumonitis, and hemorrhagic complications).

Conjunctival suffusion (Figure 4-25) is highly specific because it is rarely seen in other infectious diseases.

The hepatitis is characterized by the bilirubin being disproportionately elevated compared to the liver transaminases. The variety of presenting symptoms makes for a high incidence of initial misdiagnoses.



Figure 4-25: Leptospirosis conjunctival suffusion
Source: James Heilman, MD

Diagnose by CSF cultures on special media within the first 10 days of illness. After that, culture the urine and send serum for antileptospiral IgM, and check urine antigen.

Treat with PCN or doxycycline.

LYME DISEASE

Borrelia burgdorferi causes Lyme disease. It is transmitted by the *Ixodes scapularis* tick in the mid-Atlantic, Midwest, and Northeast U.S. and by the *Ixodes pacificus* tick in California. The protozoan *Babesia* (see [Babesia](#) on page 4-62) and the agents of ehrlichiosis and anaplasmosis are also transmitted by this tick.

Ixodes ticks have 3 stages of development: larva, nymph, and adult. Ticks transmit Lyme disease most efficiently during the nymphal stage. Nymphs are more likely to feed on humans and are rarely noticed because they are very small (< 2 mm).

Ticks require **at least 36-48 hours** of attachment before transmission of infection occurs. A tick found walking on the skin is not transmitting infection.

Manifestations

Stages of Lyme disease:

- Stage 1—**early localized**: **Erythema migrans** (EM) is the pathognomonic skin lesion of Stage 1 disease; it starts at the site of the bite and is a slowly spreading, circular, erythematous lesion, usually with a lighter center (Figure 4-26 on page 4-52). Other Stage 1 symptoms include myalgias, arthralgias, fever, headache, and lymphadenopathy. ~ 50% of patients have secondary skin lesions.

- Stage 2—**early disseminated**: Weeks to months later, Stage 2 disease occurs with **neurologic** symptoms (i.e., lymphocytic meningitis, cranial or peripheral neuritis) and/or **heart** infection (i.e., myocarditis with transient 1st, 2nd, or 3rd degree heart block). A peripheral 7th nerve palsy (Bell's palsy) is not uncommon and, if bilateral from an endemic area for Lyme disease, is diagnostic.
- Stage 3—**late**: Months to years later, Stage 3 occurs with a mono- or oligoarticular **arthritis**. This is not to be confused with so-called chronic Lyme disease, which is generally not recognized as being a real entity.



Figure 4-26: Erythema migrans
Source: CDC

Diagnosis

A diagnosis can be made in 2 ways:

- 1) presence of EM or
- 2) ≥ 1 Stage 2 or 3 manifestations and positive serology (an enzyme immunoassay [EIA] test, followed by a Western blot only if the EIA is positive).

There are a few important caveats about testing for Lyme disease:

- Do not perform serology if there are no Lyme symptoms. Patients with seropositivity and no symptoms have had prior asymptomatic exposure, but they do not warrant and do not benefit from treatment.
- Do not perform serology in patients with EM. It is diagnostic of Lyme disease and most patients are seronegative in Stage 1.
- Reserve serology for persons from endemic areas with symptoms consistent with Stage 2 or 3 Lyme disease.

Treatment

Treatment depends on the stage and type of manifestation:

- Treat Stage 1, Bell's palsy, and asymptomatic 1st or 2nd degree heart block with oral doxycycline or amoxicillin $\times$ 10–21 days.
- Treat symptomatic heart block and neurologic disease with ceftriaxone 2 g or PCN G 20 MU IV in divided doses $\times$ 14–21 days. Typically only temporary pacing is required for symptomatic heart block.
- Treat arthritis with oral doxycycline or amoxicillin $\times$ 28 days, but you may need to repeat the oral regimen or use IV ceftriaxone if there is recurrence after the initial oral regimen.

Although patients previously treated for Lyme disease more commonly have chronic neuromuscular symptoms (e.g., muscle and joint pain, fatigue, trouble with memory and formulating ideas) than do patients never infected with *B. burgdorferi*, several studies have confirmed that there is no benefit in giving additional courses of antibiotics to these individuals.

Prevention

Because transmission does not occur until at least 36–48 hours of attachment, the best prevention is to keep ticks off the body with clothing treated with insect repellents and to find and remove the *Ixodes* tick from the skin. When ticks are embedded in the skin, they should be removed by grasping them with tweezers placed on their mouthparts and pulling them straight up from the skin.

Postexposure prophylaxis: Give a single dose of doxycycline 200 mg PO if an embedded tick is found on the skin and all of the following are true:

- The tick is in the nymph or adult stage.
- The tick was attached at least 36 hours and is engorged.
- The patient presents within 72 hours of tick removal.
- The local rate of tick infection with *B. burgdorferi* is $\geq 20\%$, such as in New England, mid-Atlantic states, and parts of Minnesota and Wisconsin.

FUNGAL INFECTIONS

PREVIEW | REVIEW

- In a febrile patient who is receiving intravenous hyperalimentation, which fungal bloodstream infection might you suspect?
- When can you disregard *Candida* as a blood culture contaminant?
- What is the treatment of candidemia when a line is present?
- Which patient population typically develops hepatosplenic candidiasis?
- Patients with candidemia should have what kind of referral?
- What are the cerebral spinal fluid abnormalities in cryptococcal meningitis?
- Initial treatment for cryptococcal meningitis includes which drugs?
- Where is *Coccidioides immitis* geographically found?
- What are the clinical presentations of histoplasmosis?
- Which tests are best for diagnosing histoplasmosis?
- What are the clinical manifestations of disseminated blastomycosis?
- Which patient groups are at risk for mucormycosis?

OVERVIEW

Fungi are divided into 2 morphologic types: **yeasts** and **molds**. There are also **dimorphs** that change from a yeast to mold, and vice versa, depending on temperature. The dimorphs are the type most likely to cause **systemic** disease in the nonhospitalized, immunocompetent host. The dimorphic fungi are transmitted by spores that convert to yeast at body temperature.

Some of the clinically relevant fungi include:

- *Candida* species
- *Cryptococcus* species
- *Aspergillus* species
- Endemic fungi (*Histoplasma*, *Blastomyces*, and *Coccidioides*; found in specific regions of the U.S.)
- Dermatophytes (cause tinea capitis, tinea corporis, tinea pedis, and tinea cruris)
- *Sporothrix schenckii*
- Zygomycetes (e.g., *Mucor*, *Rhizopus*, and *Rhizomucor*)

CANDIDA

Outpatient *Candida* infections are usually caused by *Candida albicans*.

People who have recently spent time in nursing homes and have lines and tubes that go into their body, such as breathing tubes, feeding tubes, and central venous catheters, seem to be at highest risk for *Candida auris* infection. Limited data suggest that the risk factors for *C. auris* infections are generally similar to risk factors for other types of *Candida* infections. These risk factors include recent surgery, diabetes, broad-spectrum antibiotic and antifungal use. Infections have been found in patients of all ages, from preterm infants to the elderly. Further study is needed to learn more about risk factors for *C. auris* infection. Infections with this organism are more likely to occur in patients who:

- are immunosuppressed,
- are on antibacterials,
- have indwelling catheters,
- are receiving IV hyperalimentation,
- have uncontrolled diabetes, or
- have HIV infection.

Presentations vary. Disease can be localized to mucosal surfaces of the mouth (thrush), esophagus, and vagina (candidal vaginitis). Disseminated disease manifests as candidemia that can produce endocarditis, endophthalmitis, hepatosplenic infection, and renal infection. Usually, candidemia, either from an infected vascular catheter or from overgrowth of *Candida* in the gut, is the source of dissemination to these other organ systems.

Physical exam findings: Limited mucosal *Candida*, such as thrush, is visible as whitish plaques with an underlying erythematous base. Patients who have odynophagia and oral thrush can be assumed to have esophageal candidiasis; endoscopy is not required to make the diagnosis. Vulvovaginal candidiasis presents as a thick, whitish discharge along with intense vaginal itching (see [Vulvovaginal Candidiasis \(VVC\)](#) on page 4-21).

C. auris is an emerging multidrug-resistant yeast with outbreaks in health care settings. Patients with lines going into their body (e.g., feeding tube, central catheter) are more susceptible. Known risk factors for *C. auris* are the same as those for *C. albicans*. The most reliable antifungal options are the echinocandins.

Candidemia

Signs and symptoms of disseminated disease are fever; rash or painless, erythematous papules/pustules; visual complaints; and multiorgan involvement. *Candida* species grow readily in routine blood culture bottles. *Candida* in a blood culture is **never** a contaminant; it represents real disease, even if the patient is relatively asymptomatic. It can take days to grow the organisms out of the blood. If the patient is ill, consider empiric antifungal treatment (e.g., in a neutropenic patient with a prolonged fever).

Non-*albicans Candida* are common in hospitalized and immunocompromised patients. They are often resistant to fluconazole.

Treatment of candidemia includes removal of any infected catheters and administering a systemic antifungal. An echinocandin (i.e., caspofungin, micafungin, anidulafungin) is 1st line therapy in all patients, pending identification and susceptibility. Fluconazole can be considered once speciation is known.

Chronic Disseminated Candidiasis

Chronic disseminated candidiasis (a.k.a. hepatosplenic candidiasis) is seen in leukemic patients as they recover from a period of neutropenia. Symptoms include fever and pain in the right upper quadrant.

Labs show increased alkaline phosphatase +/- increased transaminases and bilirubin. Contrast CT of the abdomen shows multiple small abscesses in the liver and spleen.

As with candidemia, the main therapy is an echinocandin (i.e., caspofungin, micafungin, anidulafungin). Note that the echinocandins end in "-fungin."

Ocular Candidiasis

Ocular candidiasis presents with altered visual acuity and can manifest as endophthalmitis or chorioretinitis. Disease can occur as a result of fungemia and seeding of the eye or after cataract surgery. Early disease (especially with chorioretinitis) can be relatively asymptomatic, so any patient who develops candidemia should have a dilated eye exam by an ophthalmologist. The most common symptom is painless loss of visual acuity, and exam may show fluffy chorioretinal lesions or fungus balls in the vitreous.

Treat chorioretinitis without vitritis with systemic azoles (fluconazole or voriconazole), unless there is azole resistance, and then liposomal amphotericin should be used. If there is also macular involvement, give intravitreal amphotericin B or intravitreal voriconazole. If chorioretinitis with vitritis is present, treatment may entail vitrectomy in addition to systemic and intravitreal antifungals.

Genitourinary Candidiasis

Candiduria is fairly common, especially in hospital settings, and it often represents colonization, especially if the patient has had a urinary catheter.

Be concerned about repeatedly positive urine cultures for *Candida* in patients with diabetes or recent urinary manipulation and patients with systemic signs of infection. Urinalysis showing pyuria is not sensitive or specific for true infection. In the evaluation, include renal imaging with either ultrasound or CT of both the bladder and the kidneys.

Manage asymptomatic candiduria with negative imaging by changing the urinary catheter if present. Antifungal therapy is **not** indicated unless the patient is neutropenic or will be undergoing urologic manipulation.

Treat symptomatic candiduria with a systemic antifungal based on culture results. Fluconazole is preferred if the isolate is susceptible.

Lipid amphotericins are not excreted in high enough concentrations in the urine to be useful in treating *Candida* UTIs. Echinocandins are also not recommended, for the same reason. Bladder irrigation also is not recommended for cystitis, although it has some use in treating upper tract disease complicated by fungus balls.

Surgically remove any fungus ball if no improvement after amphotericin B upper tract irrigation.

CRYPTOCOCCUS

In immunocompetent patients, *Cryptococcus neoformans* usually causes minimally symptomatic, self-limited infection after entering via the respiratory route. Patients can have a low-grade fever, pleuritic pain, cough, and a pulmonary infiltrate. Form of treatment depends on level of symptoms. Although it is found in pigeon droppings, most patients have no recollection of being in contact with birds. Cryptococcal pneumonia can form cavitory lesions and peripheral "cannon ball" lesions. Lumbar puncture is recommended in pulmonary cryptococcosis, even if without CNS symptoms, as cryptococcal meningitis may be subtle.

Dissemination is more likely with *Cryptococcus gattii*, a related species, in immunodeficient patients (e.g., AIDS, corticosteroid therapy, Hodgkin disease, acute lymphocytic leukemia, diabetes, after organ transplant). These patients are especially likely to get **cryptococcal meningitis**—the most common presentation of severe cryptococcal infection. *C. gattii* is found in northern California and the Pacific Northwest.

Suspect cryptococcal meningitis in any immunosuppressed patient who has headache +/- skin lesions and/or pulmonary lesions +/- fever. More specific meningeal symptoms (e.g., stiff neck, photophobia) are rare. Lumbar puncture commonly shows increased CSF opening pressure, usually > 200 mmH₂O. The rest of the spinal fluid analysis may be remarkably benign with minimal leukocytosis and protein elevation. India ink testing is relatively nonspecific and insensitive and has generally been replaced by cryptococcal antigen testing.

Treatment is long term and occurs in 3 stages:

- 1) Induction with amphotericin B + flucytosine for 2 weeks
- 2) Consolidation with fluconazole 400 mg/day for ≥ 8 weeks
- 3) Maintenance with fluconazole 200 mg/day for ≥ 1 year

Additionally, daily repeated lumbar punctures are recommended in those with increased intracranial

pressure (> 200 mmH₂O) or with associated headache, clouded sensorium, visual/hearing loss, or cranial nerve palsies. Sometimes, if these do not reduce pressure, shunts are required.

Patients with AIDS require secondary prophylaxis with chronic fluconazole.

ASPERGILLOSIS

Aspergillus species are ubiquitous in the environment. *A. fumigatus* is the most commonly isolated pathogen and can cause severe infections, mostly in immunocompromised hosts. Aspergillosis can present with a spectrum of disorders spanning the following:

- Allergic bronchopulmonary aspergillosis (ABPA), an allergic reaction to colonization with *Aspergillus* (clinical presentation similar to asthma; more in the [Pulmonary Medicine](#) section)
- Aspergilloma (a fungus ball in a previously formed cavity; [Figure 4-27](#))
- Invasive aspergillosis can be an acute destructive pulmonary process in immunocompromised patients (acute invasive pulmonary aspergillosis) or chronic in those who are immunocompromised (chronic necrotizing aspergillosis) or immunocompetent (chronic cavitary aspergillosis leading to chronic fibrosing aspergillosis).



Figure 4-27: *Aspergillus* fungus ball
Source: CDC

Invasive aspergillosis can be rapidly fatal and requires prompt diagnosis and treatment. Diagnose by lung biopsy and demonstration of the organism invading the lung and on culture. Use caution in interpreting expectorated sputum and bronchoalveolar lavage (BAL) specimens because the organism is common in the environment and may represent colonization. Alternatively, measure *Aspergillus* galactomannan antigen in the blood or the BAL fluid. This test is most useful in immunocompromised hosts (particularly patients with hematologic malignancy and stem cell transplant recipients), which is also true for 1,3-β-D-glucan, which is a serum test that may support the diagnosis of invasive aspergillosis.

Treat ABPA with steroids +/- voriconazole. Aspergillomas can be observed, but if symptomatic (hemoptysis), resect. 1st line treatment for the invasive forms of aspergillosis is voriconazole.

ENDEMIC FUNGI

The American endemic fungi are *Coccidioides*, *Histoplasma*, *Blastomyces*, and *Cryptococcus gattii* (discussed in [Cryptococcus](#)). They have the following characteristics in common:

- They are found in specific areas of the U.S., and a patient becomes infected only after visiting or living in the area where the organism is endemic and participating in activities that encounter the organism.
- They are acquired by inhalation.
- They most commonly cause asymptomatic or mild, self-limited pulmonary disease.
- Less frequently, they cause significant pulmonary disease requiring medical treatment.
- Least commonly, they cause disseminated disease.
- Significant pulmonary disease and dissemination are much more common in immunodeficient patients.
- Mild disease is treated with azoles. Severe or CNS disease is treated with amphotericin B.

Coccidioidomycosis

Coccidioides immitis and *Coccidioides posadasii* cause coccidioidomycosis ([Figure 4-28](#)). The spores (arthroconidia) are highly infectious at a very low inoculum.

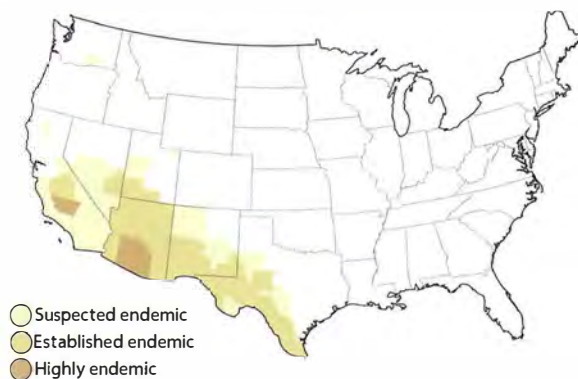


Figure 4-28: Geography of coccidioidomycosis, 2018
Source: CDC

C. immitis is found in the soil of the arid southwest U.S. and northern Mexico. This disease is frequently called **valley fever** because it is endemic to the San Joaquin Valley and Death Valley.

When inhaled, the arthroconidia convert to their yeast form that, days to weeks later, causes a self-limited, flu-like illness with arthralgias, erythema multiforme, and/or erythema nodosum. Disease can result in a pulmonary "coin lesion." People at highest risk for severe infection include Asians and African Americans, pregnant women, and the immunosuppressed.

Extrapulmonary coccidioidomycosis can involve bone, skin, or the CNS. Coccidioidomycosis and ABPA are the only 2 fungal diseases that cause peripheral **eosinophilia**.

Demonstration of spherules in body fluids or tissue is diagnostic (Figure 4-29). Culture is also diagnostic, and the organism grows well on almost all media in ~ 1 week. IgM serology is available but takes 1-3 weeks to turn positive.

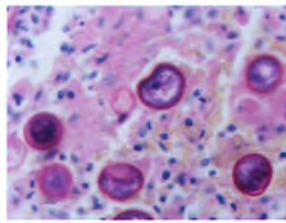


Figure 4-29: Coccidioidomycosis spherules

Most patients have self-limited disease and do not require treatment. If needed, nonmeningeal, less severe infections can be treated with fluconazole or itraconazole. Treat severe cases with amphotericin B. When treatment is indicated, continue for a prolonged duration (6-12 months).

Histoplasmosis

Histoplasma capsulatum causes histoplasmosis and is found predominantly in the Mississippi and Ohio River valleys (Figure 4-30).

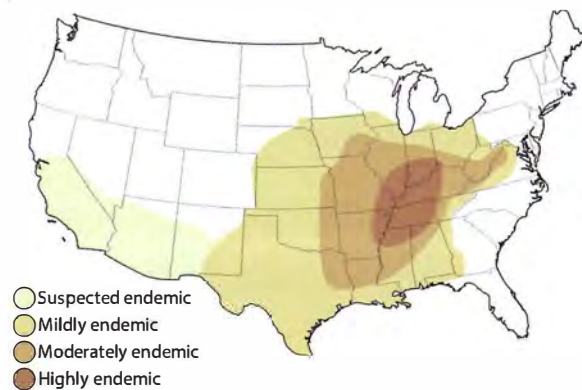


Figure 4-30: Geography of histoplasmosis, 2018
Source: CDC

H. capsulatum is especially prevalent in bat and bird droppings. Conidia or mycelial fragments are the infectious form.

Immunocompetent patients typically have a self-limited, flu-like illness with or without mild pulmonary infiltrates. *Histoplasma* can present with pneumonia, mediastinal adenopathy, superior vena caval obstruction, palate ulcers, and hepatosplenomegaly. Radiographically, it can mimic cancer, sarcoid, or TB.

In the immunocompromised patient (especially HIV/AIDS), *H. capsulatum* can disseminate, causing a rapidly progressive sepsis and/or multisystem involvement.

Demonstration of characteristic yeast forms with narrow-based budding (Figure 4-31) that are often intracellular is diagnostic. They are not as commonly detected

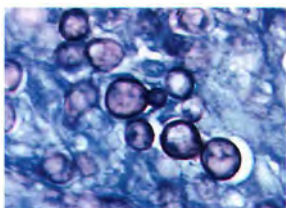


Figure 4-31: Histoplasmosis narrow-based budding
Source: CDC

as is the granuloma on biopsy. Serum and urine antigen detection is diagnostic and has the highest yield in immunocompromised hosts and/or those with disseminated disease. Antigen detection tests cross-react with *Blastomyces dermatitidis*, which diminishes the specificity of these tests.

Acute, nonsevere pulmonary disease requires no therapy. More severe but localized histoplasmosis can be treated with itraconazole. Disseminated disease requires amphotericin B (either deoxycholate or liposomal formulations; liposomal formulations are preferred because they are relatively less nephrotoxic) followed by itraconazole.

Blastomycosis

Blastomycosis is caused by *Blastomyces dermatitidis*, which, in vivo, is a broad-based budding yeast (remember the 4 Bs: blasto, broad-based, budding).

Blastomycosis was primarily seen in states bordering the Mississippi and Ohio River basins and the basins near the Great Lakes and along the St. Lawrence River but has since expanded to cover almost all of the eastern half of the U.S. (Figure 4-32).



Figure 4-32: Geography of blastomycosis, 2018
Source: CDC

Initial infection is often asymptomatic; otherwise it commonly presents as a flu-like illness. This can progress to a lobar pneumonia that is unresponsive to antibacterial agents. If it disseminates from the lung, it typically does so to the skin, usually causing verrucous (warty) lesions with central ulceration. Septic arthritis and osteomyelitis can also be seen.

Demonstration of the yeast form with its broad-based buds in secretions or tissue is diagnostic (Figure 4-33). Cultures require fungal media and turn positive in 1-4 weeks. Urinary antigen and serum antigen are usually positive in disseminated disease, with the urine being a more sensitive test.

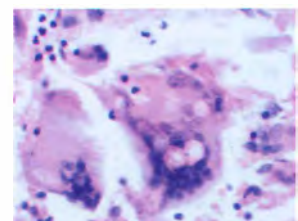


Figure 4-33: Blastomycosis; giant cell with broad-based budding

Treat mild to moderate disease with itraconazole. Severe or CNS disease requires amphotericin B.

SPOROTRICHOSIS

Sporotrichosis (a.k.a. rose gardener's disease) is caused by *Sporothrix schenckii*—a ubiquitous dimorphic fungus found in soil and plants. Gardeners are prone after being pricked by a thorn. Of the 4 clinical presentations, the cutaneous and the lymphangitic (nodules form on the skin over lymph channels) types are treated with itraconazole, and the rare pulmonary and disseminated types are treated initially with lipid amphotericin B. The disseminated type is more common in those with immunodeficiency. *Mycobacterium marinum* and *Nocardia brasiliensis* cause similar lesions over lymphatic channels.

MUCORMYCOSIS

Mucormycosis (previously zygomycosis) is caused by fungi in the order Mucorales. *Mucor*, *Rhizopus*, or *Rhizomucor* are the most common species of Mucorales that cause human disease.

Rhizopus thrives in acidic and high-glucose conditions. These conditions occur in patients with iron overload on deferoxamine chelation, in patients with diabetes, and in those with primary or secondary hemochromatosis. The severely immunosuppressed are also at risk.

Disease can present as invasive pulmonary or rhinocerebral infection. Rhinocerebral mucormycosis presents as a black necrotic spot on the paranasal skin, nasal mucosa, or paranasal sinuses that can extend intracranially. Necrotic areas can also be seen on the hard palate. It has a poor prognosis.

Pulmonary mucormycosis presents as a necrotizing, cavitating pneumonia, similar to aspergillosis. Consider mucormycosis in a patient on voriconazole treatment or prophylaxis with new or worsening pulmonary disease.

Diagnosis is made by biopsy showing broad, nonseptate hyphae with right-angle branching that are described as “ribbon-like” (Figure 4-34).

Treat with correction of predisposing factors (e.g., diabetic ketoacidosis), aggressive surgical resection, and lipid amphotericin B. Use posaconazole or isavuconazole in those who cannot tolerate amphotericin B or for salvage therapy. The other azoles (fluconazole, itraconazole, voriconazole) do not have activity against mucormycosis.

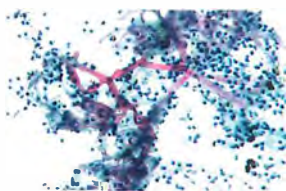


Figure 4-34: Right-angle branching in mucormycosis pneumonia

DERMATOPHYTES

Dermatophytes infect keratinized structures, such as skin and hair.

The names of the diseases caused by dermatophytes begin with “tinea” and end with the location of their infection: tinea corporis, tinea capitis, tinea pedis, and tinea cruris. See the Dermatology section.

Treat ringworm (tinea corporis) with topical clotrimazole, topical terbinafine, or undecylenic acid. Then, if there is no success, use an oral agent; the preferred ones are itraconazole and terbinafine. Infection of hair follicles (tinea capitis) requires treatment with oral agents, such as terbinafine, itraconazole, and fluconazole.

PARASITES

PREVIEW | REVIEW

- How is a *Giardia* infection diagnosed?
- What is kala azar?
- Which form of malaria is associated with banana-shaped gametocytes?
- For travel to chloroquine-resistant areas, which drugs are used for malaria prophylaxis?
- What is the presentation of *Babesia* infection?
- *Strongyloides* hyperinfection syndrome can be seen in which patient population?
- What is visceral larva migrans?
- What are the clinical manifestations and treatment of neurocysticercosis?

There are 2 main types of parasites, protozoa and helminthic organisms.

PROTOZOA

Protozoa are single-celled and can replicate within the body. With the exception of *Cystoisospora*, protozoa do not cause eosinophilia.

There are 3 types of protozoa:

- 1) Sporozoa (*Toxoplasma*, *Cryptosporidium*, *Cystoisospora* [previously *Isospora*], microsporidia, *Plasmodium*, *Cyclospora*, *Babesia*)
- 2) Amebas (*Entamoeba histolytica*, *Naegleria fowleri*)
- 3) Flagellates (*Giardia*, *Trichomonas*, *Trypanosoma*, *Leishmania*)

We classify the protozoan parasites in terms of the systems they affect (Figure 4-35 on page 4-58).

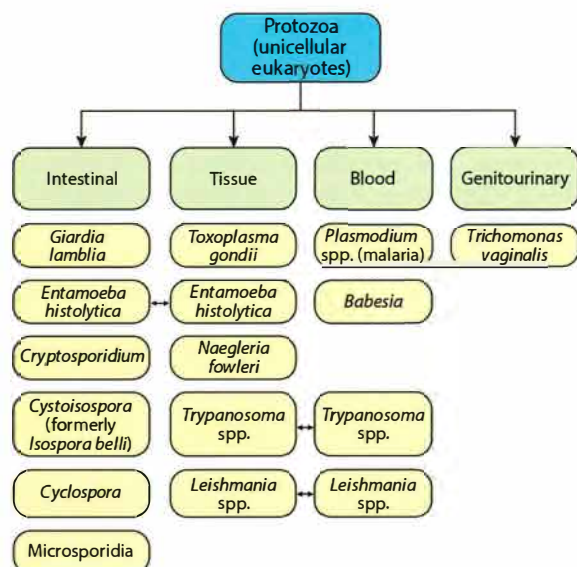


Figure 4-35: Classification of parasites—protozoa

Intestinal Protozoans

Giardia

Giardia lamblia (a.k.a. *Giardia duodenalis*, *Giardia intestinalis*) is an intestinal protozoan that infects the duodenum and proximal jejunum by adhering to the mucosa. Infected persons are asymptomatic in 75% of cases. Distribution is worldwide; it is the most common intestinal parasite in North America. Infection occurs through ingestion of infectious cysts via contaminated food, water, or fomites. Cysts turn into trophozoites in the gut, and look like a face with flagella legs when viewed under the microscope.

Groups of people at increased risk for *Giardia* infections include:

- Campers/backpackers (drinking unfiltered water)
- Travelers to endemic regions
- Young children in day care (and their parents also)
- HIV-infected persons
- Men who have sex with men, or anyone who performs oral-anal contact
- IgA deficiency (Remember: IgA is actively secreted across mucosal barriers, so this makes sense.)

Infection may be asymptomatic, posing infectious risk to others. If symptoms are present, they include foul, floating, watery diarrhea; sulfur-tasting burps; and flatulence associated with a malabsorption syndrome. A helpful distinguishing feature is prolonged diarrhea, with flatulence, frequently associated with weight loss. *Giardia* can sometimes cause a chronic syndrome of diarrhea, malabsorption, and weight loss. Diagnose by microscopic examination of fresh stool samples, antigen detection, or nucleic acid amplification assays, with the latter being the most sensitive. Excretion of the organism is intermittent, so up to 3 stools may be needed to make the diagnosis. Treat with tinidazole, metronidazole, or nitazoxanide.

Entamoeba

Human amebiasis is caused by the protozoan *Entamoeba histolytica*. Distribution is worldwide, though primary burden of disease occurs in developing countries. There are 30–50 million cases per year around the world, and it is the 3rd most common parasitic disease in the United States. Transmission occurs through ingestion of infectious cysts, typically via the fecal-oral route (e.g., food, waterborne). Acquisition through oral-anal sexual contact also occurs. In the U.S., the most commonly affected population groups include the institutionalized, immigrants, travelers, and men who have sex with men.

There are 4 major clinical syndromes:

- 1) **Asymptomatic cyst-passing carrier state** (80% of cases): risk to community
- 2) **Amebic diarrhea without dysentery**: diarrhea without mucus or blood
- 3) **Amebic dysentery** (< 20% of cases): subacute (3–4 weeks) progressively worsening diarrhea with mucus, or visible/microscopic blood, usually with abdominal pain; fever uncommon
- 4) **Amebic liver abscess** (< 1% of cases): seeded via portal system; usually presents as subacute RUQ pain, most commonly occurs in adult men; typically a solitary abscess

Diagnosis of intestinal disease is by stool for ova and parasites. Amebic liver abscesses often show no amebas or PMNs. These cases can be diagnosed by serology.

Treat with metronidazole or tinidazole for both forms of the disease. Although metronidazole treats amebas that have invaded, it does not kill intraluminal cysts. This must be accomplished with the administration of paromomycin, diiodohydroxyquin, or diloxanide furoate. Typically, amebic liver abscesses do not require percutaneous drainage, as opposed to pyogenic liver abscesses (which most commonly do).

Cryptosporidium

Cryptosporidium parvum and *Cryptosporidium hominis* are acid-fast, intestinal protozoans that cause enteric infections. *Cryptosporidium* is found worldwide. Infection occurs after ingestion of oocysts, usually from fecally contaminated water. *Cryptosporidium* is quite hardy and unique from other intestinal pathogens in that it can be acquired after swimming in recreational, chlorine-treated water, such as swimming pools or water parks. The patient's immune response influences the severity and duration of illness, as well as response to therapy. *Cryptosporidium* typically causes watery diarrhea for 1–2 weeks in immunocompetent patients, but can be quite severe and protracted (sometimes with biliary involvement) in immunocompromised patients. Patients with advanced HIV/AIDS are particularly at risk for severe disease. Diagnosis can be difficult but is typically made by stool microscopy, aided by acid-fast staining, as well

as other special stains. Additional methods, such as stool antigen detection and PCR, may be used to improve sensitivity. Therapy involves supportive care, consideration of nitazoxanide, and (if applicable) reduction of immune suppression or initiation of antiretroviral therapy.

Cystoisospora belli and *Cyclospora cayetanensis*

Cystoisospora belli (previously *Isospora belli*) and *Cyclospora cayetanensis* are two partial acid-fast protozoans that cause a secretory, self-limited diarrhea in immunocompetent patients, and more severe chronic forms of diarrhea in patients with compromised immune systems (especially those with advanced HIV/AIDS). Infections occur worldwide, though more commonly in tropic/subtropic regions. Infection develops after fecal-oral ingestion of oocysts. *Cyclospora* in particular is often the cause of outbreaks related to imported fruits or vegetables from Central America. Extraintestinal manifestations, particularly acalculous cholecystitis, sometimes occur in immunocompromised patients with severe disease. A clue to all of these intestinal protozoan infections is a longer duration of illness than most bacterial GI infections. Diagnosis is made via stool microscopy and aided by modified acid-fast staining (plus other special stains). Multiple stool samples might be needed to improve detection sensitivity. Treat with TMP/SMX—or, in the sulfa-allergic patient, use ciprofloxacin or nitazoxanide.

Microsporidia

The phylum Microsporidia encompasses a large group of organisms. They are intracellular parasites, recently reclassified as fungal organisms rather than protozoans; however, they can be thought of as protozoan-like and most commonly cause diarrhea, though they can infect any organ system. Water contact is a risk factor for acquisition. The most common microsporidia infecting humans are *Enterocytozoon bieneusi* and *Encephalitozoon intestinalis*. These organisms cause disease predominantly in the immunosuppressed patient (particularly advanced HIV/AIDS). The diagnosis is made by demonstrating spores in the stool by trichrome staining or PCR assay. Bowel disease is patchy, so biopsy does not increase the yield. Albendazole is the treatment of choice.

Tissue Protozoans

In addition to the tissue protozoans described here, *Entamoeba histolytica* can also manifest as tissue disease (see *Entamoeba*).

Toxoplasma gondii

Toxoplasma gondii is a tissue protozoan that causes toxoplasmosis. Cats are the definitive host (i.e., the host in which the adult parasite lives); they excrete the oocysts. After oocysts are ingested by other animals, they encyst in the muscles. Undercooked muscle from these animals (mainly pigs, lambs, and cattle) is then ingested

by humans, the organism excysts, and tachyzoites are released that circulate through the blood stream and infect any nucleated cell—with a predilection for neural tissue. ~ 20% of pork and lamb and 10% of beef contains *T. gondii* cysts. Thus, consumption of undercooked meat and outdoor cat contact/ownership are the modes of acquisition. Infection is common in the U.S., with 1/3 of adults demonstrating seropositivity to the organism.

There are 4 clinical presentations of toxoplasmosis:

- 1) Immunocompetent host
- 2) Congenital
- 3) CNS
- 4) Ocular

Immunocompetent hosts are usually asymptomatic, but toxoplasmosis may cause fever, lymphadenopathy, and atypical lymphocytosis similar to infectious mononucleosis; pharyngitis is conspicuously absent. Diagnose by demonstrating the presence of IgM antibody. It is self-limited and requires no treatment.

If acquired during pregnancy, *T. gondii* can infect the fetus and cause **congenital toxoplasmosis**, with a combination of necrotizing chorioretinitis, hydrocephalus, intracranial calcifications, and intellectual disabilities (see the [Women's and Men's Health](#) section).

CNS toxoplasmosis occurs in immunocompromised patients (particularly those with AIDS) from reactivation of previous infection. These patients present with new onset of seizures, neurologic deficit, and/or altered consciousness. Diagnosis is made by brain imaging revealing multiple, bilateral, ring-enhancing lesions with a predilection for the basal ganglia. When considering CNS toxoplasmosis, the other main differential diagnosis to consider in a patient with AIDS and ring enhancing lesions is primary CNS lymphoma (though lymphoma lesions are typically single). Because this is a reactivation disease, IgM antibody is not present—but IgG is. However, a negative IgG does not necessarily exclude infection in the immunocompromised patient because of difficulty making antibodies. Treat with pyrimethamine, sulfadiazine, and leucovorin. Substitute clindamycin for sulfadiazine in the sulfa-allergic patient.

Ocular toxoplasmosis causes retinal lesions that appear as yellow-white cotton patches, irregular scarring, and pigmentation. There is also reactivation in the immunocompromised host. Treat with pyrimethamine and a sulfadiazine for 3 weeks.

Naegleria fowleri

Naegleria fowleri is a free-living amoeba found worldwide in warm freshwater (not saltwater). It causes primary amoebic meningoencephalitis, a rare but rapidly fatal disease that occurs when infested water comes in contact with nasal mucosa and the cribriform

plate, usually after extensive exposure through swimming, diving, waterskiing, and surfing. The disease is rare because the risk of infection is < 1 in 2.5 million exposures.

Typical cases involve a young, previously healthy patient, ~ 2–5 days after recreational water exposure, presenting with a rapidly progressive meningoencephalitis that is almost universally fatal within 2 weeks. Spinal fluid shows a polymorphonuclear pleocytosis and is often hemorrhagic. The diagnosis can be made by demonstrating the motile organisms on a centrifuged CSF specimen.

Because of the rarity of the disease and the high mortality rate, there are no convincing trials to determine optimal therapy.

Trypanosoma

Trypanosoma is a tissue/blood protozoan that causes two distinct diseases, Chagas disease (American trypanosomiasis) and African sleeping sickness.

Chagas disease is caused by *Trypanosoma cruzi* and is transmitted to humans via the triatomine bug (a.k.a. reduviid bug or kissing bug). It has a large impact on health and wellness, affecting 6–8 million people worldwide with 50,000 deaths per year. It occurs primarily in Central and South America. Acute illness is nonspecific with fever, lymphadenopathy, and hepatosplenomegaly. There is an intermediate phase without symptoms, followed by a chronic phase with predominately GI and cardiac involvement, causing congestive heart failure and ventricular arrhythmias in particular. Congenital infection occurs as well. Make the diagnosis by microscopic identification of organisms from the buffy coat of blood during acute disease, and by tissue biopsy in chronic disease. Treat acute illness, congenital infection, reactivation in the immunosuppressed, and young people (< 18 years of age) who are asymptomatic. Do not treat people with advanced heart disease, those who are pregnant, or patients with multi-organ failure.

African sleeping sickness, caused by *Trypanosoma brucei gambiense* and *Trypanosoma brucei rhodesiense*, is much less common, affecting ~ 10,000 people per year worldwide. It is transmitted by the bite of the Tsetse fly in East, Central, and West Africa. A painful chancre develops at the bite, after which organisms disseminate to lymphatics, then blood, then finally to the CNS, where neuropsychiatric symptoms and sleep disturbances can occur. Death and coma will occur if left untreated. It is important to always rule out CNS disease with a lumbar puncture. Diagnosis is made by microscopy. Treat with pentamidine or suramin, depending on the causative species.

Leishmania

Leishmaniasis is caused by any of the following 4 species of the *Leishmania* protozoa: *L. donovani*, *L. tropica*, *L. mexicana*, and *L. braziliensis*. It is spread via the sand

fly in tropical and subtropical regions around the world. It is characterized by a chronic, progressive course with 3 main phenotypes:

- 1) **Cutaneous** (painless ulcer)
- 2) **Mucocutaneous** (destructive lesions in oral/nasal mucosa)
- 3) **Visceral** (a.k.a. Kala-Azar; hepatosplenomegaly, pancytopenia)

Of note, there is a higher susceptibility for leishmaniasis in HIV-infected patients who travel to endemic areas. Diagnosis is made by histologic examination of infected tissues for cutaneous and mucocutaneous disease, and the highest yield for visceral disease is a bone marrow biopsy. Treatment varies from observation, to local therapies, to systemic therapy, depending on the extent of disease, location, and host immune status.

Blood Protozoans

In addition to the blood protozoans described here, *Trypanosoma* and *Leishmania* can also manifest as blood disease. They are described under Tissue Protozoans in *Trypanosoma* and *Leishmania*.

Plasmodium (Malaria)

Malaria—an acute febrile illness of varying severity caused by a blood protozoan—is a very old disease, described by ancient civilizations. There are 5 clinically relevant species within the genus *Plasmodium*:

- 1) *P. falciparum*
- 2) *P. vivax*
- 3) *P. ovale*
- 4) *P. malariae*
- 5) *P. knowlesi*

The clinical significance of malaria cannot be understated. According to the WHO World Malaria Report, there were 228 million cases of malaria with 405,000 deaths in 2019 alone. Africa carries the highest burden of disease and highest mortality, which is typically attributed to *P. falciparum*.

The basic life cycle of malaria is important to consider in order to understand the disease. The female *Anopheles* mosquito releases sporozoites during a blood meal. Sporozoites travel to the liver and mature. *P. vivax* and *P. ovale* can form hypnozoites and “sleep” in the liver, allowing for recurrent infection unless appropriately treated. After maturation in the liver, merozoites are released into the blood stream and continuously infect, mature, then rupture red blood cells. In RBCs, merozoites mature into ringed trophozoites, which is the form that is typically identified on microscopy. Some merozoites in the bloodstream form gametocytes, which transmit back to uninfected *Anopheles* mosquitos and then infect additional people.

Consider malaria in any febrile traveler returning from an endemic region. Geographic hot spots include sub-Saharan Africa and tropical regions of South America, Asia, and Indonesia.

Malaria typically presents as an acute febrile illness with chills, rigors, profound fatigue, and splenomegaly. Fevers can be very high ($> 40^{\circ}\text{C}$, 104°F) and may be spaced in regular intervals, correlating with cycles of RBC rupture. In endemic regions, due to partial immunity, symptoms can be milder or more indolent. *P. falciparum* deserves special attention because it causes the majority of severe malaria due to its ability to lodge in microvasculature and obstruct blood flow. Look out for cerebral malaria (seizure, coma), shock, acidosis, severe anemia, respiratory distress (ARDS), hypoglycemia, and renal failure. Anemia occurs through a combination of hemolysis and bone marrow suppression.

Diagnosis is made by microscopic analysis of blood smears. Thick blood smears analyze a larger volume of blood by lysing RBCs and looking for parasites. Thin blood smears are used to make a species diagnosis based on the stage and appearance within intact RBCs.

Appropriate treatment of malaria depends on 3 factors:

- 1) Species
- 2) Geographic region
- 3) Illness severity

As we go through the following discussion, refer to Table 4-7.

Plasmodium falciparum

P. falciparum causes the most severe malaria and is the cause of virtually all fatal malarial infections. It has widespread chloroquine resistance.

Differentiating this species from the others is critical because *P. falciparum* causes the large majority of the mortality attributed to malaria throughout the world. *P. falciparum* has several unique findings on blood smears that facilitate this identification: banana-shaped

gametocytes (Figure 4-36); double chromatin knobs (giving the parasite the appearance of headphones); > 1 parasite per cell; and the number of infected RBCs being $> 5\%$.

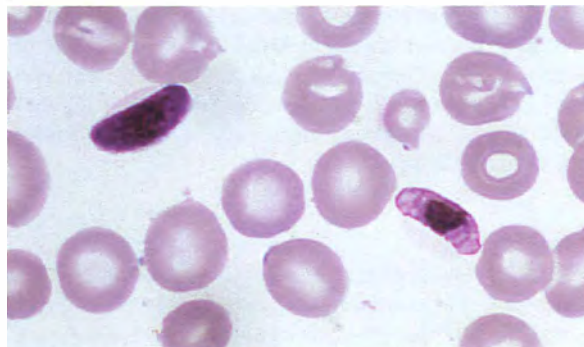


Figure 4-36: *P. falciparum* banana-shaped gametocytes
Source: CDC

Treatment for *P. falciparum* malaria depends on the country of acquisition. Chloroquine-susceptible regions are still present in 4 parts of the world. Malaria acquired from these areas can safely be treated with chloroquine:

- 1) Central America north of Panama
- 2) Haiti
- 3) Dominican Republic
- 4) Middle East

P. falciparum from other areas must be assumed to be chloroquine resistant. Treat nonsevere disease (i.e., no end-organ damage) with artemether/lumefantrine (Coartem) or atovaquone/proguanil. Treat patients with severe disease with artesunate.

Non-*P. falciparum*

Assume *P. vivax* from Papua New Guinea, Indonesia, and Southeast Asia is chloroquine resistant; otherwise, all non-*P. falciparum* species are chloroquine sensitive, so treat with chloroquine.

Table 4-7: Treatment and Prophylaxis of Malaria

Type of Malaria	Treatment	Prophylaxis
Non- <i>falciparum</i> malaria	Chloroquine, followed by primaquine	Chloroquine 500 mg (300 mg base) weekly; give daily in endemic areas, and continue for 4 weeks after return.
<i>P. falciparum</i> Chloroquine-sensitive	Chloroquine Atovaquone/proguanil	Choose any 1 of the following: • Chloroquine • Atovaquone/proguanil • Mefloquine • Doxycycline
<i>P. falciparum</i> Chloroquine-resistant Not severe	Atovaquone/proguanil or Mefloquine	
<i>P. falciparum</i> Chloroquine-resistant Severe	Artesunate Artemether/lumefantrine Alternative: IV quinidine gluconate with either doxycycline or clindamycin	Atovaquone/proguanil 1 dose daily, including 1–2 days before travel and 7 days after return, or Mefloquine 1 dose weekly, including 1 week before and 4 weeks after, or Doxycycline 100 mg 1–2 days before and continued 4 weeks after

Treat resistant isolates with artemether/lumefantrine (Coartem), atovaquone/proguanil, quinidine + doxycycline, or mefloquine.

Primaquine is adjunctive medication for infections with *P. vivax* and *P. ovale* to eradicate hypnozoites in the liver. Hypnozoites are the malarial forms responsible for relapse. Remember that primaquine induces hemolytic anemia in glucose-6-phosphate dehydrogenase (G6PD)-deficient persons, so you must screen for G6PD deficiency before prescribing it.

Prophylaxis

In chloroquine-sensitive areas: Use chloroquine. Start it 1–2 weeks before the patient departs to the endemic area and continue 4–6 weeks after they leave the area.

In chloroquine-resistant areas: Use mefloquine or atovaquone/proguanil. Start 2 weeks prior or 2 days prior to travel, respectively. Atovaquone/proguanil is preferred because of the easier dosing schedule and lack of neurologic side effects.

Doxycycline has activity against chloroquine-sensitive and chloroquine-resistant malaria, and it can be used for prophylaxis at a dose of 100 mg daily. The advantage is that it is very inexpensive; the disadvantages are that it can cause photosensitivity, must be taken daily, and must be taken for 4 weeks after leaving the endemic area.

Malaria in pregnancy can be particularly severe, so prevention is key. Deferment of travel should be considered. If travel cannot be delayed, practice mosquito avoidance in combination with chemoprophylaxis. For chloroquine-sensitive regions, use chloroquine. For chloroquine-resistant regions, use mefloquine.

Babesia

Babesia microti is an intra-RBC protozoan parasite indigenous to the U.S. that causes babesiosis. Similar to malaria, it causes a febrile hemolytic anemia, and asplenic patients are at increased risk for severe disease.

The organism is transmitted via the *Ixodes* tick, as is the spirochete *Borrelia burgdorferi*, which causes Lyme disease. It is most prevalent in the northeast U.S. and upper Midwest, usually in summer or early autumn. The primary animal hosts are the white-footed mouse and white-tailed deer. Rare cases result from blood transfusion.

Symptoms, which can persist for months, include fever, profuse sweats, myalgias, and shaking chills. Severe cases cause liver, renal, and neurologic failure and death. Hemoglobinuria is a predominant sign.

Diagnosis is made by thick and thin blood smears. These may need to be repeated if tests are initially negative but there is high clinical suspicion. Serologies and

serum PCR can be helpful with low level parasitemia and when differentiating from malaria is difficult. Travel history is important for the microbiology lab because babesiosis can be misdiagnosed as malaria.

B. microti distinguished from *Plasmodium* by being pear-shaped. *B. microti* occasionally form a tetrad, appearing as a Maltese cross.

Figure 4-37 shows the *Babesia* parasites in both ring and tetrad forms.

PCR assays are available and more sensitive than peripheral smears.

Mild babesiosis infections are usually self-limited. Treat moderate infections with atovaquone + azithromycin and severe cases with clindamycin + quinine and consider an exchange transfusion.

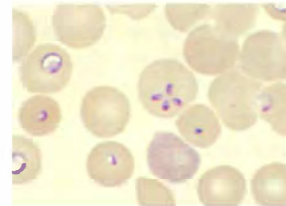


Figure 4-37: *Babesia* parasites in both tetrad and ring forms

Genitourinary (GU) Protozoans

Trichomonas vaginalis

Trichomonas vaginalis causes trichomoniasis, an STI. Treat with metronidazole. See more about this under Trichomoniasis on page 4-21.

HELMINTHIC ORGANISMS

Helminthic organisms are multicellular worms that cause eosinophilia. Helminthic organisms consist of roundworms (nematodes) and flatworms, which are divided into tapeworms and flukes. With the exception of *Strongyloides*, helminthic organisms do not replicate in the human host.

In Figure 4-38, we classify the helminthic parasites in terms of the systems they affect.

Roundworms (Nematodes)

Nematode infections are listed in Table 4-8 on page 4-64.

Intestinal Roundworms

Ascaris lumbricoides (Roundworm)

- Cause ascariasis
- Epidemiology: Worldwide, > 1 billion people are infected—predominantly in tropical and subtropical regions with poor hygiene. Humans are the sole host. In the U.S., 2% overall are infected (worse in the rural South), with up to 30% of young children affected in some areas.

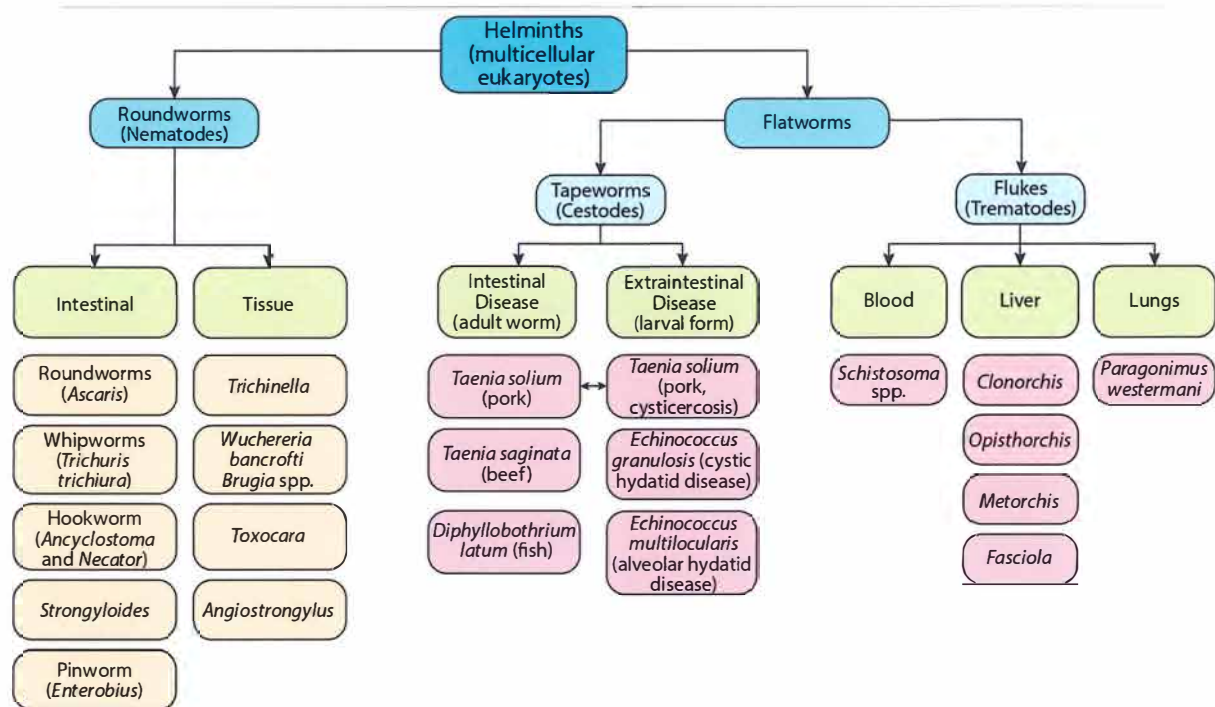
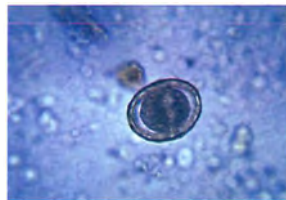


Figure 4-38: Classification of parasites—helminths

- Life cycle: Eggs (Figure 4-39) are ingested and hatch in the small intestine; the larvae penetrate the intestinal wall and migrate to the lungs, where they mature over 10 days. Then they ascend the bronchial tree, which generates a cough reflex, and are then swallowed. They mature into adult worms in the small intestine, and eggs are excreted in the stool. Eggs can live for up to 10 years in dark, moist conditions. Worms may migrate into the biliary tree and the appendix.
- Presentation (if symptomatic): pulmonary eosinophilic syndrome (a Löffler-type syndrome) in early phase of infection, malnutrition, acute appendicitis, biliary obstruction including ascending cholangitis
- Diagnosis: microscopy, demonstrating eggs (and rarely, worms) in stool
- Treatment: albendazole or mebendazole

Figure 4-39: Roundworm egg
Source: CDC

Trichuris trichiura (Whipworm)

- Epidemiology: Worldwide, > 1.5 billion people are infected (~ 25% world's population), mainly children. Found in warm, moist places with poor sanitation, similar to *Ascaris*; coinfection is not uncommon.
- Life cycle: Eggs are ingested, hatch in small intestine, and mature in caecum and ascending colon where they embed in epithelial layer; eggs are excreted in stool. There is no lung stage.
- May present with eosinophilia

- Presentation (if symptomatic): chronic colitis in children, *Trichuris* dysentery syndrome (diarrhea with mucus, blood, tenesmus, abdominal pain, and rectal prolapse)
- Diagnosis: stool microscopy demonstrating eggs in stool
- Treatment: albendazole for 3 days; repeat Rx prn.

Necator americanus and *Ancylostoma duodenale* (Hookworm)

- Epidemiology: *Necator* is endemic in the U.S. but can be found throughout the Americas, India, Africa, and Indonesia. *Ancylostoma* is found in the Mediterranean, Iran, India, Pakistan, and the Far East. Acquisition requires coming into barefoot contact with larvae in the soil that have hatched from eggs excreted by humans. People walking barefoot or with open sandals in contaminated areas are at risk.
- Life cycle: Larvae penetrate the skin, migrate to the lungs and up the bronchial tree, cough reflex occurs, and then the larvae are swallowed. Once in the small intestine, they mature and attach to the intestinal wall, where they feed. Eggs are excreted in stool.
- Presentation (if symptomatic): cutaneous itching at the site of larval entry (ground itch) and serpiginous eruption along the course of the larvae's migration (cutaneous larval migrans [CLM]). Pneumonitis can occur during pulmonary migration, although it is less severe than that of *Ascaris*. Chronic infection leads to iron deficiency anemia from chronic GI blood loss and hypoalbuminemia in persons already malnourished. Persistent eosinophilia may also be present.
- Diagnosis: stool microscopy demonstrating eggs in stool
- Treatment: single dose of albendazole

Table 4-8: Nematode Infections

Genus	Common Name	Route of Acquisition	Life Cycle in Humans	Signs and Symptoms*	Diagnosis	Treatment
<i>Ascaris</i>	Ascariasis	Ova ingestion	Eggs → larvae through lungs → swallowed → adults in bowel	PES; can obstruct bile duct or appendix	Stool ova	Albendazole or mebendazole
<i>Trichuris</i>	Whipworm	Ova ingestion	Eggs ingested → hatch in small intestine → mature in caecum and ascending colon → excrete eggs in stool	Diarrhea; abdominal pain; blood in stool; rectal prolapse	Stool ova	
<i>Ancylostoma</i> ; <i>Necator</i>	Hookworm	Larvae enter through skin	Soil larvae → penetrates skin → through lungs → swallowed → adults attach and feed in bowel	Ground itch; CLM; iron deficiency; hypoalbuminemia	Stool ova	
<i>Strongyloides</i>	Strongyloidiasis	Larvae enter through skin; only spp. to autoinfect	Soil larvae → penetrates skin → through lungs → swallowed → adults attach, mate in bowel, produce more larvae → cycle repeats	Ground itch; CLM; PES; abdominal pain; N/V/D; immunocompromised hyperinfection with multiorgan invasion and shock	Stool larvae, serology in immuno-competent	
<i>Enterobius</i>	Pinworm; threadworm	Ova ingestion	Eggs → hatch to adults → lay perianal eggs	Perianal itch	Tape test	Albendazole
<i>Trichinella</i>	Trichinellosis	Cysts in undercooked meat ingested	Excyst → adult releases larvae → blood → muscle	Muscle pain; high worm burdens can affect the CNS, lungs, heart, and kidneys	Muscle biopsy; serology	Albendazole with glucocorticoids
<i>Wucheria</i> ; <i>Brugia</i>	Filariasis	Mosquito injects larvae	Larvae in lymphatics → adult → releases microfilaria → ingested by next mosquito	Acute fever; microfilaria in lungs cause wheezing; lymphedema	Blood smears for microfilaria; best around midnight	Diethyl-carbamazine (only available from CDC)
<i>Toxocara</i>	Toxocariasis	Ova ingestion	Eggs → larvae migrate through tissues	Hepatomegaly; myocarditis; PES; eosinophilic meningitis; myalgia; ocular lesions	Serology	Albendazole
<i>Angiostrongylus</i>	Rat lungworm; angiostrongyliasis	Ingestion of larvae in snails and others	Larvae enter blood → CNS or mesenteric arteries	Headache; eosinophilic meningitis or abdominal pain; N/V; GI bleed and perforation	Organisms in CSF (rare) or on bowel biopsy (rare)	No drug available; surgery for ocular complications

*if present

CLM = cutaneous larval migrans

N/V/D = nausea, vomiting, and diarrhea

PES = pulmonary eosinophilic syndrome (fleeting infiltrates, cough, wheeze, and eosinophilia)

Strongyloides stercoralis (Strongyloidiasis)

- **Epidemiology:** endemic in soil throughout tropical regions of the world and in parts of the U.S. It is the only helminthic organism that can complete its life cycle within the human body, resulting in **autoinfection** and persistence of infection. The filariform larvae penetrate the perianal or colonic mucosa to complete the autoinfection cycle. This can lead to overwhelming worm burden in immunocompromised patients. Patients who are immune suppressed are at greatest risk for hyperinfection syndrome, including steroid use, HTLV infection, advanced HIV/AIDS, organ or bone marrow transplantation, and chemotherapy.
- **Life cycle:** Like hookworm, the *Strongyloides* larvae penetrate the skin (usually after walking barefoot on feces-contaminated ground) and migrate to the lungs. They then migrate up the tracheobronchial tree, produce a cough reflex, and are swallowed. Once in the small intestine, they attach to the mucosa and mature. Adult female worms produce eggs that hatch into **noninfectious** rhabditiform larvae, which are mostly excreted in the stool. However, some of these noninfectious larvae convert to infectious filariform larvae while still within the small intestine. These larvae penetrate the wall of the colon or perianal skin to hematogenously travel to the lung, just like exogenously introduced larvae do.
- **Presentation (if symptomatic):**
 - Like hookworm, itching at the site of larval entry (ground itch) and a fast-moving serpiginous eruption along the course of the larvae's migration (larva currens) can occur; this is pathognomonic.
 - Pulmonary eosinophilic pneumonitis can occur, causing a Löffler-like syndrome.
 - GI symptoms include abdominal pain, nausea, vomiting, and diarrhea.
 - ***Strongyloides* hyperinfection syndrome** is seen in immunocompromised hosts. Those who receive high-dose steroids, and those with advanced HIV or HTLV-1 are at particular risk. This represents an augmented and accelerated autoinfection cycle. As worms migrate out of the GI tract, they can bring bacteria with them—think of this with polymicrobial GNR bacteremia or community-acquired GNR meningitis. Perhaps counterintuitively, peripheral eosinophilia may be **absent** in these patients due to blunted immune response.
 - **Diagnosis:** Larvae in the stool are diagnostic but are seen in < 50% of those infected. Serology is useful in immunocompetent patients. In hyperinfection syndrome, many larvae can often be seen in respiratory samples. *Strongyloides* are sometimes encountered incidentally on a culture plate; see Figure 4-40.
- **Treatment:** Ivermectin is the drug of choice; albendazole is a less effective alternative. Repeat treatment after 2 weeks for eradication.

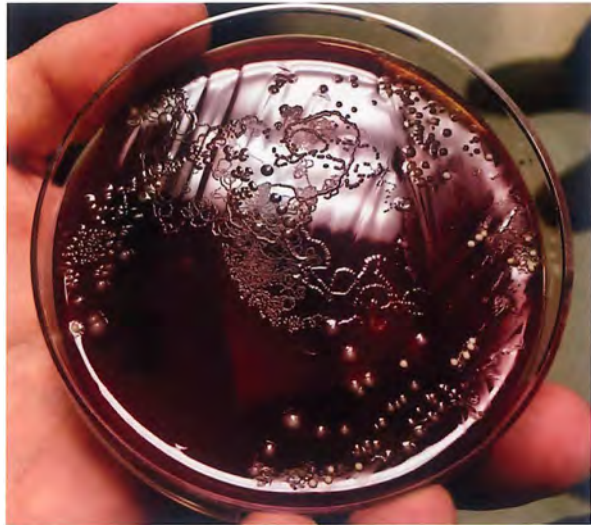


Figure 4-40: *Strongyloides* (serpiginous trail wandering around bacterial colonies)

Source: Nathaniel Warner, MD

Enterobius vermicularis (Pinworm, Threadworm)

- **Epidemiology:** **most common** helminthic infection in the U.S.; humans are the only host. Occurs commonly in school-aged children and their families.
- **Life cycle:** Eggs (Figure 4-41) are ingested and hatch in the small intestine. Gravid females migrate to the rectum and, at night, lay eggs in the perianal area. Autoinfection is possible (i.e., scratch anal area with hands and ingest eggs via contaminated hands).
- **Presentation (if symptomatic):** perianal itching
- **Diagnosis:** microscopic exam of transparent tape that was touched upon the perianal area demonstrating eggs and sometimes female worms (Scotch tape test)
- **Treatment:** single dose of albendazole, followed by repeat dose in 2 weeks to kill worms from hatched eggs. Strict hand hygiene. Treat the entire household.



Figure 4-41: Pinworm eggs

Source: CDC

Tissue Roundworms

Trichinella spp. (Trichinellosis)

- Epidemiology: ~ 10,000 cases worldwide are reported per year. *T. spiralis* is the most common *Trichinella* species in the U.S. The main sources of the disease are undercooked wild game (e.g., bear, wild boar) and domesticated pigs (pork). In the U.S., ~ 20 cases are reported each year, although there is a much higher incidence seen on autopsy.
- Life cycle: Cysts in undercooked meat are ingested then excyst and mature into adults in the small bowel, where they release larvae that invade via the blood into the muscle, where they burrow and encyst in a muscle cell.
- Presentation (if symptomatic):
 - Intestinal phase (week 1): invade small bowel mucosa, patients may experience watery diarrhea, abdominal pain
 - Muscle phase (> week 1): hematogenous dissemination and encystment into striated muscle; muscle pain, fevers, splinter hemorrhages
 - Eosinophilia is common. High worm burdens can affect the CNS, lungs, heart (e.g., fatal cardiomyopathy), and kidneys.
- Diagnosis: Serology is available and turns positive after several weeks. Muscle biopsy may be performed to look for cysts. High-grade eosinophilia is almost always present.
- Treatment for mild cases is supportive. For systemic infections, treat with albendazole for 10–14 days. Give glucocorticoids to suppress the inflammatory consequences of worm death.

Wuchereria bancrofti, *Brugia malayi*, and *Brugia timori* (Lymphatic Filariasis)

- Epidemiology: > 100 million people worldwide are infected, and 1/3 of those infected are symptomatic. These worms are transmitted via mosquito bites. Most cases occur in sub-Saharan Africa, Southeast Asia, Indian subcontinent, and Pacific islands. Epidemiology may change as countries adopt mass drug administration campaigns.
- Life cycle: A mosquito introduces larvae into the skin during feeding. Larvae enter the lymphatics and mature over 9 months. Adult worms then produce microfilariae that migrate into the cutaneous blood vessels, with timing synchronized to the specific mosquito species involved. The microfilariae are ingested by another mosquito, develop into larvae, and can be transmitted to another human.
- Presentation (if symptomatic)—primarily related to lymphatic obstruction:
 - Acute infection causes a nonspecific febrile illness in a traveler (**filarial fever**) that can be similar to malaria. There may be associated tender lymphadenopathy, which is called acute adenolymphangitis.

– **Tropical pulmonary eosinophilia** is due to microfilariae trapped in the lungs and causes nocturnal wheezing.

- Chronic infection leads to lymphatic obstruction, scarring, and severe lymphedema (**elephantiasis**).
- Diagnosis: blood smears (best obtained around midnight) to identify microfilariae from blood
- Treatment: Diethylcarbamazine kills the larvae and adult worms. It must be obtained from the CDC.

Toxocara canis and *Toxocara cati* (Toxocariasis, Visceral Larva Migrants)

- Epidemiology: *T. canis* (the dog ascarid) is more common than *T. cati* (the cat ascarid). It occurs worldwide, with a 14% prevalence in the U.S. Humans are not normal hosts for these helminths and are not a required part of their life cycle.
- Life cycle: The adult worm sheds eggs in the stool of its animal host. If humans ingest these eggs, they hatch into larvae that travel through tissue and elicit an immune response. The larvae subsequently die.
- Presentation (if symptomatic): Migrating larvae (**visceral larva migrants**) can cause injury to the liver (causing hepatomegaly), heart (causing myocarditis), lungs (fleeting pulmonary infiltrates, shortness of breath, cough, wheeze), brain (eosinophilic meningoencephalitis), muscle (myalgias), and eyes. Presentation is typically accompanied by eosinophilia.
- Diagnosis: ELISA IgG serology is available.
- Treatment: Self-limiting; antiparasitic typically not required. If necessary, give albendazole for 5 days.

Angiostrongylus cantonensis and *Angiostrongylus costaricensis* (Angiostrongyliasis, Rat Lungworm)

- Epidemiology: *A. cantonensis* is endemic in southeast Asia and tropical Pacific islands and is the most common parasitic cause of eosinophilic meningitis. *A. costaricensis* is endemic in Latin America and the Caribbean. The parasite is passed between rats and mollusks (e.g., slugs, snails) to complete its life cycle; humans are accidental hosts.
- Life cycle: *A. cantonensis* eggs found in rat stool are ingested by snails and slugs. If the snail or slug is eaten by humans, the larvae can migrate to the central nervous system, causing eosinophilic meningitis.
- Presentation (if symptomatic): *A. cantonensis* causes symptoms typical of meningitis that can be self-limiting or neuroinvasive. Headache is the most prominent symptom, and LP yields an eosinophilic inflammatory response. *A. costaricensis* causes abdominal pain, fever, and vomiting and can progress to GI bleeding and perforation.
- Diagnosis: *A. cantonensis* is rarely visualized in the CSF, so diagnose based on the presence of eosinophilic meningitis in the appropriate epidemiologic setting.

- Treatment: *A. cantonensis*—the disease is self-limited, and no antiparasitic drugs have been shown to be effective. *A. costaricensis*—antiparasitic drugs are not effective and may cause worm migration and worsening symptoms. Perform surgery for ocular complications.

Flatworms

Tapeworms (Cestodes)

Clinically important tapeworms include *Taenia solium* (pork tapeworm), *Taenia saginata* (beef tapeworm; usually asymptomatic), *Diphyllobothrium latum* (fish tapeworm; occasionally causes vitamin B₁₂ deficiency because it competes with the ileum for absorption), and *Echinococcus*.

T. solium is endemic in many regions of Central and South America, sub-Saharan Africa, India, and Asia. Although it is called the pork tapeworm, humans are the definitive host. It is important to recall the life cycle of *T. solium* in order to understand the 2 manifestations of human disease it causes: extraintestinal disease (in its larval form) and intestinal disease (when it is an adult worm).

Extraintestinal Tapeworm Disease (Larval Form)

If *T. solium* eggs are ingested, they hatch in the bowel and become oncospheres that invade the bloodstream to encyst in tissues (most commonly the central nervous system) as cysticerci—causing **neurocysticercosis**. CNS cysticerci can be in the parenchyma or be extraparenchymal in the CSF, where they usually lodge in the aqueduct of Sylvius. Cysticerci are able to suppress the human host response and thus remain asymptomatic until the organism dies, when an inflammatory response ensues. The most common presentation is seizure, followed by hydrocephalus, depending on the location of cysts within the brain or ventricles. Intraocular, subarachnoid, and extra-CNS cysts occur as well.

Patients with suspected neurocysticercosis should have a head CT as well as an MRI. Diagnosis is typically made based on characteristic findings of cysts, and confirmed with serologic testing. Screen patients who will require steroids for latent tuberculosis and *Strongyloides* to prevent reactivation and hyperinfection while on steroids. Prior to starting antiparasitics, do a dilated funduscopic exam to rule out intraocular disease.

Treatment of neurocysticercosis is complex and frequently requires a multidisciplinary approach. Type and timing of treatment depends on location, viability, and number of cysts, as well as the presence of CNS edema and hydrocephalus.

Treatment is recommended in patients presenting with seizures. For < 2 viable intraparenchymal cysts, use albendazole. If > 2 intraparenchymal cysts are present, add praziquantel to albendazole. Corticosteroids are recommended to reduce risk of seizures during therapy. Antiparasitic therapy is **not** recommended if

only calcified, nonviable cysts are present—or if cerebral edema, untreated hydrocephalus, or intraocular lesions are present. These cases are typically treated with a combination of steroids and surgery, in collaboration with infectious disease and neurosurgical specialists. Cutaneous and intramuscular disease can be treated with analgesics.

Echinococcus species also cause an extraintestinal disease—**hydatid disease**—in which hydatid cysts proliferate throughout the body. It is acquired after ingesting food contaminated with feces from the definitive hosts, which are other mammals (e.g., sheep, dogs, rodents, foxes). Most cases are diagnosed in immigrants from endemic regions (i.e., Asia, Europe, South/Central America, the Middle East); hunters and veterinarians are also susceptible. The initial phase of infection is typically asymptomatic, and most people are infected as children. The liver is the most common organ affected (especially with *E. granulosus*), followed by the lungs (especially with *E. multilocularis*). The right lobe of the liver is most commonly affected, and generally presents as a single large cyst. Complications can occur due to mass effect of the cyst, cyst rupture into the biliary tree or peritoneum, or cyst infection. Ultrasound or other imaging is diagnostic and can be confirmed with a serologic test, usually ELISA. Treatment with surgical techniques is evolving, but open surgery is recommended for large cysts (> 10 cm). Therapy with albendazole before and after surgery is useful.

Intestinal Tapeworm Disease (Adult Worm Form)

If *T. solium* cysts are ingested from undercooked pork, the organism excysts and grows into the adult tapeworm in the gut (taeniasis). A person carrying a tapeworm then starts shedding eggs. Most people with a tapeworm have no symptoms. Niclosamide is the usual treatment for all intestinal tapeworms, including beef and fish tapeworm.

Flukes (Trematodes)

Fluke common names are based on the part of the body in which the adult worm resides. In humans, there are blood, liver, and lung flukes. Liver and blood flukes increase risk of cancer. [Table 4-9 on page 4-68](#) summarizes them all.

Blood Flukes (Schistosomes)

There are 5 species of schistosomes: *Schistosoma mansoni*, *japonicum*, *haematobium*, *intercalatum*, and *mekongi*. The latter 2 species are geographically limited, uncommon, and will therefore not be discussed further.

S. mansoni is endemic to Africa, South America, and the Caribbean. *S. japonicum* is in East Asia. *S. haematobium* is found in Africa and the Middle East.

The infectious form for all species is cercariae, which are released from snails in fresh water and can penetrate intact skin. These lose their tails and become schistosomula, which migrate to the liver where they mature into

Table 4-9: Fluke Infections

Genus	Common Name	Route of Acquisition	Life Cycle in Humans	Signs and Symptoms	Diagnosis	Treatment
<i>Clonorchis</i> , <i>Opisthorchis</i> , <i>Metorchis</i> , <i>Fasciola</i>	Liver flukes	Ingestion of metacercariae in raw fish; water vegetables	Metacercariae → biliary tree → adult fluke resides	Biliary obstruction, cholangiocarcinoma	Stool or bile ova	Praziquantel; triclabendazole
<i>Paragonimus</i>	Lung flukes	Ingestion of metacercariae in crabs and crayfish	Metacercariae penetrate bowel → cross diaphragm to lung → adult fluke resides	Cough, hemoptysis, pleuritic pain, fever	Sputum/BAL ova, stool ova	Praziquantel
<i>Schistosoma</i>	Blood flukes	Cercariae enter through skin	Cercariae migrate to liver → adult fluke can then → enter mesenteric veins or vesicular plexus	Swimmer's itch, Katayama fever (fever, chills, myalgias, abdominal pain, lymphadenopathy, hepatosplenomegaly, eosinophilia), bladder cancer, portal hypertension, cirrhosis, and esophageal varices	Stool ova; urine ova (<i>S. haematobium</i> only)	Praziquantel

motile adult flukes. From there, they swim upstream through the portal vein to spend their adult lives in their preferred venous system: *S. mansoni* in the inferior mesenteric vein, *S. japonicum* in the superior mesenteric vein, and *S. haematobium* in the vesicular venous plexus.

Initial penetration of the cercariae can produce local inflammation and itching after swimming in fresh water (swimmer's itch). If large numbers invade, an acute syndrome (**Katayama fever**) occurs 3–8 weeks after inoculation. This presents with fever, chills, myalgias, abdominal pain, lymphadenopathy, hepatosplenomegaly, and marked eosinophilia. This spontaneously resolves.

The flukes themselves do not cause symptoms, but the eggs they shed do. *S. haematobium* eggs cause inflammation and fibrosis of the bladder wall with symptoms of UTI, and they predispose to bladder cancer. *S. mansoni* and *S. japonicum* shed eggs into the portal venous system, leading to portal hypertension, cirrhosis, and esophageal varices.

Diagnose by finding the eggs in the stool or urine, depending on the species. Treat with a 1-day course of praziquantel.

Liver Flukes

Clonorchis sinensis is the Chinese liver fluke, which is endemic in the Far East. *Opisthorchis felinus* and *viverrini* are endemic in Eastern Europe and Asia. *Metorchis conjunctus* is endemic in Canada. Infection from all ensues after eating the metacercariae in raw fish, which mature to adult flukes that live in the biliary tree and can cause biliary obstruction and cholangiocarcinoma. Diagnose by finding eggs in bile (from an ERCP) or stool. Treat with praziquantel. *Fasciola hepatica* is a fluke that infects livers of mammals. Its primary hosts are cattle and sheep throughout most temperate zones in the world.

Eggs shed by these develop into metacercariae that encyst on nearby watercress and, if ingested, become mature flukes in the human biliary tree. The mature fluke can obstruct or migrate through the liver. Treat with triclabendazole (available through the CDC under investigational protocol) or, as 2nd line, nitazoxanide. Praziquantel is not effective.

Lung Flukes

Paragonimus westermani is the human lung fluke. It is endemic in the Far East and West Africa but also is found in the Americas. It is acquired by ingestion of metacercariae in crabs and crayfish. They penetrate the duodenum into the abdominal cavity and then penetrate the diaphragm and pleura to enter the lung parenchyma, where they mature into adults that lay eggs. They are coughed up and then swallowed and defecated back into the environment. If symptomatic, the predominant symptoms are cough, hemoptysis, pleuritic chest pain, and fever. Pleural effusions, if they occur, are eosinophilic. Diagnose by finding the ova in sputum, BAL, or stool. Treat with praziquantel.

VIRUSES

PREVIEW | REVIEW

- Multinucleated giant cells can be seen with which viral infections?
- What is the most sensitive and specific method for diagnosing herpes simplex virus encephalitis?
- Which patients should receive the zoster vaccine?
- What is the clinical presentation of Epstein-Barr virus mononucleosis?

- What are the clinical symptoms of measles?
- How do you diagnose influenza A?
- Which class of drugs should be used to treat influenza A?
- What are complications of mumps in males?
- Which virus causes the “slapped cheek” rash?
- What does the bone marrow show in patients with pure red cell aplasia from parvovirus B19?
- How is West Nile virus encephalitis diagnosed?
- How does dengue hemorrhagic fever present?
- Characterize a patient with hantavirus pulmonary syndrome.

HERPES SIMPLEX VIRUS (HSV)

HSV (a DNA virus) is spread person to person, usually through asymptomatic shedding. Both HSV-1 and HSV-2 cause vesicular lesions, with HSV-1 predominating in the orofacial area and HSV-2 in the genital area. If the virus is in its preferred location, it is more likely to recur.

HSV-1 causes orofacial infections in ~ 40% of the population, although the seropositivity rate is much higher. In the primary infection, the vesicular lesions and ulcers are usually localized to the oral mucosa, lips, and surrounding skin and are commonly accompanied by constitutional symptoms. Recurrent infection ulcers are typically just on the outer lip. It is possible to autoinoculate the virus, so the infection can spread, for example, from the lips to the eyes of a patient.

Recurrent HSV-1 eye infection resulting in keratitis is the most common infectious cause of blindness in industrialized nations. See the [General Internal Medicine](#) section.

Tzanck smears are performed by scraping down to the bottom of a vesicle, placing the material on a slide, then staining with either Giemsa or Wright stain. In herpes simplex and varicella-zoster virus infections, it shows **multinucleated giant cells** (Figure 4-42). However, in current clinical practice, PCR and direct fluorescent antibody (DFA) are the most commonly used diagnostic tests and should be done to confirm the diagnosis if the clinical picture is not diagnostic.

HSV-2 causes ~ 75% of HSV genital infections—the rest are due to HSV-1. The prevalence of HSV-2 is 1 in 6 Americans 14–49 years of age. Most cases of neonatal

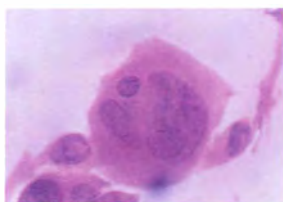


Figure 4-42: Multinucleated giant cell

HSV are from intrapartum contact, so a C-section is recommended if the mother has symptoms or signs of genital herpes or has a typical prodrome at the time of delivery. HSV reactivates in 2/3 of seropositive transplant patients within 6 weeks of transplant, but this rate is drastically **lower** in patients receiving antiviral prophylaxis.

HSV encephalitis is the most common cause of sporadic viral encephalitis and causes the highest number of deaths due to viral encephalitis in adults. Patients with HSV encephalitis usually present with fever, altered mental status, seizures, and/or focal neurologic deficits. The virus has a predilection for the frontal and temporal lobes. Prognosis is poor, and > 60% have neurologic sequelae. MRI is usually abnormal, potentially showing hemorrhage in the temporal lobe. Do not delay LP and empiric treatment to obtain an MRI. CSF typically shows increased protein, lymphocytic pleocytosis, and increased red cells, but it can be normal in early infection. Diagnosis of HSV by PCR in CSF is the most sensitive (98%) and specific (97%) test. False negative testing can occur early in clinical course, so if high clinical suspicion remains despite a negative test, consider repeating CSF HSV PCR 3–7 days later before stopping IV acyclovir.

HSV is one of many causes of erythema multiforme. See the [Dermatology](#) section.

Treatment of HSV: Initial or recurrent mucocutaneous HSV can be treated with acyclovir PO, but this is beneficial only if treatment is given within the first 72 hours. Famciclovir and valacyclovir are similarly effective but more expensive—although they have more convenient dosing. Give acyclovir after 72 hours if the patient is immunocompromised. For HSV encephalitis, give IV acyclovir for 14–21 days. Give IV acyclovir if there is disseminated HSV (e.g., lung, skin, liver). Acyclovir (or famciclovir or valacyclovir) can also be given in low doses chronically to suppress infection in those with frequent recurrences. Use foscarnet to treat those with HSV resistant to acyclovir; ganciclovir is **not** used because cross-resistance is common in acyclovir-resistant strains.

VARICELLA-ZOSTER VIRUS

Varicella-zoster virus (VZV; a DNA virus) causes varicella (chickenpox) when initially acquired and herpes zoster (shingles) if it recurs.

Varicella (Chickenpox)

Varicella is an airborne, highly contagious disease that causes a characteristic pruritic, vesicular eruption that comes in successive crops. On exam, these skin lesions are typically found in various stages, from new erythematous papules to vesicles to crusted-over lesions—this is in contrast to smallpox, where lesions are all in the same stage of development (Figure 4-43 on page 4-70).



Figure 4-43: Chickenpox lesions in various stages

Patients are contagious for 1–2 days before eruption and stay contagious until the last lesion has crusted over. These pox marks do not leave scars unless superinfected or manipulated.

Patients have a characteristic prodromal phase with fever, malaise, pharyngitis, myalgias, nausea, and headache.

Varicella symptoms are usually mild in children but can be severe in adolescents and adults, especially in pregnant women, in whom pneumonia is more likely to occur.

Diagnosis is made clinically based on the classic appearance of the rash. DFA or PCR can be used for atypical-appearing rashes.

Treat all adult patients with PO acyclovir if they present within 24 hours of rash onset. This treatment decreases the number of lesions and the duration of disease. Give IV acyclovir for noncutaneous organ involvement and to patients who are immunocompromised.

Patients at increased risk of developing severe varicella infection are those who are:

- not currently immune because they have never had varicella or the vaccine,
- currently immunocompromised, or
- pregnant.

There are two varicella (chickenpox) vaccines on the market: a single antigen varicella vaccine (Varivax), and a combination measles, mumps, rubella, and varicella vaccine. Vaccination is recommended in all infants > 12 months, children, and adults who do not have immunity to varicella.

Herpes Zoster (Shingles)

Herpes zoster manifests as grouped vesicles along a dermatome with focal pain. Older age and immunosuppression (e.g., HIV) are risk factors.

Zoster is caused by reactivation of the varicella-zoster virus. After the initial infection, the virus becomes dormant and asymptomatic in sensory ganglia neurons until it is reactivated and spreads down the nerve, causing a painful rash.

Reactivation causes a prodromal phase with constitutional symptoms followed by hyperesthesia and a burning, frequently lancinating pain over the dermatome. This is followed by the characteristic vesicular skin rash localized to that dermatome.

The most common dermatomes involved are the thoracic dermatomes. Usually 1 thoracic dermatome is involved, but occasionally it involves 1–2 more. If there are > 3 dermatomes involved, or > 30 lesions outside of the primary dermatomes, it is considered disseminated zoster.

In ~ 10–20% of patients, the ophthalmic branch of the trigeminal nerve is involved, which can be sight-threatening if zoster keratitis results. Consider this in a patient with the classic vesicular lesions appearing on one side of the face anywhere on the forehead, nose, and periorbital area. This requires emergent treatment and referral.

Herpes zoster oticus (**Ramsay Hunt syndrome**) affects several cranial nerves; it presents with vesicles in the external auditory canal and tympanic membrane, along with ipsilateral facial paralysis and ear pain.

As with varicella, zoster lesions are contagious until crusted over, and they can give a nonimmune person varicella. Unlike varicella, there is no respiratory transmission with shingles; if the patient is hospitalized, use standard precautions alone, unless the lesions are disseminated.

Rash duration is ~ 2–4 weeks. If there are any new lesions after 7–10 days, consider underlying cell-mediated immunodeficiency. Immunocompromised patients are at increased risk for dissemination, which can include internal organ involvement (e.g., CNS, lung, liver). Shingles recurs in < 5% of immunocompetent patients.

Postherpetic Neuralgia

Postherpetic neuralgia (PHN) is the most common complication (~ 10% overall) of zoster, and it is more likely to occur with increasing age (20% in those > 80 years of age). It can cause a lancinating, sometimes debilitating pain for many months to years.

Treatment

If started within 72 hours of onset, antiviral therapy with acyclovir, famciclovir, or valacyclovir decreases disease duration of disease, severity of the initial pain, and incidence of PNH.

Adding prednisone provides no additional benefit and may prolong the course of herpes zoster in immunosuppressed patients.

For pain control, tricyclic antidepressants, gabapentin, pregabalin, and lidocaine patches have some efficacy. Opiates can be useful but remain controversial due to dependency. Capsaicin cream is useful after the lesions have healed.

Regarding work restrictions for health care personnel, the following apply:

- Any health care worker with disseminated zoster should stay home until lesions are fully scabbed over.
- Immunocompromised health care personnel with dermatomal zoster (as well as immunocompetent healthcare personnel with dermatomal zoster who work with immunocompromised patients) should not return to work until all lesions are fully crusted over.
- Health care personnel with dermatomal zoster who are immunocompetent and do not work with immunosuppressed patients can return to work, as long as they can cover up their lesions with a bandage and clothing.

Vaccination for Herpes Zoster

The most recent zoster vaccine, called recombinant zoster vaccine (RZV; Shingrix), was approved by the FDA in October 2017. It is a recombinant vaccine as opposed to the previous live attenuated vaccine (Zostavax). The Advisory Committee on Immunization Practices (ACIP) and the CDC recommend the recombinant vaccine for all healthy adults > 50 years of age. The ACIP also recommends that those who received the earlier zoster vaccine be revaccinated with the newer version.

In those 50–69 years of age, recombinant zoster vaccine (RZV; Shingrix) has an effectiveness of 97% and 91% in preventing herpes zoster and PHN, respectively. At > 70 years of age, this falls a little to 91% and 89%. This is much better than Zostavax (attenuated live vaccine), with an overall effectiveness of only 50% and 75%. The longer-term immune response of Shingrix also appears to be much better.

As opposed to the first vaccine, with only 1 dose required, Shingrix requires 2 total doses repeated 2–6 months apart.

CYTOMEGALOVIRUS (CMV)

Cytomegalovirus (CMV; a DNA virus) is in the herpes virus family. CMV infection in the normal population is fairly common; 50% of the population has anti-CMV antibodies by 35 years of age.

CMV infection in the immunocompetent population is typically asymptomatic, but ~ 10% have a mononucleosis-type illness with fever, sore throat, adenopathy, fatigue, and hepatitis. Exudative pharyngitis is rare. Think of this in a monospot-negative adult with these symptoms, especially in younger to middle-aged individuals, because EBV mono usually occurs more often in adolescents. Also consider acute HIV with this presentation.

CMV is a very common infection in patients with decreased cellular immunity (e.g., posttransplant, AIDS). Pretransplant donor and recipient CMV IgG serologies are very important to guide use of antiviral prophylaxis after transplant. For example, of seronegative transplant recipients, 75% get CMV disease if the

donor is seropositive. In organ transplant recipients there are 3 main presentations:

- 1) CMV DNAemia: CMV in the blood (PCR-positive) without any attributable signs or symptoms of disease
- 2) CMV syndrome: CMV in the blood (PCR-positive) with attributable signs/symptoms of systemic disease, but no evidence of end-organ disease (e.g., colitis, pneumonitis). Typical signs and symptoms include fever, profound fatigue, and leukopenia.
- 3) Tissue-invasive CMV disease: end-organ disease due to CMV, typically (but not always) accompanied by CMV in the blood (PCR-positive). Typical signs and symptoms depend on the organ that is involved (e.g., colitis = diarrhea, pneumonitis = shortness of breath and bilateral infiltrates, chorioretinitis = decreased vision and fluffy retinal lesions).

HIV/AIDS: When the CD4 count is < 50 cells/ μ L (0.05×10^9 /L), CMV can cause chorioretinitis, pneumonitis, esophagitis, and colitis. Patients with CMV retinitis may initially complain of floaters and will then gradually lose vision. CMV retinitis is distinctive; it has both retinal blanching and hemorrhage and follows along the path of the retinal arteries. Diagnosis is typically made by an ophthalmologist based on appearance. CMV serologies and serum PCR do not play a role in diagnosing CMV retinitis. CMV esophagitis and colitis are diagnosed by endoscopy and tissue pathology.

Diagnose acute CMV infection in immunocompetent hosts by serologies, either a 4-fold rise in convalescent serologies or positive IgM. Serologies have no role in the diagnosis of active CMV disease in immunosuppressed patients. CMV DNAemia and CMV syndrome are diagnosed by demonstrating DNA in peripheral blood. For tissue invasive disease, get a biopsy of the tissue involved for pathology—the tissue will demonstrate cytopathic viral effects combined with positive immunohistochemical stains. Most patients with end-organ disease have an accompanying viremia, but not all. Always try to get tissue samples if possible (e.g., colonoscopy).

Treat susceptible CMV infection with valganciclovir or ganciclovir. For resistant virus, use foscarnet or cidofovir.

EPSTEIN-BARR VIRUS (EBV)

Epstein-Barr virus (EBV; a DNA virus) causes infectious mononucleosis. The incubation period is 1–2 months, and it is usually acquired in adolescence through contact with others who are asymptotically shedding the virus in their secretions (the so-called kissing disease).

The vast majority of adults have been infected, but most acute EBV infections are asymptomatic. If symptomatic, > 90% have pharyngitis, which is typically exudative. Tonsillitis, fever, lymphadenopathy, and elevated transaminases also occur. Splenomegaly

may be seen. A maculopapular rash occurs in ~ 20% of symptomatic patients; however, if patients are given ampicillin, 90% develop a similar rash. This can occur if the exudative pharyngitis is mistakenly treated as an *S. pyogenes* infection.

Symptomatic patients typically develop extreme fatigue, which can occasionally persist months after the initial symptoms disappear.

Lymphocytosis is found in acute EBV infection, usually with > 10% atypical lymphocytes on peripheral blood smear. Atypical lymphocytes (Figure 4-44) are enlarged T cells actively trying to fight EBV-infected B cells. They have abundant cytoplasm, vacuoles, and indentations of the cell membrane.

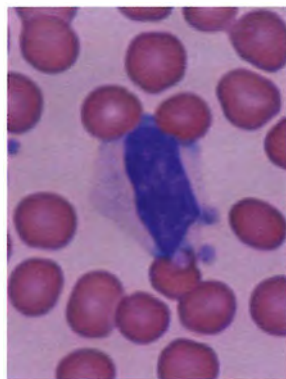


Figure 4-44: Atypical lymphocyte

Confirm diagnosis of infectious mononucleosis with serology. Heterophile antibody titers (monospot) are nonspecific antibodies that cross-react with RBCs of other mammals. They are absent ~ 25% of the time in the 1st week of illness (heterophile-negative mononucleosis). Thus, the most common cause of heterophile-negative mononucleosis of 1-week duration is still EBV. Diagnose by testing for IgM capsid antibody in these patients. Other causes of heterophile-negative mononucleosis are CMV, toxoplasmosis, acute HIV, and HHV-6 infection.

Treatment of acute EBV infection remains supportive because of its excellent prognosis and the unavailability of any antivirals active against EBV. If splenomegaly is present, patients should avoid contact sports.

EBV causes oral **hairy leukoplakia**, which can be seen as an early manifestation of HIV disease. These are white lesions on the lateral tongue (Figure 4-45) that, unlike thrush, do not scrape off.

Chronic fatigue syndrome has **no** proven association with EBV.

EBV is oncogenic and can result in nasopharyngeal carcinoma, non-Hodgkin lymphoma—specifically Burkitt lymphoma—and posttransplantation lymphoproliferative disorders (PTLD).

RUBELLA (GERMAN MEASLES)

In adults, the typical rash of rubella (a.k.a. German measles; an ssRNA virus) may be preceded by up to 5 days of fever, generalized malaise, headache, sore throat, arthralgias, cough, and coryza. The illness in adults is typically a fairly mild viral illness. Associated clinical signs



Figure 4-45: Oral hairy leukoplakia

Source: CDC

include posterior cervical, postauricular, and suboccipital lymphadenopathy and an enanthem in 20% of cases (**Forchheimer sign**) characterized by soft palate petechiae and/or larger, reddish spots. Despite its mild course in adults, if acquired by a pregnant patient in the 1st trimester, there is up to a 90% chance that the baby will develop congenital rubella syndrome (e.g., deafness, cataracts, cardiac disease).

Rubella is diagnosed by demonstrating rubella-specific IgM at least four days after development of a rash. In pregnant patients, it can be diagnosed via PCR from nasopharyngeal swab. In infants, virus can be detected from cord blood or placenta.

Due to a successful vaccination program, rubella has been declared eliminated in North and South America but is still seen elsewhere.

RUBEOLA (MEASLES)

Rubeola (an ssRNA virus) causes measles. Outbreaks continue to occur in at-risk persons who have not been vaccinated. This is one of the most contagious diseases known.

After an incubation period of 1–3 weeks with a median of 2 weeks, measles begins with a prodromal phase of fevers, malaise, and the 3Cs (cough, coryza, conjunctivitis) which lasts for 72 hours. Enanthem (mucosal rash) develops ~ 48 hours before the exanthem (rash). These are called **Koplik spots**, described as whitish spots on an erythematous base near the molars on the inner cheeks (Figure 4-46). Exanthem lasts for ~ 72 hours and evolves rapidly. It is characterized by numerous, generalized, blanching, fine, discrete, pinkish maculopapules that begin on the face and spread down the trunk, coalesce, then disappear, generally after 3 days. The rash evolves in the same way as having paint dumped on a person's head—it drips down from the top! Convalescence with immunity typically occurs after resolution of the rash. If fevers persist longer, then measles-related complications should be considered.



Figure 4-46: Measles; Koplik spots, small white spots that occur before the rash
Source: CDC

If rubella is suspected, place the patient in a room with airborne precautions and notify public health authorities. Viral encephalitis occurs in 1:1,000 of these patients. Autoimmune reaction (acute disseminated encephalomyelitis) rarely occurs, and if it does, it appears ~ 2 weeks after the rash and has ~ 20% mortality and considerable morbidity. **Subacute sclerosing panencephalitis** occurs in 1:100,000 about a decade later, and it is suspected to be from a variant virus; it is universally fatal.

RETROVIRUSES

Retroviruses are ssRNA viruses:

- HTLV-1 (human T-cell leukemia virus, Type 1) causes T-cell lymphoma and tropical spastic paraparesis, a neurologic syndrome seen in Japan and the Caribbean.
- HTLV-2 causes a rare T-cell variant of hairy cell leukemia.
- HIV-1 causes AIDS.
- HIV-2 causes AIDS (same as HIV-1); found in West Africa and parts of the U.S.

RESPIRATORY VIRUSES

Rhinoviruses

Rhinoviruses (all are ssRNA viruses) are a common cause of URI in adults.

Respiratory Syncytial Virus

Respiratory syncytial virus (RSV; an ssRNA virus) infections occur year-round, but more commonly during the autumn and winter. RSV infection has similar morbidity as influenza and especially affects the elderly and those with immunodeficiency. It is thought to be responsible for up to 25% of excess winter season mortality that was previously attributed solely to influenza.

RSV is also an important pathogen in hematopoietic stem cell transplant recipients and lung transplant recipients.

Diagnose by detecting RSV antigen or with PCR of nasal secretions. Use ribavirin, oral or inhaled, as an antiviral therapy in immunocompromised hosts, but the efficacy is limited.

Influenza

Influenza (an ssRNA virus) is a major cause of morbidity and mortality, especially in patients > 55 years of age with COPD. Annual vaccination decreases mortality.

There are 3 types of influenza viruses: influenzas A, B, and C. Subtypes of influenza A exist based on their specific neuraminidase and hemagglutinin antigens. Influenzas A and B cause the yearly epidemics of respiratory illnesses. Influenza C causes very mild symptoms, if any.

Influenza presents as an acute febrile respiratory illness with fever, cough, and myalgias. Serious complications include viral pneumonia, secondary bacterial pneumonia, rhabdomyolysis, encephalitis, and myocarditis.

A positive antigen test or PCR for influenza A and B from nasopharyngeal swab or respiratory secretions is diagnostic. Not every patient with influenza needs antiviral therapy.

Give treatment in 3 settings:

- 1) Those at high risk of complications (e.g., immunocompromised; pregnancy; underlying heart, lung, liver, or kidney disease; > 65 years of age; residents of chronic care facilities; active malignancy; diabetes; morbid obesity; hemoglobinopathies; neurologic conditions causing compromise of handling respiratory secretions; Native Americans; Alaska Natives)
- 2) Hospitalized patients
- 3) Severe, progressive, or complicated illness

In addition, anyone outside of these high-risk groups who presents with influenza within 48 hours of onset can be treated based on clinical judgment.

There are 3 classes of anti-flu drugs: neuraminidase inhibitors, cap snatch inhibitors, and adamantanes. Oseltamivir, a neuraminidase inhibitor, is the most commonly used. For a complete discussion of these medications, see [Antiviral Agents on page 4-85](#).

The prevalence of antiviral resistance to any specific agent is dependent on the circulating strains. Look to CDC guidance for up-to-date information on flu resistance to antiviral drugs.

All individuals > 6 months old should receive annual influenza vaccination with one exception: previous severe allergic reaction (i.e., anaphylaxis) to influenza vaccine. A history of Guillain-Barré syndrome is a precaution to vaccination, but not necessarily a contraindication. Egg allergy is **not** a contraindication to vaccination. If your patient reports hives only, give influenza vaccine. If your patient reports more

than urticaria (e.g., angioedema, swelling, recurrent vomiting, lightheadedness), give influenza vaccine in monitored healthcare setting with basic life support capability.

Influenza vaccines are targeted at the serotypes that are most likely to be present when the influenza season occurs. The better the antigenic match between this year's strains and next year's, the better the vaccine works. There are 3 types of influenza vaccines available in the U.S.: inactivated, recombinant, and intranasal live attenuated vaccine. Also, a high-dose influenza vaccine is available and is more effective than the standard dose vaccine in patients > 65 years of age, due to enhanced immunogenicity. Avoid the intranasal live attenuated vaccine in immunocompromised patients, pregnant patients, and healthcare workers who work with immunosuppressed populations. Regardless of which is used, administer vaccines when they become available each year, which is usually in September or October.

Adenoviruses

Adenoviruses (dsDNA) cause upper respiratory infections and conjunctivitis more often in children than adults. When they cause pharyngitis, they cause an exudative pharyngitis that is indistinguishable from streptococcal pharyngitis; however, there is a commonly associated bilateral conjunctivitis and coryza that are distinguishing clues. Diagnose by culture or PCR from secretions. In immunocompetent patients, the infection is self-limited.

Adenovirus is a feared virus in severely immunosuppressed populations. This includes patients who have undergone a bone marrow transplant, or who have severely depleted cell-mediated immunity. Pneumonia and disseminated disease carry a very high mortality. Cidofovir can be used—though nephrotoxicity is a major concern with this drug, and dialysis may be required frequently.

POLIOVIRUS

Poliovirus (an ssRNA virus) is asymptomatic in > 90% of infections. Symptomatic cases are characterized by aseptic meningitis and an asymmetric, flaccid paralysis due to infection and destruction of anterior horn cells. It has been eliminated in the Western hemisphere and in resource-rich countries worldwide secondary to vaccination, but it is still seen in resource-poor countries, especially India. In countries in which polio has been eradicated, enterovirus 68 and West Nile virus are mimics of the disease.

MUMPS VIRUS

Mumps (an ssRNA virus) occurs most commonly in winter and early spring. Although it commonly is asymptomatic, it can present with unilateral or bilateral parotitis, aseptic meningitis, and/or encephalitis.

Of postpubertal males with mumps, 15–20% get epididymo-orchitis, which is usually unilateral. Postinfection sterility is a rare occurrence. To differentiate mumps from bacterial parotitis, check a Gram stain of the parotid secretions. There are many WBCs and organisms in bacterial parotitis and **none** in mumps. Other causes of enlarged parotid glands are frequent vomiting or parotid duct stones. Always consider bulimia in an adolescent or adult with parotid gland enlargement.

PARVOVIRUS B19

Parvovirus B19 (an ssDNA virus) is spread by respiratory secretions and is usually acquired early in life, commonly manifesting as **erythema infectiosum** (fifth disease) with a high fever and a “slapped cheek” appearance. Adult-acquired illness typically consists of a self-limited fever, symmetric small joint arthritis, and a lacy rash on the trunk and/or extremities (Figure 4-47).



Figure 4-47: Parvovirus lacy rash
Source: CDC

The virus infects the red cell precursors, specifically the pronormoblasts, and causes arrest of red cell maturation. This causes a halt in RBC production for the ~ 1-week duration of the infection, resulting in pure red cell aplasia. In otherwise healthy adults, this causes a drop in Hgb of 5–10%, which is not symptomatic.

Only 3 groups of adults have any serious complications from the infection with this virus:

- 1) Immunocompromised hosts who cannot mount an antibody response have persistent red cell arrest and develop profound anemia.
- 2) Patients with chronic hemolytic anemias who rely on their reticulocytosis to maintain their Hgb levels (e.g., sickle cell disease) also become severely anemic.
- 3) In pregnant patients, if the virus is acquired during the 1st trimester, it can cause increased fetal loss due to hydrops fetalis.

Diagnosis is by assaying for IgM antibody in immunocompetent patients. In immunocompromised patients, who may not mount an antibody response, diagnosis can be made with a serum PCR assay for parvovirus DNA. Bone marrow exam, if done, shows giant pronormoblasts that are also diagnostic.

There is no specific antiviral therapy for parvovirus B19. Give immunocompromised patients passive immunity with IVIG to eradicate the virus. Maintain patients with hemolytic anemias with PRBC transfusions while they mount an antibody response to eradicate the virus.

ARBOVIRUSES

Arboviral Encephalitis

Arboviral encephalitis occurs throughout the U.S., typically in the late spring and summer. West Nile virus (WNV) is the most commonly identified arbovirus.

Arboviruses, like WNV, are named after the geographic area in which they were first found, so they carry names like La Crosse, St. Louis, Eastern equine, Western equine, Venezuelan equine, Powassan, and Colorado tick fever.

Almost all symptomatic arboviral infections have similar symptoms: fever, headache, chills, and varied severity of encephalitis or aseptic meningitis. WNV is asymptomatic in 80% of cases, but it can present as a nonspecific viral illness. Neuroinvasive disease (encephalitis, meningitis, or an asymmetric, flaccid paralysis similar to polio) occurs in only 1/150 patients. Since polio is no longer present in the U.S., test a person with a polio-like presentation for WNV. Less common presentations are tremor, myoclonus, parkinsonism, and cranial neuropathies.

Testing of patients with neurological disease should be done via sending the CSF for WNV IgM antibody. Virus concentration in the CSF is usually too low for PCR to be useful.

Treatment is supportive; no specific antiviral therapy is available.

Mosquito netting, repellents, and insect mitigation help to decrease the spread of these viruses.

Dengue Virus

The dengue virus (an ssRNA virus) causes a spectrum of disease ranging from asymptomatic infection to dengue fever to, most ominously, dengue hemorrhagic fever. It is the most common mosquito-borne viral disease and is seen throughout the tropics. The virus is transmitted to humans via the day-biting female *Aedes* mosquitoes, not the *Anopheles* mosquitoes that carry malaria.

Dengue fever symptoms are rapid onset of high fever (breakbone fever), markedly severe myalgias, arthralgias, and headache. This may be followed by a macular red rash that covers most of the body.

Dengue hemorrhagic fever is due to a diffuse capillary leak syndrome that results in hemoconcentration, anasarca, thrombocytopenia, and spontaneous bleeding. Death due to circulatory collapse may occur; it is seen in people who have had a prior infection with a different serotype of dengue.

Diagnose by a serum IgM antibody assay. Treatment is supportive with IV fluids. No specific antiviral therapy is available. There is a vaccine that causes a predictable immune response to all 4 dengue serotypes that is available in high prevalence areas, but not in the United States.

Chikungunya Virus

Chikungunya is an alphavirus endemic to West Africa and transmitted by the day-biting mosquitoes *Aedes aegypti* and *Aedes albopictus*. It has been present in the U.S. since 2014. It causes a syndrome very similar to dengue with high fever, polyarthralgia, headache, and maculopapular rash, except arthritis and arthralgias are much more prominent with chikungunya. Diagnosis is by detecting virus-specific IgM (which may not appear until 5–7 days of symptom onset) or by PCR. Treatment is supportive. Mortality is rare.

Zika Virus

Zika virus (an ssRNA virus) is a *Flavivirus* related to dengue and chikungunya viruses. It was first identified in the Zika forest of Uganda in 1947, found in a rhesus monkey in a program monitoring for yellow fever. Transmitted by the *Aedes* mosquito, Zika causes symptoms in only 20% of people infected. There is evidence of male-to-female sexual transmission.

Zika virus symptoms, if they occur, include fever, rash, muscle and joint pain, and conjunctivitis. The symptoms are usually mild and self-limited. Rarely, it can cause myelitis and/or encephalitis.

In 2015, an alarming increase in the number of infants born with microcephaly was seen in Brazil. Physicians found an association between Zika infection during pregnancy and infants born with microcephaly (see the [Women's and Men's Health](#) section). Subsequent studies have shown a 10–40% incidence of neurologic defects in babies born to women infected during pregnancy. Zika is also associated with Guillain-Barré syndrome. There was epidemic spread of the virus to South America, Central America, and the Caribbean in 2016, for which the WHO declared a public health emergency. As of 2019, there is no country worldwide with a Zika outbreak, but the virus is likely endemic in these new regions. Per the CDC, pregnant women and women of childbearing age should be cautioned against travel to Zika endemic regions, which include India, south-east Asia, Africa, the Caribbean, Central America, and South America. Zika has also been detected in Florida and Texas. Infected men can shed viral RNA in their semen for up to 6 months and place partners at risk.

The CDC has a reverse transcriptase polymerase chain reaction (RT-PCR) assay that can facilitate diagnosis in selected patients. There is no treatment for Zika virus. The CDC recommends prevention by avoiding insect bites.

Hantavirus

The primary reservoir for hantavirus (an ssRNA virus) in the U.S. is the deer mouse. The Four Corners area of the Southwest is the area of highest concern. On the East Coast and in the Southeast, the cotton rat is the reservoir. The infection occurs when the excreta or saliva of an infected rodent are inhaled (e.g., cleaning droppings, working in a barn). No human-to-human transmission is known.

Hantavirus pulmonary syndrome (HPS) starts as a non-descript viral syndrome, often with GI symptoms. Patients then develop muscle pain, fever, headache, and cough, which quickly progresses to hypoxia, hemorrhagic pneumonia, acute respiratory distress syndrome (ARDS), and death in > 50% of cases. Laboratory findings include hemoconcentration and thrombocytopenia. Diagnose by finding IgM antibodies in the blood or CSF. No specific antiviral therapy is available.

Ebola Virus

Ebola virus (an ssRNA virus)—first discovered in 1976 with an unknown reservoir, possibly fruit bats—causes episodic outbreaks of a hemorrhagic fever with severe vomiting, diarrhea, rash, and internal and external hemorrhage. Until 2014, no cases left the African continent. The 2014–2015 outbreak resulted in ~ 2 dozen cases that were exported to other continents, almost all of which were health care workers who were in the endemic areas caring for infected persons. Presentation is similar to that of dengue hemorrhagic fever, with a > 70% mortality rate. No specific treatment has been proven effective other than supportive care.

SLOW VIRUSES

There are 2 classes of slow viruses (long incubation time):

- 1) Normal viruses, such as papillomavirus (warts; [Human Papillomavirus \(HPV\)](#) on page 4-20) and polyomavirus (PML; [John Cunningham \(JC\) Polyomavirus](#) on page 4-37)
- 2) Defective viruses, such as the defective measles virus (subacute sclerosing panencephalitis; [Rubeola \(Measles\)](#) on page 4-72)

ANTIMICROBIAL AGENTS AND VACCINES

ANTIBACTERIAL AGENTS

PREVIEW | REVIEW

- Which antibiotics target deoxyribonucleic acid gyrase to interrupt protein synthesis?
- Which antibiotics antagonize folic acid?
- Which classes of antibiotics affect the developing bacterial cell wall?
- What are the definitions of minimal inhibitory concentration (MIC) and minimal bactericidal concentration?
- What is the difference between concentration-dependent and time-dependent killing?
- Which type of killing do aminoglycosides exhibit?
- What is the postantibiotic effect?
- What is the difference between concentration-dependent and time-dependent killing?
- In time-dependent killing, how long should a patient's serum concentration of a drug be higher than the infecting organism's MIC?
- What coverage does ampicillin add over penicillin?
- Which organisms do extended-spectrum penicillins cover?
- 3rd generation cephalosporins are known for their additional activity against which organisms?
- Which β -lactam drug can be given to patients with a penicillin allergy?
- Which carbapenem should be avoided in those with seizures?
- What are potential complications of linezolid use?
- Which drugs inhibit the absorption of quinolones?
- The use of which class of antibiotics increases the risk of tendon rupture?

HOW ANTIBIOTICS WORK

Most antibiotics work by disrupting bacterial protein synthesis, folate metabolism, or cell wall/membrane synthesis. First, let's review protein synthesis; then we'll tackle the mechanisms of action for specific antibiotics.

Quick Review — Protein Synthesis

Transcription: Protein synthesis requires the unwinding of DNA and having it cut and held open by DNA gyrase to be read by RNA polymerase.

RNA polymerase moves along a section of DNA to create a complementary strand of RNA, which is messenger RNA (mRNA).

Translation: The mRNA is translated into a sequence of amino acids to create the desired protein product by ribosomes. mRNA attaches to the 30S ribosomal subunit, after which a 50S ribosomal subunit binds to this complex to form a 70S ribosome.

Amino acid-specific transfer RNAs (tRNAs) bring in the corresponding amino acids to make the protein.

Antibiotics That Block Protein Synthesis

Rifampin binds to RNA polymerase and blocks transcription.

Quinolone antibiotics (e.g., ciprofloxacin, levofloxacin, moxifloxacin) block the ability of DNA gyrase to reconnect the cleaved DNA strands.

Metronidazole has a similar action to the quinolones. It also affects cell membrane function.

Aminoglycosides (e.g., gentamicin, tobramycin, amikacin) bind irreversibly to the 30S ribosomal subunit and prevent the 50S subunit from attaching.

Tetracyclines (e.g., doxycycline) and **glycylcyclines** (e.g., tigecycline) bind reversibly to the 30S subunit, distorting it so that the anticodons of the tRNAs cannot align properly with the codons on the mRNA.

Macrolides (e.g., erythromycin, clarithromycin, azithromycin) bind reversibly to the 50S subunit. They prevent peptide bond formation between the amino acids and, hence, keep the 70S ribosome from forming the desired protein.

Clindamycin works similarly to macrolides.

Oxazolidinones (e.g., linezolid, tedizolid) bind to the 50S ribosomal subunit, preventing attachment to the 30S unit.

Antibiotics That Affect DNA Replication

Trimethoprim and the **sulfonamides** block the production of folic acid from para-aminobenzoic acid (PABA). Folic acid is required to replicate DNA.

Quick Review — Cell Wall Synthesis

Peptidoglycan is a component of bacterial cell walls. It is composed of alternating polysaccharides: *N*-acetylglucosamine and *N*-acetylmuramic acid that are cross-linked to form alternating strands that make the wall solid. Gram-negative organisms have an outer membrane outside of the cell wall.

Antibiotics That Affect the Cell Wall

A variety of antibiotics act at 1 or 2 stages of peptidoglycan synthesis. In order for an antibiotic to affect the cell wall of gram-negative organisms, the drug must

pass through the outer membrane via channels called porins. Passage is affected by drug size and charge. Some gram-negative organisms have inherent resistance to certain cell wall agents because of the shape of their porins.

β -lactams are a class of antibiotics that interrupt formation of the bacterial cell wall. Because there is no analogous structure in human cells, people can tolerate relatively high doses.

Glycopeptide antibiotics (e.g., vancomycin, telavancin, dalbavancin, oritavancin) work by inhibiting cell wall synthesis of gram-positive organisms.

Antibiotics that Affect the Cell Membrane

Cyclic lipopeptides (e.g., daptomycin) insert into the plasma membrane of gram-positive bacteria, creating channels that allow the efflux of ions and disruption of membrane polarization. It also has a dual action on cell wall function.

Polymyxins (polymyxin B and colistin) bind to the cell membrane to create an efflux of ions and cell death.

Diagnostic Microbiology

When certain specimens are obtained (i.e., sputum, CSF, pleural, ascetic, urine), an attempt is made to directly visualize and identify the bacteria with a Gram stain before culturing it. For other samples, the specimen goes directly to culture (e.g., blood). The culture medium is incubated for 24 hours and observed for development of turbidity, which indicates bacterial growth.

Once bacterial growth is established, identification and sensitivity testing are done. Traditionally, the culture is then placed on various agar plates to identify the bacteria, and disk diffusion susceptibility is conducted to determine the minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) of the drug for those bacteria.

Most labs currently use an automated system that performs identification and sensitivity simultaneously, usually by a microtiter method.

Disk diffusion (Kirby-Bauer) testing is used for specific, difficult-to-treat bacteria that do not grow well in the automated media or for testing with antibiotics that are not included in the standard panels.

Minimal Inhibitory Concentration (MIC) and Minimal Bactericidal Concentration (MBC)

The **MIC** is the lowest concentration of antibiotic that **inhibits** visible growth (visible turbidity) in vitro after 24 hours of incubation. The **MBC** is the lowest concentration of antibiotic that **kills** 99.9% of the bacteria.

If the MIC of a drug vs. a specific isolate is achievable in tissue based on usual dosing of the antibiotic, the

organism is considered susceptible (sensitive) to the antibiotic and can be considered for treatment. All that needs to happen is for the drug to inhibit the growth of the organism, and the immune system does the rest to clear the infection.

In only a few circumstances, the goal is for the specified antibiotic to have an achievable MBC, not merely MIC. MBC is used to treat infections at sites that the immune system has trouble accessing (e.g., the center of an endocarditis vegetation, the CSF in meningitis) or when the patient is neutropenic.

General Rules of Antibiotic Use

Know these important points:

- Source control is key to treating serious infections. Examples of this are draining an abscess, removing dead tissue, and relieving a biliary or GU obstruction. Foreign bodies, lines, catheters, and devices may need to be removed.
- Pick the drug with the proper spectrum for the suspected or proven pathogen(s) and the site of infection.
- Adjust dosage for body size and clearance when appropriate.
- If the patient does not respond, consider 5 things:
 - 1) Is the patient getting/taking an effective drug?
 - 2) Is there resistance?
 - 3) Is there an undrained focus of infection?
 - 4) Is there a superinfection?
 - 5) Are the symptoms due to a noninfectious disease?

Concentration-Dependent Killing vs. Time-Dependent Killing

Concentration-Dependent Killing

Concentration-dependent killing means that killing increases as you increase the concentration of drug above the MIC for the bugs you are treating. This is sometimes referred to as dose-dependent killing because killing is based on concentration above MIC, not on time. Aminoglycosides and quinolones are drugs that exhibit concentration-dependent killing.

Quinolones and aminoglycosides also exhibit a **post-antibiotic effect (PAE)**. A PAE is persistent killing of bacteria even after the concentration of drug has fallen below the MIC at the site of infection. The dose-dependent killing and PAE allow these drugs to be dosed once daily, achieving a high peak concentration.

Time-Dependent Killing

In time-dependent killing, the concentration of drug above the MIC does not really matter. Instead, killing is related to how long the concentration of antibiotic remains greater than the organism's MIC at the site of

infection (a.k.a. time over MIC). β -lactams, macrolides, and glycopeptides (e.g., vancomycin) are such drugs. Aim for serum concentrations above the MIC for > 50% of the dosing interval.

Because β -lactams are time dependent, it is not important to aim for 8–10 $\times$ the MIC with each dose. Instead, patients need repeated, reliable dosing intervals so they do not have prolonged periods during the dosing interval when their serum levels fall below the MIC. The clinical relevance is that with time-dependent killing, patients who miss doses risk treatment failure.

β -LACTAM ANTIBIOTICS

Overview and Development of Penicillins

The 1st of the β -lactam antibiotics was penicillin. Its derivatives were created either to increase its spectrum of activity and/or to address developing bacterial resistance.

The development timeline of these drugs is as follows:

penicillin $\rightarrow$ semisynthetic penicillins $\rightarrow$ aminopenicillins $\rightarrow$ extended-spectrum penicillins $\rightarrow$ aminopenicillins/extended-spectrum penicillins + β -lactamase inhibitors

This topic area covers the penicillin-based antibiotics using the above developmental timeline.

Penicillin

Penicillin (PCN) is appropriate mainly for streptococci, sensitive enterococci, leptospirosis, *Listeria*, *Pasteurella*, and syphilis.

Staphylococci rapidly developed resistance by producing penicillinase, a β -lactamase enzyme that destroys the drug, so next came the...

Semisynthetic Penicillins

Methicillin (and later, **oxacillin**, **nafcillin**, and **dicloxacillin**): These are stable against staphylococcal penicillinase. These drugs are called semisynthetic penicillins or antistaphylococcal penicillins because they were synthesized from penicillin. They are the drugs of choice for methicillin-sensitive, penicillin-resistant staphylococci.

The semisynthetic penicillins lacked activity against gram-negatives, so next came the...

Aminopenicillins

The aminopenicillins are **ampicillin** and its oral formulation, **amoxicillin**. They retain the efficacy of prior penicillins but also kill many susceptible gram-negative organisms, such as *H. influenzae*, *E. coli*, *Proteus mirabilis*, and several strains of *Salmonella* and *Shigella*. Therefore, this new class added activity against urogenital and colonic bacteria. However, they are destroyed by staphylococcal penicillinase.

Unfortunately, resistance developed quickly; bacteria started producing other β -lactamases. Also, they had no activity against *Klebsiella* or *Pseudomonas*. So, the next major drug class to be developed was the...

Extended-Spectrum Penicillins

Piperacillin and **ticarcillin**: These drugs are called extended-spectrum PCNs because they take the spectrum of ampicillin and extend it to cover the more resistant GNRs, including *Pseudomonas*. Organisms created β -lactamases to this class, so the next addition to come along was the...

β -Lactamase Inhibitors

Addition of a β -lactamase inhibitor (BLI)—**sulbactam**, **tazobactam**, **avibactam**, or **clavulanic acid**—in combination with an aminopenicillin or an extended-spectrum penicillin protects the penicillin from β -lactamase hydrolysis.

Combinations include:

- IV ampicillin + sulbactam
- PO amoxicillin + clavulanic acid
- IV piperacillin + tazobactam (active against *Pseudomonas*)

The drugs retain the activity of the parent penicillin, but they are also effective against bacteria that make β -lactamase, including most anaerobes.

Evolution of Methicillin-Resistant *Staphylococcus aureus*

Staphylococci eventually acquired the *mecA* gene, which encodes a change in the penicillin-binding proteins that the β -lactams use to bind the bacteria. *MecA* transcription results in reduced affinity of all β -lactams for the organisms' cell walls—except for the newest 5th generation cephalosporin, ceftaroline. The staphylococci that express this gene are called methicillin-resistant staphylococci (methicillin-resistant *S. aureus* [MRSA], methicillin-resistant *S. epidermidis* [MRSE], and other methicillin-resistant coagulase-negative staphylococci).

Vancomycin, daptomycin, and linezolid effectively treat serious MRSA infections. Newer drugs with anti-MRSA activity include ceftaroline, oritavancin, dalbavancin, telavancin, and tigecycline; these are not for MRSA bacteremia. MRSA in skin and soft tissue infections often retains susceptibility to clindamycin, TMP/SMX, or doxycycline.

Penicillin Allergy

Most reported penicillin allergies are not true allergic responses. Penicillin allergy is often incorrectly reported by patients due to recollection of nonallergic symptoms while treated in the past (e.g., diarrhea, nausea). The American Academy of Allergy, Asthma, and Immunology recommends increased use of

penicillin skin testing, which is safe and effective. In patients in which a penicillin is the drug of choice or essential (e.g., neurosyphilis), skin testing can be performed. A negative skin test has a negative predictive value of > 95%, making an anaphylactic reaction to penicillin very unlikely. If truly allergic, patients can also be desensitized. See the [Allergy & Immunology](#) section for more on drug desensitization.

Cephalosporins

Cephalosporins also contain the β -lactam ring, but are inherently penicillinase-resistant because of their structure. Cephalosporins have no activity against enterococci or *Listeria*. With the exception of ceftaroline, all methicillin-resistant staphylococci are resistant to all cephalosporins.

1st Generation Cephalosporins

1st generation cephalosporins are active against MSSA and streptococci. There is 1 parenteral form available, IV **cefazolin**, and 2 oral forms, **cephalexin** and **cefadroxil**. They are unlike penicillin in that they have some coverage against community-acquired GNRs, such as *E. coli*, *Klebsiella*, and *Proteus*. 1st generation cephalosporins are commonly given for:

- Skin and soft tissue infections from sensitive organisms
- Surgical prophylaxis
- UTIs from sensitive organisms

2nd Generation Cephalosporins

Gram-negative coverage increases with coverage of *H. influenzae* (cefuroxime), *Moraxella*, *Enterobacter*, and *N. gonorrhoeae*. Pneumococcal coverage is retained. In this group, 2 drugs, **cefoxitin** and **cefotetan**, also have anaerobic coverage. These 2 drugs are used to treat:

- Pelvic inflammatory disease (PID)
- Postoperative abdominal infections

The 3rd generation cephalosporins have largely replaced the 2nd generation except for anaerobic infections, usually due to gut flora.

3rd Generation Cephalosporins

3rd generation cephalosporins are stable against most β -lactamases and have enhanced activity against pneumococci, *H. influenzae*, and *N. gonorrhoeae*. The GNR coverage is also enhanced over previous generations, so these drugs are better for the Enterobacteriaceae (*E. coli*, *Klebsiella*, *Proteus*, *Enterobacter*, and *Serratia*).

Remember the following facts about 3rd generation cephalosporins:

- They are great pneumococcus drugs, so they are recommended as 1st line agents for community-acquired pneumonia and meningitis in combination with vancomycin for empiric treatment.

- None of the drugs are 1st line agents for MSSA; 1st generation cephalosporins or nafcillin/oxacillin are preferred.
- None of the drugs cover anaerobes. 2nd generation cephalosporins or PCNs are better.
- **Ceftazidime** is the only 3rd generation drug that has antipseudomonal activity.
- **Ceftazidime**, **ceftriaxone**, and **cefotaxime** cross an inflamed blood-brain barrier. Any of these can be used as primary therapy for meningitis caused by *Enterobacteriaceae*.
- **Ceftolozane** was FDA approved in 2014 to treat complicated intraabdominal infections and UTIs. It is only available in combination with tazobactam.
- Cefdinir (Omnicef), cefditoren (Spectracef), cefixime (Suprax), cefpodoxime-proxetil (Vantin), and ceftibuten (Cedax) are 3rd generation cephalosporins.

4th Generation Cephalosporins

Cefepime is the only 4th generation cephalosporin. Think of it as the gram-positive activity of a 1st generation cephalosporin combined with the gram-negative activity of ceftazidime (including *Pseudomonas aeruginosa*), with enhanced stability against cephalosporinases. It has limited anaerobic coverage and is commonly used for neutropenic fever.

5th Generation Cephalosporins

Ceftaroline is the only cephalosporin that treats MRSA. Think of it like vancomycin combined with ceftriaxone. It does **not** treat *Pseudomonas* infections.

Advanced Generation Cephalosporins

Cefiderocol is a novel cephalosporin that binds with iron. It is recognized by bacteria as a siderophore-iron complex and is actively transported through the outer membrane (think Trojan horse), where it can bind to penicillin-binding proteins and halt cell wall synthesis in the same way as other cephalosporins. Gram-negative spectrum is extensive, including multidrug-resistant *Pseudomonas aeruginosa* and carbapenem-resistant *Enterobacteriaceae*. Gram-positive and anaerobic spectrum is limited. Cefiderocol is approved by the FDA for complicated urinary tract infections. Its therapeutic niche is treatment of infections caused by highly resistant gram-negative rods.

Addition of β -Lactamase Inhibitors

There are 4 newly approved β -lactam + β -lactamase inhibitor combinations available for extremely drug-resistant, gram-negative infections. These include the following:

- 1) IV ceftolozane + tazobactam
- 2) IV ceftazidime + avibactam

3) IV meropenem + vaborbactam

4) IV imipenem-cilastatin + relebactam

The specifics of when to use these agents should generally be discussed with an infectious disease specialist and/or antimicrobial stewardship department.

Monobactams

Aztreonam is the only monobactam with a β -lactam ring. It covers **only** GNBs, including *Pseudomonas*. Its spectrum is similar to aminoglycosides and 3rd generation cephalosporins. It is not active against gram-positive cocci or anaerobes. This drug can be used in patients with both a β -lactam allergy and penicillin allergy, which is its niche. It is available for intravenous or inhaled use only.

Carbapenems

Imipenem, **meropenem**, **doripenem**, and **ertapenem** are broad-spectrum β -lactams recommended **only** for use in **complicated** infections involving **multiple** organisms (such as in the abdomen or the diabetic extremity with possible bacteremia), against multidrug-resistant organisms, and for empiric treatment of the critically ill.

Carbapenem Resistance

Carbapenemases are carbapenem-hydrolyzing β -lactamases that confer carbapenem resistance. Various forms of these have been identified over the last several years.

Individual Carbapenems

Imipenem covers **most** bacterial classes: gram-positive cocci (GPC; excluding MRSA), gram-negative rods (GNRs; including *Pseudomonas* and other resistant GNRs), and mouth and gut anaerobes (particularly *Bacteroides fragilis*). It also is effective against extended-spectrum β -lactamase (ESBL)-producing organisms.

The few organisms resistant to imipenem:

- *Enterococcus faecium*
- *Burkholderia cepacia*
- *Corynebacterium jeikeium* (JK)
- *Stenotrophomonas maltophilia*
- *Acinetobacter* species
- MRSA

Also, remember that although *E. coli* and *K. pneumoniae* are typically sensitive to imipenem, the carbapenemase-producing variety can spread easily and cause major problems.

Resistance is increasingly common in *Pseudomonas* isolates, especially in those patients with recurrent infections—such as patients with cystic fibrosis.

Imipenem can lower the seizure threshold, so do not use it in patients with seizures and/or advanced-stage chronic kidney disease.

Imipenem is always formulated with equal amounts of cilastatin. Cilastatin is an enzyme inhibitor that impairs the metabolism of imipenem in the renal tubule, thereby increasing its half-life.

Meropenem is a similar carbapenem with a longer half-life, so there is no need for an enzyme inhibitor.

Doripenem is a carbapenem with similar activity and pharmacokinetics to meropenem.

Ertapenem is a carbapenem with convenient 1×/day dosing but **no** activity against *Pseudomonas*. Otherwise, its spectrum is similar to the other carbapenems. It is useful for outpatient parenteral treatment, especially of diabetic foot wounds, and for abdominal, pelvic, skin, and soft tissue infections.

GLYCOPEPTIDES

Vancomycin

Vancomycin is a glycopeptide antibiotic that is effective against most gram-positive organisms, including MRSA, MRSE, *Clostridium*, and *Corynebacterium*. It is a large molecule that diffuses poorly into most tissues, with only ~ 1/8 of the blood concentration reaching the site of infection. It exhibits time-dependent killing, so predose (**trough**) levels are measured to assure that they are ~ 8× the usual cutoff for susceptibility (2 mcg/mL), as well as to limit toxicity. For most serious infections, predose levels between 15 and 20 mcg/mL are recommended.

Clearance of vancomycin in patients undergoing hemodialysis can vary widely depending on the membranes used, so levels are needed to guide dosing.

Some strains of enterococci are vancomycin resistant. MICs are increasing in staphylococci, but vancomycin-resistant staphylococci (MIC ≥ 16 mcg/mL) are exceedingly rare. However, increases in the MIC that are still within the susceptible range (1–2 mcg/mL) can result in vancomycin treatment failure. Some experts suggest using an alternative drug to treat the infection (e.g., linezolid, telavancin, daptomycin). (Remember that daptomycin is inactive in the lungs, so use linezolid for vancomycin-resistant staphylococcal pneumonia.) It remains controversial whether to start an alternative agent as soon as the MIC is available or to wait for clinical outcome. Staphylococci with a MIC between 2 and 8 mcg/mL for vancomycin are considered to have intermediate susceptibility; use alternative drugs if possible.

Vancomycin, when it is rapidly infused, sometimes causes so-called **red man syndrome**, consisting of tachycardia, flushing, occasional angioedema, and generalized pruritus. It is an infusion rate-related phenomenon that is usually the result of mast cell degranulation and release of histamine. Red man syndrome is not a

true allergy. Patients who experience this reaction can be retreated with the drug if it is infused more slowly. Pretreat these patients with H1 blockers. Renal and ototoxicity are rare at normal doses (< 4 g/day).

The sole indication for **PO** vancomycin is *C. difficile* infection. IV vancomycin is **not** effective for *C. difficile* because it does not achieve therapeutic levels in the bowel.

Newer Glycopeptides

The FDA approved 3 glycopeptides in 2013 and 2014: **telavancin**, **oritavancin**, and **dalbavancin**. They have the same spectrum as vancomycin but have longer half-lives of 7–10 hours, 10 days, and 14 days, respectively, thus allowing for less frequent IV dosing of once daily, once weekly, or biweekly, respectively. These drugs lend themselves nicely to ambulatory treatment of infections and are FDA approved for the treatment of acute bacterial skin and skin structure infections. Telavancin is also approved for ventilator-associated and hospital-acquired pneumonia when alternatives are not appropriate. It has some cross sensitivity with vancomycin, so use caution if a known allergy exists.

OXAZOLIDINONES

Linezolid and **tedizolid** are the only oxazolidinones on the U.S. market.

They are bacteriostatic agents active against gram-positive organisms, including MRSA, MRSE, and vancomycin-resistant enterococci (VRE). Neither has an indication for bacteremia. They are highly bioavailable orally and come in IV and PO preparations. Linezolid is dosed twice daily, and tedizolid is dosed once daily.

These drugs are useful alternatives to vancomycin for MRSA. Tedizolid is only approved for skin and soft tissue infections.

Linezolid can cause reversible thrombocytopenia, anemia, and leukopenia especially if the patient has been taking it > 2 weeks. Tedizolid may cause this less frequently but has only been studied for short courses of therapy. Both drugs may cause a peripheral neuropathy. Both drugs can cause serotonin syndrome when used concurrently with selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs).

STREPTOGRAMINS

Quinupristin and **dalfopristin** are streptogramins, which are administered as a combination IV antibiotic. This compound has a narrow spectrum against certain aerobic, gram-positive organisms—specifically vancomycin-resistant *E. faecium* and MSSA—and is used when these organisms are resistant to, or patients are intolerant to, other agents. It is rarely used, given the availability of newer agents.

CYCLIC LIPOPEPTIDES

Daptomycin is a cyclic lipopeptide active against gram-positive organisms. It is a parenteral drug with a long half-life that allows once-daily dosing. It is used to treat skin and soft tissue infections, bacteremia, and right-sided endocarditis caused by MSSA or MRSA. It is reserved for resistant organisms, such as MRSA and VRE, or for patients intolerant to other drugs used for these organisms. It is also a useful drug to treat MRSA that have relatively high MICs to vancomycin.

It is inactivated by pulmonary surfactant and thus is not effective in treating pneumonia. Myopathy is a potential side effect, so monitor CK levels at least weekly during long-term use, especially in patients who are also taking a statin.

GLYCYLCYCLINES

Tigecycline is a parenteral glycylicycline that is a derivative of tetracycline. It is very broad-spectrum with activity against gram-positive organisms (e.g., VRE, MRSA), anaerobes, and GNRs. It has coverage against ESBL-producing GNRs. However, it is **not** active against *Pseudomonas* and has reduced activity against *Proteus* and *Providencia*.

Tigecycline is indicated for complicated skin and soft tissue infections and intraabdominal infections. Nausea and vomiting are its main side effects, occurring in > 20% of patients. There is a black box warning of increased mortality for tigecycline because certain patients, particularly those with pneumonia, did worse on tigecycline compared with other antibiotics. There is still a role for this antibiotic in multidrug-resistant infections, but it should generally be given in collaboration with infectious disease colleagues.

POLYMYXINS

Colistin is a nephrotoxic agent that was essentially replaced by the less (but definitely) nephrotoxic aminoglycosides, only to have a new niche with the advent of multidrug-resistant *P. aeruginosa* and *Acinetobacter*. Because nephrotoxicity occurs in 20–50% of patients, its use is limited to treatment of those multidrug-resistant organisms for which no other antibiotics are available and/or tolerable.

Polymyxin B is also available in parenteral and topical forms and is used for resistant gram-negatives. It is also toxic, and its use is limited as above.

AMINOGLYCOSIDES

Aminoglycosides (e.g., **gentamicin**, **tobramycin**, **amikacin**, **streptomycin**) are active against the following:

- Enteric GNRs (but not anaerobic GNRs, such as *Bacteroides fragilis*)
- *Yersinia pestis* (plague)
- *Francisella tularensis* (tularemia)

- *Pseudomonas aeruginosa*
- *Brucella* species (brucellosis)
- *Mycobacterium tuberculosis*
- *M. avium-intracellulare*

Aminoglycosides are also used to treat patients with febrile neutropenia, in combination with a 3rd generation cephalosporin or an extended-spectrum penicillin + β -lactamase inhibitor if local β -lactam resistance rates are too high to trust β -lactam monotherapy.

These drugs exhibit concentration-dependent killing and a considerable postantibiotic effect. Hence, they are best dosed once daily after a loading dose. Potential complications include ototoxicity and nephrotoxicity.

FLUOROQUINOLONES

Ciprofloxacin, **levofloxacin**, **moxifloxacin**, and **delafloxacin** are available in IV and oral form. **Gemifloxacin** is available only in oral form. Their oral bioavailability is ~ 100% but is reduced by chelation with divalent cations (Mg^{2+} , Ca^{2+}) that may be components of vitamins and laxatives. Other drugs can decrease absorption (e.g., aluminum/magnesium antacids, sucralfate, ferrous sulfate). They can also prolong the QT interval, so you must avoid concomitant use with other QT-prolonging agents (e.g., amiodarone).

They all have aerobic GNR coverage, and ciprofloxacin and levofloxacin have *Pseudomonas* activity. Ciprofloxacin should **not** be used for empiric *S. pneumoniae* coverage. On the other hand, levofloxacin and moxifloxacin are approved for *S. pneumoniae*, which is why some refer to them as “respiratory fluoroquinolones.” Although *S. aureus* may be susceptible in micro reports, resistance commonly develops during treatment, and fluoroquinolones should not be used, with the exception of delafloxacin.

Delafloxacin was FDA approved in 2017 for skin and soft tissue infections only, and the indication includes MRSA.

Moxifloxacin is less active than the others against GNRs, but it is the most active quinolone for *M. tuberculosis* and is active against most anaerobes.

There are many caveats with this class:

- Do not give to pregnant/lactating patients.
- Due to inhibition of tendon and bone formation, their use in persons < 18 years of age is not recommended by the FDA, with the exception of ciprofloxacin, which is approved for 2nd line therapy in children with UTIs and patients with cystic fibrosis.
- In adults, injury to tendons (specifically the Achilles tendon), muscle, joints, and peripheral nerves can occur, especially in the elderly. Thus, the FDA recommends against their use as 1st line drugs for acute bacterial sinusitis, exacerbations of COPD, and uncomplicated UTIs.

MACROLIDES

There are 4 macrolides currently available: erythromycin, clarithromycin, azithromycin, and telithromycin.

The parent drug **erythromycin** is effective against:

- *Mycoplasma pneumoniae*
- *Chlamydomphila pneumoniae*
- *Campylobacter*
- Diphtheria
- Pertussis

Erythromycin has a short half-life of 2 hours and thus must be dosed several times a day. It increases intestinal motility and may cause nausea, vomiting, and/or diarrhea. It increases the concentrations of many drugs, including theophylline, cyclosporine, and warfarin.

Clarithromycin, **azithromycin**, and **telithromycin** have better *S. pneumoniae* and *H. influenzae* coverage than erythromycin, and have better GI tolerance. Clarithromycin and telithromycin are available only orally, but azithromycin comes in both IV and PO formulations. These 3 agents have longer half-lives that permit more convenient dosing—either bid or daily for clarithromycin ($T_{1/2}$ = 3–7 hours), daily for azithromycin ($T_{1/2}$ = ~ 3 days), and daily for telithromycin ($T_{1/2}$ = 10 hours). The use of telithromycin is severely restricted due to increased toxicity in comparison to the other agents.

URINARY TRACT AGENTS

3 agents—nitrofurantoin, fosfomycin, and methenamine—are often considered together because their only indication is for the treatment of UTIs.

Nitrofurantoin has multiple mechanisms of action that disrupt protein, DNA, RNA, and cell wall synthesis; this explains why resistance is rare among species that are intrinsically susceptible, which includes most *E. coli*. All *Proteus* and most *Klebsiella* are resistant. Blood levels are not sufficient to treat pyelonephritis or systemic infections, so its use is limited to uncomplicated cystitis from susceptible strains. Toxicity is rare if renal function is normal. It is not recommended if creatinine clearance is < 60 mL/minutes/1.73m² (1.00 mL/seconds/m²). It is a 1st line drug for uncomplicated cystitis and is safe in pregnancy, except at term. It can also be used as low-dose prophylaxis of recurrent UTIs related to sexual activity in women.

Fosfomycin is a phosphonic antibiotic that has activity against most enterococci and *E. coli*, *Klebsiella*, and *Enterobacter*. For the same reasons as nitrofurantoin, it should not be used for pyelonephritis or systemic infections. It is a 2nd line agent for uncomplicated cystitis and has the advantage of only requiring a single dose.

Methenamine is a heterocyclic antibiotic made from combining ammonia and formaldehyde. In acidic urine, formaldehyde is released, which is bactericidal

to organisms. No formaldehyde is created in the alkaline environment of the blood or renal parenchyma, so toxicity is minimal. It is relegated to use in suppressing recurrent UTIs.

ANTIFUNGAL AGENTS

PREVIEW | REVIEW

- Liposomal amphotericin B preparations are used in which circumstances? Against which fungi?
- Which candidal species are usually resistant to fluconazole?
- What are the indications for voriconazole?
- What are the indications for echinocandins?

POLYENES (AMPHOTERICIN AND NYSTATIN)

Polyenes bind to ergosterol on fungal cell walls, altering their permeability and producing cell death.

The original formulation of **amphotericin B deoxycholate** has been mostly replaced by lipid polyene formulations, echinocandins, and azoles. When given intravenously, it has many side effects: acute kidney injury, anemia, phlebitis, renal tubular acidosis, hypokalemia, and hypomagnesemia. Infusion-related chills and fevers can be severe, and hypotension can occur.

Liposomal amphotericin B preparations are less nephrotoxic and have fewer infusion-related side effects but are more expensive. Lipid preparations are better for some fungal infections, especially those that enter the reticuloendothelial system, such as cryptococcal meningitis and disseminated histoplasmosis. Lipid amphotericin B is also used to treat mucormycosis (*Mucor* and *Rhizopus*) because higher doses of the preparation can be given without nephrotoxicity. They are also used when toxicity has occurred with the amphotericin deoxycholate preparation. The very low level excreted in the urine is the reason they are not indicated in treating fungal UTIs. The original version can be used to treat fluconazole-resistant UTIs.

Topical polyene macrolides are **nystatin** and **amphotericin B**. These are effective only against mucocutaneous candidiasis. Both are also available in liquid form for oral and esophageal candidiasis.

AZOLES

Azoles work by inhibiting the synthesis of ergosterol, a necessary component of the fungal cell wall.

Ketoconazole is an oral and topical preparation that is rarely used systemically because of increasing resistance and more toxicity than other azoles. It can be

used to treat refractory tinea infections. Ketoconazole is a potent P450 inhibitor and therefore has many drug-drug interactions.

Clotrimazole and **miconazole** are available in both cutaneous and vaginal (for vaginal candidiasis) preparations. Many other preparations are also available. They are also used to treat cutaneous candidiasis, tinea versicolor, and ringworm.

Fluconazole is indicated for oral and esophageal candidiasis, candidemia (for susceptible isolates), disseminated candidiasis from *C. albicans*, coccidioidomycosis, cryptococcosis, and vulvovaginal candidiasis. It has excellent penetration into the CSF. **Never** use fluconazole as empiric antifungal treatment in febrile neutropenic patients. *Candida krusei* is entirely resistant, and many *Candida glabrata* are resistant.

Fluconazole is a moderate P450 inhibitor and therefore has many drug-drug interactions.

Itraconazole is a triazole analog of ketoconazole that is more effective and safer. Capsules should be taken with food; a carbonated drink (acidity) helps with absorption. Always check levels when using itraconazole. Consider itraconazole for patients with non-life-threatening endemic fungal infections (e.g., histoplasmosis, blastomycosis) and sporotrichosis.

Itraconazole also is a potent P450 inhibitor and therefore has many drug-drug interactions.

Voriconazole is a triazole with an extended antifungal spectrum compared to fluconazole. Voriconazole is 1st line therapy for invasive aspergillosis—this is the most important indication to remember. It can also be used for certain resistant, invasive candidal infections with ocular involvement (azoles generally penetrate the blood-brain/blood-eye barrier), as well as other hyaline and dematiaceous mold infections. The drug can be given orally or by IV.

Major toxicity is transient, with reversible alterations in visual acuity and color vision. It happens in ~ 30% of patients 30 minutes after administration and lasts 30 minutes (30-30-30 rule). Check voriconazole serum levels whenever you are treating a serious infection because significant variations in levels occur from person to person.

Voriconazole is a potent P450 inhibitor and therefore has many drug-drug interactions.

Posaconazole is a triazole with the extended antifungal spectrum of voriconazole, with additional activity against the Zygomycetes (e.g., *Rhizopus*, *Mucor*). It is FDA approved for prophylaxis of *Aspergillus* and *Candida* infections in those with severe immunocompromised states, including prolonged neutropenia or stem cell transplant recipients with graft-versus-host disease. It is also used for treatment of oropharyngeal candidiasis (particularly infections refractory to itraconazole or fluconazole), invasive *Aspergillus*, and Zygomycetes.

Posaconazole is a potent P450 inhibitor and therefore has many drug-drug interactions.

Isavuconazole was FDA approved in 2015 for the treatment of invasive aspergillosis and mucormycosis. It is at least as good as voriconazole for the former and was found reasonably effective for the latter in an open-label study published in 2015. Drug levels do not need to be monitored. It is also a potent P450 inhibitor.

ECHINOCANDINS

Echinocandins inhibit β -1,3-glucan, an essential component of the cell walls of several fungi, including *Aspergillus*. They act very similarly and are used interchangeably. Think of echinocandins primarily for severe *Candida* infections in sick patients, such as candidemia. It is the 1st choice for empiric antifungal therapy in prolonged febrile neutropenia.

Caspofungin has a half-life of 30–50 hours and is dosed once daily after an initial loading dose. Caspofungin is approved for:

- Candidemia and *Candida* infections of the abdomen, peritoneum, and pleural space and fluconazole-resistant esophagitis
- Invasive aspergillosis in severely immunocompromised patients who are intolerant of lipid amphotericin B or voriconazole

Caspofungin is the only echinocandin additionally approved for invasive aspergillosis as salvage therapy. Caspofungin also has the most drug interactions. No dose adjustment is needed for renal failure.

Several drugs interfere with its metabolism: phenytoin, dexamethasone, carbamazepine, efavirenz, nevirapine, and rifampin.

Micafungin has a half-life of 11–21 hours and does not require a loading dose. It has fewer drug interactions.

Anidulafungin has a half-life of 40–50 hours and is dosed once daily after an initial loading dose. It has very few drug interactions.

OTHER ANTIFUNGALS

Flucytosine (a.k.a. 5-fluorocytosine; 5-FC) is metabolized to the antimetabolite 5-fluorouracil which competes with uracil and inhibits RNA synthesis. It is highly soluble and penetrates well into the CSF. Most *Candida* and endemic fungi are susceptible, but if used alone, drug resistance develops quickly. When combined with amphotericin B, resistance does not develop and there is a synergistic antifungal effect. This combination is used in the induction treatment of severe cryptococcosis. 5-FC can cause serious GI, hepatic, renal, and bone marrow toxicities—the latter usually presents as neutropenia and thrombocytopenia. It is renally excreted, so a decrease in renal function predisposes to toxic effects.

ANTIPARASITIC AGENTS

Praziquantel is the **only** drug effective against **all** species of *Schistosoma*. It is effective against flukes and tapeworms. It is a 2nd line drug to treat neurocysticercosis (brain cysts) caused by the pork tapeworm, *Taenia solium*.

Albendazole is a 1st line drug for all nematodes (except filariasis) and cysticercosis. It is 2nd line for strongyloidiasis and schistosomiasis. Use only in nonpregnant patients.

Niclosamide is used for the treatment of tapeworm.

Pentamidine is effective against trypanosomiasis (African sleeping sickness). For *Pneumocystis*, which is a fungus and not a parasite, treat with IV or via inhalation for prophylaxis. It is not used as a 1st line drug for treatment because of the many side effects, including azotemia, leukopenia, pancreatitis, and hypo- or hyperglycemia.

Nitazoxanide is approved for treatment of *Giardia lamblia* and *Cryptosporidium parvum*.

Miltefosine is used to treat *Naegleria* and *Leishmania*. It is only available through the CDC.

Eflornithine is used to treat *Trypanosoma brucei gambiense* meningoencephalitis (sleeping sickness).

Atovaquone is used to treat babesiosis and as a 2nd line drug for *Pneumocystis*.

Nifurtimox is used to treat *Trypanosoma cruzi* and *T. b. gambiense*.

Benznidazole, an orphan drug, is used to treat *Trypanosoma cruzi*.

Ivermectin is the drug of choice for *Strongyloides* infections.

Diethylcarbamazine is the drug of choice for all forms of filariasis. It is only available through the CDC.

Triclabendazole is used to treat *Fasciola hepatica* but is not available in the U.S.

Antimalarial drugs: See *Plasmodium* (Malaria) on page 4-60.

Valacyclovir and **famciclovir** are oral antivirals that also treat herpes simplex and varicella-zoster infections. Only acyclovir is available intravenously to treat severe infections. Valacyclovir and famciclovir drugs are used primarily for less-frequent dosing of outpatients. They are more expensive than acyclovir.

Ganciclovir is used to treat cytomegalovirus (CMV) infections, which are seen most often in posttransplant patients and those with HIV/AIDS. Typical CMV infections are retinitis, encephalitis, pneumonitis, colitis, and, occasionally, severe bone marrow suppression (neutropenia and thrombocytopenia).

Valganciclovir is an oral preparation similar to ganciclovir but with better absorption, leading to blood levels comparable to IV ganciclovir.

Foscarnet is used in patients with ganciclovir-resistant herpes infection or as an alternative to ganciclovir for CMV. Foscarnet toxicity includes decreases in serum K⁺, Ca²⁺, Mg²⁺, and phosphorus along with acute kidney injury.

Cidofovir is a 2nd line drug to treat CMV infections in immunocompromised hosts.

Ribavirin is used as part of combination therapy for hepatitis C. It can cause significant hemolytic anemias, requiring downward dose adjustments.

Neuraminidase inhibitors are the primary drugs used to treat influenza A and B. They prevent virion release from cells by inhibiting the enzyme neuraminidase. The three FDA approved drugs in this class are oseltamivir (Tamiflu), zanamivir (Relenza), and peramivir (Rapivab).

Cap snatch inhibitors interfere with viral RNA transcription and viral replication. These are active against influenza A and B. The one drug in this class that is FDA approved is baloxavir marboxil (Xofluza).

Adamantanes target the M2 ion channel protein of influenza A viruses. They are not active against influenza B. Presently, nearly all influenza A is resistant to these drugs, so they are not recommended for treatment. The two drugs in this class are amantadine and rimantadine.

See **Antiretroviral Drugs** on page 4-31.

ANTIVIRAL AGENTS

PREVIEW | REVIEW

- What are the indications for ganciclovir?

Acyclovir is a nucleoside analog used for the treatment of herpes simplex and varicella-zoster viruses. Treatment of zoster infections requires higher doses. High intravenous doses to treat herpes simplex encephalitis can crystalize in the urine, causing a microobstructive acute kidney injury that resolves with hydration.

VACCINES

PREVIEW | REVIEW

- Which vaccines contain live virus? Which patients should not receive them?
- Which vaccines are safe to administer to immunocompromised or pregnant patients?
- Which vaccines are recommended to adults and in which age groups?

- How many doses of measles, mumps, and rubella vaccine are considered most desirable and protective?
- Which patient groups should receive the pneumococcal polysaccharide vaccines and in what order?
- How do you decide how to prevent tetanus in a patient presenting with a wound?

VACCINE TYPES

Vaccines used solely in childhood are not discussed here.

Do **not** give live attenuated vaccines to the immunocompromised or pregnant patients (see the [Women's and Men's Health](#) section). **Live attenuated vaccines** include:

- MMR (measles-mumps-rubella)
- Varicella
- Zoster
- Smallpox
- Typhoid oral
- Cholera oral
- BCG (bacillus Calmette-Guérin)
- Yellow fever
- Intranasal influenza

Killed (inactivated) vaccines are safe for the immunocompromised and pregnant, and include:

- Td (tetanus-diphtheria toxoid)
- Tdap (tetanus toxoid, reduced diphtheria toxoid, acellular pertussis)
- Hepatitis A
- Hepatitis B
- Polio
- Cholera (not available in the U.S.)
- Rabies
- Japanese encephalitis
- Typhoid polysaccharide
- HPV
- Pneumococcal vaccines (PPSV23 and PCV13)
- Meningococcal
- Influenza

VACCINE SCHEDULES

Vaccine schedules are noted here with vaccine-specific discussions to follow later in this section. The specific schedule for vaccinations changes frequently. The current schedule can be found on the web page for the Advisory Committee on Immunization Practices (cdc.gov/vaccines/schedules).

Vaccinations that are recommended for adults, according to age groups:

- **Td or Tdap:** 1 dose q 10 years. Tdap is approved for **all** > 7 years of age. Tdap should be given only once as an adult if the 3-dose primary childhood series has been given; after that, Td can be given.

- **HPV:** 2 or 3 doses (depending on age at which the 1st dose is administered) for 9–26 years of age for both males and females
- **Varicella (chickenpox vaccine):** 2 doses, if no history of immunity or vaccination
- **Zoster (booster to prevent shingles):** adults > 50 years of age
- **MMR:** For patients born after 1956 or those who have not had naturally occurring infection or laboratory evidence of immunity, give 2 doses if not vaccinated or 1 more if received only 1 vaccine as a child.
- **Influenza:** given annually to **all** persons > 6 months of age
- **Pneumococcal vaccination:** > 65 years of age and those at risk. There are 2 vaccines that should be given to most individuals.
- **Hep A:** at-risk adults (chronic liver disease, men having sex with men [MSM], travelers to endemic countries, and intravenous drug abuse [IVDA])
- **Hep B:** at-risk adults (health care/safety workers, chronic liver disease, end-stage renal disease, HIV, IVDA, and MSM) without evidence of immunity and no history of childhood vaccination
- **Meningococcal polysaccharide or conjugate:** everyone 11–18 years of age and at-risk adults 19–55 years of age

Zoster vaccines: There are two zoster vaccines currently available. The Advisory Committee on Immunization Practices (ACIP) and the CDC recommend the recombinant vaccine for all healthy adults > 50 years of age. The ACIP also recommends that those who received the earlier zoster vaccine (live attenuated) be revaccinated with the newer version (recombinant).

Recombinant zoster vaccine (RZV; Shingrix): In those 50–69 years of age, recombinant zoster vaccine has an effectiveness of 97%; it is 91% effective in preventing herpes zoster and postherpetic neuralgia, respectively. At > 70 years of age, this falls a bit to 91% and 89%, respectively. Two total doses are required, 2–6 months apart.

Attenuated live vaccine (Zostavax): The attenuated live vaccine has an overall effectiveness of 50% and 75% to prevent herpes zoster. Because it is a live virus, this vaccine is contraindicated in immunodeficient and pregnant patients. Both the varicella and the zoster vaccine have the same virus, but the latter has a much higher dose. One total dose required.

MMR: It is recommended that persons born after 1956 receive 2 doses of live measles vaccine. These should be given at least 1 month apart, but they can be given years apart. Any adults born after 1956 who have had only 1 live measles vaccine should receive another.

Pneumococcal vaccine: The 2 pneumococcal vaccines include the 23-valent polysaccharide vaccine (PPSV23), which was approved in 1983 and contains 60–70% of prevalent serotypes, and the 13-valent conjugate vaccine (PCV13), which was approved in 2010 and contains the 13 most common serotypes. The approach to giving

these vaccines is a little complicated. First, decide whether PCV13 is indicated; if so, give it before the PPSV23. If PCV13 is **not** indicated, decide whether PPSV23 is indicated. There is no circumstance in which PPV13 is given alone.

PPSV23 should be given:

- Alone to adults < 65 years of age if at risk because of:
 - Smoking
 - HF
 - COPD
 - Cirrhosis
 - Diabetes mellitus
 - Ethanol abuse
- In combination with and after PCV13 in persons ≥ 65 years of age, or if very high risk, defined as:
 - CSF leak or cochlear implant
 - Asplenic
 - Chronic kidney disease or nephrotic syndrome
 - Immunocompromised
 - Leukemia, lymphoma, or myeloma
 - Disseminated cancer
- With an interval between doses:
 - If given because of high risk (≥ 8 weeks)
 - If given because ≥ 65 years of age (≥ 6 months)
 - In patients who have already received PPSV23 and now have an indication for PCV13, the latter should be given ≥ 1 year after the former.

Hepatitis A vaccine: Unless otherwise contraindicated, inactivated HepA vaccine is universally recommended at or after 1 year of age. It is also recommended for men who have sex with men; patients with chronic liver disease, including hepatitis B and/or C; patients with clotting disorders; and travelers to countries with high rates of hepatitis A.

Hepatitis B vaccine: This vaccine is universally recommended at birth and for all adolescents who were not immunized in childhood. Chronic hepatitis B is a risk factor for hepatocellular cancer. Vaccination is recommended in high-risk adults.

According to the CDC's Advisory Committee on Immunization Practices (ACIP):

- All unvaccinated adults at risk for hepatitis B infection should be vaccinated. This includes:
 - Sex partners of people infected with hepatitis B
 - Men who have sex with men
 - People who inject street drugs
 - People with > 1 sex partner
 - People with chronic liver or kidney disease
 - People < 60 years of age with diabetes
 - People with jobs that expose them to human blood or other body fluids
 - Household contacts of people infected with hepatitis B

- Residents and staff in institutions for the developmentally disabled
- Kidney dialysis patients
- People who travel to countries where hepatitis B is common
- People with HIV infection
- Other people may be encouraged by their doctor to get the HepB vaccine; for example, adults ≥ 60 years of age with diabetes.
- Anyone else who wants to be protected from hepatitis B infection may get the vaccine.
- Pregnant women who are at risk for 1 of the reasons stated above should be vaccinated (see the [Women's and Men's Health](#) section). Other pregnant women who want protection may be vaccinated.

Serologic testing for immunity is recommended only for specific groups:

- Health care and public safety workers
- Chronic hemodialysis patients
- HIV-infected persons
- Immunocompromised persons
- Sexual partners of HBsAg-positive persons

Give persons who do not develop a protective response (anti-HBs concentration of < 10 mU/mL) another full vaccine series.

Meningococcal vaccines: Meningococcal disease is devastating; therefore, preventing disease is of paramount importance. Remember the risk factors for severe disease to help remember the vaccination recommendations. They include:

- Asplenia
- Complement deficiencies (See more on complement deficiencies in the [Allergy & Immunology](#) section.)
- 1st year college students who live in dorms
- Military recruits
- People who are traveling to the meningitis belt of sub-Saharan Africa, Saudi Arabia (e.g., for the Hajj), or Nepal
- Lab workers who work with *Neisseria*

There are two broad groups of meningococcal vaccines; only those available in the U.S. will be reviewed.

Quadrivalent polysaccharide conjugate vaccine: Serogroups A, C, W, and Y are covered by the quadrivalent conjugate. Two quadrivalent vaccines are approved for use in the U.S.:

- MenACWY-DT (Menactra)
- MenACWY-CRM (Menveo)

Indications for quadrivalent vaccination are all individuals 11–18 years of age and individuals ≤ 10 or ≥ 19 years of age who are at risk for invasive meningococcal disease.

Monovalent vaccine: Serogroup B in the U.S., other serotypes (C and A) are used outside of the U.S. Two serogroup B vaccines are approved for use in the U.S.:

- MenB-FHbp (Trumenba)
- MenB-4C (Bexsero)

Indications for MenB vaccination:

- Individuals ≥ 10 years of age who are at increased risk for invasive meningococcal disease
- During outbreak scenarios
- Individuals 16–23 years of age who are at average risk for invasive meningococcal disease for short-term protection (e.g., new college students in dorms or new military recruits in barracks)

Pertussis: Adults are the major reservoir for pertussis. Although it is usually self-limited in adults, it can be deadly for infants.

To help protect children, it is recommended that all adults receive 1 booster with Tdap sometime in adulthood. In addition, give pregnant women Tdap with each pregnancy.

APPROACH TO TETANUS PREVENTION

Tetanus can be prevented with the appropriate use of tetanus toxoid (Td) and tetanus immunoglobulin (TIG). The use of these depends on the type of wound and the vaccination status of the patient.

Tetanus-prone wound: Tetanus-prone wounds include crush injuries, bite injuries, dirt- or fecally contaminated wounds, puncture or missile wounds, deep penetration wounds, wounds containing foreign bodies (e.g., wood splinters), and reimplantation of an avulsed tooth. Tetanus can be prevented based on how certain it is that patients have had the primary series of 3 injections of Td or not.

Give a booster dose of Td to those who have had a primary series if they have not received Td in the last 5 years. This stimulates sufficient production of antitoxin antibodies before the tetanus toxin can travel from the wound site to the CNS.

Patients with a tetanus-prone wound who have **not** received the primary series or have uncertain immunization history are considered at high risk for tetanus. Give these patients Td to begin the primary series. However, since they have not had adequate prior immunization, boosting of their immune response cannot be relied upon. Therefore, these are the patients for whom tetanus immune globulin (TIG) is indicated.

Non-tetanus-prone wound: Persons who do not have tetanus-prone wounds (often called “clean wounds”) are not at risk for tetanus from the wound. However, the patient encounter provides an opportunity to begin immunization in the previously unvaccinated or to boost immunity in people who haven’t received a booster in the last 10 years. Thus, give those who have not received

all 3 primary series injections of Td (or are uncertain) as many Td injections as needed to complete the 3-shot primary immunization sequence. Give a Td booster to those who have completed the primary series but have not been boosted in the last 10 years. TIG is **never** indicated in the management of non-tetanus-prone wounds.

UNCOMMON VACCINES FOR SPECIAL SITUATIONS

Japanese encephalitis vaccine is recommended for travelers who plan to stay a long time in rural Asia.

Rabies vaccine is discussed under [Rabies on page 4-24](#).

Typhoid vaccine is recommended for travelers > 2 years of age who go outside of the usual tourist areas within Latin America, Asia, and Africa. An oral live attenuated vaccine is recommended for those > 2 years of age. It has a protection rate of only 35–60% and can be repeated every 5 years. A parenteral polysaccharide vaccine has an efficacy of 60–70% and can be repeated every 2 years.

Polio vaccine is not routinely recommended to persons > 18 years of age. Polio vaccine is recommended for previously unimmunized travelers to endemic areas. A booster is indicated for travelers who have had only the primary vaccination and who travel to areas where exposure to the wild-type virus is likely. Only the inactivated vaccine is recommended in the U.S.

Yellow fever vaccine is recommended for travel in equatorial Africa and much of tropical South America. It is a live vaccine; therefore, do not give to immunosuppressed patients. As of early 2020, supply of yellow fever vaccine was totally depleted, and the manufacturer is expected to have an update by the end of 2020.

Cholera vaccine was approved in the U.S. in 2016 and is a live attenuated oral vaccine that can be given to adults traveling to regions with active cholera cases within the last year.

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Geriatric Medicine

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DEMOGRAPHICS

Life expectancy correlates with race and gender. Caucasian women live the longest. African American women and Caucasian men tie for 2nd place. African American men have the shortest lifespans. Generally, women live longer than men, are less likely to remarry, lack money to take care of all their needs, and are more often disabled as they age.

61–79% of patients > 65 years of age have hypertension, and roughly 27% have diabetes. Mortality data from the Centers for Disease Control and Prevention (CDC) for 2017 shows that heart disease is the leading cause of death, followed by cancer, in older adults (a.k.a. the elderly). Many studies show that elderly patients are **not** offered the same life-saving procedures as younger patients with the same disease states, even though age alone has no adverse effect on outcomes of the interventions. **Age alone is not enough of a reason to withhold an intervention.**

THE PHYSIOLOGY OF AGING

PREVIEW | REVIEW

- Know the meaning of these terms: senescence, normal aging, usual aging, life expectancy, and maximum life-span potential.
- Explain the various theories for the causes of aging.
- What are the cellular processes involved in aging?
- What is sarcopenia?
- What are the physiologic changes that occur in the various sense organs of the body with aging?

OVERVIEW

In 2016, 49.2 million people in the U.S. were ≥ 65 years of age (15% of the total population), with projections to be 98.2 million in the year 2060. The fastest-growing segment of the population is those > 85 years of age. If the present growth rates continue, there will be about 834,000 centenarians by 2050, and 82% will be women. It is very important to understand the physiology of aging, as this helps differentiate between normal age-related physiologic changes from pathologic processes and aging.

Aging is a progressive process that is associated with declines in structure and function, impaired ability to maintain and repair tissues, and increased susceptibility to disease and death. The aging process is the most significant risk factor for disease and disability.

While recognizing aging is easy, defining aging is a little more difficult. There are certain phenotypic components of aging that can be subclassified into the following:

- Primary aging changes: e.g., gray hair, decreased muscle mass (sarcopenia)
- Age-related diseases: e.g., dementia, osteoporosis, osteoarthritis, increased insulin resistance

Additionally, in contrast to the younger cohort, older people have multiple comorbidities and chronic diseases and are more vulnerable to malnutrition. Microvascular dysfunction, mitochondrial impairment, and oxidative injury are typical changes associated with aging and underlie many of the pathologic changes.

Some terms:

- **Senescence** refers to postmaturational processes that lead to diminished homeostasis and increased vulnerability of the living person.
- **Normal aging** refers to physiologic processes that occur at certain points during the aging process. A good example of this is menopause in females.
- **Usual aging** refers to age-related disease processes that occur in older individuals. Examples of these processes include hypertension and coronary artery disease, which occur more frequently as one grows older.
- **Life expectancy** refers to the average age expected to live based on current age, race, gender, and other demographic factors (e.g., financial, marital, health status).
- **Maximum life-span potential** is the age obtained by the longest living member of the given population.

In human beings, the maximum life-span potential for a male is approximately 120 years and for a female is approximately 122 years. The approximate life expectancy is 76 years for males and 81 years for females. In general, females outlive males in most species in the animal kingdom.

THEORIES OF AGING

There is no single, definitive theory that gives a satisfactory explanation for the aging process.

The **stochastic theory of aging** hypothesizes that random damage to cellular structures accumulates and results in progressive decline in cellular function and eventual death. The various processes under this theory include mutations and free radical-induced injuries. Free radicals are highly reactive byproducts of metabolism, and they can affect the cells and their various components. Accumulation of free radicals results in dysfunctional cells and subsequent cell death.

Genetic theories of aging state that genes are programmed for a person's growth from birth to death. About a quarter of human lifespan variation is believed to be genetic. For example, longevity appears to correlate with the presence of the apolipoprotein E (*APOE*) e2 allele and/or the absence of *APOE* e4.

According to the **neuroendocrine theory of aging**, the hypothalamic-pituitary-adrenal axis plays a significant role in the various stages of development, and as its function declines, aging occurs.

The **vascular aging** theorists believe that changes in the endothelial structure of the blood vessels correlate with significant changes in all body parts. They conclude that

age-related changes in the arteries (such as vascular stiffening and abnormal vasomotor regulation with alterations in arteries [e.g., coronary arteries]) adversely affect cell function.

The **immunologic theory of aging** proposes that alterations in the immune system increase susceptibility to disease and, therefore, affect longevity.

AGING AT THE CELLULAR LEVEL

At the cellular level, the following processes seem to cause aging:

- Oxidative stress and increase in free radical formation
- Mitochondrial dysfunction causing altered mitochondrial adenosine triphosphate (ATP) formation, again leading to increased free radical formation
- Progressively shortening telomere length and replicative senescence (Hayflick limit refers to the limit at which the cell stops dividing when the telomere length reaches below a critical limit.)
- Altered gene expression due to epigenetic changes (e.g., DNA methylation, chromatin remodeling, histone acetylation)
- Impaired autophagy causing defective cell repair

AGE-RELATED CHANGES

Height

Bone is built until the 3rd decade of life and then loss of bone starts to occur. Height loss averages 1/2 inch every 10 years and is even more rapid after 70 years of age. This is caused by decrease in vertebral body height, thinning of the intervertebral discs, slight flexion at the hips and knees, and flattening of the arches of the feet.

Weight and Body Composition

Weight is not directly related to aging and is influenced by multiple factors, including diet, activity level, and socioeconomic status. However, **body composition** does change with age. Total body water decreases with age. Lean body mass decreases by 1% per year from approximately 55 years of age. The fat component doubles from 15% to 30% of the body weight by the 7th decade of life in men. Across the board, the fat component is slightly higher in women across all ages. As aging occurs, fat becomes more centrally distributed—mainly in the abdomen.

Musculoskeletal System

Sarcopenia is decreased muscle mass with decrease in strength caused by aging. This occurs due to a decrease in lean body mass, alterations in neuronal and neuromuscular transmission, and muscular changes that occur with aging. This muscle loss mainly involves the Type II fibers. Lipofuscin accumulation is a pathologic feature observed in sarcopenia. One muscle that is notably spared in aging is the diaphragm.

Joints and cartilage become concomitantly stiffer with aging. In postmenopausal females, estrogen loss causes a significant increase in bone loss, leading to osteoporosis.

Gait and Balance

Gait velocity correlates with functional status. The slower the gait, the higher risk for health decline and mortality. Decreased gait correlates with decrease in arm swing. Sarcopenia, slower gait, and decreased arm swing contribute to imbalance and cause a slightly increased propensity to fall. In addition to these, concomitant disease processes, impaired vision, and medications also independently increase the risk of falling. See more under [Mobility and Gait on page 5-5](#).

Skin

Skin turnover time is increased in aging. Blood supply to the skin is also decreased, resulting in dry skin (xerosis) with decreased functioning of both sweat and sebaceous glands. All of these not only cause the skin to become more prone to injury but also prolong the healing time with even minor injuries. Wrinkling of the skin occurs due to loss of elastin and collagenous and subcutaneous fat. Hair loss is increased. Graying of hair occurs because of progressive loss of melanocytes. Synthesis of vitamin D is less efficient in sunlight-exposed aging skin, which contributes to this vitamin deficiency.

Sensory Changes

Vision

Several changes occur across various parts of the eye with aging. **Important changes:** the iris responds more sluggishly to light stimulation due to increased rigidity, and the lens becomes yellowed due to photo oxidation of tryptophan, which affects blue color perception. Significant glare can occur when light is scattered into the eyes, and this adversely affects driving, among other things. Presbyopia refers to the process of decreasing lens elasticity and ciliary muscle atrophy. Both light and dark adaptation are impaired, and contrast sensitivity is diminished. Because of these, the use of night lamps and glare-free lights are important to decrease the risk of injury from falls.

Hearing

As we age, the auditory canals become narrowed, predisposing older individuals to cerumen impaction. Cerumen impaction also occurs because the cerumen is drier and the hair in the canal gets coarser. These independently can cause conductive hearing loss in older patients in addition to the sensorineural hearing loss that occurs with aging. Presbycusis describes the bilateral, symmetric hearing loss involving higher frequencies in older patients. Hearing aids can be beneficial. Be sure to check for cerumen impaction.

Taste and Smell

Taste perception and smell perception both decrease significantly with normal aging. Smell acuity declines to about 50% of its peak by 80 years of age. The number of taste buds declines after 60 years of age, and the remaining buds shrink in size, resulting in reduced taste. Common medications such as antihypertensives, antibiotics, and cholesterol-lowering drugs can also decrease smell and taste. These sensory alterations can contribute to anorexia and decreased appetite. However, profound anorexia is almost always pathological. Flavor enhancers, such as pepper, cinnamon, vinegar, and ginger, may be helpful in increasing appetite. While sugar and salt addition may achieve the same thing, excessive use of sugar and salt are associated with adverse health consequences and, therefore, preferably avoided.

Immunity

There is an age-related decrease in immunity. The total number of T cells declines, and there is a change in T-cell subsets. CD4 T cells decrease with age, and the number of CD8 T cells increases with age. CD4 decline causes less stimulation of B cells; also, the bone marrow makes fewer B cells with a net result: less antibody production. Also, only half of the T cells remain competent, which is why herpes zoster and reactivation tuberculosis are often seen in older adults.

CLINICAL PEARL

As aging occurs, smaller doses of water-soluble drugs (e.g., aminoglycosides) achieved therapeutic levels as compared to their use in younger people. In contrast, lipid-soluble drugs like benzodiazepines (BDZs) accumulate in the fat in elderly people. This causes the effect of these fat-soluble medications to be present long after withdrawal of the medications.

EPIDEMIOLOGY OF AGING

PREVIEW | REVIEW

- What are the 3 Ds in aging?
- What factors influence disease and disability in older adults?
- Do gender and race affect morbidity and mortality?
- What are the major causes of mortality in older adults?
- What are ADLs and IADLs?

OVERVIEW

The main health concerns of older patients can be summarized as 3 Ds: disease, disability, and dependency. Various factors influence the 3 Ds: age, gender, race,

education, and income level. Epidemiology of aging refers to the disability, morbidity, and mortality caused by various diseases, including their effect on independent living in older adults.

The simplest and often the best way for you to assess your patient's health is to ask them to rate their health on a scale of 1–5:

- 1—Poor
- 2—Fair
- 3—Good
- 4—Very Good
- 5—Excellent

A patient's self-assessed health correlates significantly with their clinical condition and is a good predictor of their health outcomes, including hospitalizations, health care expenditure, nursing home placements, morbidity, and mortality.

AGE

As people age, the incidence and prevalence of chronic diseases, such as arthritis, cancer, hypertension, and heart disease, increase. Mortality and morbidity rates also increase with age.

GENDER

Females have a longer life expectancy than males—although the exact cause of this is unclear. Premenopausal women suffer less from heart disease due to the protective effect of estrogen. Additionally, in general, women notice problems sooner and seek attention faster than men. In contrast, a higher percentage of men indulge in high-risk behaviors like smoking or alcohol or drug use and are likely to work in occupations that involve higher risk and higher occupational exposure to toxins. These reasons may explain why men have a shorter life expectancy than women.

Paradoxically, women have higher disability and morbidity rates compared to men, but again, the exact causes are unclear.

RACE

African American, Hispanic, and Native American populations have higher mortality rates when compared to Caucasian Americans of the same age. Overall, rates of chronic diseases (including arthritis, diabetes, hypertension, coronary artery disease, and strokes) are significantly higher in minority populations. Asian Americans are a notable exception to the rule—although even they have slightly poorer health care outcomes.

EDUCATION AND INCOME LEVEL

Higher levels of education are associated with better health; similarly, lower levels of education are associated

with poor health outcomes. Higher education is associated with better physical health behaviors (e.g., more time spent on exercise, lower smoking rates, lower BMIs). Higher subjective levels of happiness are also reported in people who have attained higher education. Similarly, higher income levels are also consistently associated with better health outcomes.

MAJOR CAUSES OF MORTALITY IN OLDER ADULTS

The majority of deaths in the early 1900s were due to infectious disease. In contrast, in 2017, nearly half of all older Americans died from heart disease (25%) and cancer (21%), followed by chronic lower respiratory diseases, stroke, Alzheimer disease, and other diseases. Currently, infections such as influenza and pneumonia account for only about 2% of all deaths in older Americans. Although women have a lower mortality rate at a given age than men, the causes of death in older women are the same as older men.

MORBIDITY

Morbidity refers to the burden of disease. Chronic diseases form the bulk of these problems. Nearly 2/3 of older adults have hypertension, 1/2 have elevated blood lipids, and arthritis, diabetes, and heart disease each affect 1/3.

Comorbidity refers to the presence of > 1 disease. About 85% of older Americans have 1 chronic disease and 60% have ≥ 2 chronic diseases. Even at 60 years of age, 25% of Americans have a chronic disease that significantly impacts their ability to perform at least 1 of the activities of daily living (ADLs; see [Disability](#)). Comorbid diseases are a significant cause of loss of independence. Chronic diseases and mental health account for 90% of American health care expenditures. When hospitalized, older adults have a longer length of stay compared to younger adults, primarily due to the comorbidities.

DISABILITY

As previously mentioned, women have a higher rate of disability than men. Age is a major risk factor for loss of independence; 20% of women are dependent at 70 years of age, and this number increases to 60% by 90 years of age.

Disability is assessed through activities of daily living (ADLs) and instrumental activities of daily living (IADLs). ADLs are the basic self-care activities necessary for independent living, while IADLs are higher-level activities required to function independently in society.

ADLs can be remembered by the mnemonic **DEATH**:

- Dressing
- Eating
- Ambulating
- Toileting
- Hygiene

IADLs can be remembered by the mnemonic **SHAFT**:

- Shopping
- Household work
- Account management (managing finances)
- Food-making (cooking)
- Transport (ability to move around from place to place)

Most people with ADL limitations have limitations in IADLs, whereas the converse is not true: people with IADL limitations need not have any ADL limitations. This is because ADLs assess more basic functions as compared to IADLs.

RECENT TRENDS IN LIFE EXPECTANCY

The encouraging news is that with medical advancement and understanding of disease processes, total life expectancy and disease-free life expectancy have mostly increased. Declines in life expectancy largely related to drug overdoses and unintentional injuries began to reverse in 2018, aided by lower death rates due to cancer. Threats to continued improvement include rising rates of liver disease, diabetes, and obesity. Other potential threats to human longevity are pandemics (such as the one caused by the novel coronavirus SARS-CoV-2 in 2020), epidemics, and nuclear warfare. Despite these unknowns, medical science strives to usher in a golden period in human history in terms of improvements in life expectancy.

GERIATRIC ASSESSMENT

PREVIEW | REVIEW

- How do you diagnose frailty?
- What assessments should be done periodically in older patients?
- What are the major features of delirium, using the Confusion Assessment Method?

Frailty affects a large number of older adults. It can be caused by comorbid illness and/or disability, but not necessarily so. Frail patients are more likely to fall, become disabled, or die. Make a diagnosis of frailty if ≥ 3 of the following are present:

- 1) Unintentional loss of ≥ 10 lb/1 year
- 2) Exhaustion due to lack of endurance
- 3) Decreased hand strength
- 4) Walking slowly
- 5) Reduced activity

All geriatric patients should have a specific interval assessment of **function** because functionality is related to longevity. Functional assessment evaluates several components:

- ADLs
- IADLs

- Cognition
- Hearing
- Vision
- Nutrition (See [Nutrition and Gastroenterology on page 5-10.](#))
- Gait and balance (See [Mobility and Gait.](#))
- Driving ability (See [Older Adults and Driving on page 5-23.](#))

Start by assessing **ADLs**: Can the patient dress, bathe, feed, use the bathroom, and move around without help? IADLs are those activities that connect the patient with the community: Can the patient manage their money, take their own medication, manage transportation, make phone calls, do the shopping and housework, and make their own meals? To perform IADLs requires effective executive functioning, an umbrella term that refers to a set of mental skills that allow us to plan, juggle tasks, call up from memory, and focus attention.

To assess **cognition**, look for evidence of dementia and delirium:

- Assessing **dementia**: A quick way is to use the Mini-Mental State Exam (MMSE) or the Mini-Cog (easier to remember) to assess dementia. To perform the Mini-Cog, ask the patient to remember 3 words, and then ask them to draw a clock showing a specific time. After drawing the clock, ask the patient to recite the 3 words. Score by giving 1 point for each word remembered correctly and 2 points for an accurate clock (0–2 points = dementia). The Montreal Cognitive Assessment (MoCA) test is more sensitive for mild cognitive impairment than the MMSE or Mini-Cog.
- Assessing **delirium**: The best tool to assess delirium is the Confusion Assessment Method (CAM; 94–100% sensitive; 90–95% specific). See [Table 5-1](#). Delirium is present when the patient has features 1 and 2 along with either 3 or 4.

Table 5-1: Confusion Assessment Method (CAM)

Feature	Description
1	Acute onset and fluctuating course: Is mental status acutely changed from baseline, and does the change fluctuate throughout the day?
2	Inattention: Is there a problem focusing attention (e.g., easily distracted)?
3	Disorganized thinking: Is conversation rambling or irrelevant? Are ideas illogical in flow?
4	Altered level of consciousness: Is the patient alert (normal state), hyper-alert, drowsy but easily aroused, difficult to arouse, or unarousable?

Read more under [Delirium on page 5-13](#) and [Dementia on page 5-14](#).

Assess **hearing** and **vision** using traditional instruments such as the whisper test and the Snellen eye chart. The whisper test is performed by covering the ear that is

not being tested, then whispering a question while standing about 2 feet away. If the patient responds correctly, then no more testing is required. Give the patient 6 tries. Refer for further audiometric testing if the patient answers ≥ 3 questions (out of 6) incorrectly.

Gait and balance are assessed by observing gait and by watching the patient get up from a chair, walk across the room, turn around, walk back, and sit down (the **Get Up and Go** test).

Older adults (and teens) have more driving violations compared to the general population. Usually, patient performance on the vision, hearing, and gait assessment gives you an adequate estimate of a patient's physical ability to operate a vehicle. Formal assessment is offered for older adults through departments of motor vehicles.

Assess for safety annually and potential abuse at each visit. Patients often do not voice these types of concerns unless asked directly. See more under [Elder Mistreatment on page 5-21](#).

MOBILITY AND GAIT

PREVIEW | REVIEW

- What are risk factors for falls in older adults?
- What is the most common foot deformity among older adults?
- What factors can contribute to the development of decubitus ulcers?
- What is the role of wet-to-dry dressings in decubitus ulcer treatment?

FALLING

Aging contributes to **increased instability and falls**. 50% of patients ≥ 80 years of age fall each year! Older adults have a stiffer, less agile gait with decreased position reflexes. 5% of falls result in fractures, and, if the patient cannot get up, there is an increased possibility of hypothermia, dehydration, pressure injuries, and rhabdomyolysis.

Aging is also associated with decreased proprioception and baroreceptor reflexes, so orthostatic hypotension and swaying are common. Carotid sinus hypersensitivity increases with aging and can increase the risk of falls and fractures. Postprandial hypotension occurs frequently in older adults—risk can be decreased by eating smaller meals and fewer carbs per meal.

Risk factors for falls:

- Age
- Female gender
- History of falls
- Rugs, untidiness, and dim lighting
- Poor vision

- Orthostatic hypotension
- Unsteady gait
- Cognitive impairment
- Musculoskeletal disease
- Cardiovascular disease (e.g., syncope)
- Psychotropic drug use
- Peripheral neuropathy

Use of physical restraints (e.g., arm or leg restraints, hand mitts, vests) increases the risk of injuries, so avoid physical restraints when possible.

Fall risk assessment in older adults includes 5 quick office tests:

- 1) Get Up and Go test
- 2) Gait speed (slower = ↑ risk)
- 3) Tandem (heel-to-toe) walk
- 4) Visual acuity
- 5) Calf circumference (smaller = ↑ risk)

Workup for the patient with falls includes a good history and physical exam with emphasis on a multidisciplinary assessment and evaluation for a cardiovascular cause. Do a syncope workup if the patient does not remember the fall or if the history is suggestive. Also think about weakness caused by osteomalacia—especially in nursing home patients who are bedridden and never exposed to sunlight. Check 1,25-(OH)₂-D if you suspect osteomalacia and treat any deficiency, because treatment decreases fall risk. Bone mineralization is impaired without adequate vitamin D. Look for other laboratory clues to osteomalacia such as low serum levels of calcium (leading to increased parathyroid hormone levels) and decreased serum phosphate. Another finding is increased alkaline phosphatase, a result of increased osteoblast activity.

Anticipatory guidance for fall reduction includes restriction of certain activities, improving the lighting at home (e.g., use night-lights), decreasing hazards (e.g., remove rugs and loose carpets), and placing extra supports (e.g., bars in the shower). If possible, discontinue medications known to increase fall risk (e.g., diuretics, anticholinergics, BDZs, muscle relaxants, antidepressants, neuroleptic agents, antihypertensive medications). Exercise, especially focused on balance and resistance training, is **very important** in reducing fall risk.

Falls and osteoporosis are major risk factors for hip fractures in older adults. 90% of hip fractures occur from a simple fall. Women are at higher risk compared to men due to higher rates of osteoporosis. See the [General Internal Medicine](#) section for more on osteoporosis and falling.

COMMON FOOT PROBLEMS

After 75 years of age, < 30% of patients are able to care for their feet due to physical and cognitive limitations.

Lack of preventive care can lead to common foot problems in older adults. The ankles, subtalar joints, and first metatarsophalangeal (MTP) joints frequently develop arthritis. Bunions account for 75% of foot deformities. Their etiology is unknown and likely contributing factors are altered foot mechanics or anatomy and genetics. Hammer toes are deformities due to high tension in muscles and tendons in toe joints. Toenails usually become thicker and brittle with aging and onychomycosis, poor circulation, or hypothyroidism. Ingrown toenails can lead to pain and infection. Other foot health issues include foot ulcers from diabetes and lower extremity edema from cardiovascular diseases, a medication side effect, and poor nutrition. Properly fitting shoes, routine foot care, and treatment of underlying conditions prevent long-term complications.

IMMOBILITY

Immobilization causes muscle atrophy. Patients adapt to bed rest, and the longer a patient is immobilized, the harder it is to ambulate again. Immobilization causes decreased ADH secretion → diuresis → decreased blood volume → orthostatic symptoms. The heart continually deconditions after 2 days of bed rest. Treat with rehabilitation.

The goal of rehabilitation is to get the patient to function at the highest level possible given the physical impairment. Enhance functional abilities and limit demands. This can be achieved by limiting medications, enhancing nutrition, providing assistive devices and human help, modifying living arrangements, and providing adaptive training. The greatest rehabilitation potential is achieved with coordinated care with the patient, family, and caregivers. This is often achieved across multiple settings, including the hospital, nursing home, and home health services.

Geriatric patients struggle with the decision to stay in their home vs. an alternative location such as a nursing home or assisted living facility. Most studies show no differences in health outcomes between rehabilitation at home vs. nursing homes. The best results involve decisions made between the patient, family, and caregivers regarding where the best care can be delivered. Often, home care can be cost prohibitive, and the level of care needed by the patient is best delivered in a nursing home.

PRESSURE INJURIES

Pressure injuries (a.k.a. decubitus ulcers) occur most commonly on the heels, greater trochanter, sacrum, and iliac crest. The main etiology is sustained pressure over a prominent bone. Shearing and friction tear the skin and cause necrosis with ulceration. **Moist** environments (notably, in urinary incontinence), neurologic impairment (e.g., dementia), and **malnutrition** (i.e., ≥ 10-lb weight loss in the past 6 months) also increase the risk for developing pressure injuries.

Pressure injuries in **nursing home patients** increase mortality (usually from osteomyelitis and bacteremia/sepsis).

There are 4 stages of pressure injury:

- Stage 1 is nonblanching erythema (reddish macules).
- Stage 2 is partial-thickness skin loss (small, superficial ulcer).
- Stage 3 is full-thickness skin loss (fat visible).
- Stage 4 is loss of tissue down to the muscle, tendon, or bone.

Bed-bound patients should be rotated from side to side (30° angle) every 2 hours. This prevents continued contact against bony prominences. Special mattresses and heel/elbow pads also help.

In **established ulcers**, keep pressure off the area, and if an eschar exists, remove it for proper staging. Then determine whether any arterial or venous insufficiency exists, treat infection if present, and maintain a “clean” ulcer.

Effective healing requires **debridement** of necrotic tissue back to healthy granulation tissue, using either chemical topical treatments or a scalpel.

Next, the wound must be cleaned and dressed. **Saline cleansing** is best because it is gentle on growing tissue, and iodine or peroxide hinder wound healing if used repeatedly. The choices for wound dressings are wide and variable. Follow the advice given by the wound care therapist. As a means for debriding wounds, wet-to-dry dressings have fallen out of favor, because too often they damage friable new tissue.

Give antibiotics, in addition to local wound care, if the patient is systemically ill. Use deep wound cultures to guide your choice.

Wounds do **not** heal in malnourished patients, so follow the recommendations of the registered dieticians to provide adequate increased nutrition.

Know: Wounds that develop in the setting of arterial or venous insufficiency do not heal unless the local blood flow is corrected—most often via surgical intervention. Sometimes this is feasible, sometimes not, depending on the patient’s comorbidities.

Stage 1 and 2 ulcers typically heal quicker than Stage 3 and 4 ulcers, which can take months or longer.

A chronic wound is defined as a wound that does not heal within 1 month. Chronic venous insufficiency can lead to progressive edema and ulceration. Management of chronic wound and venous ulcers is similar to that of an acute wound, requiring debridement and proper wound dressing. For venous ulcers, reducing the edema via leg elevation and compression therapy is paramount to wound healing.

HIP FRACTURE

PREVIEW | REVIEW

- What are the risk factors for hip fracture in older adults?
- What are the different classifications of hip fractures?
- Which type of hip fracture is subject to avascular necrosis?
- Which type of hip fracture has the greatest risk for hemodynamic compromise?
- What is the primary management for hip fracture?
- Which anticoagulants are used for venous thromboembolism prophylaxis and for how long after hip fracture?

OVERVIEW

In the United States, hip fractures represent the 2nd leading cause of hospitalizations among older adults. Every year more than 300,000 people > 65 years of age are hospitalized for hip fractures. It is imperative that you recognize, prevent, and correctly manage hip fractures in older patients.

> 95% of hip fractures are caused by falling, most commonly from a standing position, with osteoporosis as the major comorbid factor. Other risk factors include cardiovascular disease, diabetes, low BMI, sedating medications, and low socioeconomic status.

PRESENTATION

Hip fractures are classified by anatomic location (Figure 5-1):

- Intracapsular (femoral neck and head)
- Extracapsular (intertrochanteric and subtrochanteric)

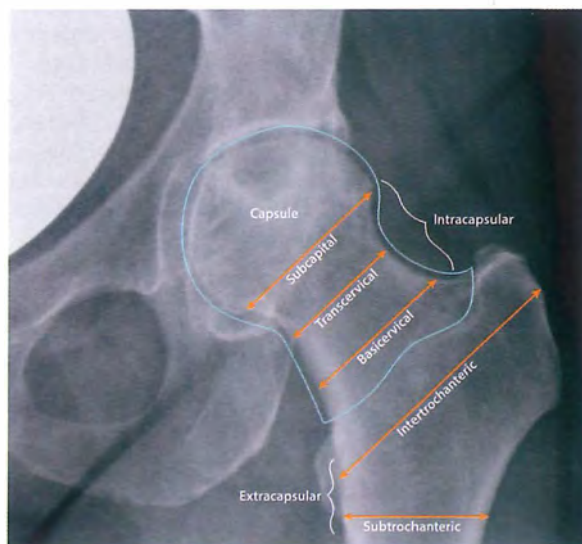


Figure 5-1: Types of hip fractures

Intracapsular fractures have a higher rate of malunion and avascular necrosis compared to extracapsular fractures; this is because the collateral blood circulation to the head of the femur is limited. Intracapsular fractures can be subdivided by anatomic location into subcapital, transcervical, and basicervical. They can also be subclassified by the degree of displacement (Garden classification from anteroposterior radiograph). Symptomatically, some patients can bear weight (e.g., nondisplaced fractures) but will be non-weight-bearing if the fracture is displaced and the limb is externally rotated and shortened on the physical exam.

Extracapsular fractures have a decreased risk of avascular necrosis due to rich dual irrigation by the medial and lateral femoral circumflex arteries (branches of the deep femoral artery). Both arteries encircle the base of the femoral neck around the trochanter. Due to their rich vascularization, extracapsular fractures present with ecchymosis and can have significant hemodynamic compromise due to blood loss. They also have an increased need for implant devices and have higher rates of implant failure due to the high stresses placed upon the femur. Extracapsular fractures are subdivided into intertrochanteric and subtrochanteric fractures, with subtrochanteric fractures presenting with groin pain.

DIAGNOSTIC IMAGES

Order a 2-view hip x-ray with comparison with the uninjured hip as the 1st diagnostic test. If x-ray is negative but clinical suspicion is high, MRI can be diagnostic. If MRI is contraindicated, bone scan is another acceptable option.

MANAGEMENT

The goal of managing hip fractures is to restore the patient's functional status to their preinjury level. Surgical management is best if the patient is medically fit for surgery. Do not delay surgery > 24 hours because delay slows recovery and increases mortality and postsurgical complication risks. Assess the preinjury functional level and risk of surgery before deciding if the patient would benefit from surgical management. In a bed-bound patient with multiple comorbidities, nonoperative management can be undertaken. On admission, all patients require orthopedic consultation and appropriate pain management.

Intracapsular Fractures

There are 4 types of intracapsular fractures, as described in the Garden classification of hip fractures:

- Type 1—incomplete or impacted bone injury with valgus angulation of the distal component
- Type 2—complete (i.e., across whole femoral neck); nondisplaced

- Type 3—complete; partially displaced
- Type 4—complete; totally displaced

Femoral neck Type 1 and 2 fractures are managed with internal fixation and a screw-type device. For Type 3 and 4 fractures, arthroplasty is preferred. Total hip arthroplasty has increased risk of postoperative dislocation and blood loss compared to hip hemiarthroplasty (prosthetic replacement of only femoral head and neck).

Extracapsular Fractures

As mentioned, there are 2 types of extracapsular fractures.

Intertrochanteric fractures have increased risk of displacement; therefore, treatment is open reduction with internal fixation. Severely comminuted fractures are often treated with long-stemmed implants and can require calcar bone graft. An alternative used with unstable fractures, especially in frail patients at increased risk for another fall, is hemiarthroplasty with a calcar-replacing prosthesis.

Subtrochanteric fractures are treated with open reduction and internal fixation.

CLINICAL PEARL

For all extracapsular fractures (both intertrochanteric and subtrochanteric), open reduction and internal fixation is the treatment of choice. If surgery is an option, it should be performed no less than 3 days from injury with early mobilization after surgery.

VENOUS THROMBOEMBOLISM PROPHYLAXIS

Deep venous thrombosis occurs in 27% of patients after hip fracture who are not prophylaxed, while pulmonary embolism occurs in about 5% in the first 3 months following hip fracture surgery. The greatest risk for venous thromboembolism (VTE) is during the first 7–14 days following hip surgery.

The 2016 American College of Chest Physicians (ACCP) guidelines recommend the use of low molecular weight heparin (LMWH), fondaparinux, direct anticoagulant (DOAC, e.g., rivaroxiban, apixaban), low-dose unfractionated heparin, vitamin K antagonist, aspirin, or intermittent pneumatic leg compression for at least 10 days after surgery. If surgery is initially delayed, VTE prophylaxis is recommended until surgery is scheduled.

Of these, fondaparinux is recommended as 1st line by the ACCP. Aspirin is significantly less effective than the above-mentioned anticoagulant agents, but it reduces the rate of VTE when compared to a placebo. Its use is only recommended in patients with high risk for hemorrhagic complications, and is always used with mechanical thromboprophylaxis. The recommended aspirin dosage is 325–650 mg/day.

OTHER RECOMMENDATIONS

Pain management is the initial therapy for any patient with hip fracture. Inadequate pain control is the main cause of delirium. Epidural pain management and nerve block are recommended and are effective controlling pre- and postoperative pain and decreasing opiate requirements and subsequent delirium.

Pressure reduction mattresses are recommended because they reduce the risk of pressure injury complications.

Poor nutritional status carries increased morbidity and mortality risks; therefore, appropriate evaluation and treatment is recommended postoperatively.

To reduce the risk of infection, remove indwelling urinary catheters within 24 hours of hip replacement surgery.

Administer blood transfusion when hemoglobin is < 8 g/dL (80 g/L), unless the patient has clinical indications for earlier transfusion, such as symptoms of anemia or symptoms of active cardiac disease.

At initial presentation, do a complete assessment to identify the possible etiology of the fall. This not only helps with the patient's diagnosis but also with appropriate discharge disposition and prevention of future falls. On discharge, physical therapy is recommended across the continuum of care, including at home, to improve functional outcomes and reduce subsequent falls.

The 2014 National Osteoporosis Foundation guidelines recommend pharmacologic intervention for osteoporosis in any patient with a history of vertebral or hip fracture regardless of bone density findings. Bone densitometry is merely a tool to assess baseline and monitor treatment response; it is not necessary for the decision to initiate treatment. Realize that fragility fractures, i.e., those that result from a fall from a standing height or less, are themselves evidence of underlying weakened bone.

Bisphosphonates are the 1st line of treatment with concomitant Ca^{2+} and vitamin D replacement; smoking cessation, exercise, and avoidance of heavy alcohol intake are also important. Use of zoledronic acid with vitamin D initiated within 90 days of surgical hip repair shows significant reduction in mortality rates and vertebral fracture risks.

Older adults are very sensitive to drugs for the following reasons:

- Pharmacokinetics change with aging (affecting absorption and metabolism), causing increased drug concentrations.
- The volume of distribution for a drug increases because of the proportional increase of body fat compared to muscle.
- Excretion decreases, consistent with age-related decreases in renal and hepatic function.
- Pharmacodynamics of aging → **increased effects** of drugs, especially **opioids** and **BDZs**.

General rules for medication use in older adults:

- Start meds at a **low dose**—usually about 1/2 the dose required for the general population—and gradually titrate up to the normal therapeutic dose. (**Start low and go slow.**) If the patient gets into trouble at the therapeutic dose, try reducing the dose gradually—many older adults get satisfactory responses with lower doses.
- Assume that **any** adverse event is drug-related until proven otherwise.
- Always look to see if a prescribed drug is the cause of new symptoms before prescribing a new drug to treat the new symptoms.
- Look at a geriatric patient's medicine record for atypical antipsychotics if the patient is institutionalized and falling. (See [Delirium on page 5-13](#).) These are the most common causes of falls in nursing homes.
- Errors in self-administration increase dramatically once a patient is prescribed ≥ 3 medications. Geriatric patients may get confused with pills that look alike and with distinguishing between generic and brand names.

Some geriatric patients are dependent on low-dose BDZs or opiates. For these patients, attempt a slow withdrawal of these medications. These have often been prescribed as treatment for anxiety, insomnia, depression, chronic pain, and drug withdrawal. Slowly taper following these general principles: Taper BDZs over 3–6 months after switching to an equivalent dosage of a water-soluble BDZ, such as oxazepam (slower onset, less addictive potential). With opiate dependence, first determine the cause of pain (if any) and treat it with a nonnarcotic drug (e.g., acetaminophen, NSAID in patients without renal disease) or alternatives such as a lidocaine patch. The American Geriatrics Society recommends acetaminophen as the 1st line therapy for chronic noncancer pain. Limit dosage to ≤ 3 g in 24 hours to prevent toxicity. Avoid long half-life opiates in treating pain in the geriatric population.

Be familiar with the Beers criteria (updated every 3 years by the American Geriatric Society) to assess possible

PHARMACOLOGY

PREVIEW | REVIEW

- What should you do for an elderly woman who is on low-dose benzodiazepines for chronic anxiety?

inappropriate drug prescribing for older adults. The 2019 version includes examples of medication classes to consider avoiding in older adults and possible alternatives. Changes in this recent update included a call for caution using aspirin in patients 70 years of age or older for primary prevention of heart disease or colon cancer. Some of the other medication classes that warrant scrutiny in geriatric use are:

- First-generation antihistamines for allergies (e.g., diphenhydramine; alternative: cetirizine)
- Tricyclic antidepressants (e.g., amitriptyline; alternative: sertraline)
- Barbiturate antiseizure medications (e.g., phenobarbital; alternative: lamotrigine)
- Sleep aids (e.g., zolpidem; alternative: nonpharmacologic sleep hygiene)
- Anxiolytics (e.g., diazepam; alternative: buspirone)
- Narcotic pain relievers for acute moderate to severe pain (e.g., meperidine; alternative: tramadol)

Know that, in some studies, up to 75% of the geriatric population use herbal supplements. Many do not give information about supplements and over-the-counter medications unless you ask directly.

NUTRITION AND GASTROENTEROLOGY

PREVIEW | REVIEW

- What criteria diagnose malnutrition?
- What is the usual cause of fecal incontinence?

NUTRITION

We become less active as we age, and we lose muscle and body fat (more muscle than fat). Nutritional requirements are reduced, so generally, older people eat less. Malnutrition is still an issue, though, because of declining abilities and comorbid systemic disease.

≥ 2 of the following parameters diagnose malnutrition:

- 1) Unintentional weight loss (i.e., ≥ 10 lb/6 months)
- 2) Loss of cutaneous fat
- 3) Loss of muscle mass
- 4) Decreased functional status
- 5) Decreased calorie intake
- 6) Localized edema

When malnutrition is diagnosed, assess for modifiable risks (e.g., decreased access to nutritious food, denture or teeth problems, untreated medical illness, inability to perform IADLs [such as grocery shopping]).

The age-related decline in appetite and energy needs is often accompanied by dietary replacement of

carbohydrates with fats. Counsel geriatric patients to increase their daily fluid and fiber intake, obtain the recommended 0.8 g/kg protein/day, and eat healthy fats (i.e., monounsaturated, omega-3s)—such as olive oil, nuts, avocados, and fish. Vitamin supplements are useful in those with poor oral intake because this age group is especially vulnerable to deficiencies of vitamins D and B₁₂ and Ca²⁺.

For those > 65 years of age, the National Institute on Alcohol Abuse and Alcoholism and the American Geriatrics Society recommend lower-risk limits of no more than 2–3 drinks/day and/or 7 drinks/week, with lower amounts for people taking medications with alcohol-potentiated side effects.

DISORDERS OF SWALLOWING

Among older adults, disorders of swallowing are common, which can lead to dehydration, weight loss, aspiration pneumonia, and airway obstruction. Structural and functional causes include stroke, cancer, neurologic disorder (e.g., Parkinson, dementia, myopathy), gastroesophageal reflux disease (GERD), esophageal dysmotility, medication side effects (e.g., antipsychotics, antihistamines, antidepressants), and inflammation or infection. Evaluate with a video fluorographic swallowing study to identify the disorder and to test therapeutic and compensatory techniques. Endoscopy is sometimes needed to further evaluate the disorder. Treatment is targeted at the underlying condition and initiation of rehabilitative measures, which can include dietary modification and adjusted swallowing techniques. Severe forms of swallowing dysfunction can require bypass of the oral cavity with a feeding tube or IV total parenteral nutrition.

CONSTIPATION

Constipation in older adults is either due to functional chronic constipation or secondary to other causes. Functional causes include slow transit, dyssynergic defecation, and irritable bowel syndrome with predominant constipation. Secondary causes include metabolic derangement, such as hypothyroidism; neurologic disorders, such as stroke and Parkinson disease; and medication side effect, especially from opiates. Treat with dietary and lifestyle modifications. Use of laxatives, stool softeners, enemas, and biofeedback are alternative options.

FECAL INCONTINENCE

Geriatric fecal incontinence is usually caused by fecal impaction and secondary overflow incontinence. The impaction is normally a result of lax muscles and neuronal degeneration. Typical presentation is an older adult with complaints of diarrhea and abdominal discomfort who has hard stool in the rectal vault on physical exam. Treatment is disimpaction and a subsequent bulking agent such as psyllium.

ENDOCRINE SYSTEM

PREVIEW | REVIEW

- What is the median age of menopause?
- What is andropause?
- What is the typical presentation of Paget disease?
- What complications are geriatric patients specifically at risk for developing as they are being treated for diabetes?
- Metformin should not be given to patients with estimated glomerular filtration rate below what calculated level?
- What are the symptoms of apathetic hyperthyroidism?

AGE-RELATED DEFICIENCIES

The only **specific** female hormonal change that occurs with aging is **ovarian failure**. The median age of menopause is 51 years of age.

The hypothalamic-pituitary-gonadal axis is also disturbed in men, but not as predictably as in women. In both sexes, the adrenal zona reticularis declines in synthesis of dehydroepiandrosterone (DHEA) and the pituitary secretion of growth hormone wanes (and, subsequently, also levels of insulin-like growth factor-1 [IGF-1]). Many other hormones are produced in normal amounts but do not function as well.

Many of these hormone perturbations are thought to occur with the aging process, but none are conclusively linked except ovarian failure. Growth hormone reduction appears to coincide with loss of muscle mass and strength; supplementation is discouraged because it has too many side effects.

The pineal gland's **melatonin** production is disrupted with aging. This can cause poor sleep and insomnia. Melatonin supplementation can help some patients.

Aging patients have reduced clearance of **thyroid hormone**, so thyroid hormone replacement for hypothyroidism can be started at a lower than usual dose. Thyroid-stimulating hormone (TSH) increases with age, especially in women (see the **Endocrinology** section), so a rising TSH without an accompanying decrease in T_4 levels does **not** merit treatment for hypothyroidism. However, most experts recommend starting treatment if the TSH > 10 mU/L.

Testosterone production decreases in the aging male, but the effect is variable. However, the **rate** of sperm production is stable from 20–70 years of age. Follicle-stimulating hormone (FSH) and luteinizing hormone (LH) also decline, but disproportionately compared to the more drastic decline in testosterone. The low testosterone production is most likely due to declining testicular function and not to hypothalamic disease.

Low testosterone is believed to be related to decreases in the following, although direct causation has not been proven:

- Sexual function
- Bone mineral density
- Muscle mass (and increased fat)
- Muscle strength
- Mentation

These symptoms, in association with reduced free testosterone, are sometimes called **andropause**. The Endocrine Society set forth treatment guidelines in 2018 for symptomatic males with testosterone deficiency who have a serum testosterone < 264 ng/dL (9.2 nmol/L) and with a treatment goal of 350–600 ng/dL (14.1–24.5 nmol/L). If there are no symptoms of low testosterone, do **not** screen. Do not treat men with low levels if they do not have symptoms. Testosterone promotes red cell proliferation and is trophic to prostate tissue. Men receiving testosterone therapy need to have periodic monitoring of their blood for polycythemia and rapid rises in PSA (prostate specific antigen).

Vitamin D deficiency is common in older adults because of decreased intake, decreased absorption (reduced melanocytes), reduced sun exposure, and poor conversion of storage to the active form of vitamin D. Vitamin D supplementation in older adults for the prevention of osteoporosis is controversial, but it appears to play an important role in the prevention of falls. Calcium supplementation in geriatric patients without osteoporosis is likewise controversial. Fracture risk appeared decreased in two meta-analyses with the use of high-dose vitamin D (≥ 800 IU/day; 2012) and when vitamin D was given together with calcium (2009).

BONE

Osteoporosis

Most women > 80 years of age have osteoporosis. According to the 2018 U.S. Preventive Services Task Force (USPSTF) guidelines, screen women ≥ 65 years of age with a dual energy x-ray absorptiometry (DEXA) scan at least once. If the patient has any risk factors for vitamin D deficiency (especially poor diet or lack of sun exposure), check stores by measuring 25-OH-D.

Paget Disease

Paget disease of bone occurs in about 1% of people > 40 years of age in the U.S. It is usually diagnosed after discovering an isolated elevation of alkaline phosphatase in an asymptomatic person. The disease results from a mismatch of osteoclast and osteoblast activity (e.g., remodeling), causing changes seen on x-ray, bone scan, CT, or MRI in localized areas. The bones are more brittle, hypervascular, and larger—leading to arthritis, high-output heart failure, nerve compression, and hearing loss (if the skull is involved).

Etiology: There is a clear genetic predisposition; other than that, the etiology is unknown.

Diagnosis is strongly suggested by a cotton-wool appearance on plain skull films that results from the disordered bony trabeculae and bone scan results. Patients with Paget disease have focal areas of marked increased uptake.

In most patients, treatment is neither required nor curative. However, treatment is often needed if heart failure, bone pain, nerve compression, or hearing loss develop.

Treatment: Bisphosphonates (e.g., risedronate, tiludronate, alendronate) given orally are effective. Give IV zoledronic acid for severe disease. Calcitonin is an alternative if the patient is intolerant to bisphosphonates.

DIABETES

With aging, there is **decreased** carbohydrate tolerance, with a slight increase in fasting glucose. Both insulin sensitivity and production decline. Older adults with diabetes get the same micro- and macrovascular complications as younger patients, but this patient group must be **specifically watched** for life-threatening hypoglycemia and drug-drug interactions.

Geriatric patients with hypoglycemia present more often with **cognitive impairment** rather than tremulousness and sweats. The most likely causes of hypoglycemia are **insulins** and the **insulin secretagogues** (e.g., sulfonylureas, meglitinides). **Glyburide** has about 2× the incidence of hypoglycemia in older adults compared to glipizide (27% vs. 14%). Sulfonylureas are not recommended by the American Diabetes Association (ADA) as 1st line medications in older adults.

Be cautious with **metformin** use in older adults because of the high prevalence of **chronic kidney disease** in this population and the increased risk of lactic acidosis (a side effect of metformin). Assess the estimated glomerular filtration rate (eGFR) prior to use of metformin in patients and do **not** give the drug to any patient with an eGFR < 30 mL/minute/1.73 m², regardless of age. Hemoglobin A1c levels ≤ 8% are acceptable in older adults with comorbidities, importantly to avoid the risk of hypoglycemia, which can affect cognition and increase fall risk.

Thiazolidinediones enhance insulin sensitivity and can help preserve some function of pancreatic beta cells. (See more on thiazolidinediones in the [Endocrinology](#) section.) Pioglitazone or rosiglitazone can cause fluid retention and precipitate heart failure. Pioglitazone can reduce recurrence of stroke but has a higher risk of bone fractures and bladder tumors.

Remember to lower insulin doses as renal function declines with age, especially as eGFR drops < 50 mL/minute/1.73 m².

THYROID DISEASE

Patients > 60 years of age with thyroid disease are more likely to have vague symptoms that can indicate either hyper- or hypothyroidism. Features of classic **hyperthyroidism**, such as hyperreflexia, heat intolerance, tremor, nervousness, polydipsia, and increased appetite, are often absent in older adults. **Apathetic hyperthyroidism, also called apathetic thyrotoxicosis**, can be seen in elderly patients and presents as apathy, fatigue, anorexia/weight loss, and tachycardia. **Subclinical hyperthyroidism** is diagnosed when TSH is low in the presence of normal serum-free T₄ and T₃; symptoms of mild hyperthyroidism may be present or absent. Confirm this biochemical diagnosis by repeating these studies at 1–3 months. If the TSH is not persistently below 0.1 mU/L and the patient is not at high risk for complications (e.g., heart disease, osteoporosis), follow with observation and repeat TSH and free T₄ and T₃ levels every 6 months.

Atrial fibrillation and anorexia can occur in older patients with **hypothyroidism**; these symptoms are rarely seen in younger patients with hypothyroidism and are possibly related to overtreatment of hypothyroidism in the geriatric population. Atrial fibrillation is more commonly seen in hyperthyroidism.

HORMONE REPLACEMENT THERAPY

According to the North American Menopause Society (NAMS), for women < 60 years of age or within 10 years of menopause, the risk:benefit ratio favors the use of hormone replacement therapy (HRT) to ease troubling vasomotor symptoms (e.g., hot flashes, night sweats) and mitigate bone loss or fracture in at-risk women. However, the risk:benefit ratio of HRT is not as favorable for women > 60 years of age or those with menopause that began more than 10–20 years prior to starting HRT because of increased risk for heart disease and stroke, venous thromboembolic disease, and dementia. For women with resistant vasomotor symptoms or bone loss, HRT is sometimes continued past 60 years of age and reassessed periodically.

Cessation or continuation of HRT after 60 years of age is best approached on an individual basis by assessing risks, considering the formulation and administration route (e.g., intravaginal instead of oral), and aiming to optimize the shortest duration and lowest dose of HRT. Individualization is tailored to risks for breast cancer, venous thromboembolism, stroke, and osteoporosis. For women with a uterus on combination (i.e., estrogen and progesterone) therapy, stopping HRT at ~ 5 years is recommended. Women on estrogen alone without a uterus can sometimes continue HRT for a few years longer if necessary because therapy-related increased risk for breast cancer has not been shown in this patient subgroup.

The Beers criteria consider hormone therapy in the form of pills and patches as a medication class potentially inappropriate for older adults. Topical estrogen creams are alternative treatments for vaginal dryness. Vasomotor symptoms can otherwise be alleviated by nonhormonal drugs such as gabapentin, selective serotonin reuptake inhibitors (SSRIs), and serotonin-norepinephrine reuptake inhibitors (SNRIs).

See more on hormone replacement therapy in the [Women's and Men's Health](#) section.

NERVOUS SYSTEM

PREVIEW | REVIEW

- What are the main features of delirium? Precipitating factors?
- How is delirium different from sundowning?
- What is the recommended initial therapy for elderly patients with delirium? What are some options for drug therapy, and what are their associated risks?
- How is dementia different from delirium?
- What are the 3 most common causes of dementia in the U.S.?
- When do patients derive the greatest benefit from Alzheimer disease treatment?
- What are common symptoms of geriatric depression?
- What are common side effects of medications for depression?
- Name some medications typically linked to insomnia in older adults.
- What is the role of benzodiazepines (BDZs) in the treatment of insomnia?
- What dangerous side effects are sometimes seen with both BDZ and non-BDZ sleep agents?
- Which secondary conditions can cause restless leg syndrome?
- What type of dizziness is caused by deficits in visual, hearing, orthopedic, and neurologic functioning? What can help the symptoms?
- Which maneuver helps identify benign paroxysmal positional vertigo?

DELIRIUM

Delirium is a transient alteration in consciousness related to systemic factors. It is a common problem

in older adults. Patients with underlying dementia and/or stroke are at highest risk. The main features of delirium are:

- **Abnormal** attention span (e.g., easily distracted)
- **Disorganized** thinking (e.g., may hallucinate)
- **Altered** consciousness (with increased or decreased mental activity) that **fluctuates** during the day and typically worsens at night

Common precipitating causes of delirium include drugs (especially psychoactive medications), poor nutritional status, and acute illness (e.g., infections, volume depletion). Know that physical restraints and bladder catheters can incite delirium as well. In the post-op period, uncontrolled pain is a major cause, especially in geriatric patients with hip fractures.

1/3 of cases are caused by drugs. Medications should be particularly suspected in patients taking 5 or more drugs, called polypharmacy. Be **especially** aware of meperidine, NSAIDs, any new antimicrobial, diphenhydramine, all cardiovascular drugs and antidepressants, antiemetics, baclofen, H₂ receptor blockers, sleep inducers, and herbals (e.g., St. John's wort, valerian root). Also, acute discontinuation of alcohol, BDZs, SSRIs, and pain medications can cause **withdrawal** delirium.

Differentiate delirium from sundowning. **Sundowning** is a disturbance in behavior that occurs predictably in the evening among some patients who live in chronic care environments. It does not occur with a precipitating illness and is not delirium. With sundowning, usually the caregivers can tell you that the patient predictably deteriorates at night.

Know that in older adults, delirium can sometimes be the only manifestation of illness. Thoroughly evaluate any patient who becomes delirious for a serious precipitating cause, such as an underlying UTI or pneumonia.

Evaluate the confused patient with an objective tool such as the MMSE or the CAM ([Table 5-1 on page 5-5](#)). On the physical exam, focus on identifying an **underlying acute illness** with the potential to cause confusion (e.g., infections, hypoglycemia, drug abuse, hepatic failure, uremia, head injuries, stroke, seizures). Work up the central nervous system (imaging and lumbar puncture [LP]) if no cause is found after a thorough search.

Initial treatment of delirium is supportive, with focus on diagnosis and treatment of the underlying cause. Calendars and orienting signs, night-lights, newspapers, a radio, glasses, and hearing aids help stabilize and prevent decompensation. It is also necessary to minimize daily stress.

Pharmacologic treatment of delirium in older adults is challenging because the medications themselves can worsen the confusion. Low-dose haloperidol is an option, but watch for prolongation of the QT interval.

This increases the risk of an arrhythmia known as *torsades de pointes*, a polymorphic ventricular tachycardia. Do **not** use haloperidol in patients with parkinsonism as it can exacerbate parkinsonian symptoms. Alternative drugs include the atypical antipsychotics: risperidone, olanzapine, and quetiapine. These drugs have fewer short-term side effects but increased mortality among older adults have been reported (e.g., with their use in patients with dementia and those with pneumonia). Do not use BDZs in delirious patients because they make patients more confused and drowsy.

Use of a sitter and other nonpharmacologic interventions are always the best 1st choices. Remember to avoid physical restraint of geriatric patients at all costs because it precipitates delirium and increases the risk of injuries.

DEMENTIA

Patients with dementia have a progressive deterioration of cognitive function that is mostly insidious and chronic—but **without** altered consciousness, as with delirium. The deterioration can be either very gradual or stepwise (depending upon the underlying cause). The cognitive impairment presents as:

- Difficulty learning and remembering new information
- Decreased problem-solving of both simple and complex tasks
- Decline in spatial organization, which can lead to getting lost
- Trouble with impulse control, which can lead to unusual behavior

Some decline in cognition occurs with normal aging, but in contrast to dementia, memory loss seen in aging is mild, does not affect the patient's daily living, and is not especially noticeable by family.

Most patients in the U.S. with dementia are diagnosed with **Alzheimer** disease (80%), **multiinfarct** dementia, or Lewy body dementia (LBD). Dementia is a common development in patients with Parkinson disease as well. See the **Neurology** section for a more thorough discussion of dementia.

Depression can look like **dementia**, especially in older adults. A couple of ways to tell the **difference**: Depressed patients often present complaining of memory loss, while patients with dementia are brought in by family or friends. Depressed patients often have a depressed affect and slowing with completion of the MMSE or Mini-Cog, while patients with dementia have a more normal affect. Assessment tools can help identify the true cognitive defects of dementia. A score of < 24/30 points on the MMSE is consistent with dementia/delirium. See more under **Depression**.

The position of the USPSTF on screening for dementia is that there is insufficient evidence to recommend for or against it.

First-line treatment for Alzheimer disease is the cholinesterase inhibitors (CIs), donepezil (Aricept), rivastigmine (Exelon), and galantamine (Razadyne). Best results with CIs are achieved in mild-to-moderate Alzheimer dementia, but other causes of dementia (e.g., multiinfarct, LBD) sometimes also improve. CIs do not help patients with Huntington disease, however. CIs can be combined with memantine (Namenda), an *N*-methyl-*D*-aspartate receptor antagonist.

CIs provide a small benefit and help some patients carry out their activities of daily living (ADLs). CIs may be particularly useful in controlling behavioral problems in patients with dementia. There are conflicting data on their long-term effects. Not every patient receives benefit. The combination of CI plus memantine appears to be better than CI alone.

CI side effects often involve the gastrointestinal tract (i.e., nausea, vomiting, diarrhea, anorexia, weight loss). Severe bradycardia due to atrioventricular (AV) block from excessive acetylcholine has been reported. The bradycardia from CIs can occur with or without syncope.

The benefit from treating Alzheimer disease is greatest early in the course of the disorder; therefore, stop CIs in patients with severe dementia or if no improvement is noted.

LBD is marked by progressive cognitive decline with concomitant hallucinations, sleep disturbances, and parkinsonian features. Use CIs. Treatment of LBD with neuroleptics can bring on a paradoxical psychosis and worsening of parkinsonism. The same can occur with the use of dopaminergic agents, making behavioral therapies preferable to medications when possible.

The American Academy of Neurology (2001; reaffirmed 2004) recommends checking TSH and B₁₂ for metabolic reversible causes in the evaluation of dementia.

DEPRESSION

Depression is the **most common** mental problem in the geriatric population. It is particularly likely to occur in those who live in institutionalized settings and/or have chronic diseases, especially just after a severe sickness or in states of chronic pain. Depressed older adults (especially men) complete 25% of the successful suicide attempts in the U.S.

Look for dysphoria, psychomotor slowing, anorexia, weight loss, and multiple aches and pains. **Insomnia** frequently occurs with depression, especially in older adults, although it is not known whether it is a symptom or a cause. Depression-associated **delusions** are more common in elderly patients than in the general population. Pay special attention to the elderly man with depressed mood, hopelessness, chronic pain, and insomnia because his suicide risk is particularly high. The best predictor of future suicide is a previous attempt. Other risk factors include male sex, substance

abuse, psychiatric disorder, recent major stressor, family history of suicide, and age > 45 years. Half of suicides in 2016 involved a firearm, and access to a firearm increases the risk of successfully completing suicide.

A host of substances and drugs can exacerbate depression, including alcohol, BDZs, opiates, and barbiturates. Untreated thyroid disease, diabetes, and pain are organic causes. Always assess thyroid function, especially if symptoms and signs of thyroid disease are present, prior to initiating antidepressant therapy.

Treatment is usually psychotherapy as a standalone modality or combined with antidepressants; electroconvulsive therapy can be considered in severe cases. **Exercise** helps, too. SSRIs are the 1st line drugs because they have fewer side effects than other choices. Watch for the side effects of hyponatremia and tremor in elderly patients on SSRIs. SSRIs can cause sexual dysfunction (in about 50% of patients) and sedation (< 20%). Patients intolerant of one SSRI can often be switched to another. See [Table 5-2 on page 5-16](#) for treatment options.

As with most medications, when using antidepressants in older adults, **always** start with low doses (typically 1/2 the normal dose) and increase **slowly** with the goal of eventually reaching the normal therapeutic dose. See patients (or call them) within 2 weeks of starting a medication. It takes about 8 weeks to see improvement; 6–12 months is the usual duration of treatment.

Depression or reduced sociability can be a sign of elder mistreatment. Victims are unlikely to report mistreatment. Unexplained injuries or a low BMI prompt you to evaluate for possible elder mistreatment. Routinely ask older patients about mistreatment and whether they feel safe.

SLEEP DISTURBANCES

Sleep disturbance is a common problem in geriatrics; normal aging is associated with more frequent awakenings. Other disturbances include difficulty falling asleep (> 30 minutes), waking too early, and feeling generally unrestored. When the disturbance also causes problems for the patient during the day (e.g., poor concentration, moodiness, sleepiness, fatigue), it is classified as **insomnia**.

Sleep disturbances that are **not** insomnia:

- Some people can sleep well for only a few hours and have no problem functioning the next day. These patients simply have **short-duration sleep**.
- People who have chosen not to sleep at night (due to work or other reasons) and easily fall asleep during the day are classified as having **insufficient sleep** (a.k.a. **sleep deprivation**), not insomnia.

Insomnia, especially in older patients, is associated with worsening of hypertension, heart disease, lung disease, urinary incontinence, chronic pain, and depression.

When taking the patient's history, focus on characterizing the sleep disturbance (sleep logs help) and identifying any untreated comorbidities and/or precipitants (e.g., napping stress, newly stopped or started medications, alcohol, caffeine, nicotine, depression).

Medications specifically linked to insomnia include corticosteroids, β -blockers, and β -agonists. Stopping sedatives or pain medications can also cause insomnia.

Labs are recommended only to diagnose potential comorbidities (e.g., hyperthyroidism, restless legs). Sleep studies are unnecessary until a patient has failed to respond to conservative management.

Direct treatment toward improving any poorly managed comorbidities and advising the patient on **good sleep hygiene**:

- Set a schedule for sleep and stick to it.
- Get in the bed only when you're sleepy, and get up when you're rested.
- Minimize excessive light and sound in the bedroom.
- Exercise during the day, at least 4 hours before bedtime.
- Maintain a bedroom environment and ambient temperature conducive to sleep.
- Avoid caffeine, nicotine, alcohol, and excessive intake of fluids near bedtime.
- Eat dinner or an evening snack to prevent bedtime hunger.
- Do not fight sleep. If you cannot sleep for > 20 minutes, get up and do something relaxing (e.g., reading, listening to music). Avoid bright lights, electronic screens, or TV.

The **most effective** treatment in patients with uncomplicated insomnia is **behavioral**—not pharmacologic. Elderly patients are especially susceptible to bad outcomes from sleep drugs.

Ramelteon (Rozerem), a melatonin agonist, improves sleep for some patients. It is a **good choice** for older adults, albeit with variable efficacy.

BDZs and non-BDZ insomnia drugs (such as zolpidem [Ambien], zaleplon [Sonata], and eszopiclone [Lunesta]) in **older adults** can cause confusion, wandering, imbalance, and daytime grogginess—hence, **avoid** both drug classes in geriatric patients.

Stay away from 1st generation antidepressants (e.g., amitriptyline), diphenhydramine, haloperidol, and barbiturates because of side effects.

RESTLESS LEG SYNDROME

Restless leg syndrome (RLS) is a common sleep disorder in older adults (prevalence = 20% in those > 80 years of age). The hallmark of RLS is leg discomfort +/- paresthesias at rest, relieved immediately with movement. Usually, pain is deep seated and localized below the knees. Symptoms are worse in the evening and at night.

RLS can be primary or caused by other conditions, such as iron deficiency (even without anemia), dialysis, diabetic neuropathy, multiple sclerosis, and Parkinson disease. Make sure that the patient's complaints aren't due to akathisia caused by medications (e.g., phenothiazines, SSRIs).

Diagnosis is based on clinical history, a normal neurologic exam, and absence of kidney disease. Always check ferritin level to rule out iron deficiency, even if the patient does not have anemia.

Table 5-2: Antidepressants and SSRIs

Drug	Half-Life (Hours)	Mechanism of Action / Blocks	Drug of Choice for...	Notes	Caution (!) in Patients...
Fluoxetine* (Lexicomp)	72	SSRI		Can cause anxiety and insomnia	With insomnia
Paroxetine (Paxil, Pexeva)*	20	SSRI		Most anticholinergic of the SSRIs Sedating in some Weight gain more common Worst for SSRI withdrawal symptoms	In whom anticholinergics are to be avoided With insomnia
Sertraline (Zoloft)*	25	SSRI		GI discomfort is common.	With insomnia With irritable bowel
Fluvoxamine (Luvox)*	15	SSRI	Patients with agitation, insomnia, or obsessive-compulsive disorder	Most sedating of the SSRIs	With irritable bowel
Citalopram (Celexa)*	35	SSRI		Can cause anxiety and insomnia, N/V, headache, and QT prolongation	With long QT syndrome
Escitalopram (Lexapro)	30	SSRI		S enantiomer of citalopram; can cause QT prolongation	With long QT syndrome
Nefazodone (Serzone)	3†	SSRI and 5-HT ₂ Has anti- α -adrenergic activity	Patients with insomnia; to maintain sexual activity	Maintains sleep architecture Sexual dysfunction unlikely	On BDZs or antihistamines (interact with cytochrome P-450 system)*
Venlafaxine (Effexor)	4	SSRI and norepinephrine reuptake and some dopamine reuptake			With insomnia; With HTN—usually increases blood pressure, so not used in these patients
Duloxetine (Cymbalta, Irenka)	12	SSRI and norepinephrine reuptake and some dopamine reuptake	Patients with chronic pain syndromes	Also indicated for fibromyalgia	
Bupropion	15	Reuptake of dopamine and some norepinephrine		Sedation and sexual dysfunction unlikely	With insomnia With HTN—may increase blood pressure
Mirtazapine (Remeron, Remeron SolTab)	20	Presynaptic α_2 -receptor (increases serotonin and norepinephrine release) and 5-HT ₂ and 5-HT ₃	Patients with insomnia; to maintain sexual activity	Agitation and sexual dysfunction unlikely Good for insomniacs Weight gain more common	Most anticholinergic of all these With HTN—may increase blood pressure

Note: Bupirone is a 5-HT_{1A} agonist that can be combined with an SSRI to decrease the dose or improve efficacy.

* All the SSRIs tend to cause agitation, sedation, and sexual dysfunction. Pure SSRIs are not likely to increase blood pressure.

† Half-life is higher than this in older adults, especially women.

‡ Can use loratadine (Claritin) or lorazepam (Ativan) with nefazodone

Treatment of RLS:

- **Intermittent symptoms:** Try nonpharmacologic therapy first—iron-replacement therapy; mentally stimulating activities (such as video games or crosswords); avoidance of caffeine, nicotine, and alcohol. Then, if needed, try 1 of the following:
 - Dopamine agonists (e.g., pramipexole or ropinirole) are usually the drugs of choice.
 - Levodopa: Be careful—can cause augmentation (worsened symptoms or rebound).
 - BDZs (generally avoided)
 - Low-potency opioids (generally avoided)
- **Daily symptoms:** Try nonpharmacologic therapy first, then dopamine agonists, gabapentin, and, lastly, low-potency opioids.
- **Refractory symptoms** to dopamine agonists: Try gabapentin, a different dopamine agonist, combination therapy, then tramadol, and, lastly, high-potency opioids.

PERIODIC LIMB MOVEMENT OF SLEEP

Periodic limb movements of sleep (PLMS) are periodic episodes of repetitive movements lasting 1–10 seconds separated by intervals of 20–40 seconds. They occur in 60% of older adults and 80% of patients with RLS. The diagnosis is made on polysomnography showing excessive limb movement beyond what is expected as physiologic limb movement of sleep. Treatment of PLMS uses the same approach as RLS.

DIZZINESS

Dizziness is common in older adults but is **not** a normal consequence of aging. Probe patient complaints of dizziness diligently, remembering the risks and consequences of falls and fractures in this age group. Take a good **history** (more accurate in making the diagnosis than physical exam, labs, or studies) to determine which of the following the patient is describing:

- Vertigo: spinning, whirling, or moving of either the patient or the environment that is often worse with head movement and can occur in spells (days to weeks), then eventually resolves. A complete discussion about the workup of vertigo is included in the **Neurology** section.
- Presyncope: almost fainting or blacking out while either standing or seated (not supine), possibly with sweating, a sensation of warming, visual blurriness, and nausea
- Disequilibrium: imbalance with standing and walking, especially with turning
- Nonspecific dizziness: unable to characterize into one of the other categories

Presyncope: Dizziness that sounds like presyncope or faintness should be taken seriously and evaluated with a cardiovascular workup, especially if the patient has known heart disease, palpitations, or a history of true syncope. However, some causes of presyncope can be diagnosed by the history and physical examination (e.g., postural hypotension).

Multisensory deficits: Think about multisensory deficits as a cause for disequilibrium in the patient with a mix of visual, hearing, orthopedic, and neuropathic impairments. (This form of dizziness is sometimes called benign disequilibrium of aging.) Multisensory deficits causing disequilibrium and benign positional vertigo are common. In geriatric patients, the cause is more often **vestibular** than in other patient groups. The history is of feeling unsteady, which improves with a walker or when someone holds the individual's arm. Treat disequilibrium by maximizing support for each sensory impairment and providing assistance devices (e.g., canes, walkers).

Benign paroxysmal positional vertigo (BPPV) presents as recurrent (lasts for weeks in spells), short-lived (< 1 minute) episodes of vertigo that predominantly occur when the patient changes head position. The vertigo can be bad enough to cause nausea and vomiting, but otherwise, the patient has no symptoms (e.g., hearing loss, headaches). BPPV can occur with aging, head trauma, labyrinthitis, giant cell arteritis, migraine, hypertension, hyperlipidemia, and stroke. Be sure to take a good history in the dizzy elderly patient to determine whether symptoms of vasculitis or polymyalgia rheumatica are also present (e.g., weight loss, fevers, musculoskeletal pain).

In **uncertain** cases, BPPV can be diagnosed by the Dix-Hallpike test. This maneuver involves turning the patient's head, then rapidly tilting the patient backwards for 30 seconds, then upright again, with subsequent observation for nystagmus. Repeat the maneuver with the head turned in the opposite direction. A positive test is visible nystagmus in either the recumbent or the upright position. Warn patients ahead of time that the maneuver sometimes triggers nausea and vomiting.

In BPPV, the differential diagnosis includes **central causes of vertigo** such as cerebellar lesions (i.e., strokes, masses). So, if the history is suggestive (e.g., diplopia and ataxia or cerebellar signs), do further workup with imaging and electronystagmography (i.e., water calorics).

Treatment of BPPV can be accomplished through maneuvers; Epley or Semont. Both are equivalent in efficacy and designed to reposition the misplaced otoliths thought responsible for the vertigo. The maneuvers are extensions of the Dix-Hallpike test. Alternatively, home exercises can be prescribed that aim to have the same result (but are less effective). No drugs are used to treat BPPV.

CARDIOVASCULAR SYSTEM

Walking > 4 hours per week is associated with a dramatic decrease in cardiovascular-related hospitalizations in persons > 65 years of age.

Isolated systolic hypertension is a common finding in elderly patients. It increases the risk of myocardial infarction and stroke 2–4×. Several studies show these patients benefit from treatment as long as the diastolic pressure does not fall below 60 mmHg. Low diastolic pressures have been associated with increased cardiovascular events.

In older patients with hypertension, start with about 1/2 the standard dose of any 1 of the following:

- 1) Thiazide diuretics (e.g., chlorthalidone)
- 2) Dihydropyridine calcium channel blockers (e.g., amlodipine)
- 3) Angiotensin-converting enzyme (ACE) inhibitors/angiotensin II receptor blockers

Avoid β-blockers for treatment of **systolic** hypertension in **older adults** because they are less effective than other treatments and have been associated with increased mortality.

The 6-month mortality rate after a myocardial infarction (MI) increases with age (e.g., from 4% at 66 years of age to 12% when > 80 years of age), with 1st MI, with thrombolytics, and when discharged from the hospital. Only about 75% of eligible patients receive aspirin on discharge from the hospital and about 1/3 are referred for cardiac rehabilitation—both interventions after MI markedly reduce the risk of death. Be sure to prescribe an antiplatelet drug to these patients and ensure their participation in cardiac rehabilitation!

Heart failure: The prevalence of heart failure (HF) is increasing due to the aging of the population. It is the **#1 cause of hospitalizations** in older adults. (#2 is pneumonia.)

Treat HF itself primarily with diet, diuretics, β-blockers (specifically metoprolol, carvedilol, or bisoprolol), and ACE inhibitors. Spironolactone lowers mortality for systolic HF. Digoxin is indicated only for more severe HF and reduces hospitalizations but **not** overall mortality. Isosorbide dinitrate and hydralazine lower mortality, especially in African Americans with systolic HF. The use of NSAIDs is an important precipitant of HF in older patients who already have risk factors for HF.

Note: ACE inhibitors, β-blockers, and low-dose spironolactone lower mortality rates in HF. If you prescribe spironolactone, follow K⁺ closely. Spironolactone provides benefit in patients with Class III or IV heart failure with ejection fraction (EF) of ≤ 35%.

PULMONARY SYSTEM

PREVIEW | REVIEW

- What is an important comorbidity to know about in treating asthma?
- What happens with spirometry results as we age?

ASTHMA

Geriatric patients with asthma can have long-standing disease acquired in childhood or young adulthood, or asthma that developed during aging adulthood. Around 8% of adults > 65 years of age are diagnosed with adult-onset asthma. Be aware that it is **commonly misdiagnosed** as chronic obstructive pulmonary disease (COPD) because COPD is more likely to occur in this age group.

Risks for development of adult-onset asthma are the same as for younger patients: allergens and irritants (e.g., tobacco smoke, occupational vapors, air pollution).

Comorbidities are important—especially coronary artery disease because treatment of asthma with β-agonists can cause myocardial ischemia. Also, β-blockers used as anti-hypertensive drugs can exacerbate airway obstruction, although this is primarily the case with older, nonselective β-blockers.

Asthma in the older patient can present the same as in the younger patient, although older patients tend to have **fewer symptoms** with the same amount of disease. Definitive diagnosis is made with **spirometry**, when the FEV₁ and FEV₁/FVC are reduced.

A response to bronchodilators is still expected for the diagnosis of airway reversibility, as per the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria: > 200 mL increase in FEV₁ after bronchodilator and > 12% of predicted.

Separating COPD and COPD with overlap syndrome from asthma alone can be difficult in geriatric patients, where rates of underlying COPD are high. All lung volumes decrease with age and the chest wall gets stiffer; therefore, even in an elderly patient with no prior smoking history, the PFTs tend to overdiagnose airflow obstruction. Know: Reversible obstruction is consistent with asthma, and a low diffusing capacity of the lungs for carbon monoxide (DLCO) with airflow obstruction is consistent with emphysematous COPD.

Bronchoprovocation is used to diagnose asthma in older patients with normal spirometry, the same way it is used in younger people.

Management of geriatric asthma is the same as for younger patients, but theophylline is not recommended, even as an alternative drug, because of the significant potential for toxicity.

SLEEP APNEA

Think about sleep apnea as a potential cause of reduced cognition in geriatric patients. Know that apnea that results in poor sleep and excessive daytime somnolence carries a higher rate of morbidity in patients who are frail and already prone to falls. Untreated, sleep apnea in older adults carries an increased risk for ischemic stroke and coronary artery disease. Diagnosis and management is the same as in younger patients.

UROLOGIC SYSTEM

PREVIEW | REVIEW

- Is urinary incontinence considered a normal consequence of aging?
- What are the 4 types of incontinence?
- What is the best treatment for urge incontinence?
- What is the best initial treatment for stress urinary incontinence?
- What is a common cause for incomplete bladder emptying in males?
- What is the role of bladder catheterization in the treatment of geriatric incontinence?
- What are symptoms of UTI in older adults?
- How is UTI in older adults treated?

URINARY INCONTINENCE

Normal micturition is dependent on an intact neurologic pathway from the brainstem to the bladder, which causes relaxation of the sphincter muscle's tonic contractile state just milliseconds before contraction of the detrusor (bladder muscle). Additionally, voluntary control of micturition requires communication between the cerebral cortex and the brainstem.

Urinary incontinence, although a common geriatric problem, is always considered a pathologic condition that is **not** a normal consequence of aging! Always consider the possibility that the patient has a serious underlying condition responsible for the leakage.

Normal, age-related changes to the urinary tract include **decreased** flow rate, decreased bladder capacity, and **increased** residual volume. As a function of these changes, it is normal for patients to get up once during the night to void. Patients can have **functional incontinence** caused by physical or mental impairment that limits their ability to reach the bathroom in time.

Urinary incontinence can be thought of as either a storage problem (detrusor or bladder over- and under-contraction) or an outflow problem (outlet obstruction or incompetence). Remember too that lifestyle factors—obesity, excess beverage consumption (especially carbonated, caffeinated, and alcoholic drinks), smoking, and for some, constipation—can contribute to or worsen incontinence.

There are 4 types of urinary incontinence:

- 1) **Urge** = leakage (a lot or a little) with the feeling of urgency
- 2) **Stress** = leakage with increased intraabdominal pressure (e.g., coughing, sneezing)
- 3) **Mixed** = leakage with both an urgency and increased intraabdominal pressure
- 4) **Incomplete bladder emptying** (overflow) = leakage (a lot or a little) after voiding

Urge Incontinence

Urge incontinence (UI) is a **common** cause of geriatric incontinence. With UI, there is passage of either **small** or **large** amounts of urine, with a sense of urgency often set off by a **precipitating stimulus** (e.g., hearing running water, unlocking the door to the house, entering cold environments).

UI is related to overactive bladder. They are both caused by uncontrollable bladder contractions (**detrusor instability**)—usually caused by **CNS problems** (termed detrusor hyperreflexia) but sometimes caused by **cystitis**.

Detrusor hyperreflexia is due to progressive loss of communication between the frontal lobes and the micturition center in the brainstem. As the bladder loses the modulating influence from the brain, it tends to spasm more often.

After ruling out a bladder infection, treat UI with behavioral therapy, called bladder training. When an urge to void becomes intense, the patient is instructed to attempt relaxation techniques that help the urge subside and allow short-term voiding delay. Once the urge is controlled, the patient can walk calmly to the restroom and urinate. The eventual goal is to delay voiding to every 4 hours with no interval leakage.

Bladder training is more effective than the more commonly prescribed therapy of antimuscarinic agents (e.g., oxybutynin, tolterodine, fesoterodine, trospium, darifenacin, hyoscyamine, tricyclic antidepressants), all of which relax the bladder muscle and are equivalent in efficacy. They have **anticholinergic** side effects (e.g., dry mouth, tachycardia, constipation).

Remember that anticholinergics can precipitate acute angle-closure glaucoma! Also, do not use them for incontinence in patients who are taking cholinesterase inhibitors for dementia because the combination **accelerates** cognitive decline. Even so, these antimuscarinic agents are helpful when used as an adjunct to bladder training—short term, as needed. Consider a β_3 -agonist, mirabegron. Also consider intravesicular botulinum toxin injections in refractory cases.

Pelvic muscle exercises (Kegel exercises) and lifestyle modifications such as weight loss in obese patients are also helpful for UI.

Stress Urinary Incontinence

Stress urinary incontinence (SUI) is the 2nd most common cause of urinary incontinence in elderly **women**. With SUI, the urethra cannot maintain the pressure gradient required for urinary control when there is an increase in intraabdominal pressure (e.g., coughing, jumping). SUI is associated with multiple vaginal deliveries, pelvic surgery, postmenopausal hormonal changes (low estrogen → atrophic relaxation of the vaginal wall → lack of support for the urethra), but SUI is sometimes seen in males after prostatectomy. During the physical exam, focus on the presence of uterine prolapse/cystocele, pelvic floor laxity, and cough leak.

Stress incontinence is best treated initially with behavioral therapy, especially **Kegel exercises** (i.e., perineal muscle contractions). Referral to a pelvic floor physical therapy specialist can be helpful in effective teaching of Kegel exercises. Note that some women with urinary incontinence have a mixture of SUI and UI. Vaginal pessary devices, usually made of silicone, are nonsurgical options that can be used as a therapy adjunct or for certain situations to avoid incontinence incidents. Impressa is a disposable over-the-counter option that can be self-inserted and does not require fitting by a health care provider. Although surgery has high cure rates, it also has high risk of complications.

Patient **history** gives you the clues to determine whether incontinence is due to urge or stress incontinence—ask about the stimuli that precipitate leakage in a patient with UI and look for leakage associated with increased intraabdominal pressure with SUI.

Mixed Incontinence

Mixed incontinence is a combination of UI and SUI. The etiology is unknown. Bladder training and Kegel exercises help these patients.

Incomplete Bladder Emptying

Incomplete bladder emptying is sometimes still called **overflow incontinence**. It is caused by either an overactive bladder +/- an outlet obstruction or by an underactive bladder that has trouble contracting (e.g., diabetes, Parkinson's, multiple sclerosis, alcohol abuse).

Incomplete emptying is rare in females. In males, it is usually caused by prostatic hyperplasia. The **outlet obstruction** causes a distended bladder and high-volume postvoid retention. Physical exam may show a distended bladder, an enlarged prostate, and a postvoid residual volume that is ≥ 150 mL. Anticholinergic drugs are the most common causes of drug-induced incomplete emptying. Psychogenic retention can also be a cause.

Treat the underlying cause if possible; use intermittent catheterization for neurogenic bladder and diaper-like garments if needed. Treat men with benign prostatic hyperplasia (BPH) with α -blockers and/or 5- α reductase inhibitors and consider surgical consultation.

Review of Treatment

Treatment includes:

- Bladder training, lifestyle modifications, and Kegel exercises: urge, stress, and mixed
- Drugs for urge and mixed incontinence: anticholinergics with antimuscarinic effects, β 3-agonist, botulinum toxin
- Drugs for stress incontinence: None! Bladder training, pessaries, lifestyle modifications, and Kegel exercises only!
- Surgery: last resort for refractory incontinence of all types

Note: Asymptomatic bacteriuria, common in older adults, is **not** a cause of incontinence. Also, incontinence is **never** an indication for a long-term bladder catheter.

URINARY TRACT INFECTION

The most common infectious illness among older adults is urinary tract infection (UTI). Because the geriatric population often has noninfectious causes of urinary symptoms such as incontinence or prostatic hyperplasia, making a diagnosis of UTI is sometimes difficult. Another confounder is the increased prevalence of asymptomatic bacteriuria with aging. Older adults living or participating in communal settings such as care facilities or senior daycare are at higher risk for UTIs. Also at higher risk are older adults with underlying conditions known for impaired immunity, such as diabetes and chronic heart failure. Symptoms can be nonspecific to the urinary tract or present as fever, dysuria, gross hematuria, worsening incontinence, and suprapubic or costovertebral angle pain. Know that in especially in frail older adults, fever can be low-grade (i.e., 99°F) or absent. In geriatric patients, symptoms of UTI may present as confusion or altered mental status and can be masked by presentation as a fall.

If nitrites or leukocyte esterase are positive by urinalysis, order a urine culture and sensitivity. Diagnose asymptomatic bacteriuria when bacteria are cultured from 2 sequential specimens but without the development of any new urinary tract-related symptoms. Uncomplicated lower UTI can be treated with antibiotics for 3–6 days, while complicated lower UTI (UTIs among men are considered complicated) requires a longer course of antibiotics (10–14 days). Do not treat asymptomatic bacteriuria with antibiotics.

SEXUAL DYSFUNCTION

Sexual dysfunction increases with aging. Men and women experience decline in libido, sexual responsiveness, comfort level, and sexual frequency. Many factors are causal, including lower levels of testosterone. Other comorbid conditions, medications, and psychosocial stressors impact sexual dysfunction among older adults. Sexual disorders in men are usually erectile dysfunction and delayed ejaculation. In women, they include arousal and orgasmic

disorders and pain with intercourse. Treatment includes reassurance, sex therapy, and medications. See the [Women's and Men's Health](#) section for more information.

ELDER MISTREATMENT

PREVIEW | REVIEW

- What is the definition of elder mistreatment?
- What are the various forms of elder mistreatment?
- What are the risk factors for elder mistreatment for victims? For caregivers?
- What physical exam findings suggest elder mistreatment?
- What are the management principles of elder mistreatment in a victim who lacks decision-making capacity?

OVERVIEW

Elder mistreatment in individuals > 65 years of age (a.k.a. elder abuse) is less recognized by health care providers than child abuse.

Passed in 2010 to combat elder abuse, the Elder Justice Act provides for freedom from abuse and exploitation.

The World Health Organization defines elder mistreatment as a single or repeated act or lack of appropriate action occurring within any relationship where there is an expectation of trust that causes distress or harm to an elderly person.

Elder **neglect** refers to the withholding of physical, psychological, or financial resources that the elderly person needs to be happy and healthy.

Many people prefer to avoid the use of terms like elder mistreatment, elder abuse, and elder neglect, instead preferring terms like inadequate care of the elderly or mistreatment of the elderly to refer to both acts of omission and commission that result in harm or potential harm to older individuals.

Forms of elder mistreatment:

- Physical abuse is the use of physical force that can result in bodily injury, physical pain, and/or physical impairment.
- Sexual abuse is nonconsensual sexual contact. This can be sexual contact of any kind.
- Emotional or psychological abuse is the act of inflicting anguish, pain, or distress through verbal or nonverbal activities.
- Financial/Material exploitation is the illegal or improper use of financial resources, including funds, property, or other assets.
- Neglect is the refusal or failure to fulfill any part of a person's obligations or duties to a person they are caring for.

- Self-neglect is behavior that threatens an individual's own health or safety.
- Abandonment is the desertion of a person by an individual who has physical custody of the individual or by a person who has responsibility for providing care to the individual.
- Institutional abuse is physical, psychological, sexual, or neglect that occurs in institutional settings where care is provided.

INCIDENCE OF ELDER MISTREATMENT

The National Council on Aging reports that 10% of older adults suffer from elder mistreatment. The most common form of elder mistreatment is verbal abuse followed by financial abuse. Physical abuse is the least common form of elder mistreatment.

Victim-related risk factors for elder mistreatment include:

- Female sex
- Advanced age
- Total dependence on caregiver
- Social isolation
- Behavioral disorders
- Physical and cognitive impairment
- Dementia

Caregiver-related risk factors for elder mistreatment include:

- Use of alcohol or illegal drugs
- History of abuse as a child
- Financial dependency on the victim
- Inexperience in providing care
- Unrealistic expectations and overwhelming situations
- Psychiatric diseases
- Economic or other life stresses
- History of violent behavior

When caring for older adults, it is important to consider elder mistreatment when something in the clinical picture doesn't make sense. Look for incongruity between what the patient says is happening and what appears to actually be happening (e.g., they report all is well at home, yet they appear disheveled with poor hygiene). Screening for elder abuse was included in the 2018 update of the U.S. Preventive Services Task Force recommendations. In 2007, the AMA recommended screening for elder abuse in all clinical settings. The AMA has made routine screening for psychological, physical, and sexual abuse part of its Code of Ethics. Observations suggestive of elder mistreatment include:

- Poor supervision by caregiver
- Delays in seeking medical care
- Unexplained injuries
- Missed medical appointments

- Inconsistency of history between patient and caregiver
- Discrepancy of lab results and patient history
- Reluctance to answer questions and vague explanations
- Recurrent hospitalizations
- Attempts by caregiver to prevent interaction between patient and health care provider
- Extreme fear of the caregiver by the patient
- Living arrangements not compatible with assets
- Unexplained withdrawals from bank account of the elderly individual
- Presentation of a frail elderly patient without a designated caregiver

It is very important to obtain a good history in an environment where the elderly individual feels secure. Questions to ask:

- Do you feel safe where you live?
- Who prepares your meals?
- Do you have to wait long or ask for food or medication?
- Who handles your finances?
- Is anyone trying to hurt you, or are you afraid of anyone?
- Has anyone touched you in a way that makes you feel uncomfortable?
- Have you been slapped, punched, kicked, or otherwise physically hurt?
- Have you been yelled at?
- Have you been closed in a room alone for a long period of time?

It is also important to speak to the caregivers and ask them questions to investigate suspicions of elder mistreatment. Handle these situations with the appropriate delicateness, consult other members of the care team, and engage social services to help if indicated.

You must perform a good physical examination when elder mistreatment is suspected. The following physical examination findings can be seen in victims of elder mistreatment:

- General appearance
 - Problems with hygiene, dressing, and cleanliness
- Skin and mucous membranes
 - Skin lesions and bruises in various stages
 - Signs of dehydration and deficient care of established skin lesions
- Head and neck
 - Hematoma on the scalp
 - Traumatic alopecia
 - Lacerations and abrasions on the head and neck area
- Eyes, nose, and throat
 - Subconjunctival or vitreous hemorrhage
 - Whiplash injuries from repeated shaking
 - Deviated septum from repeated trauma

- Oral cavity
 - Tooth fractures
 - Oral lesions suggestive of sexually transmitted diseases
 - Cigarette burns on lips
- Chest
 - Bruises and rib fractures
- Abdomen
 - Unexplained rectal bleeding
 - Bruises and intraabdominal hemorrhage
- Pelvic
 - Unexplained vaginal bleeding
 - Foreign bodies in the vulva or rectum
- Extremities
 - Signs of restraint use on wrists or ankles
- Musculoskeletal system
 - Occult fractures
 - Unexplained pain
- Neuropsychiatric examination
 - Rapidly worsening cognitive impairment
 - Worsening depressive symptoms
 - Severe anxiety

MANAGEMENT OF ELDER MISTREATMENT

It is important that when elder mistreatment is recognized that the patient be placed in a safe environment, including potential hospitalization. Adult Protective Services should be called immediately. In certain regions, there are designated area agencies of aging to deal with such complicated matters.

However, the situation is often complicated by the elderly individuals refusing any intervention. If they are capable of making their own decisions, then honor their wishes but educate them about the various resources available. It is important to make them aware that the abuse may escalate in the future and is unlikely to end without any intervention. For victims who do not have decision-making capacity, take steps to safeguard them as soon as possible. The American Bar Association recommends contacting state adult protective services (in most states it's a law, and failure to report is a crime), which can arrange for safe care, as well as be an important source for evidence keeping.

It is very important to document the event(s) accurately. As far as possible, use the patient's own words during documentation to avoid errors in translation. For health care providers, it is important to know that reporting elder mistreatment is confidential, and you are protected from litigation unless the complaint was made maliciously.

Every clinician must know how to get in touch with their local area agency for aging. It is important that you take a nonconfrontational, nonjudgmental, and methodical approach and involve a multidisciplinary team to assess and handle situations where elder mistreatment is suspected.

OLDER ADULTS AND DRIVING

PREVIEW | REVIEW

- What are the physiologic changes that affect driving in elderly individuals?
- What are important points to consider while examining the patient to assess their ability to drive?
- What are the steps you can take when you suspect your patient is an unsafe driver?

OVERVIEW

Driving is an important factor in the independence and freedom in American life. The primary goal of the health care provider is to maximize older patients' potential for independent functioning and living. However, the patients' autonomy cannot override concerns for their safety and the public's safety in general.

The rate of motor vehicle crashes is lowest between 20 and 65 years of age. After 65 years of age, it gradually increases, and the crash risk for drivers > 85 years of age is 2.5× the average risk. Traffic violations involving right of way or sign errors are early indications of problems affecting driving in older adults. The most common form of driving accidents involving older adults take place while turning at intersections, especially when making left turns against oncoming traffic.

Physiologic changes with aging and pathologic processes that may adversely affect driving:

- Physiologic changes
 - Visual
 - Presbyopia
 - Diminished visual acuity
 - Decreased visual fields
 - Decreased resistance to glare
 - Delayed response to accommodation and light reflexes
 - Auditory
 - Presbycusis
 - Cognitive
 - Slower reaction times
- Medical illnesses and medications
 - Arthritis
 - Cardiovascular diseases
 - Cerebrovascular diseases
 - Dementia
 - Diabetes, especially diabetic retinopathy and diabetic neuropathy
 - Parkinson disease
 - Sleep apnea
 - Alcohol
 - Psychotropic medications

Perform a comprehensive geriatric examination in individuals when driving is a concern, focusing on the following:

- Complete history
- Detailed physical examination, including:
 - Visual acuity and visual field assessment
 - Joint range of motion, especially in the neck
 - Gait and balance evaluation
- Mental status examination
- Driving history
- Driving simulation with an occupational therapist

CLINICAL PEARLS

Elderly patients are very sensitive to even small amounts of alcohol. Alcohol has a significant effect on driving in older people, even if the levels are less than the legal limits allowed.

Many older adults take medications, including BDZs, psychotropic medications, anticholinergic medications, and/or diphenhydramine, which cause significant mental impairment adversely affecting their driving.

REGULATIONS AND DRIVING

Governmental regulations concerning elderly drivers vary from state to state in the U.S. In most states, physicians do not face liability issues if they report the patient to the Department of Motor Vehicles (DMV) for concerns with driving. However, in some states, physicians are not protected from liability for such reporting, and must decide between liability in disclosing patient confidentiality and public safety. Have a detailed discussion with the patient and family members and, when appropriate, report concerns to the DMV or other pertinent authorities. The physician can order a driving test that is necessary for the patient to maintain their driver's license.

It is worth noting that some of your elderly patients may not care if they have a license and continue to drive, especially if they have mild cognitive impairment or early dementia. In such cases, the family may need to get involved by cutting off access to the vehicle by removing the keys and/or the vehicle itself.

When possible, it is important to make every effort to maximize the patient's ability to drive safely. It has been found that the rates of depression and other medical illnesses significantly increase in patients who have their ability to drive taken away from them. Therefore, consider psychological support for your patients when they lose their ability to drive independently. Remind families and patients that their local independence can be maintained through alternative means (e.g., rideshares, senior driving programs).

TAKE-HOME MESSAGE

Loss of driving is equal to loss of freedom for many patients. Deterioration of vision and slowing of reflexes are 2 of the most significant physiologic changes that occur in older adults and can impact their ability to drive. Diminished hearing capacity, arthritis, and cognitive decline are other important contributing factors. Evaluate the elderly patient for the capacity to drive safely, and when they cannot, you need to have this important discussion with the patient and their family.

HOME HEALTH CARE

PREVIEW | REVIEW

- What is home health care?
- What is skilled home health care?
- What is the role of home health aides?

Home health care is medical treatment or assisted care for patients who do not require hospitalization or facility care but do need additional support to live safely at home. The goal of home health care is to treat patients in the emotional comfort of their home while helping them to become self-sufficient and regain their independence in their ADLs (including bathing, transferring, toileting, and eating) and IADLs (including daily tasks of light work, meal preparation, grocery shopping, transportation, and medication management).

In the U.S., most people receiving home care are > 65 years of age.

Since the 1980s, the types of services offered by home care have expanded, with the inclusion of intravenous antibiotics, oncology, hemodialysis, and parenteral and ventilator care. Hospice care is also included for terminally ill patients with a life expectancy of < 6 months; this service includes a bigger team of integrated medical professionals. Provision of any of these services requires prescription from a licensed physician.

Home health care is divided into skilled and unskilled care.

Skilled home health care is medical treatment provided by medical professionals, including registered nurses, licensed practical nurses, physical/occupational therapists, and speech therapists. Examples of skilled home health care include wound care (e.g., after surgery, pressure ulcers), monitoring serious illness and unstable health status (e.g., heart failure), patient and caregiver education, injections, and intravenous or nutrition therapy.

Unskilled home health care is provided by home health aides. Home health aides are trained and certified health workers who provide assistance to patients in their homes. Their various roles include help with personal care (e.g., hygiene, grooming, activities) and

light household help (e.g., grocery shopping, meal preparation). They also help monitor the patient's clinical condition, even though they cannot provide formal medical care. Family members continue to be the main caregivers, as home health aides only provide care for certain hours in a week, depending on the patient's need.

Home health telemonitoring has shown benefit for patients with chronic conditions, such as heart failure, to reduce hospital readmissions and decrease overall health care expenditure.

While we've focused here on formal home health care, note that most home health care is unpaid and provided by families and friends of the patients. Without these caregivers, the health system would probably become insolvent.

The government and insurance providers are funding this level of formal care as an alternative for inpatient care and long-term facilities. While 48% of older adults receiving paid care will require less than a year of such care, 19% will need it for 1–2 years, 21% for 2–5 years, and 13% for 5 or more years. As the elderly population grows, so does the government health expenditure. The Centers for Medicare & Medicaid Services spent \$102.2 billion on home health care in 2018.

NURSING HOME CARE

PREVIEW | REVIEW

- What are the 3 categories of nursing home care?
- What is the tool used to assess the acuity of illness for nursing home patients?
- What are the negative impacts of using restraints in nursing home patients?
- What is the average infection rate in nursing home residents?

OVERVIEW

The geriatric population in the U.S. is growing, and the highest growth rate is among those ≥ 85 years of age. This is significant because nursing home utilization rates are 4% for those > 65 years of age but dramatically rise to 17% for those > 85 years of age. Even though nursing home care is heavily regulated and utilizes a significant proportion of health care dollars, quality care continues to be a struggle. Nursing home care is an integral part of patient care today and acts as a bridge between hospital care and home care.

Nursing home care can be divided into 3 categories:

- 1) Long-term care (~ 6%)
- 2) Subacute care
- 3) Specialized care

Long-term care is appropriate for individuals who suffer from multiple chronic diseases and are no longer able to care for themselves. Nursing homes provide custodial care for these patients for the remaining duration of their lives. The most common reason for seeking placement in long-term care is the caregivers' inability to provide optimal help with ADLs. These include incontinence care, worsening neurologic function, and significant dementia-related behaviors. This type of care is not reimbursed by Medicare. Consequently, patients must pay out of pocket for their care until they meet income levels to qualify for Medicaid.

In contrast, **subacute care** is designed for posthospital patients. Typically, these patients stay for a short time in nursing homes, and the ultimate discharge plan is usually back to the home. Rehabilitative care, complex medical care, and wound care are among the diagnoses that qualify patients for subacute nursing care. The most common reasons for subacute nursing care admission are orthopedic surgeries (e.g., after hip and knee replacements), stroke, heart failure, COPD and other pulmonary disorders, and care for pressure ulcers.

Specialized care is designated for specific programs, such as dementia care, dialysis, and hospice, in a smaller category of patients.

Nursing home care is increasingly being used by non-geriatric patients (<65 years of age), predominantly for mental health care.

In 2016, the average length of stay of older adult nursing home residents was 485 days with 43% staying less than 100 days and 57% staying 100 days or longer. Women make up 60–68% of nursing home patients, primarily because women have a higher life expectancy compared to men. On average, women need longer care than men.

ADMISSION EVALUATION

During the nursing home admission process, all patients need an individualized focused care plan, which should be reviewed on a regular basis. This requires a comprehensive geriatric assessment of all elderly patients evaluating functional, physical, cognitive, emotional, and psychological well-being. The Minimum Data Set (MDS) is the universal tool used at the time of admission, as well as for quarterly reassessments for long-term residents, to define complexity of care in nursing home patients. It includes a comprehensive assessment of the patient's functional, cognitive, psychosocial, and overall health status. The MDS includes assessment of cognition, vision, hearing, communication, physical functioning, continence, and psychological and nutritional status—besides, of course, disease diagnoses and associated treatment needs.

The care goals in a nursing home setting differ from the hospital setting. Nursing homes emphasize maximizing function and improving quality of life, rather than curing a disease. It is very important to communicate with patients and their families periodically. Typically,

this communication occurs once a week, or every 2 weeks for subacute patients, or every 2 months for long-term care patients.

The goal of long-term care admission planning is to maintain the best possible quality of life.

ADVANCED DIRECTIVES AND LIVING WILLS

A conversation regarding advanced directives is the most important step to initiate quality care at admission. First and foremost, evaluate patients for medical decision-making capacity. If they have the competency to do so, then talk about a **living will** and **health care proxy appointment**. Both are prepared in case the patient later loses the capacity to make decisions on their own. A living will consists of instructions regarding a person's desired future care. A health care proxy is a trusted agent and alternative agent who have been appointed to make health care decisions on the patient's behalf.

Discuss and clearly document patients' wishes regarding resuscitation, rehospitalization, and medical interventions. Several states have forms to document these decisions, including allow natural death (AND), do not resuscitate (DNR), and physician orders for life-sustaining treatment (POLST), and questions regarding intubation, artificial feeding, dialysis, and the use of invasive procedures. This information is important to make sure that the medical personnel respect patients' known wishes and values.

USE OF RESTRAINTS

The use of physical and chemical restraints is not infrequent in nursing home care, but increasingly, nursing homes are going restraint free. If restraints are used, Joint Commission standards must be followed. This certainly comes with a lot of controversy.

Restraints are used as a modality to:

- Promote safety
- Control violent behavior

The negative impacts of restraints include:

- An associated increased risk of injury
- Increased mental impairment
- Decubitus ulcers
- Nosocomial infections
- Agitation
- Loss of dignity for the patient

Use **physical** restraints only as a last resort after demonstrating that less restrictive measures were unsuccessful. **Chemical** restraints refer to the use of psychoactive medications. Use these only to treat specific symptoms, such as psychosis, and when there are clear behaviors that cause the patient to be a danger both to others and themselves.

Never use restraints to control patient behavior solely for the convenience of the nursing home personnel. Nursing home personnel should receive appropriate education and adhere to monitoring guidelines when overseeing residents. Establish interdisciplinary teams to minimize the use of restraints. When needed, obtain a psychiatric consultation, especially with a geropsychiatrist (if available).

PREVENTIVE CARE

Preserving function and maintaining quality of life are the most important preventive interventions in a nursing home. For long-term care residents, continue routine use of appropriate clinical and laboratory screening unless the patient's life expectancy is < 5 years. (If life expectancy is < 5 years, cancer screening is not needed.) Nursing home patients need certain specific screenings, including screening for hearing problems, cognitive impairment, gait impairment, nutrition, and incontinence. In addition, optometry, podiatry, and dental needs must be addressed.

Prevention of infectious diseases in nursing homes is very important. Screen all nursing home residents with purified protein derivative (PPD) for tuberculosis. Tetanus and diphtheria vaccinations are recommended in the absence of appropriate vaccination history. All nursing home residents should receive appropriate influenza and pneumococcal vaccinations. For vaccine schedules, see the [Infectious Disease](#) section.

When influenza outbreaks occur, oseltamivir is effective in early treatment and prevention of influenza. When influenza is diagnosed or strongly suspected, treat with oseltamivir at 2×/day dosing (dose adjustment is needed for renal failure). Chemoprophylaxis with oseltamivir once a day is recommended for all nursing home residents in case of an epidemic. Once-daily oseltamivir should be given to all nursing home residents when an epidemic starts and should be continued for a minimum of 14 days and a week after the last case of influenza in the nursing home.

INFECTION CONTROL

The institutionalized elderly are at significant risk for infections given their decreased immunity, advanced age, and comorbid diseases. Subacute patients from acute hospital settings can harbor virulent and resistant organisms, such as methicillin-resistant *Staphylococcus aureus* (MRSA), carbapenem-resistant Enterobacteriaceae (CRE), vancomycin-resistant *Enterococcus* (VRE), and *Clostridioides difficile* (formerly known as *Clostridium difficile*). The average incidence of infections in nursing homes in the U.S. is 1–2 infections/resident/year. These infections increase not only rehospitalizations but also patient morbidity and mortality rates.

For successful infection control programs, include appropriate screening of patients and procedures for preventing, identifying, and treating infections. Staff must be educated on the use of universal precautions, especially simple handwashing, aseptic techniques, and appropriate disposal of contaminated materials. Ideally, all facilities should have an infection control nurse.

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Pulmonary Medicine

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DIAGNOSTIC TESTS

PREVIEW | REVIEW

- What are the primary computed tomography (CT) chest types, and which has the highest radiation exposure?
- Which conditions are diagnosed by high-resolution CT (HRCT) scan?
- What are the results of VC, TLC, FEV₁, and FEV₁/FVC in patients with intrathoracic restriction? In extrathoracic restriction?
- What are the results of VC, TLC, FEV₁/FVC and RV in patients with obstruction?
- What is VC? Which smaller lung volumes make up VC?
- Characterize the differences in the flow-volume loops for obstructive and restrictive airway diseases. (See Figure 6-2 on page 6-4, Figure 6-3 on page 6-4, Figure 6-4 on page 6-4, Figure 6-5 on page 6-5.)
- When is the methacholine bronchoprovocation test performed?

COMPUTED TOMOGRAPHY (CT) CHEST

Table 6-1 reviews the most common types of chest computed tomography (CT) scans, including radiation dose exposure. For reference regarding comparative effective radiation dose exposure in millisieverts (mSv), a 2-view chest radiograph has a score of 0.02 mSv and a transcontinental airline flight scores 0.02 mSv.

HRCT assesses the lung parenchyma rather than the vasculature or other tissues of the thorax. Certain HRCT patterns and distributions can correlate well

with histopathology in some instances of ILD. In some cases, a diagnosis can be made using characteristic HRCT findings without a lung biopsy (the diagnostic gold standard).

HRCT is used when disease is suspected by history and physical exam but the chest x-ray is normal, has a subtle abnormality, and/or considerable detail is needed to characterize the disease further. Such instances include interstitial lung diseases (ILDs), emphysema from α_1 -antitrypsin deficiency, bronchiectasis, and lymphangitic spread of malignancy. If you suspect ILD or bronchiectasis, make HRCT the initial study.

Obtain prone positioning and end-inspiratory images to distinguish dependent atelectasis from ILD. Obtain images at the end of inspiration and expiration to evaluate for air-trapping in the lung. In contrast, when acquiring CT images, patients hold their breath at the end of inspiration.

HRCT is sometimes used to guide biopsies of focal diseases, such as solitary pulmonary nodules or localized parenchymal abnormalities.

MAGNETIC RESONANCE IMAGING (MRI)

MRI is useful only in the following specific situations when evaluating for pulmonary disease:

- Evaluation of tumors near adjacent blood vessels or nerves
- Differentiation of tumors and nonneoplastic entities; examples include tumors of the superior sulcus, brachial plexus, mediastinum, and tumors near the aorta, spine, or heart.
- Evaluation of venous thrombosis with magnetic resonance angiography (MRA) and magnetic resonance venography (MRV). These are used in very few centers.

Table 6-1: Common Chest CT Scans

Type	Millisieverts (mSv)	Key Imaging Protocol Features	Important Points About When to Use
CTPA	15 mSv	Uses a rapid-timed infusion of IV contrast dye to enhance the imaging of the pulmonary vasculature	Diagnosis of PE during the bolus phase
CT chest without contrast	8 mSv	Usually ≤ 5 mm for the mediastinal and lung sections	• Assesses the mediastinum, pleura, and parenchyma • Workup of a solitary pulmonary nodule (CT > HRCT)
LDCT	1.5 mSv	Uses no contrast and 1 breath hold	Screening tool for lung cancer and follow-up imaging of identified abnormalities during screening regime
HRCT	Dose can be > or < conventional CT, varying with protocol used, but < CTPA	Uses thinner slices, 1.5 mm, and no contrast	• Diagnosis of ILD or bronchiectasis • Workup of a solitary pulmonary nodule (CT > HRCT) • Do not select HRCT to diagnose a PE!

CT = computed tomography
CTPA = CT pulmonary angiography
HRCT = high-resolution CT
ILD = interstitial lung disease
LDCT = low-dose CT
PE = pulmonary embolism

LUNG BIOPSY

Consider using a lung biopsy to assist in diagnosing ILD with **atypical** clinical and HRCT features, especially when you need to differentiate among forms of ILD or to exclude infectious and other causes of an interstitial pattern. Choose a lung biopsy technique based on the type, extent, and location of the pulmonary abnormalities. Use chest x-ray and HRCT findings to guide this choice. For example, in sarcoidosis, transbronchial biopsy yield is highest when infiltrates are obvious on the chest x-ray and lowest when hilar adenopathy is the only abnormality. Lung biopsy is generally pursued in consultation with a pulmonary specialist.

Bronchoscopic transbronchial biopsy is useful in the diagnosis of suspected sarcoidosis, some cases of cryptogenic organizing pneumonia (COP), lymphocytic interstitial pneumonia, eosinophilic pneumonia, lymphangitic spread of cancer (though this is generally suggested by the clinical picture and CT appearance), and certain infections. The chief problem with transbronchial biopsy is the small amount of tissue afforded by the biopsy forceps, with resulting low sensitivity and low specificity from sampling error. Cryobiopsy is another option performed at specialized centers and is performed via bronchoscope. Sample size is larger but comes at higher risk for pneumothorax.

If the diagnosis is not obtained or unlikely to be obtained bronchoscopically or radiologically, **open lung biopsy** or **video-assisted thoracoscopic surgery (VATS)**

may be pursued. This step is dependent upon the clinical condition of the patient, the risks and benefits of such an operation, and whether empiric treatment is problematic. The surgeon obtains multiple biopsies at different affected sites. These biopsies yield larger tissue samples than transbronchial biopsies.

The radiographic pattern on HRCT has increasingly obviated the need for lung biopsy in classic or typical cases of idiopathic pulmonary fibrosis (IPF).

OTHER PULMONARY TESTS

Bronchoalveolar lavage (BAL) is an important pulmonary diagnostic tool. It is used to obtain material for microbiologic data, cytology, and leukocyte count with differential from the lung. Know [Table 6-2](#). BAL with cell count and differential can be used to diagnose eosinophilic pneumonia. In cases of suspected sarcoidosis or berylliosis, a CD4:CD8 ratio of > 4 in BAL lymphocytes is suggestive in the absence of an increased proportion of other inflammatory cell types in BAL. If the ratio is reversed, consider hypersensitivity pneumonitis, silicosis, COP, or drug reaction. Examining the BAL effluent is useful for alveolar proteinosis (periodic acid-Schiff positive) as well as pulmonary hemorrhage.

Endobronchial ultrasound (EBUS) is used to guide biopsy of suspicious or enlarged central lymph nodes. In experienced hands, it is increasingly regarded as the procedure of choice for staging of lung cancer.

Table 6-2: Findings in Bronchoalveolar Lavage (BAL)

Results	Causes
< 1% neutrophils, < 16% lymphocytes, no eosinophils	Normal findings
Increased neutrophils	IPF, collagen vascular disease, asbestosis, suppurative infections, GPA, and ARDS
Increased lymphocytes	Hypersensitivity pneumonitis and sarcoidosis, but also COP, nonspecific interstitial pneumonitis, and collagen vascular disease with lung involvement
Increased eosinophils	Acute and chronic eosinophilic pneumonia, some ARDS, EGPA, Löffler syndrome, tropical eosinophilia, parasite infection (esp. ascariasis), TB, collagen vascular disease, malignancy (esp. lymphoma), asthma, bone marrow transplant, and drug reactions
Diagnosis of specific types of pneumonias and other infectious diseases	95% sensitive for PJP in AIDS patients* CMV pneumonia (identifies inclusion bodies)* TB or fungal infection* Pneumonia in ARDS patients*
Turbid, periodic acid-Schiff (PAS)-positive material	Alveolar proteinosis*
Langerhans cells	Langerhans cell histiocytosis*
Bloody with a large amount of hemosiderin in the alveolar macrophages (increase with serial aliquots)	Diffuse alveolar hemorrhage*
Hyperplastic and atypical Type 2 pneumocytes	Cytotoxic lung injury*
Foamy changes with lamellar inclusions	Amiodarone exposure: seen with and without lung disease
* In these, BAL results are sufficient for diagnosis.	
ARDS = acute respiratory distress syndrome EGPA = eosinophilic granulomatosis with polyangiitis IPF = idiopathic pulmonary fibrosis CMV = cytomegalovirus GPA = granulomatosis with polyangiitis PJP = <i>Pneumocystis jiroveci</i> pneumonia COP = cryptogenic organizing pneumonia TB = tuberculosis	

Transthoracic needle biopsy is done with CT guidance for peripheral lesions, such as suspicious lung nodules.

Pulmonary angiogram was considered the gold standard for the diagnosis of pulmonary embolism; however, it is **rarely required** anymore because CTPA has high sensitivity and specificity for diagnosing acute pulmonary embolism. When chronic thromboemboli are suspected, such as during the workup of pulmonary hypertension, ventilation/perfusion scan (a.k.a. V/Q scan) is recommended.

PET (positron emission tomography)/CT scan is useful in differentiating some benign lesions, such as scars, from pulmonary lesions that are malignant, infectious, or inflammatory. Note that PET cannot distinguish between malignant, infectious, and inflammatory lesions, but the intensity of the 18F-fluorodeoxyglucose (FDG) uptake can guide clinical decision-making. The PET scan is paired with a CT to localize FDG avidity by metabolically active cells. PET/CT is most useful with nodules > 1-2 cm but has a lower limit of resolution of approximately 8 mm. This study is also used to identify suspicious lymph nodes for biopsy in cases of suspected lung cancer or other cancers. False negatives can occur (e.g., adenocarcinoma in situ, renal cell metastasis, carcinoid tumors).

Pulmonary function tests (PFTs) are outlined under [Pulmonary Function Tests \(PFTs\)](#), **V/Q scan** is discussed under [Review of Lab and Radiological Tests for PE on page 6-41](#), and **thoracentesis** is covered under [Exudative vs. Transudative on page 6-49](#).

PULMONARY FUNCTION TESTS (PFTs)

Using spirometry in the office, you can determine vital capacity (VC), forced vital capacity (FVC), tidal volume (TV), inspiratory reserve volume (IRV), expiratory reserve volume (ERV), expiratory flows, and flow-volume loops and also assess bronchodilator response. Spirometry cannot measure reserve volume. Indications for spirometry:

- Aid in diagnosis of dyspnea or lung disease
- Assess the severity of a known lung disease in many cases
- Evaluate variability of lung disease (e.g., asthma)
- Evaluate the impact of prescribed treatment
- Assess the role of environmental exposures

- Assess the impact of exercise on airflow
- Evaluate for potential respiratory disability (generally with full PFTs)
- Assess for possible restrictive vs. obstructive disease

A pulmonary function lab is needed for:

- Total lung capacity (TLC) determination
- Residual volume (RV) determination and its derived values, including TLC and functional reserve capacity
- Diffusing capacity of the lungs for carbon monoxide (DLCO) determination
- Methacholine or other challenge tests (specific training of technicians needed)

For FEV_1 , FVC, and TLC, **< 80%** is generally considered abnormal and for RV > 120% also may be significant.

When reviewing PFT results, keep in mind the following:

- **TLC** is decreased in restrictive lung disease, and degree of restriction is determined by FVC.
- Expiratory flow rate (ratio of forced expiratory volume in 1 second to FVC [FEV_1/FVC]) is used to assess **obstructive** lung disease. Airway obstruction is diagnosed when the FEV_1/FVC is **< 70% or less than a lower limit of normal (LLN)** provided by the laboratory.

For a summary of typical PFT results for restrictive and obstructive lung disease, see [Table 6-3](#).

Lung Volumes

Review the lung volumes diagram in [Figure 6-1 on page 6-4](#). The lung is made of 4 basic functional volumes:

- 1) Inspiratory reserve volume (IRV) = normal unforced end-inspiration to maximum end-inspiration
- 2) Tidal volume (TV) = volume used in normal unforced ventilation
- 3) Expiratory reserve volume (ERV) = from the lowest point of tidal volume exhalation to maximum forced end-expiration
- 4) Residual volume (RV) = unused space

A capacity is ≥ 2 of these basic volumes and gives even more functional significance to them. For example, VC is the volume you have available for breathing (makes sense) and is comprised of the IRV, TV, and ERV.

Table 6-3: Typical Pulmonary Function Test (PFT) Results

	VC	TLC	FEV_1	FEV_1/FVC	RV	DLCO
Restrictive Intrathoracic	↓	↓ (< 80%)	↓ or normal	NI	↓	↓
Restrictive Extrathoracic	↓	↓ (< 80%)	↓ or normal	NI	↓	NI
Obstructive	↓	NI to ↑	↓	↓ (< 70% or less than LLN)	↑↑	NI to ↓

DLCO = diffusing capacity of the lung for carbon monoxide
 FEV_1 = forced expiratory volume in 1 second
 FVC = forced vital capacity
 LLN = lower limit of normal

NI = normal
 RV = residual volume
 TLC = total lung capacity
 VC = vital capacity

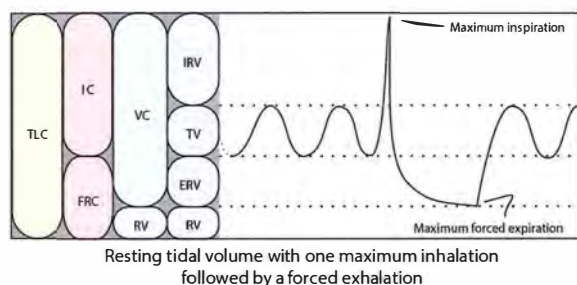
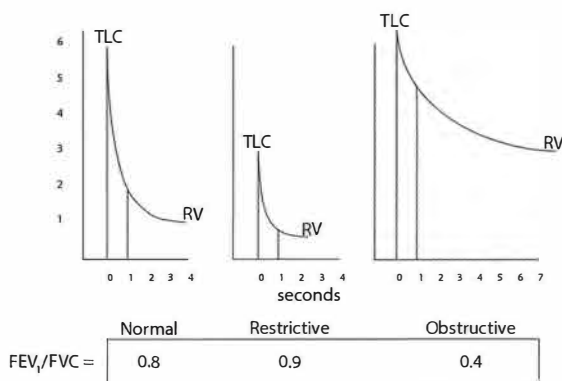


Figure 6-1: Lung volumes

The TLC is the sum of the VC and RV. In severe chronic obstructive pulmonary disease (COPD), TLC is increased (even though VC is decreased) due to a greatly increased RV—air trapping—seen as a barrel chest. In restrictive disease, the TLC is decreased due to both a decreased VC and RV. TLC is determined in the lab by helium dilution, nitrogen wash-out, or plethysmography (the latter provides more accurate results in patients with airflow obstruction).

The tracing in Figure 6-1 shows a forced expiration from maximum inspiration. Figure 6-2 shows a comparison of similar expirations for patients with normal, restrictive, and obstructive airways. This is an easy test and an important result, but you will not usually see it diagrammed this way.

Figure 6-2: Forced expiratory volumes and FEV₁/FVC

Although the TLC cannot be determined from spirometry (you must know the RV, which is calculated and not measured), you can determine the presence of **obstruction** by the ratio **FEV₁/FVC**. In a patient with a healthy lung, the ratio is about 0.8. It is always less than 0.7 or below the LLN in a patient with COPD or a patient with asthma experiencing bronchospasm. It may be normal or increased in a patient with restrictive disease—even though the VC is small—because this patient has no trouble getting air out. A patient with asthma has reversible disease and, if not having active bronchospasm, can have a normal FEV₁/FVC, a common situation with intermittent asthma,

Flow-Volume Loops

The diagrams of flow-volume loops shown in Figure 6-3, Figure 6-4, and Figure 6-5 are a more common way of expressing airflow in the different lung diseases. These

loops are derived from the spirometry data and are calculated and plotted by an attached computer, where the FEV₁/FVC is automatically determined. Note that the y-axis illustrates the flow rate.

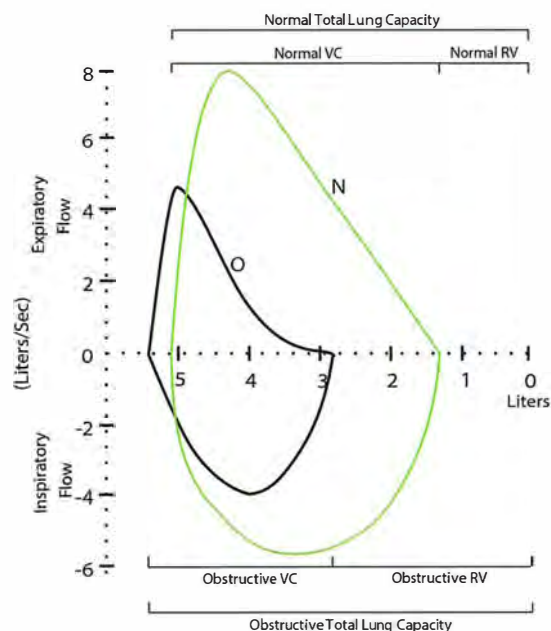


Figure 6-3: Flow-volume loops—normal vs. obstructive

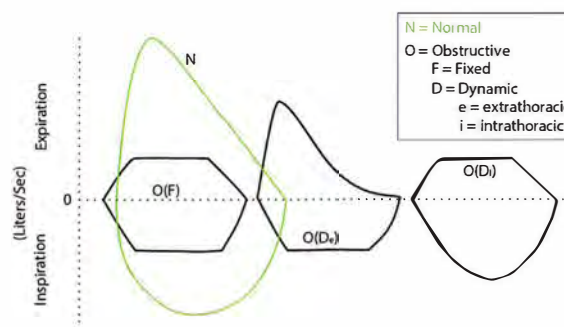


Figure 6-4: Upper airway obstruction

Because you cannot determine RV from spirometry, you get most of your information from the **shape** of the loop. The exception is in restrictive disease. Although the shape is similar to normal, the VC (represented by the curve from TLC to RV or the loop width) is much smaller than normal.

Figure 6-3 compares normal and obstructive lung-flow loops. Figure 6-4 compares the different types of obstructive disease. Figure 6-5 includes restrictive diseases. Know the shapes and sizes of these loops!

In obstructive disease (Figure 6-3), increased expiratory airway resistance causes a decreased expiratory flow rate. Again, while normal FEV₁/FVC = 80%, obstruction is defined as **< 0.7 or below the LLN**. (In very severe obstruction, it may be even < 35%!) Additionally, there is a **scooping or concavity** of the tracing in the latter half of expiration. Common causes of lower airway obstruction include asthma, COPD, bronchiectasis, and cystic fibrosis (CF).

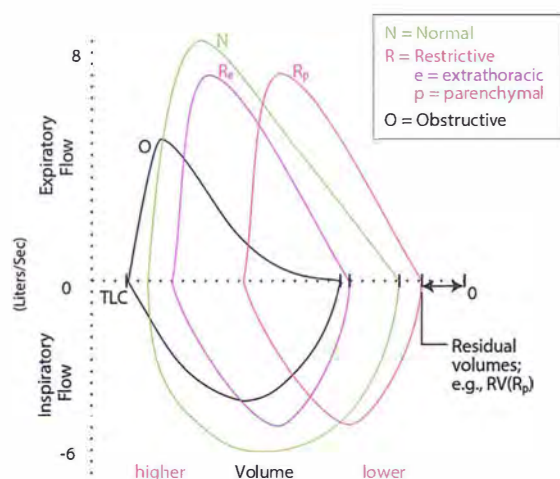


Figure 6-5: Flow-volume loops—all

When analyzing an obstructive disease of the **upper airway** (from the pharynx to the origin of the mainstem bronchi), you can derive much information from the **shape** of the flow-volume loop. See Figure 6-4.

Fixed upper-airway obstruction: If the upper-airway obstruction is fixed, the graph is flattened on the bottom **and** the top; i.e., during both inspiration and expiration. Examples of fixed obstruction are conditions due to compressive tumors (e.g., thyroid tumors) and tracheal stenosis (e.g., history of intubation).

Dynamic upper-airway obstruction: With dynamic **extra-thoracic** obstruction, such as in tracheomalacia and vocal cord paralysis, the obstruction occurs on inspiration. Think of a thin rubber wall in the neck (instead of the normal trachea) collapsing from the negative pressure of inspiration.

If the tracheomalacia is **intrathoracic**, the flow is impeded on expiration due to the increased intrathoracic pressure pressing on the malacic trachea.

Restrictive disease is shown in Figure 6-5. Note that in intrathoracic restrictive disease (e.g., parenchymal disease, ILD), the RV is decreased, unless there is concomitant marked obstructive disease. In extrathoracic restrictive disease states (e.g., obesity, kyphosis), the RV can be normal, but the loop shape and size are similar.

Bronchodilation

Bronchodilator response during pulmonary function testing is done for 2 reasons:

- 1) To determine if the obstruction is responsive to β_2 -agonists. Before testing, withhold β_2 -agonists for 8 hours and theophylline for 12-24 hours.
- 2) To test for the efficacy of a current regimen. In this case, medications are not withheld. If treated patients have a response to β_2 -agonists, it suggests they are not on an optimum regimen or are not using them properly.

Methacholine or other bronchoprovocation challenges determine if patients have **bronchial hyperreactivity**. This testing is done in patients with normal spirometry and intermittent asthma-like symptoms (or other symptoms suggestive of airflow obstruction). It is often done in the workup of **chronic cough** (see **Asthma** on page 6-11) and occasionally in patients with cold air-induced or exercise-related bronchospasm.

Protocols using inhaled escalating doses of methacholine or histamine are given to the patient while monitoring for a 20% drop in FEV_1 . Know that patients with asthma bronchoconstrict at a **very low dose** of the irritant, whereas those without asthma do not.

Also know that PFTs are always the 1st test in the evaluation of possible COPD or asthma. Bronchoprovocation should be done **only** when initial PFTs are **normal** and the **diagnosis remains obscure**.

Pre-Op

PFTs are **not** routinely indicated in preoperative evaluation.

PFTs with or without arterial blood gases (ABGs) **may be** indicated in the following circumstances:

- If the surgical procedure is close to the diaphragm (e.g., gallbladder)
- If the patient has moderate or severe lung disease. In these cases, an $FEV_1 < 1$ L or an **elevated pCO_2** indicates that the patient is at risk for postoperative pulmonary complications.
- If the patient requires presurgical evaluation for lung **cancer** or lung **resection**. Assuming a worst-case scenario (pneumonectomy), the patient must still have adequate lung function postoperatively. High risk of postoperative morbidity is suggested by a predicted $FEV_1 \leq 0.8$ L after surgery.
- If a patient has a preoperative FEV_1 of, for example, ≤ 1.6 L, you can estimate the postoperative FEV_1 by obtaining a quantitative ventilation and perfusion lung scan. You then multiply the percent perfusion (or ventilation) to the lobe to be removed by the FEV_1 in order to obtain the estimated postoperative FEV_1 .

Now, let's look at what PFTs show in the major lung diseases. In subsequent discussions, we focus on the clinical aspects of the major lung diseases.

PFTs for Specific Lung Diseases

The following lists detail potential PFT findings for common chronic pulmonary diseases, but not all features may be present:

- Emphysema
 - Decreased expiratory flow volume (a shortened top portion of the flow-volume loop)
 - Concave expiratory flow-volume loop tracing, if there is concomitant obstructive airway disease

- Minimal response to β_2 -agonists ($< 12\%$ improvement or < 200 mL improvement in FEV_1 or FVC)
- Increased TLC with reduced VC (hyperinflation with trapped air)
- DLCO is **decreased** due to the destruction of the alveolar-capillary interface.
- Early on, patients may have low DLCO and radiographically demonstrable emphysema but relatively normal spirometry and lung volumes.
- Chronic bronchitis
 - Decreased expiratory flow volume
 - Concave expiratory flow-volume loop tracing, if concomitant obstructive disease
 - Variable response to β_2 -agonists
 - Normal or only slight increase in TLC (normal or slightly reduced VC)
 - DLCO is **normal** to slightly decreased, but it is not as low as in patients with emphysema. Remember: DLCO is the test that allows you to differentiate emphysema from chronic bronchitis and asthma. Understand that most cases of COPD have mixed physiology, with components of both chronic bronchitis and emphysema.
- Asthma
 - PFTs can be normal if there is no active bronchoconstriction at the time of testing, as occurs in intermittent asthma.
 - Decreased expiratory flow volume
 - Concave expiratory flow-volume loop tracing, if active bronchoconstriction present
 - Significant response to β_2 -agonists
 - Normal or increased TLC (due to hyperinflation) and a normal or reduced VC
 - **Normal** DLCO
- Interstitial lung disease
 - Normal to increased FEV_1/FVC
 - Straight or slightly convex expiratory flow-volume loop tracing
 - Proportional decreases in all lung volumes, that is, restriction
 - DLCO is **reduced** (due to the thickening of the alveolar-capillary interface) and is the 1st pulmonary parameter to change with disease progression.

When approaching a PFT scenario, think in terms of:

- Expiratory flow
- Lung volumes
- Diffusion capacity
- Response to bronchodilators

FVC, FEV_1 , or TLC $< 80\%$ of predicted is an abnormal finding. Generally, the actual FEV_1/FVC value is used. FEV_1/FVC is age adjusted. The percent predicted is sex, age, race, and height adjusted. (Note: If a patient is unable to stand, height can be estimated by measuring the arm span; i.e., both arms spread in parallel.)

Review the following 4 steps and apply them to the 6 sets of PFT results in Table 6-4. Write your conclusions in the Analysis column. Remember, we are looking for normal findings, restrictive disease, or obstructive disease.

1) Look for all normals:

- Circle everything $\geq 80\%$. Label these values **normal**.
- If all the values are $\geq 80\%$, the results are normal.
- Remember that most smokers have **normal** values.

2) Look for restrictive disease:

- Any TLC $< 80\%$ is by definition restrictive. Label these results as **restrictive**. If the TLC is not known, restrictive disease is reflected in a proportional decrease in both the FEV_1 and FVC (i.e., $FEV_1/FVC = 80\%$ but the FVC is $< 80\%$).
- If restrictive, check the DLCO. This determines if it is extrathoracic or intrathoracic.
 - If the decrease in the DLCO is **proportional** to the decrease in the TLC, the restriction is commonly caused by an extrathoracic origin. Label it **extrathoracic** and think of obesity, neuromuscular disease, or kyphosis. **Pulmonary resection** can also cause this.
 - If the decrease in the DLCO is **disproportionately** low compared to the decrease in the TLC, label it **intrathoracic** and think of parenchymal disease or ILD.

3) Look for obstructive disease:

- Obstruction is defined by a disproportionately low FEV_1 . So, both the FEV_1 and FEV_1/FVC are low, $< 70\%$ or below the LLN. Label these lines **obstructive**.
- If obstructive, check the TLC, DLCO, and reactivity to β_2 -agonists.
 - Label it **emphysema** if the TLC is high but the DLCO is low. There is minimal to no response to β_2 -agonists.
 - Label it **asthma** if the DLCO is normal. There is typically improvement with β_2 -agonists.

4) In some instances, results represent combinations of obstructive and restrictive diseases, such as in:

- patients with concomitant asthma and obesity or
- patients with concomitant asthma and certain diseases, especially sarcoidosis, lymphangioleiomyomatosis, and Langerhans cell histiocytosis.

Okay, now look at your completed table of PFT results. **Know!** This is not only for exam questions but also for clinical practice. PFT results are shown as a percentage of predicted. Remember that for FVC, FEV_1 , and TLC, $< 80\%$ of predicted is abnormal. If a percent predicted for FEV_1/FVC rather than the actual ratio is given, a value $< 80\%$ of predicted would be abnormal. Confusingly, the actual FEV_1/FVC is often also reported as a percentage rather than as an actual ratio, so it is important to note the difference.

Table 6-4: Pulmonary Function Test (PFT) Analysis*

Set	% FEV ₁	% FVC	FEV ₁ / FVC	% TLC	% DLCO	Analysis
1	83	89	93	92	85	
2	58	62	93	68	64	
3	52	80	65	110	65	
4	55	87	63	100	88	
5	57	87	65	70	68	
6	66	72	92	75	33	

* Except for the FEV₁/FVC ratio, results are reported as a percentage of predicted values.

DLCO = diffusing capacity of the lung for carbon monoxide

FEV₁ = forced expiratory volume in 1 second

FVC = forced vital capacity, TLC = total lung capacity

Set 1: You should have all these values circled. These are, of course, normal. Remember that normal results are seen in most smokers!

Set 2: Extrathoracic restrictive mechanics (non-parenchymal).

All restrictions, intra- and extrathoracic, are defined by a decrease in the TLC. The normal FEV₁/FVC ratio proves that there is no obstructive mechanism involved. The FEV₁ is decreased in proportion to the decrease in FVC, so the FEV₁/FVC is $\geq 80\%$. Extrathoracic involvement is indicated by the proportional decrease in the TLC and the DLCO—that is, the decrease in the DLCO is due to the decrease in the TLC.

Pure extrathoracic restriction is seen with **kyphosis** and **obesity**. Kyphoscoliosis is usually a result of compression fractures of the thoracic vertebral bodies, secondary to long-standing osteoporosis. It also occurs in a small percentage of neurofibromatosis (von Recklinghausen disease) and tuberculosis patients who have thoracic vertebrae involvement. Obesity may be associated with a reduced ERV.

If a patient is post-CABG (coronary artery bypass graft) and suffering from orthopnea, check PFTs, but also check FVC values while the patient is both standing and lying down. If the patient has extrathoracic restrictive mechanics and the difference in the FVC values is $> 20\%$ (decreases with lying down), consider bilateral hemidiaphragmatic paralysis from the cold cardioplegia. (This is exam-question specific—a chest x-ray will tell you this!) Unilateral phrenic nerve problems can be diagnosed by a sniff test with fluoroscopy or with bedside ultrasound evaluation. Also note that a decrease in FVC (from standing to lying) in the high-to-normal range (15–20%) is commonly seen with obesity. Maximum inspiratory pressure (MIP), measured in the PFT lab, may be reduced. The DLCO can be disproportionately low (say, 54%) if this post-CABG patient also has some postoperative atelectasis.

Question: Besides cold cardioplegia, what are the other possible causes of a bilateral elevated hemidiaphragm? Answer: Poor inspiration, systemic lupus erythematosus (SLE), bilateral phrenic nerve paralysis such as from spinal injury, tumors, neurological disorders, diaphragmatic weakness from amyotrophic lateral sclerosis (ALS), large-volume ascites, and bilateral subpulmonic effusions can all cause bilateral elevated hemidiaphragms. These all make sense, so just think about them, but do not memorize them!

Set 3: Pure obstruction with low DLCO and a high TLC.

The FEV₁/FVC is $< 70\%$. The TLC is high and the DLCO is disproportionately low, indicating a loss of alveolar-capillary units. Emphysema (from either smoking or α_1 -antitrypsin deficiency) with COPD is the most common cause of this finding.

Set 4: Pure obstruction with normal DLCO.

It is the same as Set 3, except the DLCO is normal, indicating asthma. In both Sets 3 and 4, the FVC can be low if the obstruction is so severe that the patient does not have enough time to fully expire before getting short of breath. The FEV₁/FVC remains $< 70\%$.

Set 5: Combined obstruction and extrathoracic restriction.

The low FEV₁/FVC indicates obstruction. The low TLC indicates restriction, while the proportionate decrease in the DLCO narrows it to an extrathoracic etiology. Possible etiologies include an obese patient with asthma or an osteoporotic, kyphotic patient with asthma.

Set 6: Intrathoracic restriction.

As in extrathoracic restriction, the FEV₁ and the FVC are **proportionately low** (so the FEV₁/FVC is $> 80\%$). Contrary to extrathoracic restriction, DLCO is disproportionately lower than the decrease in the TLC in intrathoracic restriction. This is seen with many forms of ILD.

RESPIRATORY PHYSIOLOGY

PREVIEW | REVIEW

- In which diseases do you see a reduced diffusing capacity of the lung for carbon monoxide (DLCO)?
- What is a simple formula for calculating the A-a gradient?
- Name 3 factors that, for a specific P_aO₂, cause a decrease in hemoglobin O₂ saturation.
- What does CO poisoning do to the oxyhemoglobin dissociation curve?
- What are the symptoms of methemoglobinemia?
- What is the treatment for methemoglobinemia?
- What is the DLCO in ILD? In asthma? In emphysema?

NOTES

Acid-base analysis is covered in depth in the [Nephrology](#) section.

Know **respiratory physiology well**. The information is used extensively in clinical practice and is often tested on exams.

SHORT REVIEW

Atmospheric pressure (P_b) varies. At sea level, at 59.0°F (15.0°C), it is 760 mmHg (29.92 inches Hg). The medical standard is to use mmHg. Atmospheric pressure decreases as you get further away from the surface of the earth and also as the temperature increases. The component gases of the atmosphere each exert a consistent partial pressure to the atmospheric pressure. For example:

$$\begin{aligned}\text{Partial pressure } O_2 &= F_{iO_2} \times P_b \\ &= 0.209 \times 760 \text{ mmHg}\end{aligned}$$

F_{iO_2} = fraction of inspired oxygen

P_b = atmospheric pressure

The partial pressure $O_2 = 158.84$ mmHg in the air surrounding us at sea level at 59.0°F (15.0°C). This pressure is called the P_{iO_2} (inspired). This fraction of 20.9% remains constant as atmospheric pressure decreases with increasing altitude.

The following is the **alveolar gas equation**, which calculates the partial pressure of O_2 in the alveoli:

$$P_{AO_2} = [(P_b - P_{H_2O}) \times F_{iO_2}] - [P_aCO_2/0.8]$$

This equation looks different from the simpler P_{iO_2} equation just discussed. The reason is that the partial pressure of inspired gases changes a little when it gets into the damp alveoli where the $O_2 \leftrightarrow CO_2$ exchange occurs. Here, you must account for the additional partial pressure of water vapor P_{H_2O} (47 mmHg at sea level) and the shifts in the concentrations of O_2 and CO_2 in the alveoli. The respiratory quotient (0.8) is the production of CO_2 /minute by the consumption of O_2 . This quotient allows you to use the measurable P_aCO_2 (arterial) in the alveolar gas equation instead of the P_aCO_2 (alveolar), which you cannot readily measure.

So, to get back to the alveolar gas equation ...

$$P_{AO_2} = [(P_b - P_{H_2O}) \times F_{iO_2}] - [P_aCO_2/0.8]$$

The P_b is still multiplied by the F_{iO_2} but only after its value is decreased to account for the water vapor. The second term decreases this product by an amount that takes into account the $O_2 \leftrightarrow CO_2$ exchange in the alveoli.

Other terms:

- P_aO_2 = partial pressure of oxygen in the arterial blood; commonly called the **pO₂**
- P_aCO_2 = partial pressure of carbon dioxide in the arterial blood; commonly called the **pCO₂**
- S_aO_2 = oxygen saturation of hemoglobin in the arterial blood

- S_vO_2 = oxygen saturation of mixed venous blood. Mixed venous blood is in the pulmonary artery.
- $S_{cv}O_2$ = oxygen saturation of central venous blood. Central venous blood is obtained from the superior vena cava.

HYPOXEMIA

Hypoxemia (low oxygen tension) has 6 causes:

- 1) **Ventilation/Perfusion (V/Q) mismatch** is the main cause of hypoxemia in chronic lung diseases and responds well to 100% O_2 . It is due to inadequately perfused airspaces or perfused areas that are inadequately ventilated. Examples include asthma, COPD, alveolar disease (e.g., pneumonia), interstitial disease, and pulmonary vascular disease (e.g., pulmonary hypertension, pulmonary embolism). The hypoxemia improves after oxygen administration.
- 2) **Right-to-left (R-to-L) shunting** is seen in, for example, acute respiratory distress syndrome (ARDS), where hypoxemia is due to perfusion of nonventilated alveoli. ARDS does **not** respond well to 100% O_2 but responds better to positive end-expiratory pressure (PEEP). See [Ventilator Support for ARDS on page 6-77](#). Other causes of R-to-L shunting, besides alveolar collapse, include intraalveolar filling (e.g., pneumonia, pulmonary edema), atelectasis, intracardiac shunt, and vascular shunt. PEEP can worsen a R-to-L intracardiac shunt by increasing the shunt fraction as a result of increased right-sided pressures.
- 3) **Decreased alveolar ventilation** is seen with decreased tidal volumes, low respiratory rates, and apnea. By definition, decreased alveolar ventilation **always** has a high P_aCO_2 with hypoxemia. The A-a gradient ($D_{A-a}O_2$, discussed below) is normal. Common causes are drug overdose, neuromuscular diseases, and CNS disorders.
- 4) **Decreased diffusion** actually has **little** effect on hypoxemia at rest, but it can play a role in exercise-induced desaturations. It takes a **tremendous** amount of membrane thickening or loss of the alveolar-capillary interface to markedly decrease the diffusion of O_2 . The **DLCO** test measures how well inspired CO diffuses from the alveoli to the RBC hemoglobin and acts as a surrogate marker for CO_2 and oxygen diffusion. Low DLCO occurs with **ILDs** and **emphysema**, in which symptoms improve with supplemental O_2 . Other causes include pulmonary vascular disease and significant anemia. Hypoxemia at rest occurs when the DLCO is approximately $\leq 30\%$ of predicted. It can occur at higher DLCO if there is an increased cardiac output, as with a rapid heart rate or if there is additional lung pathology. With an increased cardiac output, the time for diffusion is limited, so decreased O_2 transfer occurs. **Increased** DLCO is seen with alveolar hemorrhage, polycythemia, and sometimes with acute asthma attack.

- 5) **High altitude** decreases atmospheric pressure and results in a reduced $P_{A}O_2$. The A-a gradient is normal unless lung disease is present.
- 6) **Low mixed venous O_2** (i.e., venous oxygen pressure [P_vO_2]) can decrease the P_aO_2 during resting conditions, secondary to the normal shunt that exists (~ 5%). It can also exaggerate all other causes of low P_aO_2 . A low mixed venous O_2 is caused by low cardiac output or an increased tissue extraction of oxygen. A lower P_vO_2 can induce hypoxic vasoconstriction, increasing R-to-L baseline anatomical shunting.

Again:

- Supplemental O_2 does **not** cause a significant increase in P_aO_2 when there is R-to-L shunting or shunt physiology.
- The A-a gradient is **normal** with hypoventilation and with high altitudes.

A-a GRADIENT

The alveolar-arterial gradient (A-a gradient, A-a O_2 , or $D_{A-a}O_2$) is the difference between the partial pressure of oxygen in the alveoli (A) and that in arterial blood (a):

$$D_{A-a}O_2 = P_{A}O_2 - P_{a}O_2$$

For details on the A-a gradient and how to calculate it, see [Appendix A on page 6-89](#).

Calculate the gradient for every arterial blood gas you get. It helps you to quickly identify whether hypoxemia exists because of a problem in the alveolar-capillary unit (e.g., pulmonary embolism, pneumonia) or if some other cause is to blame (e.g., hypoventilation).

OXYGEN DELIVERY TO TISSUES

Oxygen delivery to the tissues is dependent upon **both** of the following:

- The amount of oxygen transported to the tissues
- How much of the transported oxygen is taken up and subsequently utilized by the mitochondria and/or cells

For more details on oxygen transport to tissues (DO_2) and how to calculate, see [Appendix B – Oxygen Transport to Tissues on page 6-90](#).

$$DO_2 = \text{cardiac output} \times (1.34 \times \text{Hgb} \times S_aO_2)$$

Cardiac output (heart rate $\times$ stroke volume), Hgb, and S_aO_2 are the 3 factors you look at when a critically ill patient requires better oxygen delivery. In exam questions, you are typically given a critically ill patient with either a low cardiac output or an obvious anemia with an O_2 saturation of 90% and P_aO_2 of 60 mmHg. The answer is to address the obviously low hemoglobin or cardiac output—the P_aO_2 is fine because the S_aO_2 is fine!

Note: Cardiac output is the variable that can usually affect DO_2 the most, potentially doubling or tripling it, while significant differences in hemoglobin are generally less common.

Oxyhemoglobin Dissociation Curve

The oxyhemoglobin dissociation curve (or oxygen saturation curve; [Figure 6-6](#)) shows the percent of O_2 saturation of hemoglobin (S_aO_2) for a certain P_aO_2 . It is the amount of O_2 -saturated hemoglobin that is important. You can see from the graph that, everything else being normal, a P_aO_2 of 60 mmHg results in an S_aO_2 of ~ 91%.

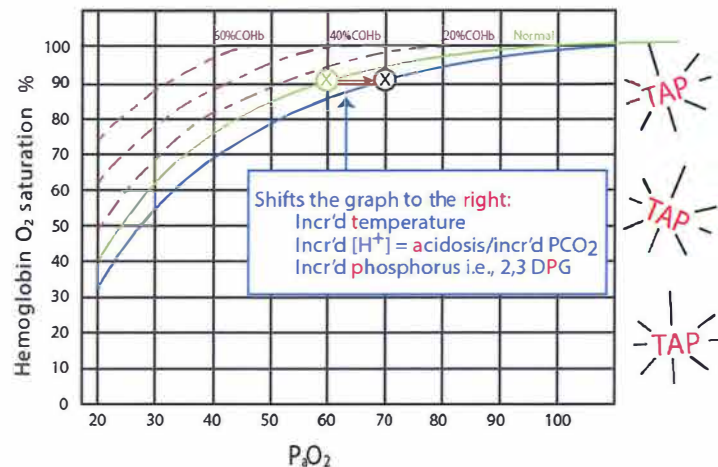


Figure 6-6: Oxyhemoglobin dissociation curve

The actual oxygen saturation of a particular hemoglobin molecule at a particular P_aO_2 is dependent on temperature, erythrocyte 2,3-diphosphoglycerate (2,3-DPG) level, and pH status. High or low levels of serum phosphorus cause an increased or decreased 2,3-DPG level. The oxyhemoglobin dissociation curve shows the S_aO_2 for a certain P_aO_2 —given variations in these 3 factors:

- 1) Temperature
- 2) Acidosis (pH)
- 3) Phosphorus (2,3-DPG)

This gives you the mnemonic **TAP** for remembering what shifts the curve.

When the curve is shifted to the **right**, with **increased levels** of TAP, it reflects a decreased hemoglobin affinity for O_2 (i.e., a decreased O_2 uptake by the hemoglobin). The red arrow on the graph indicates a shift to the right. With this given shift, you can see that maintaining an O_2 sat of 91% now requires a P_aO_2 of 70 mmHg (vs. 60 mmHg previously). Decreased affinity promotes off-loading of the O_2 to the tissues.

With a shift to the **left**, with **decreased levels** of TAP, it reflects an increased hemoglobin affinity for O_2 (i.e., an increased S_aO_2 for a particular P_aO_2).

Note that the “TAP, TAP, TAP” on the right of the graph is to remind you of the factors that shift the graph to the right—increased temperature, acidosis, and phosphorus.

Additional Causes of Reduced Hemoglobin Oxygen Saturation

Carboxyhemoglobin occurs when CO binds tightly to hemoglobin, preventing O₂ from binding. Additionally, the binding of CO causes the other oxyhemoglobin to bind even more tightly to O₂—shifting the curve to the left. The typical noninvasive saturation test (i.e., pulse oximeter) does **not** distinguish between oxyhemoglobin and carboxyhemoglobin, so the oxyhemoglobin curve not only shifts to the left but also appears to be 100% saturated with normal P_aO₂. Patient appears pink to cherry red in color. Treatment begins with high flow oxygen. With severe CO poisoning, the majority of hemoglobin is saturated with CO, leaving little room for O₂. The **red** tracing in [Figure 6-6 on page 6-9](#) shows how the graph shifts to the **left** with increasing amounts of carboxyhemoglobin.

Methemoglobin is produced when the iron in the hemoglobin molecule is oxidized from the ferrous (Fe²⁺) to the ferric (Fe³⁺) form. The resulting methemoglobin molecule cannot hold onto O₂ or CO₂—with disastrous results to the tissues. In addition, methemoglobin causes the regular ferrous hemoglobin to hold much more tightly to O₂, thereby shifting the oxyhemoglobin dissociation curve to the **left**. A typical bedside evaluation reveals generalized cyanosis with a pulse oximetry of ~ 85%. ABGs show a normal P_aO₂. The net result is a left shift of the oxyhemoglobin saturation curve that climbs to 100% at lower P_aO₂ levels. This is similar to the carboxyhemoglobin effect, but for completely different reasons.

Methemoglobinemia can be acquired (commonly due to medications) or hereditary. Clinical effects of methemoglobinemia include:

- > 25% = perioral and peripheral cyanosis
- 35–40% = fatigue and dyspnea begin
- > 60% = coma, death

Treat methemoglobinemia by removing the cause and with 100% O₂ and **methylene blue** (which causes rapid reduction of methemoglobin back to hemoglobin). Chronic hereditary methemoglobinemia is best treated with oral methylene blue and 1–2 g of daily ascorbic acid, which is a form of vitamin C that can help with cyanotic symptoms.

Think cyanide poisoning if the history includes breath with an almond odor and lab draw with bright-red venous blood. Cyanide immediately binds to the **ferric** molecule in the mitochondrial cytochrome oxidase complexes, thereby blocking cellular aerobic metabolism. Treatment goal for cyanide poisoning is to **induce methemoglobinemia** because cyanide preferentially binds methemoglobin and produces a less toxic reaction.

Carbon monoxide poisoning and cyanide poisoning are also discussed in the [General Internal Medicine](#) section.

Know that the standard pulse oximeter, which measures the absorption of 2 wavelengths of light, is **inaccurate** when there are significant levels of **carbon monoxide** or **methemoglobin**. Also understand that the oxygen saturation reported on an arterial blood gas analysis is a calculated value, not a measured one. Measuring a true level of the different hemoglobin saturations requires inserting blood into a special CO-oximeter that uses a spectrophotometer to make the measurements of oxygen saturation, methemoglobin, carboxyhemoglobin, and sulfhemoglobin levels. (Lipemic serum results may be inaccurate because the fat potentially interferes with light absorption.)

Bottom line: Realize that the standard bedside pulse oximeter is not always helpful in CO poisoning and methemoglobinemia because the value is often falsely normal—you must order measurements of the various hemoglobins on blood samples.

For more on methemoglobinemia, see the [Hematology](#) section.

Oxygen Release to Tissues

Oxyhemoglobin Dissociation Curve

We discussed oxygen transport to the tissues. What about oxygen release to the tissues? Here again, look at the oxyhemoglobin dissociation curve as it applies to oxygenated blood in the tissues. Any factor that shifts the graph to the right/down reflects a decreased affinity between oxygen and hemoglobin and, in the local tissue environment, causes a release of oxygen to the tissues.

For example, in the vicinity of the capillaries of working muscles, there is an increase of lactic acid due to normal metabolism → **local acidemia** → decreased affinity of hemoglobin for O₂ → release of O₂ to the tissues. Recall “TAP, TAP, TAP” on the right of the graph in [Figure 6-6 on page 6-9](#). The Bohr effect is the decreased association of oxygen and hemoglobin due to acidosis resulting from carbon dioxide.

Similarly, RBCs produce 2,3-DPG as a byproduct of anaerobic metabolism. (All RBC metabolism is anaerobic.) The more 2,3-DPG there is, the more O₂ is released from hemoglobin for use by the RBCs. Similarly, patients with chronic anemia have increased 2,3-DPG.

Blood stored > 1 week has a decreased level of 2,3-DPG, and large transfusions of this blood result in a shift to the left.

When there is **systemic acidosis** (or high temperatures or high 2,3-DPG levels), the decrease in affinity for O₂ by hemoglobin results in less O₂ picked up in the lung, as well as more O₂ released in the tissues. So, although the S_aO₂ is lower for a certain P_aO₂, more of the oxygen carried by the hemoglobin is released to the tissue. The

net result is to dampen the effect of low S_aO_2 caused by acidosis, high temperatures, and high 2,3-DPG levels. It dampens but does not negate or reverse the effect.

Conditions that shift the curve to the left (e.g., alkalemia; low temperatures; low 2,3-DPG levels; CO; fetal hemoglobin; methemoglobin; myoglobin) work similarly, although more O_2 is bound by the hemoglobin and less is released to the tissues. Again, it dampens but does not negate the effect.

Diffusing Capacity of the Lung for Carbon Monoxide (DLCO)

The DLCO is **decreased** by anything that interrupts the gas-blood oxygen exchange.

A decreased DLCO implies the loss of an effective alveolar-capillary interface. It is usually seen in **emphysema** (due to the loss of alveolar-capillary units), **ILD**, and **pulmonary vascular** diseases. **Anemia** also causes a decreased DLCO.

Know that the DLCO is the 1st parameter to decrease in ILD. Thus, it is important to follow DLCO when prescribing medications that can cause ILD, such as amiodarone or lung-toxic chemotherapy. Also, DLCO may be the only abnormal pulmonary function parameter in pulmonary vascular disease.

A **normal** DLCO is typically seen in asthma and chronic bronchitis. Despite bronchoconstriction, there is **no** alveolar disease. Therefore, recognize that the DLCO is the major pulmonary function parameter that helps you to distinguish **emphysematous** COPD (**low** DLCO) from chronic bronchitis and asthma (**normal** DLCO).

An **increased** DLCO is seen in problems that increase effective blood flow to the functional lung. Examples include heart failure, diffuse alveolar hemorrhage, pulmonary infarction, acute asthma exacerbation, and idiopathic pulmonary hemosiderosis (IPH). A perforated eardrum can cause a very high DLCO value due to the leakage of CO through the ear during testing!

OBSTRUCTIVE LUNG DISEASES

OVERVIEW

Obstructive lung diseases are characterized by decreased expiratory airflow. They may exhibit air trapping on PFTs (increased TLC, RV, and/or RV/TLC). While the hallmark of COPD on pulmonary function tests is persistent airflow limitation (usually $FEV_1/FVC < 0.70$), patients with asthma may have normal PFTs, as variable airflow limitation is seen with asthma. That is, at the time of spirometric measurement, the asthma may not be active. Patients with COPD tend not to have significant bronchodilator responses, while patients with asthma can, in some cases, normalize their airflow after bronchodilator administration.

ASTHMA

PREVIEW | REVIEW

- Which skin finding is a predisposing factor for IgE-mediated asthma?
- What is the asthma triad?
- Which comorbidities exacerbate asthma?
- Which spirometry findings support a diagnosis of asthma?
- How can you diagnose exercise-induced bronchospasm (EIB)?
- In the management of asthma, the initial treatment is based on _____. After therapy is started, assessment is directed toward _____.
- What is the preferred treatment course if an asthmatic is not controlled in Step 1?
- What is the preferred strategy for Step 5 patients?
- Describe the relationship between symptom-based monitoring and the peak expiratory flow (PEF).
- What is the short-acting drug of choice for asthma exacerbations?
- What is the preferred maintenance-type drug for the chronic treatment of persistent asthma?
- When is ipratropium bromide used during inpatient treatment of an asthma exacerbation?
- What is a therapeutic level of theophylline?
- What are signs and symptoms of theophylline toxicity?
- What is the preferred treatment for patients with exercise-induced bronchospasm (EIB)?
- For patients being treated for asthma exacerbation in the emergency department, when do you consider hospitalization?
- What are 2 consequences of dynamic hyperinflation?
- Explain permissive hypercapnia.
- Which ventilator settings are appropriate for a patient intubated for a severe exacerbation of asthma?

Asthma is a heterogeneous, chronic **inflammatory** condition of the airways with a multifactorial etiology and varying presentations. The symptoms are due to bronchoconstriction, airway wall thickening, and increased mucus secretion. Patients can have intermittent, persistent, acute, or chronic manifestations. The primary manifestations of bronchoconstriction are recurrent episodes of wheezing, shortness of breath, chest tightness, and cough—that vary over time.

Asthma is usually reversible either spontaneously or with treatment. However, with chronic inflammation, fixed airway disease, which is irreversible, may develop.

Causes of Asthma

Asthma often develops early in life. However, the cause is often not discovered, especially in adult-onset asthma. Asthma appears to develop from complex interactions within and between 3 groups of factors:

- 1) Host factors
 - Atopy (IgE mediated)
 - Eczema
 - Allergic asthma
 - Allergic rhinitis
 - Aspirin-sensitive (or, more accurately, aspirin-exacerbated) asthma
- 2) Environmental factors
 - Airborne allergens and viral respiratory infections
 - Other environmental agents
 - Occupational causes (e.g., isocyanates)
- 3) Comorbid conditions

Host Factors

Genetic susceptibility is especially associated with the development of asthma, although the role of genes is complex and not well defined at this point. Some asthma cases are IgE mediated. **Atopic** (allergic) eczema dermatitis is the strongest identifiable predisposing factor for developing **IgE-mediated** asthma. Atopy is a predisposition toward developing certain allergic hypersensitivities. Many doctors use the term atopy for any IgE-mediated reaction. A person with atopy usually presents with ≥ 1 of the following:

- 1) Eczema (atopic dermatitis)
- 2) Allergic asthma
- 3) Allergic rhinitis (e.g., hay fever)

The term hay fever is a misnomer. Hay is not the usual cause of this problem, and it does not cause fever. The early description of sneezing, nasal congestion, and eye irritation while harvesting field hay promoted this popular term.

Allergic rhinitis and asthma are both systemic inflammatory conditions that affect the upper and lower airways and may reflect a spectrum of the same disease. Up to 80% of patients with asthma have rhinitis. The treatment of allergic rhinitis with intranasal glucocorticoids improves asthma symptoms and decreases emergency department visits and hospitalizations.

Patients with aspirin-exacerbated asthma often have the **asthma triad** (a.k.a. **Samter triad**): acetylsalicylic acid (ASA) sensitivity, asthma, and nasal polyposis. Patients are generally young- to middle-aged adults. Symptoms start with rhinitis or congestion and then progress to asthma,

polyposis, and ASA sensitivity. The asthma is typically ongoing and markedly worsened by aspirin or NSAIDs. The ASA sensitivity can be extreme and cause anaphylaxis. Patients with ASA-exacerbated asthma may also be sensitive to other NSAIDs and tartrazine dyes but **not** to **Na⁺** and **choline** salicylates.

Environmental Factors

The development of asthma is also associated with the exposure to certain **environmental agents** at critical points in immune development. **Triggers** are environmental factors that cause asthma, but they can also exacerbate symptoms in a person with asthma.

Triggers can be broadly categorized into 6 areas: allergens, irritants, chemicals, respiratory infections, physical stress, and emotional stress. Airborne **allergens** and respiratory viral **infections** play important roles in the **development** of asthma in susceptible individuals and have been studied the most.

Examples of environmental agents that contribute to the development of asthma are pollution, tobacco smoke, and airborne agents prevalent in certain occupations (causing “occupational” asthma). Occupational causes are limited to the workplace and are usually due to a **single** substance that is not found outside of the workplace. These factors include isocyanates found in paints, varnishes, and insulation material and are used in auto body repair shops. Isocyanates are primarily potent sensitizers, eliciting an inflammatory response, but they are also irritants to the mucous membranes of the eyes, the gastrointestinal tract, skin, and the respiratory tract.

Occupational asthma can be IgE dependent, which causes an early or biphasic reaction. It can also be IgE independent, which causes a late reaction. Both a history of smoking and atopy are important sensitizing factors for occupational asthma.

Asthma can be exacerbated by occupational exposures also. Common workplace respirable substances that worsen regular asthma: cotton dust, formaldehyde, volatile organic compounds, toluene diisocyanate, fluorocarbons, grain dust, wood dust (especially western cedar), and nitrogen oxide from unvented gas stoves.

Comorbid Conditions

Asthma is known to be exacerbated by certain comorbid conditions including, but not limited to:

- Allergic bronchopulmonary aspergillosis (ABPA)
- Obstructive sleep apnea-hypopnea syndrome (OSAHS)
- Stress
- Smoking and inhalation of tobacco, cocaine, or heroin
- Allergic rhinitis
- Gastroesophageal reflux disease (GERD)
- Obesity

Changes in the Lung with Asthma

The airway inflammation associated with asthma, whatever the etiology, causes a nonspecific airway hyperresponsiveness, leading to airway edema and bronchoconstriction. Persistent airway inflammation leads to remodeling of the airways with fibrosis and muscular hypertrophy, resulting in a continuous nonresponsive airflow obstruction as a component of the clinical picture.

Acute Exacerbation of Asthma

Early in an asthmatic attack, bronchospasm is the major factor. Later on, increased airway inflammation, airway edema, and airway secretions with possible mucous plugging dominate, especially in patients with status asthmaticus.

Asthmatics usually experience episodes of some combination of dyspnea, cough, chest tightness, and wheezing. However, on the initial presentation, the patient may complain only of a chronic cough. (Remember: Patients with GERD who do not have asthma can also present with cough that typically occurs when supine.)

Diagnosis of Asthma

The diagnosis of asthma is a clinical amalgam of history, symptoms, physical findings, and spirometric findings. The patient generally has evidence on spirometry of variable airflow limitation over time and/or airway obstruction reversibility postbronchodilator, as well as a compatible history and characteristic symptoms of wheezing, cough, shortness of breath, and/or chest tightness. In some cases, the spirometry does not capture bronchospasm at the time of testing. However, a compelling history and symptom improvement with inhaled bronchodilators or corticosteroids strongly suggest the diagnosis. Consider performing a challenge test to induce bronchospasm if these features are not demonstrated.

Measure the FEV₁, FVC, and FEV₁/FVC—before and after use of a bronchodilator—in all patients. Again, response to a short-acting bronchodilator is defined as an increase in the FEV₁ or FVC of $\geq 12\%$ and an increase of at least 200 mL.

Obtaining a fractional exhaled nitric oxide (FeNO) concentration helps in the diagnosis of eosinophilic-induced asthma with levels > 50 ppb in individuals who do not smoke to be considered inflamed. At present, optimal frequency of FeNO monitoring is not known.

Bronchoprovocation tests are done in a patient who has normal spirometry and ≥ 1 of the following characteristic symptoms of asthma:

- Chronic cough
- Intermittent symptoms of cough, wheeze, and/or chest tightness
- Exertional dyspnea without other cause

Methacholine, histamine, and thermal (cold air) challenges can be used to confirm the diagnosis of asthma. These work on the principle of nonspecific hyperirritability. For the diagnosis of asthma (which requires reversible bronchoconstriction), the patient's airways must both tighten up with the challenge and relax with the administration of a bronchodilator.

Exercise-induced bronchospasm (EIB) occurs after exercise after several minutes and causes chest tightness, dyspnea, or wheezing. It may be confirmed by a decrease in the FEV₁ of $\geq 10\%$ after graded exercise on a treadmill or a stationary bicycle. The shape of the flow-volume loop can be used to rule out other etiologies, such as extrathoracic obstruction. Patients who have EIB exclusively elicited by cold air can have false-negative exercise tests. Bronchoprovocation using methacholine, cold air, or eucapnic voluntary hyperventilation can be used to confirm a diagnosis of cold air-induced EIB. It is also useful in patients who might otherwise have a false-negative exercise test. The DLCO is normal.

The initial evaluation of an untreated patient determines the severity and, consequently, the treatment of the asthma. After the initial therapy is started, the focus is on asthma control and response to treatment, rather than the asthma's severity.

The 2020 Global Initiative for Asthma (GINA) guidelines stress assessment of control of asthma symptoms. 4 questions are asked to assess control over the 4 weeks preceding the clinical encounter. Patients are queried regarding:

- the presence of daytime symptoms more than 2 $\times$ /week,
- any nighttime awakening due to asthma,
- use of SABA reliever more than 2 $\times$ /week, and
- any activity limitation due to asthma.

The well-controlled asthmatic has none of these, while the partly controlled asthmatic has 1 to 2 of these and the patient with uncontrolled asthma has 3 to 4 of these.

Patients with asthma should also be assessed for risk factors for poor asthma outcomes, such as acute exacerbations, fixed airway obstructions, and medication side effects. The risk factors for these adverse outcomes are the presence of comorbidities such as obesity, GERD, chronic sinusitis, depression, anxiety, and food allergy; pregnancy; reduced FEV₁, especially if $< 60\%$; high SABA use; lack of ICS in the regimen; inhaled triggers (e.g., allergens, pollution, tobacco smoke); and adverse socioeconomic factors that interfere with asthma treatment and control.

Treatment recommendations follow a step system: Step up care if symptoms are not controlled; when controlled, attempt to decrease to a lower step. For Step 1 symptoms (mild intermittent) initiate therapy with ICA-LABA on an as-needed basis for symptoms occurring less than twice a month. Hint: Never prescribe an asthmatic a LABA or SABA without an ICS. The use of SABA without ICS has been associated with frequent exacerbations. If control is

not optimal, the asthma symptoms are then considered persistent, and treatment progresses to Step 2 (mild persistent) with the use of daily ICS with SABA or leukotriene inhibitor. If patients are not controlled with symptoms most days, they are treated with Step 3 (moderate persistent) medications: low-dose ICS-LABA or medium-dose ICS or ICS-leukotriene receptor antagonist. If control is still not sufficient, asthma is considered severe and requires Step 4 or 5 treatment modalities. Step 4 treatment consists of medium- or high-dose ICS-LABA, with or without added tiotropium or leukotriene inhibitor. Step 5 consists of medications with high-dose ICS-LABA and based on phenotype such as anti-IgE, anti-IL-5, anti-IL-4, and/or low-dose oral corticosteroids. Phenotypic medications are continued during pregnancy if risk of cessation results in worsening respiratory status (the FDA has not assigned pregnancy category with the caveat that the provider discuss potential unknown risks of therapy).

Asthma severity is retrospectively determined by what medication is needed to control the patient's symptoms. If patient exacerbates or presents in an elevated stage, once symptoms are under control, may be able to deescalate treatment to a lower stage of treatment. corticosteroids. See the **Severity** column under **Initial Evaluation** in [Table 6-5](#) and see [Table 6-6](#).

Treatment of Asthma

At patient visits, utilize the asthma control cycle: assess, adjust treatment, and review the response to treatment. The patient also needs to have a written action plan should symptoms worsen (i.e., when to use an oral corticosteroid (OCS), when to go to the emergency department).

The assessment should focus on:

- Diagnosis (ascertain if symptoms and signs are related to asthma and assess their severity)
- Symptom control and risk factors for poor outcomes
- Inhaler technique and adherence
- Patient preference

During the assessment, determine if the patient has characteristic asthma symptoms and/or needs to use the rescue (a.k.a. reliever) inhaler > 2×/week, has > 1 episode of nocturnal awakening due to asthma, or experiences any activity limitation. The well-controlled asthmatic has none of these findings, the partly controlled asthmatic has 1 or 2 of these, and the poorly controlled asthmatic has 3 or 4 of these findings.

Identify risk factors for poor outcomes, which include exacerbations: prior intubations for asthma, uncontrolled asthma symptoms, prior exacerbation in the last 12 months, low FEV₁, poor inhaler technique and/or adherence, smoking, obesity, pregnancy, blood eosinophilia, and delayed or insufficient ICS use. Fixed airflow is associated with lack of ICS use, smoking, occupational triggers, and eosinophilia.

Based on the level of control and/or the presence of risk factors for poor outcomes, adjust treatment (pharmacological and nonpharmacological) using stepwise management and ensure proper inhaler technique and adherence. In general, the guidelines for pregnant patients with asthma are the same; however, these patients need to be monitored closely because uncontrolled asthma increases the risk of preeclampsia, low birth weight, and preterm labor. The risk of poorly controlled asthma outweighs the risks of asthma

Table 6-5: Initial Tx and Maintenance Tx of Asthma for Patients ≥ 12 Years of Age

Clinical Features (with initial evaluation) and Control (while on treatment)					Initial Evaluation: Treatment Is Based on Clinical Features		Continuing Therapy: Treatment Is Based on Control	
Days with Sx	SABA Use (Control Only)	Nighttime Awakenings	FEV ₁ or PEF *	Impairment of Activity	Severity	Treat per Step Level	CONTROL Level	Changing Tx Based on CONTROL Level
≤ 2 days/ month	≤ 2 days/week	0	Usually ≥ 80%	None	Mild	Step 1	Well controlled	Maintain the current step
> 2 days/ month but not daily	> 2 days/week but not daily and not > 1× on any given day	3–4×/ month	≥ 80%	Minor limitation	Mild	Step 2	Well controlled	Maintain the current step
Daily	Daily	> 1×/week but not nightly	> 60%, < 80%	Some limitation	Moderate	Step 3 and 4	Not well controlled	Step up 1 step; reevaluate in 2–4 weeks
Throughout every day	Several times per day	Often 7×/ week	≤ 60%	Frequently limited	Severe	Step 5	Very poorly controlled	Add short course of OCS; step up 1–2 steps; reevaluate within 1 week

*Use only FEV₁ for the initial evaluation. Use either the FEV₁ or PEF for determining control and continuing therapy.

FEV₁ = forced expiratory volume in 1 second
OCS = oral corticosteroid

PEF = peak expiratory flow rate
SABA = short-acting β-agonist

Table 6-6: Treatment Steps Used in Asthma

Step	Preferred	Alternative
1	ICS-LABA prn	ICS with SABA prn
2	Low-dose ICS daily or ICS-LABA prn	LTRA, ICS with SABA prn
3	Low-dose ICS-LABA	Medium ICS or low-dose ICS + LTRA
4	Medium-dose ICS-LABA	High-dose ICS, add on LTRA or add on long-acting muscarinics
5	Refer for phenotypic add-on therapy with anti-IgE, anti-IL-5, anti-IL-4	Add low-dose OCSs, long-acting muscarinics

ICS = inhaled corticosteroid, LABA = long-acting β_2 -agonist, LTRA = leukotriene-receptor antagonist, OCS = oral corticosteroid, SABA = short-acting β_2 -agonist

medications during pregnancy. Asthma exacerbations usually start in the 2nd or 3rd trimester, and the rule of thirds applies during pregnancy: 1/3 get better, 1/3 get worse, and 1/3 stay the same. The asthmatic pattern established in the 1st pregnancy usually applies to subsequent pregnancies. For more on asthma during pregnancy, see the [Women's and Men's Health](#) section.

In the initial assessment, determine whether the patient should be prescribed an ICS with or without additional pharmacologic agents. If the patient has asthma symptoms > 2 $\times$ /week, experiences nocturnal awakening due to asthma > 1 $\times$ /month, or has asthma symptoms with risk factors for poor outcomes, prescribe an ICS, possibly with another agent, such as a long-acting β_2 -agonists (LABA) or SABA, depending on frequency and severity of symptoms.

Patients with persistent asthma symptoms should have their environment assessed for unidentified irritants and allergens. This includes looking for seasonal variation of symptoms, home and workplace evaluation, and skin testing.

The most effective intervention for most asthma is stopping the exposure to any **environmental agents** that are known to act as triggers for the patient. Advise patients who smoke or inhale asthma-exacerbating drugs to give up those habits. The goal is to remove the trigger entirely, but when unable, the patient should minimize the exposure. Inhaling a bronchodilator before the exposure—a common way to handle unavoidable triggers, such as visiting a house with a pet—is also helpful.

The GINA guidelines recommend **treatment of symptomatic gastroesophageal reflux disease (GERD)**, which is commonly done. Treating allergic rhinitis with nasal corticosteroids is associated with improved asthma status only in those not on an ICS.

Treat GERD with the following:

- Avoid consuming foods that lessen the lower esophageal sphincter tone (e.g., alcohol, caffeine, nicotine, peppermint).
- Avoid eating within 3 hours before bed.
- Elevate the head of the bed.
- Treat with proton pump inhibitors (PPIs).

Asthma symptoms improve with weight loss, especially after bariatric surgery.

Address comorbid ABPA, OSAHS, and stress.

Monitor the peak expiratory flow (PEF; a.k.a. peak expiratory flow rate [PEFR]) in patients with **moderate-to-severe** asthma and in patients who cannot reliably describe symptoms of an exacerbation. Note that **symptom-based** monitoring is as effective as PEF in **all other** groups.

Prescribe pharmacologic treatment when needed. These medications are categorized into quick relief and long-term control categories.

Quick relief (rescue therapy for acute exacerbations):

- Short-acting β_2 -agonists (SABAs)
- Systemic corticosteroids
- Anticholinergics

Long-term control:

- ICSs, which are the most potent and most effective
- LABA with ICS
- Long-acting muscarinic antagonists (i.e., tiotropium)
- Leukotriene modifiers (i.e., montelukast)
- Immunomodulators (e.g., omalizumab, mepolizumab, reslizumab)
- Methylxanthines (e.g., theophylline)

The following text is a review of these drugs followed by the recommended treatment regimens. Also refer to [Table 6-5](#) and see [Table 6-6](#) and [Table 6-7](#).

Table 6-7: Classification of Asthma Severity in Well-Controlled Patients

Step	Classification of Asthma Severity		
	Mild	Moderate	Severe
Step	1-2	3	4-5

Short-Acting β_2 -Agonists (SABAs)

The 1st choice for the rescue treatment of an acute exacerbation is the inhaled short-acting β_2 -agonist albuterol, even if the patient routinely uses it.

For chronic asthma treatment, albuterol is indicated for patients in the U.S. who have intermittent symptoms, though, as previously discussed under [Diagnosis of Asthma on page 6-13](#), the 2020 GINA guidelines recommend an ICS with albuterol or, alternatively, the use of budesonide/formoterol. Know that SABA use > 2 days/week indicates **poor control** of symptoms and treatment should be stepped up to include a controller, usually an inhaled steroid.

Inhaled Corticosteroids (ICSs)

An ICS is the preferred drug for the chronic treatment of persistent asthma when the symptoms are not controlled with a SABA. Some may require addition of a LABA. Why is this? Asthma is an inflammatory process and ICSs subdue the inflammation where it occurs—with minimal side effects. β_2 -agonists are merely bronchodilators and provide only symptomatic treatment.

The bid dosing of ICS is as effective as qid treatments in patients with mild-to-moderate asthma. The dose-response curve for ICS is flattened in the mildly affected patient group—more is not better, and low doses are best. However, in patients with severe asthma, the dose-response curve is not flattened, and this group benefits from increasing the ICS dose early in treatment.

A spacer greatly reduces the amount of metered dose inhaler (MDI) drug deposited in the oropharynx. Large particles are trapped in the spacer, thereby decreasing the systemic effects from swallowed drug. A spacer also increases the amount of drug reaching the lungs.

ICS and safety:

- There is little, if any, effect on the pituitary-adrenal axis.
- There is no increase in fractures.
- Long-term use of high doses over years can contribute to reduced bone mineral density.
- Cataracts and glaucoma are less of a problem with inhaled than with oral corticosteroids.
- Budesonide is the preferred ICS in pregnancy because it has been the most studied. However, if the mom is stable on another ICS, then she should continue that agent.
- ICS can cause easy bruising in elderly patients.
- ICS can cause initial slowing of growth in children, but there is a catch-up period that results in normal height.
- Higher doses can cause oral thrush and dysphonia and have been implicated in recurrent pulmonary infections.

Systemic Corticosteroids

An oral corticosteroid (OCS) is an effective, short-term treatment for acute asthma. It potentiates the effect of β_2 -agonists and has an antiinflammatory effect that decreases the frequency of return visits to the emergency department.

An OCS is indicated in the acute treatment of asthma when the peak flow is < 80% after 3 treatments of rescue SABA.

OCSs have near complete bioavailability and an onset of action within 1 hour. They can be used instead of IV or IM steroids if the patient is not vomiting.

Use IV steroids, at least initially, in respiratory failure.

Due to its side effects, the chronic administration of an OCS for asthma should be prescribed by highly trained asthma specialists and only under strict circumstances. The asthma algorithm does not include chronic OCS therapy until Step 5 (refer to [Table 6-6 on page 6-15](#))—after the institution of all other therapeutic options.

Anticholinergics

Anticholinergics cause a decrease in cyclic guanosine monophosphate (cGMP) that relaxes the contractions of the bronchial smooth muscle. Ipratropium bromide is a short-acting anticholinergic, and tiotropium is an example of a long-acting one. Ipratropium bromide is usually used in acute severe asthma treatment, while long-acting anticholinergics are used in the chronic management of asthma (especially when LABAs are contraindicated or ineffective).

For acute asthma, the use of ipratropium bromide with albuterol for treatment of severe exacerbations in the emergency department or intensive care unit (ICU) can reduce hospitalizations. This combination is also recommended in the 2020 GINA guidelines for use in acute exacerbations of asthma when admitted.

In 2015, the long-acting anticholinergic (a.k.a. long-acting muscarinic antagonist [LAMA]) tiotropium was approved by the FDA for the treatment of chronic asthma. It is typically added to a regimen that already includes the use of an ICS, a LABA, and prn SABA.

Oxygen

Oxygen is given during an asthma exacerbation with a goal of keeping a P_aO_2 of ≥ 60 mmHg or an $S_aO_2 \geq 90\%$.

Long-Acting β -Agonists (LABAs)

Like SABAs, LABAs (e.g., salmeterol, formoterol) induce an increase in cyclic adenosine monophosphate (cAMP), which results in the relaxation of bronchial smooth muscles. Unlike SABAs, however, LABAs cause a sustained effect. Still, LABAs do not address the inflammatory component of asthma, and as such, they are used only with ICS per treatment guidelines.

LABAs are indicated for the treatment of moderate-to-severe asthma with ICS and a SABA. LABAs alone are not recommended for asthma or acute rescue treatment. As noted previously (refer to [Diagnosis of Asthma on page 6-13](#)), GINA guidelines have recommended use of ICS-LABA starting with Step 1.

LABAs should **never** be used as monotherapy in asthma but should always be added to the current use of an ICS! LABA monotherapy correlates with more frequent exacerbations.

LABAs are recommended only in combination with ICS in an asthma regimen either as initial therapy or for patients who are uncontrolled on a SABA and an ICS.

LABAs with low-dose ICS is recommended by the GINA guidelines for EIB.

Leukotriene Modifiers

Leukotrienes are chemical mediators released from mast cells, basophils, and eosinophils. They are potent:

- Smooth muscle contractors
- Promoters of mucus production
- Causes of airway edema
- Vasoconstrictors
- Stimulators of more arachidonic acid release

Montelukast (Singulair) and **zafirlukast** (Accolate) are leukotriene-receptor antagonists (LTRAs), and **zileuton** (Zyflo) is a 5-lipoxygenase pathway inhibitor.

Leukotriene modifiers are less potent than ICSs and are not as effective as LABAs. They are more often used in children and are **not** the preferred treatment in adults.

Leukotriene modifiers also have some utility in the treatment of EIB, but they are effective in only ~ 50% of patients. Patients with an aspirin allergy are more likely to benefit.

Rarely, a patient treated with a leukotriene modifier has been diagnosed with eosinophilic granulomatosis with polyangiitis (EGPA). The agent does not cause EGPA. However, preexisting vasculitis may be unmasked when patients are weaned off corticosteroids and started on a leukotriene modifier. This is a vasculitis discussed in greater detail under **Eosinophilic Granulomatosis with Polyangiitis** on page 6-38.

Theophylline

Theophylline, a methylxanthine, is a less effective bronchodilator than the β_2 -agonists. Some mechanisms of action include bronchodilation and mild antiinflammatory activity brought about through the inhibition of phosphodiesterase. Unfortunately, theophylline has a narrow therapeutic index and an increased risk for toxicity.

Theophylline is **not** recommended for the **acute** treatment of any asthma exacerbation (including in-hospital management) because the benefit does not exceed the risks of toxicity and drug interactions.

For chronic treatment, theophylline is indicated as an adjunct or add-on to a regimen for difficult-to-control asthma. Know that theophylline with an ICS is inferior in efficacy to the combination of a LABA and an ICS. Other

add-on treatments should be used before theophylline such as leukotriene inhibitors, LABAs, and potentially biologic agents, such as omalizumab or dupilumab, if appropriate.

Ideally, give theophylline as a sustained-release preparation and maintain the serum concentration in the therapeutic range of 5–15 mcg/mL (27.75–83.25 μ mol/L). Adverse effects can occur even within the therapeutic range. Definitely know the symptoms of theophylline toxicity and drug interactions. Toxicity symptoms include nausea and vomiting (the first symptoms), headache, tremulousness, and palpitations. Toxic patients may die or suffer morbidity from seizures, hypotension, and cardiac arrhythmias.

The list of drug interactions with theophylline is long but important. Exam-relevant interactions to remember are listed in Table 6-8.

Table 6-8: Drug Interactions with Theophylline

Interaction	Agents
Increase theophylline levels (causing toxicity)	Ciprofloxacin, clarithromycin, zileuton, allopurinol, methotrexate, estrogens, propranolol, verapamil, cimetidine
Decrease theophylline levels (possibly exacerbating asthma)	Various antiseizure medications, rifampin, St. John's wort, and smoking (more of an issue when patients stop smoking and theophylline levels subsequently increase on the same dose)
Decrease levels of coadministered drugs	Phenytoin, lithium

See the **General Internal Medicine** section for an in-depth discussion on theophylline toxicity, including treatment.

Long-Term Control — Immunomodulators

Omalizumab (an anti-IgE agent) is a monoclonal antibody that blocks the IgE receptors on mast cells and basophils. It is indicated in patients who have allergies and severe, uncontrolled persistent asthma currently on high doses of an ICS and a LABA (Steps 5 on the asthma treatment algorithm; refer to Table 6-6 on page 6-15).

Monoclonal antibodies for eosinophilic asthma approved by the FDA: **mepolizumab**, **benralizumab**, and **reslizumab**, which are monoclonal antibodies that bind to and inactivate interleukin-5 (IL-5). **Dupilumab** is an anti-IL-4 receptor antagonist to treat asthma with or without eosinophilia, though it has greater effect with the former.

Long-Term Control — Bronchial Thermoplasty

Bronchial thermoplasty is a bronchoscopic procedure that delivers radiofrequency energy to the airway wall, thereby reducing airway smooth muscle. Purported benefits include improved asthma-related quality of life and reduced emergency department visits and hospitalizations. Long-term effects on lung function are not known.

This technique is not used for acute treatment. This is not commonly done but may be available in some centers for selected patients with severe or persistent asthma not controlled by a robust regimen of inhaled steroids, bronchodilators, and additional medications.

Management of Asthma

Notes on the Guidelines

As discussed under [Diagnosis of Asthma on page 6-13](#), the 2020 GINA recommendations classify asthma by control rather than severity. For chronic asthma management, think about asthma as 2 separate types of clinical encounters: **treatment initiation** and **continuing therapy** (rather intuitive). Refer to [Table 6-5 on page 6-14](#) during this discussion.

Treatment initiation occurs when a patient initially presents with the signs/symptoms of asthma and is not on chronic management. Assess disease severity based on a number of factors (including the FEV₁, but not the peak flow!), then prescribe a step level of treatment.

If your patient's risks include > 1 category, then classify according to the most severe category. Use the purple part of [Table 6-5 on page 6-14](#) to classify the patient, and find the patient's initial severity level by reading the green section of the table in the Severity column. The initial medications you start are based on the initial severity classification and are designated as Steps 1-5.

Continuing Therapy

After instituting the proper initial step level of treatment, reevaluate the patient again in 1 to 2 months to assess the level of **control** using the same set of factors (now you can use either FEV₁ or PEF).

At the initial follow-up visit and all future visits, determine the **control level** of asthma using the purple part of the table and reading the green section in the Control column to determine whether the asthma is well controlled, not well controlled, or very poorly controlled. Based on the level of control, modify the step level of treatment if needed (per [Table 6-6 on page 6-15](#)).

The 2020 GINA guidelines recommend the approach described in [Treatment of Asthma on page 6-14](#).

Once the patient is well controlled for 3 months, look at the regimen required to maintain control and assign the patient a category of severity that corresponds with that step level of treatment (refer to [Table 6-7 on page 6-15](#)). Note that it is only at this point, when the patient is well controlled, that you can define how severe the disease is because the severity of asthma is based on the steps needed to control it. The control aspect of care is dynamic. Every 3 months, step up if the patient is not controlled or step down if controlled. The goal is to maintain control on the fewest medications.

So, the initial assessment is based on the **severity** of the presenting symptoms. Determination of continuing therapy is

based on the **control** of symptoms with treatment. Lastly, the determination of the **severity of disease** is based on how much medication is required to maintain good control. Be careful that you do not confuse these 2 uses of **severity**.

The Treatment Steps

Again, refer to [Table 6-6 on page 6-15](#) for this discussion.

The stepwise approach to treatment relies on the assessments previously discussed (refer to [Continuing Therapy](#)). Patients who have asthma symptoms more than twice a month, who have nocturnal awakening due to asthma no more than once a month, and who do not have risk factors for poor outcomes are generally candidates for Step 1 therapy, ICS for mild intermittent asthma. If they exceed these symptom thresholds, they are considered persistent and treatment escalates to Step 2 therapy, ICS with LABA. An alternative is a leukotriene inhibitor or the next step up. Higher-dose ICSs can be used with more-difficult-to-control asthma, and subsequent add-on therapy includes leukotriene inhibitors, and tiotropium. For severe persistent asthma phenotypes, Step 5 treatment can include oral corticosteroids, anti-IgE (e.g., omalizumab) or anti-IL-5 therapy (e.g., mepolizumab, reslizumab) or anti-IL-4 therapy (i.e., dupilumab). Alternative agents at each step include medications from the next step up or an add-on agent.

The continuous use of oral prednisone is only recommended once other therapies have been exhausted and should be done with expert consultation. Give chronic OCS **only** for severe asthma (or for an acute asthma exacerbation) and, even then, **repeat** attempts to wean. Steroid-sparing drugs have been tried, including methotrexate, cyclosporine, and troleandomycin, but these are not recommended for acute or long-term treatment of asthma.

When an exacerbation occurs, chronic management can be stepped up 1 or 2 levels, then slowly stepped down until symptoms recur, and then stepped up 1 level. When treatment is initially started, it is usually started 1 or 2 levels above the presumed severity level and then gradually stepped down in the same way.

Use LABAs only in combination with an ICS for asthma. ICS is the cornerstone of asthma therapy.

Treat **acute exacerbations** at any level the **same way**: inhaled **SABAs** and oxygen as needed. Add an OCS if the patient's peak flow is < 80% after 3 treatments with an inhaled SABA or if inhaled therapy is unlikely to effectively treat the acute exacerbation due to its severity. Patients should have written action plans to address worsened symptoms and acute exacerbations.

Studies show that guideline-based treatment of asthma is superior to other methods.

Management of Exercise-Induced Bronchospasm (EIB)

Treat EIB with low dose ICS-SABA.

Management of Acute Exacerbations

Algorithms for managing acute asthma exist in the guidelines; the one you use depends upon whether you are treating patients at home, at the clinic, or in the emergency department.

Assess the **severity** based on clinical history, pulse, respiratory rate, PEF (initial contact can be by phone to initiate triage), and physical exam if able.

The 2020 GINA guidelines define mild-to-moderate exacerbations as those patients with the ability to talk in phrases, respiratory rate elevated but < 30 breaths/minute, no accessory muscle use, HR 100–120 bpm, O_2 saturation 90–95%, and PEF $> 50\%$ of predicted. These guidelines recommend that mild-to-moderate asthma exacerbations should be treated in primary care with SABA, supplementary O_2 , and oral corticosteroids. If there is significant objective improvement with initial treatment, the patient can be considered for discharge with a 5–7-day steroid taper and stepped-up controller therapy for 1–2 weeks with a follow-up visit within a week. Patients in exacerbation who are on chronic β -blockers may not respond as well to β -agonists, such as albuterol, and should receive ipratropium.

Severe asthma exacerbation is defined in the GINA guidelines as consisting of being able to talk only in words and not phrases, agitation, the inability to sit still, O_2 saturation $< 90\%$, respiratory rate > 30 breaths/minute, HR > 120 bpm, accessory muscle use, and PEF $< 50\%$. Life-threatening exacerbation is defined as patients who may be drowsy or confused or have a silent chest. They should be treated in an acute care facility with SABA, ipratropium bromide, oral or IV corticosteroids, supplemental O_2 , intravenous magnesium, and possibly high-dose ICS.

A patient who has a sustained PEF > 60 – 80% of predicted or personal best 1 hour after the last SABA treatment and who looks good can potentially be discharged home with a prescription for continued outpatient frequent SABA, OCS, and a close follow-up. However, risk factors for exacerbation, including nature and severity of past exacerbations, should be considered, as well as likelihood of being able to assiduously adhere to the stepped-up regimen for treatment of the acute exacerbation. Close follow-up within a week is recommended.

Consider a patient for hospitalization if despite treatment in the emergency department with repeated doses (usually 3) of inhaled bronchodilators the patient continues to maintain a PEF of 40–69% (e.g., severity of airflow obstruction). As well, consider admitting the patient to the hospital if there is a known severity of prior exacerbations (i.e., required intubation), poor support at home, or underlying psychiatric illness.

If there is deterioration in the emergency department with a drop in the PEF to $< 40\%$, or the patient continues to have signs of severe exacerbation, admit the patient to the ICU. Inpatient care consists of a SABA, oxygen prn, and systemic steroids. If the patient was on an ICS prior to the exacerbation, continue the ICS

during hospitalization. Some spontaneously breathing patients who are awake and can guard their airways may benefit from noninvasive ventilation with bilevel positive airway pressure (BiPAP), but they must be closely monitored as they may require intubation.

Intubation and the Asthma Patient

During a severe asthma attack, the patient initially hyperventilates and the pCO_2 is low. As the chest wall and the diaphragm muscles fatigue, the patient starts to breathe more and more slowly, normalizing the pCO_2 , and later becoming hypercapnic. Mild hypoxemia and **hypocapnia** are the norm with acute asthma attacks. **Normocapnia** or **hypercapnia** indicates impending respiratory failure and possible need for **intubation or noninvasive ventilatory support!**

If intubation is required, first sedate, but paralyze **only** if needed. Try to avoid use of neuromuscular-blocking drugs to avoid a prolonged blockade (this makes weaning more difficult). Avoid morphine because it can cause histamine release.

Once intubated, do not ventilate too quickly! These patients require a prolonged expiratory period, and ventilating at too high a rate causes progressive air trapping. This could happen particularly when assist-control/volume control is used, as every inspiratory effort triggers a full ventilator breath. Patients with severe airflow obstruction do not have enough time for a full exhalation, so as a result of the **dynamic hyperinflation** that happens when the next breath is taken above the functional residual capacity (FRC), breath stacking (a.k.a. auto-PEEP) develops. This causes decreased venous return and hypotension or can lead to barotrauma. Both tension pneumothorax and dynamic hyperinflation cause a decrease in venous return $\rightarrow$ decreased filling pressure $\rightarrow$ decreased cardiac output $\rightarrow$ hypotension and poor perfusion of vital organs and, potentially, cardiac arrest. In patients who succumb to a fatal asthma attack, the amount of auto-PEEP they experience predicts mortality. For patients with significant auto-PEEP, it is the high respiratory rate that causes the problem, and the rate must be reduced, often requiring sedation. This may cause some hypoventilation.

Permissive hypercapnia is a technique of controlled hypoventilation with small tidal volumes. It is no longer recommended to try to get the pCO_2 down to 40 mmHg to resolve the acute respiratory acidosis. This effort in just-intubated asthmatics has had bad outcomes (due to auto-PEEP)! Initially, the focus is maintaining an O_2 saturation of 90%. Do not worry about the pCO_2 —a reasonable level is 60–70 mmHg or even 80 mmHg with a serum pH of 7.20–7.25. The initial blood gas may have an even lower pH and higher pCO_2 , but this generally improves with mechanical ventilation on the next blood gas in 30–60 minutes, depending on these blood gas values.

Besides maintaining an adequate O_2 saturation, you must ensure enough time for the inspired air to get out! Listen with your stethoscope and check that the ventilator is not kicking in while the patient is still exhaling. Monitor the expiratory flow waveform on the ventilator to ensure a return to baseline flow prior to the next inspiratory cycle to look for risk for auto-PEEP. Some ventilators measure auto-PEEP during an expiratory hold maneuver.

When putting an asthmatic patient on a ventilator, use a **low respiratory frequency**, a **small tidal volume**, and **high inspiratory flow rate**. Be aware that with AC/VC mode, if the patient is breathing faster than the set respiratory rate, they will get full tidal volumes and can develop air trapping. These settings cause a prolonged expiratory phase and reduce peak inspiratory pressure. The **high flow** on inspiration allows for more time devoted to expiration. A high flow can result in a slightly higher circuit pressure, but this rarely affects our main concerns—the end-inspiratory plateau pressure and the avoidance of auto-PEEP.

CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

PREVIEW | REVIEW

- What is the specific definition of chronic obstructive pulmonary disorder (COPD)?
- What are the effects of COPD on the alveoli?
- What is the specific definition of chronic bronchitis?
- What is the significance of clubbing in a patient with COPD?
- What is a strong prognostic indicator in COPD?
- A COPD patient with evidence of right heart failure has a resting P_aO_2 of 58 mmHg. How many hours a day should he be on supplemental oxygen?
- What are the benefits of pulmonary rehabilitation?
- Describe the emergent workup of a patient with an apparent COPD exacerbation.

COPD is diagnosed when patients have symptoms of dyspnea, cough, and sputum production **with** evidence of **irreversible** airflow **obstruction** ($FEV_1/FVC < 0.70$ or less than the LLN provided by the PFT lab) without another explanation for disease. This common condition affects 6% of the population and is the 3rd leading cause of death in the U.S.

COPD results from chronic exposure to an inflammatory stimulus (e.g., cigarette smoke, pollution, dust). The lungs respond with inflammatory cell infiltrates and eventually develop structural changes due to the repeated repair attempts. These structural changes are

usually permanent, even after smoking cessation. Chronic exposure causes varying degrees of damage to the large airways, small airways, and lung parenchyma that evolves over time. In later stages, chronic hypoxic vasoconstriction of the small pulmonary arteries causes pulmonary hypertension. If pulmonary hypertension progresses, right heart failure ensues with cor pulmonale.

Although smoking is definitely a cause of COPD, not all cigarette smokers develop COPD. Disease expression is mediated by additional factors, such as genetics and environment. However, the number of pack years smoked contributes to severity.

Pathophysiology

Cigarette smoking damages both large and small airways, as well as the alveoli.

Large airway damage causes the cough and mucus production that are clinically diagnosed as **chronic bronchitis**.

Small airway damage causes **airflow obstruction** with hyperinflation. Airflow obstruction is caused by the narrowing of these small airways in response to smoke. Inflammatory cells are recruited and infiltrate the walls, secreting mucus. Fibrosis ultimately contributes to chronic airflow obstruction and intermittent bronchoconstriction.

Over time, the smallest airways and alveolar spaces increase in size to try to overcome the airway resistance instigated by the narrowing—a phenomenon called **hyperinflation**. As a compensatory maneuver, it works nicely at first and is expressed as a spirometric increase in the RV and even in TLC.

However, as the lungs lose elastic recoil, the stretched-out small airways and the alveolar sacs trap air, rather than forcing it out against the resistance. Clinically, you will see this as the development of a barrel chest and a prolonged expiratory phase, manifested as an increase in TLC.

Alveolar damage also leads to impaired **gas exchange**. Over time, the alveolar sacs become distended and perforated units full of an “inflammatory soup” of macrophages and other immune cells. Pathologically, these changes are described as emphysema. However, not all patients develop emphysema.

Emphysema can occur focally in the bronchioles (centriacinar) or it can occur evenly across the lung (panacinar). Centriacinar emphysema is seen most often in smokers, and it usually affects the upper lungs. Panacinar emphysema is seen most often in α_1 -antitrypsin deficiency, and it typically affects the lower lungs. Advanced COPD from cigarettes usually involves both types.

Small airway and alveolar disease are present in almost all people with COPD, but the damage does not universally correlate with a specific presentation. That is, the damage to these units causes symptoms that vary from person to person.

Diagnosis and Assessment of COPD

Suspect COPD in any patient who presents with dyspnea, chronic cough, and sputum production—whether they smoke or not. Know that, by definition, bronchitis without objective evidence of airway obstruction is **not** COPD.

Recognize that some patients do not complain of shortness of breath. Rather, they progressively restrict their exertion in order to avoid activities that make them short of breath. For example, they might start taking elevators instead of using the staircase, or they might give up riding a bicycle.

Chronic bronchitis is defined as cough with sputum production for at least 3 consecutive months within at least 2 consecutive years. Patients may have a bronchospastic component responsive to bronchodilators.

Physical exam classically shows an obvious prolonged expiratory phase, wheezing, barrel chest, and increased lung sizes to percussion. Late-stage patients or those in exacerbation often sit forward on their elbows in the tripod position in order to harness strength from their accessory muscles. These patients are often cyanotic in the nail beds and lips.

The traditional descriptions of pink puffers and blue bloaters have fallen out of favor because COPD is **always** a mixed pathologic picture of chronic bronchitis and emphysema. Differentiation between the 2 clinical presentations is artificial because the overwhelming majority of patients do not present that way and treatment is the same.

Know: COPD, as an isolated disease process, does not cause clubbing. If you see clubbing in a patient with COPD, look for other lung pathology, such as IPF or lung cancer.

The Global Initiative for Chronic Obstructive Lung Disease (**GOLD**) is a worldwide association that sets the criteria for the diagnosis, severity grading, and management of COPD.

The GOLD criteria categorize COPD into 4 levels of severity based on the reduction of the FEV₁ compared to the predicted value. All 4 groups require spirometric diagnosis of irreversible obstruction as defined by an FEV₁/FVC < 0.70. The COPD levels are:

- GOLD 1 = mild (FEV₁ ≥ 80% of predicted)
- GOLD 2 = moderate (FEV₁ = 50–79%)
- GOLD 3 = severe (FEV₁ = 30–49%)
- GOLD 4 = very severe (FEV₁ < 30%)

The GOLD spirometric diagnostic criteria are controversial because they overdiagnose COPD in the elderly and underdiagnose it in patients < 45 years of age with mild disease. An alternative criterion for COPD, is a FEV₁/FVC below the LLN provided by the PFT lab.

The GOLD guidelines are updated regularly, including in 2020. Recent updates have emphasized that spirometry

alone does not capture COPD's full impact on individual patients. Therefore, it is recommended to assess COPD addressing:

- the GOLD **spirometry** criteria (1–4),
- the assessment of symptoms with the COPD Assessment Test (CAT) or the modified Medical Research Council (mMRC) Dyspnea Scale,
- the risk of **exacerbations** (based on history of previously treated exacerbations), and
- the presence of other **comorbidities**.

In this revised combined assessment, patients are divided into 4 groups based on symptoms using the CAT score and their exacerbation history:

- A = fewer symptoms (CAT < 10 or mMRC 0–1) and low exacerbation history
- B = more symptoms (CAT ≥ 10 or mMRC < 2) and low exacerbation history
- C = fewer symptoms (CAT < 10 or mMRC 0–1) and high exacerbation history
- D = more symptoms (CAT ≥ 10 or mMRC < 2) and high exacerbation history

For example, examining the assessments, a GOLD 4 with low exacerbation history and minimal symptoms would be assessed as GOLD 4A, but a GOLD 4 with high exacerbation history and more symptoms would be GOLD 4D. Together this approach assesses the level of airflow obstruction and ranks the severity of symptoms and frequency of exacerbations (A–D).

The **BODE** index (body mass index, airflow obstruction, dyspnea, and exercise capacity) adds a little to the GOLD severity criteria by considering how outcomes are affected by some extrapulmonary manifestations. Patients get points according to body mass index, FEV₁, dyspnea, and a 6-minute walk test. The result helps to prognosticate 4-year survival and assess response to treatment changes. Higher BODE scores correspond to an increased risk of death.

Again: COPD pathology results in airflow obstruction, hyperinflation, and problems with gas exchange.

Some must-know items and useful clinical pearls:

- Diagnosis is based on FEV₁/FVC < 0.70 by GOLD criteria or alternatively by a FEV₁/FVC less than the LLN.
- BODE index and exercise tests, such as a 6-minute walk test, are strong prognostic indicators in COPD. Low FEV₁ also can correlate with mortality.
- **Pack years** of cigarette smoking is the best predictor of FEV₁. The normal age-related decrease in FEV₁ is ~ 15–30 mL/year. COPD patients can lose 60–120 mL/year of lung function.
- Cessation of smoking is most beneficial to the lungs when accomplished at a **younger** age and before there is any loss of pulmonary function.
- P_aO₂ does not usually fall until late in the disease, when the FEV₁ is < 50% of predicted (or even lower in many patients).

- Chronic **retention** of CO_2 does not generally occur until very late in the disease, usually when the FEV_1 is < 1 liter.
- Cor pulmonale (right ventricular [RV] dysfunction due to chronic lung disease) occurs only after prolonged, marked reductions in the FEV_1 (usually $< 25\%$ of predicted) with severe chronic hypoxemia.
- Hypoxemia in COPD is almost exclusively due to V/Q mismatching. Therefore, COPD exacerbations **are** responsive to low-flow oxygen (2–3 L/minute). If a patient with an apparent COPD exacerbation is not responsive to moderate amounts of oxygen, consider another cause for the decompensation, such as a shunt process.

Let's review the lung mechanics of emphysema. Decreased elastic recoil means increased compliance and an increased TLC. Although there is an increase in TLC, there is an even greater increase in RV from air trapping, so VC (or FVC) is decreased! This air trapping leads to the process of dynamic hyperinflation and can result in a large amount of auto-PEEP (intrinsic PEEP). DLCO is reduced in patients who have a great amount of emphysema. [Figure 6-7](#), [Figure 6-8](#), and [Figure 6-9](#) show classic COPD changes on CT and on chest x-rays.

Treatment of COPD

General Treatment Principles

Management is based on the 2020 GOLD updates:

- Educate each COPD patient; encourage smokers to quit. Effective nicotine replacement therapy comes in many forms (i.e., gum, nasal spray, patch, tablet, lozenge, inhaler). Other pharmaceutical options include varenicline, bupropion, and nortriptyline. Review inhaler technique regularly.
- Use SABAs as needed in all patients.
- Use **long-acting bronchodilators** when SABAs fail to control symptoms. These drugs **reduce exacerbations and hospitalizations**.
- Long-acting anticholinergics (e.g., tiotropium) improve the efficacy of pulmonary rehab if the patient is enrolled and decrease exacerbations and hospitalizations.
- ICSs are no longer routinely recommended. They should be considered in Group D patients with asthma overlap, eosinophilia > 300 cells/ μL , or as trial in some cases. ICSs may cause an increased risk for pneumonia in severe COPD. ICSs are not recommended as long-term monotherapy for COPD.
- Patients already on LABA/LAMA with or without ICS who continue to have frequent exacerbations, may benefit from roflumilast, a phosphodiesterase-4 inhibitor, or azithromycin to reduce acute exacerbations. Roflumilast does not have any direct bronchodilator activity and is primarily directed at patients with predominant bronchitis, not emphysema.



Figure 6-7: CT—bullous emphysema
Source: Vinay Maheshwari, MD



Figure 6-8: Emphysematous COPD
James Heilman, MD

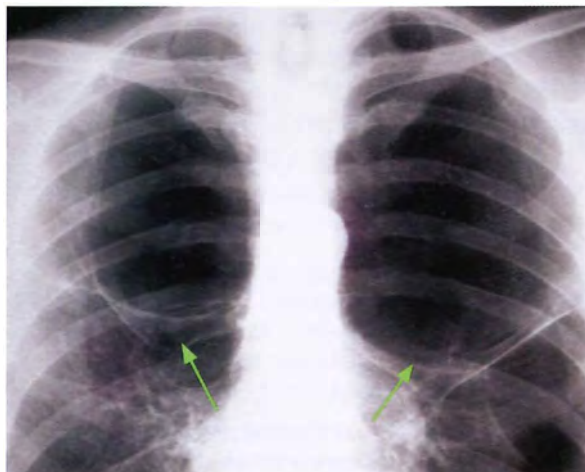


Figure 6-9: Chest x-ray showing emphysema bulla

- Patients with frequent exacerbations may benefit from azithromycin 3x/week, but they may infrequently experience hearing loss and harbor resistant bacteria. There can be a small risk of arrhythmias. A discussion with the patient of the risk/benefits of azithromycin should occur.
- Reserve theophylline for use in those who are on maximum therapy. It adds a slight bronchodilator effect to salmeterol, and this relieves breathlessness and reduces exacerbations. It may also have salutatory effects on the diaphragmatic function and the hypoxic drive to breathe in higher doses, but there is a narrow therapeutic index.
- Do not use leukotriene modifiers unless there is clearly asthma overlap syndrome. These agents are ineffective in pure COPD.
- Give pneumococcal (PCV13 and PPSV23) and influenza vaccines.
- Use oxygen as needed when patients meet the criteria (see below).
- Screen for α_1 -antitrypsin deficiency in all patients < 45 years of age who get COPD and in those who have a lower lobe prominence of bullae. The WHO 1997 guidelines recommend screening all COPD patients once at some point, especially in areas of high prevalence.
- Consider a referral for pulmonary rehabilitation.

Oxygen therapy for patients with COPD: The focus of O₂ therapy in patients with COPD (or in any other patient in respiratory distress, for that matter) is to give them enough O₂ to achieve a 90% O₂ saturation (S_aO₂)—or as close to that as possible. The 2016 Long-Term Oxygen Treatment Trial (LOTT) via the National Institutes of Health (NIH) Centers for Medicare and Medicaid Services (CMS) showed that there was no survival benefit to prescribing supplemental O₂ to those with moderate resting desaturation (S_pO₂ 89–93%). While CMS guidelines for supplemental oxygen prescription have not been revised as a result of this 2016 study, it appears that long-term oxygen therapy to prolong survival among patients with COPD would benefit those who have chronic (> 3 weeks) severe resting P_aO₂ of $\leq$ 55 mmHg or S_pO₂ of < 88% on room air. The LOTT study would also move the threshold for prescribing oxygen for ambulation to $\leq$ 89% or for those hypoxemic individuals whose dyspnea is significantly relieved by oxygen. However, these findings have not been officially incorporated into current U.S. oxygen-prescribing guidelines at this time. Not treating hypoxia causes further end-organ damage, worsens pulmonary vasoconstriction, and leads to the downward spiral to death.

The CMS criteria for starting continuous O₂ are:

- a resting P_aO₂ $\leq$ 55 mmHg or an S_aO₂ $\leq$ 88% or
- a resting P_aO₂ $\leq$ 59 mmHg or an S_aO₂ $\leq$ 89% in a patient with evidence of cor pulmonale.

The criteria of cor pulmonale include:

- Clinical evidence of right heart failure
- P pulmonale on ECG (a > 2.5 mm P-wave height in leads II, III, and aVF)
- Hct > 56% (Cor pulmonale causes chronic hypoxia leading to polycythemia.)

Continuous O₂ use, if needed for resting hypoxemia, increases the life span. Keep these patients on supplemental oxygen 24 hours/day (if not possible, at least 15 hours/day).

Intermittent O₂ use: Some patients have similar findings of hypoxia and desaturation during low-level exercise or sleep. Giving these patients supplemental O₂ during these activities can improve the exercise capacity and the quality of life, but it does not improve survival.

After 2 months of a stable drug regimen, reassess COPD patients placed on oxygen during an exacerbation—oxygen can be discontinued in up to 40% of these patients!

Pulmonary rehabilitation: A pulmonary rehabilitation exercise regimen results in a small but significant improvement in overall strength and endurance and is encouraged for those with high CAT scores and frequent exacerbations. Unfortunately, pulmonary rehabilitation does not improve PFT or ABG parameters. Know: Pulmonary rehabilitation improves symptoms and the quality of life and reduces the number of hospitalizations and days in the hospital. The 2020 GOLD update states that pulmonary rehab improves dyspnea, health status, and exercise tolerance in stable patients. Many of the immediate benefits of pulmonary rehabilitation are lost without subsequent maintenance exercise.

Lung volume reduction surgery (LVRS): LVRS can be useful for emphysematous patients with upper lobe disease and low exercise capacity. Those with diffuse emphysema are not likely to benefit. The 2003 National Emphysema Treatment Trial (NETT) was a large, randomized trial of LVRS for emphysema that showed an improved exercise capacity but no overall mortality benefit in patients with severe emphysema. There was benefit for a subset of study participants with predominantly upper lobe emphysema and low exercise capacity who showed improvement in exercise, quality of life, and mortality. LVRS can be done in such patients who are symptomatic despite the use of optimal bronchodilator therapy and pulmonary rehabilitation. However, those in the most severe group (those with an FEV₁ < 20% or a DLCO < 20%) should not undergo LVRS due to high mortality. Lung volume reduction via endoscopic bronchial valves or lung coils in select cases of hyperinflation refractory to medical therapy may be considered, but evidence of benefit is not as robust.

Know: No medication prevents the decline of FEV₁ in COPD! The only interventions that affect long-term COPD outcomes are smoking cessation, oxygen therapy in hypoxemic patients, and LVRS or lung transplantation in appropriately selected patients.

Treatment of Stable COPD

As discussed previously under [Diagnosis and Assessment of COPD on page 6-21](#), the GOLD COPD assessment classifies patients into Groups A, B, C, and D. Note: In the following treatment guidelines, **bronchodilator** means either an anticholinergic or a β -agonist. Thus, a short-acting bronchodilator can refer to either a short-acting anticholinergic or a SABA. A long-acting bronchodilator can refer to either a long-acting anticholinergic or a LABA.

The following treatments are based on the 2020 GOLD COPD guidelines:

- Group **A** patients: A short- or long-acting bronchodilator is used to improve breathlessness.
- Group **B** patients: A **long-acting bronchodilator** is used, but for patients with persistent breathlessness, long-acting bronchodilators can be combined.
- Group **C** patients: The first choice is a LAMA. Second choice is LAMA + LABA. Third choice is LABA + ICS (if there is asthma-COPD overlap or eosinophilia of at least 300 cells/ μ l, but this may increase risk of pneumonia).
- Group **D** patients: First choice is LAMA + LABA. Second choice is either LABA + LAMA + ICS or LABA + ICS. Adding an ICS is useful in asthma-COPD overlap (see [Asthma-COPD Overlap \(ACO\)](#)) patients or if there is eosinophilia of at least 300 cells/ μ l. If there are frequent exacerbations, azithromycin may be given 3 $\times$ /week (i.e., MWF) or roflumilast may be used if FEV₁ < 50% and chronic bronchitis is present.

Treatment of COPD Exacerbations

An exacerbation is a worsening of respiratory symptoms beyond the normal variation requiring a change in medication. Patients frequently present with worsening shortness of breath, coughing, wheezing, sputum production, and hypoxemia.

The **assessment** of COPD exacerbations depends upon the nature and severity of the symptoms:

- Consider obtaining a **chest x-ray**. This can help diagnose or rule out pneumonia, pulmonary edema, or pneumothorax. Up to 23% of presenting patients show new infiltrates that can change the chosen therapy.
- Consider obtaining an **ECG**. Pay attention to the history for clues suggesting pulmonary embolism, such as S₁Q₃T₃, anterior T-wave inversions, new right bundle branch block (RBBB), or reactive airway disease. Pulmonary emboli are often an unsuspected trigger of COPD exacerbations. Remember that the most common ECG abnormality in a pulmonary embolism is sinus tachycardia.
- Assess the S_aO₂ and draw an **arterial blood gas** if respiratory failure is suspected. Hypoxia not improving on oxygen, elevated pCO₂ above baseline, or acute respiratory acidosis indicate life-threatening respiratory failure.

- Do **not** use spirometry or peak flows to diagnose or to assess the severity of a COPD exacerbation.
- COPD exacerbations contribute to advancement of disease.

For the **treatment** of COPD exacerbations:

- Start treatment with a **SABA** and add an anticholinergic agent if the patient does not quickly improve.
- Give low-flow oxygen (1–2 L/minute) with close observation to keep the saturation > 90%. Note that patients with initial abnormal blood gases are at risk for hypercarbia and subsequent respiratory failure with supplemental O₂ administration.
- Begin **systemic corticosteroids**. These drugs shorten recovery time, reduce the risk of early relapse, and decrease the length of hospital stays. Treatment with 40 mg of oral prednisone for 5 days generally is as good as a 14-day taper for most patients with acute exacerbations. In some instances, additional steroids are required, up to a 14-day course. Patients with severe exacerbations, such as those admitted to the ICU or with a history of requiring a repeated or an extended course of steroids, often require a more individualized approach, including the use of IV steroids.
- Start antibiotics with increased sputum production, dyspnea, and purulent secretions. The recommended 5- to 7-day course of broad-spectrum antibiotics should be guided by local bacterial resistance patterns; consider **amoxicillin/clavulanic acid**, **azithromycin**, or tetracyclines. If the patient has underlying severe GOLD with high CAT and exacerbation scores, cover for *Pseudomonas* or resistant organisms with addition of **respiratory quinolones**.
- Noninvasive positive pressure ventilation (**NiPPV**), generally with BiPAP, is used to treat patients who are awake and spontaneously breathing but have labored breathing or hypercapnia. NiPPV reduces hospital stays, intubations, and mortalities in exacerbations. However, for patients with contraindications to BiPAP or for those rapidly progressing to respiratory failure, endotracheal intubation with mechanical ventilation is recommended. Remember, these patients are at risk for development of dynamic hyperinflation with increase in auto-PEEP, resulting in venous collapse and pneumothorax. Prolonging expiratory time and increasing inspiratory flow rates is protective.
- For patients who experience frequent exacerbations, consider prescribing azithromycin 3 $\times$ /week or roflumilast (if FEV₁ < 50% and chronic bronchitis is present).

Asthma-COPD Overlap (ACO)

ACO is a category (estimated to be 15–32%) defined by GINA 2020 as comprised of patients with both COPD and asthma features. ACO can stem from various underlying

mechanisms. Like COPD, it usually occurs after 40 years of age. The outcomes tend to be worse than in COPD or asthma alone, with more frequent exacerbations, more rapid decline in lung function, decreased quality of life, and higher mortality. Use ICS along with other controller medications. Evidence-based therapy for this category is lacking. However, patients may be treated with both asthma and COPD medications on an individual basis.

α_1 -ANTITRYPSIN DEFICIENCY

PREVIEW | REVIEW

- A 30-year-old smoker presents with COPD and emphysematous bullae in the bases. Which factors make you suspect α_1 -antitrypsin deficiency?
- What is the single environmental agent or exposure that worsens lung disease in all types of α_1 -antitrypsin deficiency?

α_1 -Antitrypsin deficiency causes 1–2% of COPD cases, so it is rather **rare**. Consider it in **young** smokers with bullous emphysematous COPD in the lung bases and in patients with family histories of both liver and lung disease.

The alleles responsible for α_1 -antitrypsin deficiency occur on a locus called *Pi*. The most common allele is *Pi^M*. The *M* means it moves moderately fast on an electrophoretic strip. There are other variants of *Pi*—some move faster (*Pi^F*) and some slower (*Pi^Z*). Null alleles do not code for any α_1 -antitrypsin. Patients homozygous for the slower allele (*Pi^{ZZ}*) or heterozygotes for *Z* and null alleles (both groups are referred to as *Pi^Z*) have severely decreased levels of α_1 -antitrypsin. Levels of α_1 -antitrypsin in heterozygotes (*Pi^{MZ}*) are ~ 60% of normal.

Disease severity is variable. For example, some *Pi^Z* individuals do **not** get COPD, and airflow obstruction among *Pi^{MZ}* individuals is unpredictable. Contrary to previous teachings, some studies show that heterozygote (*Pi^{MZ}*) nonsmokers have more airflow obstruction than patients with normal α_1 -antitrypsin levels (*Pi^{MM}*). One unifying factor in disease progression is cigarette smoking. Smoking **worsens lung disease in both groups**. Genetic factors, other than *Pi* locus alleles, likely account for the variability in disease expression.

Do not forget! Patients with α_1 -antitrypsin deficiency can also develop progressive **liver fibrosis** and **cirrhosis**. Expression of the genetic defect in the liver is variable and, as with the lung disease, *Pi^Z* patients are most affected. With cirrhosis of any cause, there is an increased incidence of hepatocellular carcinoma.

α_1 -Antitrypsin deficiency presents as airflow obstruction in a young person with unusual bullous formation in the lung bases. Chest x-ray often shows hyperinflation and bullae. There may also be elevated serum aminotransferase levels. In severe *Pi^Z* cases, liver disease can progress to cirrhosis in childhood.

Diagnosis of α_1 -Antitrypsin Deficiency

Diagnose α_1 -antitrypsin deficiency by measuring the serum level of α_1 -antitrypsin followed by the genetic testing of the *Pi* locus. Once you know the phenotype and the genotype, you can better counsel the patient and the patient's family members. The 2020 GOLD guidelines suggest a screening serum level in all patients who develop COPD at some point as well as in family members with α_1 -antitrypsin deficiency.

Treatment of α_1 -Antitrypsin Deficiency

α_1 -Antiprotease (pooled human α_1 -antitrypsin) can be given in weekly IV infusions in patients with severe disease. These infusions are expensive!

Selection criteria for IV augmentation:

- *Pi^Z* genotype
- Serum α_1 -antitrypsin level < 11 μ mol/L (equal to 50–80 mg/dL, depending on the assay)
- Abnormal chest CT
- Abnormal spirometry
- Nonsmoking or ex-smoking patient

Some experts advocate treating all individuals who have α_1 -antitrypsin deficiency with low levels of α_1 -antitrypsin to help maintain the current lung function. However, the expense of this intervention is hard to justify in COPD patients with end-stage lung damage.

In addition to the IV infusion, continue to treat patients with bronchodilators, antibiotics, oxygen as needed, and yearly vaccines. Please do not forget the vigorous anti-smoking message!

When the COPD is severe, the only treatment is lung transplantation. Note that IV infusion has no effect on liver disease and the only treatment for cirrhosis is liver transplantation.

BRONCHIECTASIS

PREVIEW | REVIEW

- What is the classic presentation in a patient with bronchiectasis?
- Which organism is particularly contagious in cystic fibrosis (CF)?
- What is the next test to perform in a patient with new diagnosis of CF?
- What are the inhaled treatments for CF?

Bronchiectasis is a persistent, pathologic, permanent dilatation of the bronchi caused by inflammation and destruction of the airway walls. The bronchi fill with mucus and pus and then become fibrotic. The infectious

or inflammatory insult is sometimes primary (e.g., adenoviral infection), or it can be secondary due to an underlying lung disease that prevents adequate clearance of organisms from the respiratory tree (e.g., *Cystic Fibrosis* (CF)).

Consider bronchiectasis in an older or middle-aged individual with a **chronic** productive cough with copious **purulent** sputum, with or without hemoptysis, that either arose insidiously over years or followed a dramatic lung event (e.g., chemical inhalation, severe pneumonia).

Specific causes of bronchiectasis include:

- Severe infections, such as viral pneumonia (from adenovirus or influenza), staphylococcal or gram-negative pneumonia (severe, untreated, or poorly treated), *Bordetella pertussis*, and mycobacteria (especially if there is a focal area of involvement). It is often difficult to tell whether the organisms growing in the patient's lungs initiated the bronchiectasis or are just colonizers. (For example, *Mycobacterium avium* complex is sometimes a colonizer of bronchiectatic lungs, but it can also cause bronchiectasis.)
- Focal lung obstructions (e.g., endobronchial tumors, lymph nodes, foreign bodies)
- Systemic diseases that reduce mucociliary clearance or prevent an adequate immune response (e.g., CF, primary ciliary dyskinesia, HIV/AIDS, immunoglobulin deficiency). These allow the colonization of destructive bacteria.
- Inhalation of a toxin (e.g., chemical fumes); aspiration of gastric contents
- ABPA (a favorite test question)
- α_1 -Antitrypsin deficiency (rare)
- Gastroesophageal reflux (increasingly implicated as a potential cause)
- Collagen vascular diseases, such as rheumatoid arthritis
- Anatomic defects of trachea or bronchi; enlargement of either can decrease mucus clearance (i.e., Mounier-Kuhn syndrome)

Diagnosis

Diagnose bronchiectasis with an HRCT of the chest, although many cases of bronchiectasis may be evident on standard CT of the chest as well (Figure 6-10). A bronchiectatic airway will be wider than the accompanying blood vessel. Chest x-ray findings are usually nonspecific but may show surrounding infiltrates. Sometimes classic "tram tracks" can be seen. Treatment decisions are not only driven by symptoms, marked changes in sputum color, consistency, and volume, but also by Gram stains with bacterial sputum culture and acid-fast bacteria (AFB) smears with cultures. Based on the clinical history and physical exam, consider testing for HIV and rheumatoid arthritis, measuring quantitative immunoglobulins, performing the prick test for ABPA, and ordering a sweat chloride measurement.

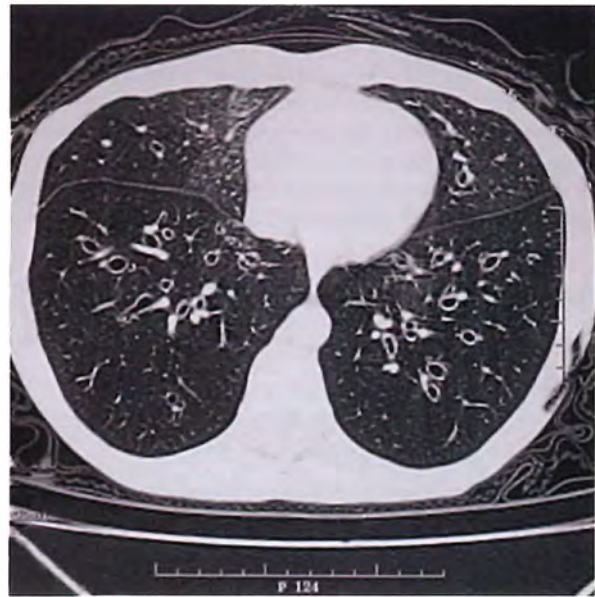


Figure 6-10: HRCT—bronchiectasis

Source: Thomas Roy, MD

Treatment

Clearance of respiratory secretions is a mainstay in the management of bronchiectasis. This includes coughing, chest physiotherapy, postural drainage, and eliciting sputum, often with the use of an expectorant such as guaifenesin as well as adequate hydration. An oscillating positive expiratory pressure (PEP) device such as a flutter valve or chest percussion can help mobilize mucus by oscillating the air column within the trachea and bronchi. The evidence base for these interventions is not solid, but they are commonly employed and generally afford some symptom relief.

Bronchiectasis exacerbations are generally treated with a 14-day course of antibiotics (though the evidence base is inconclusive) to reduce the burden of pathogenic organisms in the small airways (or treat ABPA if that is the underlying cause).

Microbiologic data from sputum drives the antibiotic choice. An organism of concern is *Pseudomonas*. However, patients with exacerbations frequently respond to antibiotics that do not treat *Pseudomonas*. In this case, there may be a colonization of *Pseudomonas* and also a proliferation of other organisms causing the exacerbation.

Chronic antibacterial **prophylaxis** for bronchiectasis is usually reserved for those with frequent exacerbations who are not able to take prophylactic macrolides. Inhaled alternating monthly tobramycin is also used in those with frequent exacerbations and *Pseudomonas* in sputum. **Macrolides** can provide antiinflammatory and antibiotic effects. The European Respiratory Society 2017 guidelines on bronchiectasis recommend, based on several studies, treating patients with several exacerbations with extended macrolide preventive therapy, such as MWF azithromycin, in non-CF bronchiectasis. If long-term macrolides

are considered, obtain sputum culture first to assess for atypical mycobacterial or pseudomonal presence; if present, do not use.

Massive hemoptysis or unresolving focal infections require vascular embolization by interventional radiology or even surgical resection for localized bronchiectasis.

Do **not** treat bronchiectasis with aerosolized recombinant DNase (because it can cause harm), except in patients who have underlying CF.

Cystic Fibrosis (CF)

Cystic fibrosis, an autosomal recessive disease, occurs as a result of a mutation in the CF transmembrane conductance regulator (*CFTR*) gene on chromosome 7. This protein normally controls Na^+/Cl^- transport on the epithelial membranes of the lung, GI tract, sweat glands, and the urogenital system. The gene mutation results in decreased Na^+ absorption and Cl^- secretion. Lung mucus is dehydrated, sticky, and low in oxygen. This contributes to bacterial superinfection with particularly virulent and refractory organisms.

Diagnosis

Only 5% of patients with CF initially present in adulthood, and the median survival is 29 years.

Initial diagnosis: Consider adult CF in a patient with a history of recurrent sinusitis, nasal polyps (found in 25%), weight loss, chronic cough productive of thick, purulent sputum, and recurrent febrile respiratory infections requiring antibiotics. Sputum Gram stain often reveals gram-negative rods (GNRs), and cultures often grow *Staphylococcus*, *Haemophilus influenzae*, *Pseudomonas*, or enteric GNRs (e.g., *Proteus*, *E. coli*, *Klebsiella*). Growth of less common organisms such as *Alcaligenes xylosoxidans*, *Burkholderia gladioli*, or *Burkholderia cepacia* raises the suspicion for CF. *Aspergillus* and nontuberculous mycobacteria are also commonly found. CF patients tend to go through a progression of colonization and infection with gram-positive organisms and then gram-negative bacteria, the most concerning of which is *Burkholderia*. This particular organism is highly contagious among CF patients, causes further decline in the lung function, and can lead to death.

Most **male** patients with CF are **infertile**, providing an additional historical clue. Females may not be infertile.

Clubbing and the signs and symptoms of cor pulmonale occur in late-stage disease.

Chest x-ray changes are nonspecific (hyperinflation and bronchial cuffing), but **bronchiectasis**, which can become extensive, is common. Pneumothorax occurs in 10%. Spirometry shows reductions in the FEV_1/FVC ratio and the FEV_1 , some of which are reversible until late in the disease process.

Screen for CF by performing the **sweat chloride** test. Approximately 1–2% of patients with CF have normal

sweat chloride tests, so pursue further testing if the patient has a strong clinical history and a negative sweat chloride test. The nasal potential difference (NPD) test and a **genetic analysis** are confirmatory tests of CF. If CF is confirmed, then proceed to *CFTR* genotyping.

Management

Manage CF with aggressive pulmonary toilet (percussion and exercises preserve lung function), oral pancreatic enzymes, ADEK fat-soluble vitamin supplementation, and culture- and susceptibility-guided antibiotics for exacerbations. Inhaled bronchodilators may help with obstructive lung disease and mucus clearance. Routine use of inhaled steroids is not recommended as benefit has not been shown and it may increase infections.

Two inhaled medications for CF management are recombinant human **DNase** and inhaled **hypertonic saline**. DNase degrades accumulated DNA in the airways and provides for better airflow. Hypertonic saline improves airway clearance.

IV antibiotics are used for more severe pulmonary exacerbations or resistant organisms. All gram-negative organisms get 2 antipseudomonal antibiotics to cover mucoid and nonmucoid strains until you obtain the identification and susceptibilities. In **CF patients**, *Pseudomonas* is often multidrug resistant. The empiric treatment for exacerbations related to *Pseudomonas* is a combination of piperacillin-tazobactam, ceftazidime, imipenem-cilastatin, or meropenem plus an aminoglycoside or a fluoroquinolone. Treatment is adjusted according to drug susceptibility results.

For the **chronic** management of CF, **antibiotic prophylaxis** using drug rotations helps to prevent exacerbations by reducing microbial colonization. Inhaled aminoglycosides, inhaled aztreonam, and oral azithromycin are commonly used. Azithromycin is used as an antiinflammatory medication, and it reduces the adherence of *Pseudomonas* to the pulmonary epithelial cells, thereby preventing its growth within biofilm.

Bilateral lung transplantation is a treatment option in patients with end-stage lung disease secondary to cystic fibrosis, with a 65% 5-year survival rate.

Complications of CF include respiratory failure, pulmonary hypertension with cor pulmonale, pneumothorax, and hemoptysis.

CFTR modulator therapies are designed to correct the function of the defective *CFTR* protein. The correction allows Na^+ and Cl^- to move properly in and out of the cells lining the lungs and other organs. In 2012, the FDA approved ivacaftor (Kalydeco) for patients over age 6, and in 2019 approved use for infants, with a certain mutation of CF. The combination drug lumacaftor/ivacaftor (Orkambi) was approved in 2015 to treat CF in patients ≥ 12 years of age and in 2018 approved for CF patients ≥ 2 years of age. The combination drug tezacaftor/ivacaftor (Symdeko) was approved in 2018 for

homogenous F508 deletions and residual function mutations. Elexacaftor/ivacaftor/tezacaftor (Trikafta) was approved in 2019 for patients ≥ 12 years of age who have at least one *F508del* mutation, the most common CF gene mutation.

INTERSTITIAL LUNG DISEASES (ILDs)

PREVIEW | REVIEW

- Name the common clinical features of all interstitial lung diseases.
- Which disease do you think of when a patient presents with recurrent pneumonia each time she cleans her birdcage?
- Characterize the chest x-ray abnormalities in patients with a history of significant asbestos exposure.
- Smoking and asbestos exposure increase the risk of which types of lung cancer?
- Which type of CT scan assists with the diagnosis of idiopathic pulmonary fibrosis (IPF)? Which findings are seen in early IPF?
- What is the typical presentation of a patient with IPF?
- Lung cancer is associated with what nail finding?
- How do you evaluate patients with IPF?
- Characterize the differences in presentation between IPF and cryptogenic organizing pneumonia.
- Which findings in a pleural effusion can be helpful in distinguishing rheumatoid arthritis as an etiology?
- In which autoimmune diseases is pulmonary hypertension a prevalent clinical presentation (sometimes out of proportion to the amount of pulmonary disease)?
- Which pulmonary function test results are seen with sarcoidosis?
- What are the indications for the treatment of sarcoidosis with corticosteroids?
- What is a potential lung complication of lymphangioleiomyomatosis?
- Which vasculitis is cytoplasmic-antineutrophil cytoplasmic antibody positive (c-ANCA+) and anti-proteinase-3 antibody positive (anti-PR3+)?
- Characterize the typical presentation of a patient with granulomatosis with polyangiitis.
- An asthma patient with worsening symptoms and peripheral eosinophilia makes you think of which diseases?

- Eosinophilic granulomatosis with polyangiitis is associated with which medications?
- Describe the differences in the presentations of Löffler syndrome, acute eosinophilic pneumonia, and chronic eosinophilic pneumonia.
- What is the workup of the uncontrolled asthmatic that you suspect has allergic bronchopulmonary aspergillosis?

OVERVIEW

ILDs are a diverse (> 100!) group of disorders that affect the supporting tissue of the lung, including the structural portions of the alveolar walls, often with diffuse airway and alveolar involvement.

The interstitium is usually a potential space between the capillaries and the alveoli. In ILDs, specifically fibrotic ILDs, primary or secondary collagen deposition in the interstitium creates fibrosis and changes the architecture of the alveoli and surrounding airways.

ILDs have **common** factors in their clinical presentation: dyspnea, diffuse disease on chest x-ray, restrictive PFTs with a decreased DLCO, and an elevated A-a gradient (Figure 6-11 and Figure 6-12 on page 6-30).

ILDs are grouped into those that have a **known** cause and those that are **idiopathic**. Those with a known cause are usually due to **dust** (organic or inorganic) from occupational or environmental exposures. We will discuss the groups of ILDs as follows:

- Occupational and environmental ILDs
- Idiopathic interstitial pneumonias
- ILDs with other causes

DIAGNOSIS OF ILDs

PFTs in ILD patients may show a classic **restrictive** pattern. This means normal airway flow rates but decreased lung volumes. With decreased compliance, there is increased lung stiffness from increased elastic recoil caused by pulmonary fibrosis (this recoil is decreased in emphysema). A chest x-ray with diffuse interstitial infiltrates is often the 1st suggestion of disease, but it correlates poorly with the severity of disease. High-resolution CT (HRCT) is integral to the workup of ILD.

Chest x-ray clues suggesting the cause of ILD:

- Asbestosis: lower lung field predominance of infiltrates (+/- pleural calcifications and plaques)
- Silicosis: hilar eggshell calcifications; nodular lesions
- Sarcoidosis: bilateral symmetrical hilar and paratracheal lymphadenopathy. See the **Dermatology** section for more on sarcoidosis.
- Lymphangioleiomyomatosis (LAM): ILD with a pneumothorax in a premenopausal woman; there can also be chylous effusions and characteristic diffuse, thin walled cysts on CT.



Figure 6-11: PA chest—diffuse interstitial fibrosis
Source: Thomas Roy, MD

Bronchoscopy with transbronchial biopsy is limited by the small tissue specimens acquired. However, this technique (when combined with bronchoalveolar lavage) can be helpful in diagnosing and ruling out infections, lymphangitic spread of carcinoma (though this may not be indicated in some cases), cryptogenic organizing pneumonia (COP), sarcoidosis, and airway centered ILDs like respiratory bronchiolitis-ILD.

Video-assisted thoracoscopic surgical (VATS) biopsy (minimally invasive thoracoscope through the chest wall) and open lung biopsy generally give the best yield for diagnosing interstitial pneumonitis.

Remember that the DLCO is the 1st test to become abnormal in ILD, so follow this parameter in patients receiving potentially lung-toxic drugs (e.g., amiodarone, chemotherapy).

OCCUPATIONAL AND ENVIRONMENTAL ILDs

The 2 categories of occupational and environmental ILDs are:

- 1) Organic dust-induced ILD: hypersensitivity pneumonitis and byssinosis
- 2) Inorganic dust-induced ILDs: asbestosis, silicosis, coal worker's pneumoconiosis, and berylliosis

Organic Dusts that Cause ILD

Hypersensitivity Pneumonitis

Hypersensitivity pneumonitis is an **immune-mediated** granulomatous reaction to organic antigens. Not many people get it—just those who are susceptible to it. Poorly formed granulomas are typical. (The granulomas in sarcoidosis are more dense and better organized.)

Hypersensitivity pneumonitis has a wide range of causes. An occupational history can be highly revealing; for example:

- Moldy hay—farmer's lung (thermophilic actinomycetes)
- Pet birds—bird fancier's or bird-breeder's lung (feathers and bird droppings)
- Grain dust—miller's lung (grain elevators)
- Isocyanates—chemical worker's lung (paints, resins, and polyurethane foam)
- Air conditioning systems (organic dusts, fungi, and molds)

Hypersensitivity pneumonitis has acute, subacute, and chronic forms. Usually, the onset is insidious. Consider this diagnosis in a patient with recurrent or persistent pneumonias who gives you a history of exposure to 1 of the above. Symptoms tend to wax and wane with exposure. In occupational lung diseases, symptoms occur during workdays and abate during days off.

Diagnose by history. Chest x-rays reveal recurrent infiltrates, but these are **transient**. Serum precipitins are **nonspecific** for hypersensitivity pneumonitis because they only indicate exposure. Most people exposed to these antigens have no immune reaction. Eosinophilia is **not** a feature of acute hypersensitivity pneumonitis.

Subacute hypersensitivity pneumonitis eventually evolves into chronic hypersensitivity with irreversible, parenchymal, fibrotic changes that are typically localized to the upper lobes.

The differential diagnosis of acute hypersensitivity pneumonitis includes other causes of recurrent or persistent pneumonias, including **eosinophilic pneumonia** and cryptogenic organizing pneumonia (COP; an idiopathic form of organizing pneumonia, formerly called bronchiolitis obliterans with organizing pneumonia [BOOP]). Note that bronchoalveolar lavage (BAL) may show an increased number or percentage of lymphocytes, with a CD4/CD8 helper/suppressor ratio of < 1 (while sarcoidosis has a ratio of > 4:1).

The best treatment is to **remove** the patient from the offending antigen or site of exposure. Corticosteroids appear to be beneficial in acute disease.

Byssinosis

Byssinosis is caused by the inhalation of cotton, flax, or hemp dust. It is **not immune** mediated, so no sensitization is needed. Early-stage disease occasionally presents with chest tightness. Late-stage disease can present with **Monday chest tightness** (regular chest tightness towards the end of the 1st day of the work week). The frequency of symptoms increases with continued exposure. Chest x-ray is normal. Flock worker's lung occurs from inhalation of ultra-fine nylon fabrics, and HRCT shows diffuse micronodules and ground-glass opacities.

Inorganic Dusts that Cause ILD

ILDs caused by inorganic dusts are asbestosis, silicosis, coal worker's pneumoconiosis, and berylliosis.

Asbestos

Asbestos causes some conditions that can occur independently of asbestosis, the ILD. Asbestos exposure causes bilateral, midthoracic pleural thickening, plaques, and calcification. The pleural thickening usually involves the midthorax (posterolateral) and spares both the costophrenic angles and the apices. Remember that pleural plaques and pleural thickening are **benign**, but when they are extensive, they can cause pulmonary restriction. Asbestos-related pleural plaques (Figure 6-12) are often erroneously called asbestosis.



Figure 6-12: PA lateral chest—*asbestos pleural plaques*

Rounded atelectasis is most commonly due to asbestos and occurs when fibrosis on the visceral pleural surface invaginates and may trap lung tissue, causing localized atelectasis. These may appear classically as a “comet tail” but are sometimes masslike.

Benign asbestos pleural effusions (BAPE) are a common manifestation of asbestos exposure in the first 10 years after exposure. These vary from serous to bloody and tend to occur early in the exposure history (within 5–10 years). About 1/3 of patients have eosinophils in the pleural fluid.

Asbestosis is pulmonary parenchymal fibrosis caused by asbestos exposure. This fibrosis develops mostly in the bases and is subpleural, but often there are longer fibrotic streaks. Other radiologic manifestations of asbestos exposure may or may not be present. Asbestosis generally occurs with > 10 years of moderate exposure, although the latency period can be > 30 years! There is no specific treatment for asbestosis.

Smoking has a synergistic effect with asbestosis in the development of lung cancer. The associated lung cancers are **squamous cell** and **adenocarcinoma** (not small cell cancer).

Malignant mesotheliomas are tumors arising from the mesothelial cell of the pleura, often where there was preceding asbestos-related pleural disease. 80% of mesothelioma patients have prior asbestos exposure. Pleural plaques do not necessarily progress to mesothelioma and in fact rarely do. The latency period is on the order of decades and can be > 40 years. Mesothelioma is **not** due to smoking. It is usually a rapidly fatal disease. A keypoint: If you have a patient who was exposed to asbestos with progressive dyspnea, pleuritic chest pain, and a bloody pleural effusion, think mesothelioma!

Silica

Silicosis is one of the most common occupational ILDs in the world. It generally requires years of exposure to crystalline silica in order for it to develop. Exposure comes from occupations such as mining, glassmaking, ceramic manufacturing, sandblasting, metal casting, and brick making. There is a demonstrable trend in construction workers who cut natural stone (quartz, marble, granite) for home renovations. The latency is 20–30 years.

Silicosis is characterized by **silicotic nodules** and **hilar lymph node involvement** (hilar eggshell calcifications). There is an increased susceptibility to **TB disease**. See Figure 6-13 and Figure 6-14. Silica ingested by alveolar macrophages renders them ineffective.



Figure 6-13: PA chest showing simple nodular silicosis with diffuse 1–3 mm nodules

There is no specific treatment for silicosis—but if symptoms such as cough rapidly worsen, or the patient presents with hemoptysis, consider a concurrent TB or other infection. A positive interferon- γ release assay (IGRA) is preferable to a positive purified protein derivative (PPD) and is diagnostic for TB in these patients. Patients with silicosis are at high risk of concurrent mycobacterial infection and should be evaluated for latent and active tuberculosis in the context of constitutional symptoms, hemoptysis, or lung cavitation on radiograph.



Figure 6-14: PA chest—hilar eggshell calcifications in silicosis
Source: Vinay Maheshwari, MD

Since it usually involves the **upper lung**, the differential diagnosis includes TB, coal worker's pneumoconiosis, and berylliosis.

Silica is also a human carcinogen. Patients with silicosis have an increased risk for malignancy development. Silicosis is also associated with scleroderma and rheumatoid arthritis.

Simple nodular silicosis presents with small lung nodules and is also called fibrocalcific.

Complicated nodular silicosis presents with big lung nodules and is also called progressive massive fibrosis. It has nodules > 1 cm that tend to coalesce in the upper lobes.

Silicoproteinosis may develop from overwhelming exposure in ~ 5 years. This results in the alveoli filling with eosinophilic material similar to that found in pulmonary alveolar proteinosis (discussed under **Alveolar Proteinosis** on page 6-39). These patients present with symptoms easily mistaken for pulmonary edema.

Corticosteroids are thought to be beneficial in acute silicosis but not in chronic disease. Consider lung transplant for those with severe disease.

Note: Asbestosis involves the **lower lung**, while silicosis involves the **upper lung**.

Coal

Coal worker's pneumoconiosis (CWP) also has simple and progressive forms. The chest x-ray shows **upper lung** field nodules (similar to that of silicosis and berylliosis). Progression of simple CWP correlates with the amount of coal dust deposited in the lungs, whereas complicated CWP does not. Complicated CWP is a progressive massive fibrosis defined by lung nodules > 2 cm without hilar involvement. With large depositions of coal dust, patients can have melanoptysis. As expected, cigarette smoking accelerates the deterioration of pulmonary function. There is no association with TB, and there is no specific treatment.

Caplan syndrome is a seropositive rheumatoid arthritis associated with pneumoconiosis related to inorganic occupational dust (coal, asbestosis, silica). This syndrome is heralded by the development of peripheral basilar lung nodules (in addition to the upper lung field nodules seen in pneumoconiosis related progressive massive fibrosis).

Beryllium

Berylliosis (a.k.a. chronic beryllium disease [CBD]) is caused by a cell-mediated immune response that can occur from ≥ 2 years of exposure to even slight amounts of beryllium. This is especially suspected in persons who have worked with high-tech electronics, alloys, or ceramics or in the aerospace industry, the nuclear industry, or pre-1950 fluorescent light manufacturing.

It usually causes a **chronic interstitial pneumonitis** that tends to affect the **upper lobes** (similar to silicosis, TB, and CWP). Patients often have hilar lymphadenopathy that looks identical on chest x-ray to that caused by **sarcoidosis**—a key point.

Diagnosis of CBD:

- History of beryllium exposure
- Positive beryllium lymphocyte proliferation test (BeLPT)
- Characteristic radiologic changes
- Lung biopsy showing interstitial cell infiltrates (with mononuclear cells) and/or noncaseating granulomas

This ILD can be responsive to ongoing corticosteroids. Methotrexate (MTX) or azathioprine can be tried if steroids fail or a steroid-sparing agent is desired, but no data supports this.

IDIOPATHIC INTERSTITIAL PNEUMONIAS

We will now discuss the second category of ILDs—**idiopathic** interstitial pneumonias (IIPs). Here is a list of IIPs:

- 1) Idiopathic pulmonary fibrosis (IPF; usual interstitial pneumonitis [UIP] is the prototype)
- 2) Nonspecific interstitial pneumonia (NSIP)
- 3) Cryptogenic organizing pneumonia (COP, an idiopathic form of organizing pneumonia)
- 4) Acute interstitial pneumonia (AIP)
- 5) Respiratory bronchiolitis-associated ILD (RB-ILD)
- 6) Desquamative interstitial pneumonia (DIP)
- 7) Lymphocytic interstitial pneumonia (LIP)
- 8) Pleuroparenchymal fibroelastosis
- 9) Unclassifiable IIPs

Each of these entities has specific histopathologic findings. IPF also has typical clinical and radiologic findings. We will discuss 2 of the most frequently encountered IIPs: **IPF** and **COP**.

Idiopathic Pulmonary Fibrosis

As its name implies, idiopathic pulmonary fibrosis (IPF) has uncertain etiology. It is a diagnosis of exclusion that remains when known causes of pulmonary fibrosis have been excluded. There are **limited extrapulmonary** manifestations in IPF, although **clubbing** is seen in up to 50–60% of patients and tends to occur more frequently in men. The typical presentation is a male > 60, prior smoker, who presents with an insidious dry cough and dyspnea on exertion in the setting of bibasilar predominant fibrotic changes on HRCT without apparent cause. However, it may occur in middle aged populations as well. As before, smoking exacerbates the disease. ~ 10% of patients have low titers of ANA or RF, which are acute-phase reactions to lung inflammation.

IPF, by definition, has the specific histopathologic findings of UIP, including varying degrees of fibrosis, bronchiectasis, honeycombing, and mild interstitial inflammation interspersed with normal lung tissue. IPF ranges from an early stage—with radiographic findings of early fibrotic interstitial changes—to a late, lower lobe predominant fibrotic stage, with severe restrictive disease, pulmonary hypertension, and cor pulmonale (with diffuse, fibrotic-appearing parenchymal infiltrates on HRCT).

HRCT in early IPF shows a subpleural reticulation and traction bronchiectasis (Figure 6-15).

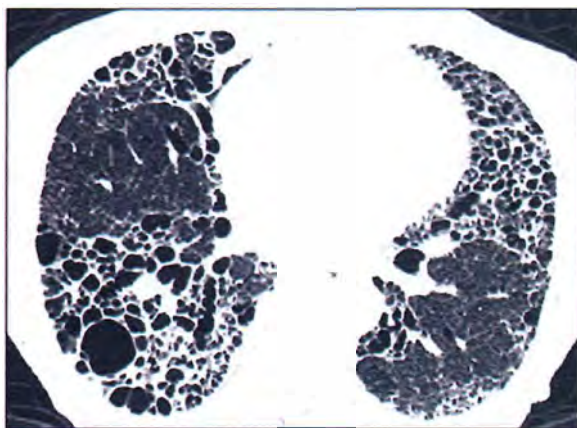


Figure 6-15: HRCT of idiopathic pulmonary fibrosis

Early IPF is characterized by leakiness of the capillaries and alveolar walls (from damage to the capillary endothelial cells and the adjacent Type I alveolar epithelial cells). This leads to interstitial and alveolar edema, which ultimately causes intraalveolar collagen deposition.

Late IPF leads to fibroblast-mediated collagen deposition in the interstitial space at the interface between abnormal lung adjacent to normal lung. HRCT shows fibrosis with **bibasilar honeycomb** pattern and traction bronchiectasis.

In IPF, the fluid in the alveoli and the interstitial edema increases the number of alveolar macrophages. They release profibrotic cytokines and proinflammatory mediators which mediate fibrinogenesis and inflammatory cascades (tumor necrosis factor [TNF], interleukin 8,

and leukotriene B₄)—some of which attract neutrophils. This is reflected in the BAL results of increased macrophages, neutrophils (PMNs > 5%), and eosinophils (> 2%) and increased BAL neutrophilia has been associated with worse prognosis. Importantly, the BAL is typically lymphopenic in IPF.

Consider IPF in a patient who presents with dyspnea; non-productive cough; mid-inspiratory, Velcro-like crackles; and a diffuse interstitial process on chest x-ray or HRCT. Patients often report a progressive decline in exercise tolerance. Velcro crackles are loud and coarse. They mimic the sound made when a Velcro patch is opened and sound different from the fine crackles made when hair is rubbed together. **Clubbing** of the nails is common, and is secondary to enlargement of the soft tissue of the distal nail, with subsequent exaggerated curvature of the nails. A widening of the angle between the proximal nail fold and the nail bed is observed (> 180°). Clubbing may be acquired or congenital, and 80% of cases are due to a pulmonary disorder like advanced pulmonary fibrosis, infections, or lung cancer.

Like many ILDs, PFTs show a restrictive intrathoracic disease (i.e., low TLC, normal FEV₁/FVC, low DLCO). Know that in IPF, a low DLCO out of proportion to restriction may correlate with the presence of pulmonary arterial hypertension (and thus, a poor prognosis).

Diagnosis

The diagnostic workup of IPF includes chest x-ray; HRCT showing characteristic features of subpleural reticulation, traction bronchiectasis, and bibasilar honeycomb formation; PFTs; ABG; and a functional assessment and oxygen requirements with exercise (e.g., 6-minute walk test). The diagnosis of IPF needs to be established by ruling out other progressive fibrotic lung diseases including NSIP and chronic HP.

When the diagnosis is in question because of an **atypical presentation**, consider a lung biopsy to characterize the pathology of the HRCT abnormalities and to exclude inflammatory-mediated disease, cancer, and infections. This is important because empiric treatment with steroids can cause harm in IPF patients and treatment should be targeted at the antifibrotic pathway.

Definitely avoid lung biopsy in a patient who has a negative environmental and rheumatologic history (corroborated by negative serologic workup), significant medical comorbidities, significant pulmonary hypertension, significant debility, and/or FVC or DLCO < 40% predicted—which suggests advanced disease that would not tolerate such a procedure. In these cases, empiric therapy can be trialed.

Once a diagnosis of IPF is established, patients are followed with serial evaluations with PFTs (including spirometry lung volumes), DLCO, and a 6-minute walk with oximetry and symptoms. Abnormalities in the above may prompt further workup with radiologic testing or bronchoscopy.

IPF has a relentless progression, but the severity and time course vary.

Treatment

In 2014, 2 drugs—**nintedanib** (a tyrosine-kinase inhibitor) and **pirfenidone** (an antifibrotic agent)—were approved by the FDA for patients with mild-to-moderate UIP (who meet specific criteria) to **slow the progression of disease**. They are frequently used in severe UIP, but data is less robust regarding proven efficacy. There is insufficient evidence to recommend a choice between nintedanib and pirfenidone. Consider patient preference, side effect profile, and tolerances.

Nintedanib is taken by mouth 2×/day. Patients with known liver disease are not candidates for nintedanib. Diarrhea, nausea, vomiting, and liver function test elevation are the common side effects of nintedanib. Nintedanib is also associated with a slightly increased risk of bleeding.

Pirfenidone is taken by mouth 3×/day. Rash, photosensitivity, nausea, diarrhea, and abdominal discomfort are the common side effects.

Studies taking both nintedanib and pirfenidone have shown overall tolerability, but further evaluation is needed to determine if they add benefit.

Routine maintenance care for patients with IPF/UIP **no longer** includes systemic glucocorticoid monotherapy; combination therapy with azathioprine, prednisone, and *N*-acetylcysteine; or monotherapy with *N*-acetylcysteine. There has been no demonstrated efficacy, and these treatments may be potentially harmful. Therapy to prevent acid reflux, such as a PPI, may be beneficial in patients with IPF. For patients who seem to have a condition other than UIP, such as NSIP, a trial of steroids may be considered. Lung transplantation is an option for patients with progressive disease and minimal comorbidities. 60% of all lung transplants result from progressive ILD.

Steroids are utilized for IPF patients with an **acute exacerbation of IPF** (i.e., a sudden acceleration of the disease with a significant decline in lung function), typically administered as high-dose IV glucocorticoids. Broad-spectrum antibiotics are typically initiated until infection can be excluded.

Cor pulmonale is treated symptomatically. Lung transplantation is an option for some end-stage IPF patients with single organ failure. Give IPF patients **pneumococcal** and **influenza** vaccines, evaluation for oxygen, palliative care consultation, and enroll in pulmonary rehab.

Organizing Pneumonias

Causes of Organizing Pneumonias

There are various types of organizing pneumonias that have the common finding of a chronic alveolitis. 50% of

organizing pneumonia cases are idiopathic. The other 50% are caused by the following:

- Inhalation of toxic fumes (e.g., smoke, paint aerosols, nylon flock fibers)
- Exposure to drugs (e.g., amiodarone, bleomycin, carbamazepine, minocycline, nitrofurantoin, phenytoin, penicillamine, sulfasalazine)
- Immunodeficiencies
- Infections (e.g., respiratory viruses, *Mycoplasma*, *Pneumocystis*, GNRs, fungi)
- Connective tissue disorders (e.g., rheumatoid arthritis)
- Myelodysplasia
- Radiation

Cryptogenic Organizing Pneumonia

Cryptogenic organizing pneumonia (COP) is an idiopathic form of organizing pneumonia. COP is a **bronchiolitis** (inflammation of the small airways) and a chronic **alveolitis** (the organizing pneumonia). The bronchiolitis causes a proliferation of granulation tissue within the small airways and alveolar ducts.

Consider COP in a patient with an insidious onset (weeks to 1–2 months) of cough, fever, dyspnea, malaise, and myalgias. Often, patients have had multiple courses of antibiotics without effect. Rales are common. Chest x-ray shows some interstitial disease, bronchial thickening, and patchy bilateral alveolar infiltrates. Chest CT shows bilateral, peripheral-based infiltrates, but these can become confluent. PFTs demonstrate a restrictive pattern with a reduced diffusion capacity.

You must differentiate COP from IPF because, contrary to IPF, COP has a **good** prognosis and a good response to steroids. To differentiate IPF from COP, know that IPF is **even more** insidious in onset (> 6 months) and the patients do **not** have fever (Table 6-9). Radiographically, the consolidative infiltrates of COP differ from the subpleural reticulations and fibrosis with traction bronchiectasis and honeycombing of UIP. Bronchoscopic lung biopsy is the definitive means of diagnosing COP.

Table 6-9: Comparison of COP and IPF

	COP	IPF
Signs	Acutely ill appearing Fever	Not acutely ill No fever
Onset of Symptoms	Days to weeks	Very slow —at least 6 months
HRCT	Patchy peripheral based infiltrates	Honeycombing, peripheral reticulation, traction bronchiectasis

Corticosteroids are the **treatment of choice** for COP. COP does not respond to antibiotics. **Slowly** taper corticosteroids over 6–12 months because exacerbations can occur with rapid tapering. Corticosteroid-sparing treatment can be used if relapses occur with steroid weaning.

OTHER CAUSES OF INTERSTITIAL LUNG DISEASE

Other causes of ILD and diffuse lung disease are:

- Drug-induced interstitial lung disease
- Collagen vascular diseases
- Sarcoidosis
- Langerhans cell histiocytosis
- Lymphangioleiomyomatosis
- Vasculitides causing ILD: granulomatosis with polyangiitis (GPA), lymphomatoid granulomatosis
- Eosinophilic ILDs: acute and chronic eosinophilic pneumonia, ABPA, EGPA
- Autoimmune-associated ILDs: systemic sclerosis, rheumatoid arthritis, Sjogren syndrome, SLE, polymyositis/dermatomyositis, MCTD, interstitial pneumonia with autoimmune features
- Pulmonary alveolar proteinosis

Drug-Induced Interstitial Lung Disease

There are hundreds of drugs that have reported pulmonary toxicities. These include antibiotics that may cause hypersensitivity and/or eosinophilic responses and chemotherapeutic agents that may cause a variety of findings. Drugs may cause pulmonary toxicity in an idiosyncratic manner—usually an acute exposure and illness—or it may be dose-related, where the cumulative dose may lead to chronic toxicity.

Mechanisms of pulmonary injury include direct toxic effects such as generation of free radicals, immune-mediated reactions, fibrotic reactions, vascular injury, and others. A broad array of findings can be seen with different medications, including:

- Hypersensitivity reactions
- Eosinophilic pneumonia (i.e., gemcitabine, cocaine, heroin, nitrofurantoin)
- Nonspecific interstitial pneumonitis
- Other ILDs
- Pulmonary edema
 - Cardiogenic (i.e., cocaine, heroin, amphetamines, rituximab)
 - Noncardiogenic (i.e., cocaine, MDMA, heroin, interferons, MTX)
- Diffuse alveolar damage (i.e., amiodarone, bleomycin, cocaine, cyclophosphamide, MTX, radiation)
- Pulmonary hemorrhage (i.e., penicillamine, tumor necrosis factor- α (TNF- α), propylthiouracil)
- COP (i.e., amiodarone, bleomycin, cocaine, MTX)
- Granulomatous interstitial disease (i.e., MTX, interferons, rituximab, TNF- α)
- Pulmonary nodules (i.e., amiodarone, MTX)
- Lipoid pneumonia (e.g., aspiration)

- Pulmonary alveolar proteinosis (i.e., sirolimus)
- Pleural effusions (i.e., penicillamine, nitrofurantoin, MTX)
- Other histopathologic findings

Airway disease can also result from drug-induced pulmonary toxicity and includes bronchospasm, hoarseness, cough, and bronchiolitis obliterans. Pulmonary vascular disease manifestations potentially include thromboembolism, alveolar hemorrhage, vasculitis, and pulmonary vascular disease. Crack lung (from inhalation of cocaine) can present with acute dyspnea with hemoptysis due to diffuse alveolar damage as well as with a pneumothorax. Consider obtaining a urine drug screen. Electronic vaping-associated lung injury can also present with diffuse alveolar hemorrhage, COP, hypersensitivity pneumonitis, and acute eosinophilic pneumonia.

Epidemiology

Prescription drug-induced pulmonary toxicity is generally an uncommon side effect. Older patients appear to be more susceptible, as well as those with prior lung injury such as from radiation or chemotherapy. In some cases, hyperoxia with prior exposure to certain medications may precipitate pulmonary toxicity.

Diagnosis

Drug-induced lung disease is a diagnosis of exclusion. Generally, infection, collagen vascular disease-associated ILD, vasculitis, and other etiologies need to be excluded. In some cases, the absence of fever, absence of purulent sputum, negative serologies, and negative cultures help exclude these etiologies. A temporal relationship and exposure should be compatible, and discontinuation of the offending or suspected agent leads to the disappearance of the manifestations. Rechallenge to establish the diagnosis is not usually done in pulmonary toxicity. Physical findings are nonspecific and can include clear lungs, crackles, or wheezes.

Radiologic findings are generally nonspecific, but other diagnoses such as COP and sarcoidosis may be suggested by their classic findings, discussed earlier.

Testing

There are no specific tests for drug-induced lung disease. Index of suspicion must be high (always consider iatrogenesis). Sputum culture and BAL with cultures, direct fluorescent antibody for *Pneumocystis*, differential cell count, and CD4/CD8 ratio may also be helpful in excluding diagnoses. Lung biopsy, whether transbronchial or open, cannot provide any specific histopathologic pathognomic finding of drug-induced lung toxicity. Biopsy is done when other etiologies are strongly suspected and there is a need to differentiate from other non-drug-related etiologies.

Treatment

Any potential offending agents should be discontinued, particularly when more acute or severe pulmonary toxicity occurs. This is also the case with known or suspected hypersensitivity or eosinophilic reactions, pulmonary edema, diffuse alveolar damage, alveolar hemorrhage, and other more severe and acute reactions. Steroids may be useful in immune-mediated reactions, some pulmonary hemorrhage situations, vasculitis, and in other situations where the etiology is not clear but the acuteness of the situation calls for a trial of steroids.

Connective Tissue Collagen Vascular Diseases and ILD

Rheumatoid arthritis (RA): > 1/3 of patients with RA get ILD! The most common lung problem in RA is pleurisy (with or without pleural effusion). Pleural effusions are **exudative** and can have uniquely very **low** glucose levels with pseudochylous findings. See **Exudative Effusions** on page 6-50. Occasionally, these patients have **necrobiotic nodules**—usually in the **upper** lung zones. ILD can also be due to a complication of gold and MTX treatment in RA patients. COP rarely results from penicillamine treatment but may occur in association with RA itself. Pleuropulmonary manifestations can occur before the articular manifestations of RA appear. The most common form of chronic ILD in RA patients is histologically UIP.

Systemic lupus erythematosus (SLE) can cause painful pleuritis (+/- effusion). It additionally causes diffuse atelectasis and sometimes diaphragmatic weakness—and, therefore, orthopneic dyspnea that is **out of proportion** to the chest x-ray findings. The chest x-ray may show elevated diaphragms. The uncommon “shrinking lung syndrome” consists of unexplained dyspnea, an elevated diaphragm, and restriction on PFTs. SLE diffuse alveolar hemorrhage (similar to that seen in idiopathic pulmonary hemosiderosis) may or may not manifest as hemoptysis. SLE affects both the lung and pleura more frequently than any other collagen vascular disease (60%). Other manifestations include acute lupus pneumonitis, pulmonary vasculitis, pulmonary hypertension, and pulmonary embolism (associated with APLA).

Systemic sclerosis (scleroderma) affects the lung 100% of the time—but there are no pleural changes! Nintedanib was FDA approved for systemic sclerosis ILD in 2019 to decrease rate of decline in lung function. Patients are treated with immunosuppression and, depending on the severity of their disease, can be considered for autologous hematopoietic stem cell transplant.

Patients with systemic sclerosis are more susceptible to pneumonia. Chronic aspiration and gastroesophageal reflux are common, and possibly related to the development and/or progression of pulmonary fibrosis.

Systemic sclerosis, rheumatoid arthritis, and systemic lupus erythematosus.

Isolated pulmonary hypertension (**without** ILD) occurs more often in patients with limited cutaneous systemic sclerosis (previously CREST syndrome) than in patients with diffuse cutaneous systemic sclerosis.

Both RA and systemic sclerosis can be associated with exposure to silica, and both have an increased incidence of bronchogenic carcinoma!

Sjögren syndrome causes desiccation of the airways and is also associated with lymphocytic interstitial pneumonia (LIP) and interstitial lung disease.

Sarcoidosis

Sarcoidosis is a multisystem disease that can affect any organ. This commonly comes to medical attention with complaints of fever, joint pains, and constitutional symptoms. ~ 50% of patients have dyspnea, chest pain, cough, and/or hemoptysis (more with established disease). A subset of patients may present with acute fever, hilar lymphadenopathy, polyarthralgia, and/or erythema nodosum, a.k.a. Löfgren syndrome. This type of presentation has a good prognosis as it is highly likely to resolve spontaneously, but NSAIDs can be used. Another syndrome is uveoparotid fever (a.k.a. Heerfordt syndrome), which is anterior uveitis, parotitis, cranial nerve 7 paralysis, and fever. It may also spontaneously resolve, but some need treatment. A significant number are asymptomatic and come to attention with an incidental abnormal chest x-ray demonstrating hilar/mediastinal adenopathy with or without parenchymal changes.

Findings

Physical examination may be normal, but findings can include uveitis, parotid tenderness, lymphadenopathy (including epitrochlear), rashes (e.g., erythema nodosum; plaquelike lesions; subcutaneous nodules; maculopapular rash; raised, indurated, purplish skin lesions on the nose known as lupus pernio), crackles on lung exam, and an array of neurologic manifestations, from neuropathy to optic nerve dysfunction, meningeal findings, myelopathic findings, and other changes.

Sarcoidosis is characterized by noncaseating granulomas in affected organs, and its cause is unknown. The granulomas are an inflammatory collection of cells that have a typical appearance on biopsy of lymphocytes around multinucleated giant cells. Skin involvement is common and may be the presenting manifestation. Cardiac involvement is variable and can cause life-threatening arrhythmias. Uveitis is a frequent ocular manifestation. Sarcoidosis affects a bimodal distribution of patients, first in the 20–30s and again in 50–60s, and is more common in females and in African Americans in the United States.

Pulmonary involvement can be an incidental finding on chest x-ray. Usually, there is bilateral hilar and/or mediastinal adenopathy (+/- reticulonodular or alveolar infiltrates). PFTs can either be normal or show **restrictive** (+/- **obstructive**) mechanics. The radiographic staging of

sarcoidosis (Table 6-10) illustrates the interesting point that hilar adenopathy disappears in advanced stages of the disease (see Figure 6-16 and Figure 6-17).

Serum angiotensin-converting enzyme (ACE) level is **nonspecific** in diagnosing sarcoidosis, but it **is sometimes** useful in the correct clinical context. However, its utility in practice has been modest, at best. Hypercalcemia (due to hydroxylation of vitamin D in granulomas and elevated 1,25 (OH)-vitamin D₃), hypercalciuria, and hypergammaglobulinemia are common.

Table 6-10: Sarcoidosis Staging

Stage	Chest X-Ray Findings
0	Clear
1	Bilateral hilar adenopathy
2	Adenopathy + parenchymal infiltrates
3	Diffuse parenchymal infiltrates
4	Fibrosis, bullae, cavities, architectural destruction (primarily upper lobe)



Figure 6-16: PA chest—Stage 1 sarcoidosis
Source: Vinay Maheshwari, MD

Diagnosis

Sarcoidosis is a diagnosis of exclusion. It is **imperative** to exclude the other granulomatous diseases, including hypersensitivity pneumonitis, berylliosis, and infectious diseases caused by mycobacteria and fungi. A positive BAL shows an increased number of lymphocytes, with a CD4/CD8 helper/suppressor ratio of $> 4:1$. (Hypersensitivity pneumonitis has a ratio of < 1 .) Material for histological exam should be cultured and examined for organisms.

While ensuring the absence of organisms and negative cultures, flexible bronchoscopy with transbronchial biopsy



Figure 6-17: PA chest—Stage 2 sarcoidosis
Source: Vinay Maheshwari, MD

of lung parenchyma or endobronchial ultrasound (EBUS) biopsy of lymph nodes showing **noncaseating granulomas** is the best method for diagnosing sarcoidosis.

Erythema nodosum is an associated skin lesion that denotes a **good prognosis**! This form of sarcoidosis is called **Löfgren syndrome**. When sarcoid presents in a classic form such as Löfgren's, biopsy confirmation is not necessary.

Treatment

Overall, 75% of sarcoid patients recover without treatment. It rarely progresses to pulmonary fibrosis or pulmonary hypertension. Treat only severe or symptomatic disease. Patients without pulmonary physiologic compromise do not need treatment unless they meet conditions below. There is no set regimen. Corticosteroids have **not been proven to induce remissions** in sarcoidosis, although they do decrease the symptoms and improve PFTs. Inhaled corticosteroids decrease the respiratory symptoms and can be used instead of systemic corticosteroids if the disease is primarily in the bronchi but not for parenchymal lung disease.

Corticosteroids are indicated for persistent hypercalcemia and evidence of other organ involvement:

- Eyes (e.g., conjunctivitis, uveitis)
- Heart (conduction abnormalities)
- CNS (signs of optic nerve or optic chiasm involvement)
- Lungs (in the presence of significant pulmonary symptoms)
- Skin (severe skin lesions)

If the case is refractory to steroids, or treatment is expected to be long term (with the goal of minimizing steroid related side effects), consider leflunomide, mycophenolate, infliximab (Remicade), adalimumab (Humira), MTX, and azathioprine. Occasionally MTX or azathioprine are combined with leflunomide.

Lung transplantation remains an option for advanced disease and associated pulmonary hypertension. Sarcoidosis can recur after transplant, but does not necessitate retransplantation.

Langerhans Cell Histiocytosis

Langerhans cell histiocytosis (LCH) causes characteristic lytic bone lesions (eosinophilic granulomas). Langerhans cells are the predominant cell form. LCH sometimes involves the posterior pituitary—leading to **diabetes insipidus**.

In the lung, it causes nodules which can cavitate and small, thick-walled cystic spaces in the upper lung fields, both of which are visible on chest x-ray and HRCT.

Virtually all affected patients are **smokers**, and males are affected more than females. Patients have ILD with normal or **increased** lung volumes. (Most ILDs have decreased lung volumes.)

Pneumothorax is a major feature, accounting for 10% of the initial presentations. Up to 50% of these patients have a pneumothorax sometime in the course of their illness. Cysts and nodules are evident on HRCT scan.

Diagnose LCH with suggestive CT findings or by Langerhans cells on lung biopsy or BAL. Electron microscopy demonstrates the presence of Birbeck granules (remember tennis rackets), and histopathologic markers for S-100 antigen, CD1a, and CD207 are positive in this disease.

Treatment: Stop smoking! Many do a trial of steroids, although drugs generally do not help. Occasionally there is spontaneous resolution.

Again: Think about LCH in a young, male smoker with recurrent pneumothoraces.

Lymphangioleiomyomatosis

Lymphangioleiomyomatosis (LAM) is the result of immature smooth muscle proliferation in the lymphatic, vascular, alveolar, and peribronchial structures. This proliferation results in the formation of constrictions and cysts in the affected structures. There is a genetic relationship to tuberous sclerosis.

LAM occurs almost exclusively in premenopausal women. Symptoms and signs included worsening shortness of breath, fatigue, and often spontaneous pneumothorax.

Chest x-ray in LAM is nonspecific. See **Figure 6-18**. HRCT can identify the characteristic multilobar, thin-walled cysts.

Thoracic and abdominal lymphatics are often involved, resulting in **chylous** pleural effusions—with triglycerides > 110 mg/dL (1.24 mmol/L; +/- chylomicrons in the fluid). Pneumothorax can occur in up to 36%.

First-line treatment for those with symptoms is inhibiting the rapamycin target (mTOR) with sirolimus (mTOR kinase inhibitor) and avoiding exogenous estrogen. Lung transplant remains an option.

Again: LAM = premenopausal, pneumothorax, chylous effusion (TG > 110 mg/dL [1.24 mmol/L; +/- chylomicrons]), and seen in tuberous sclerosis.

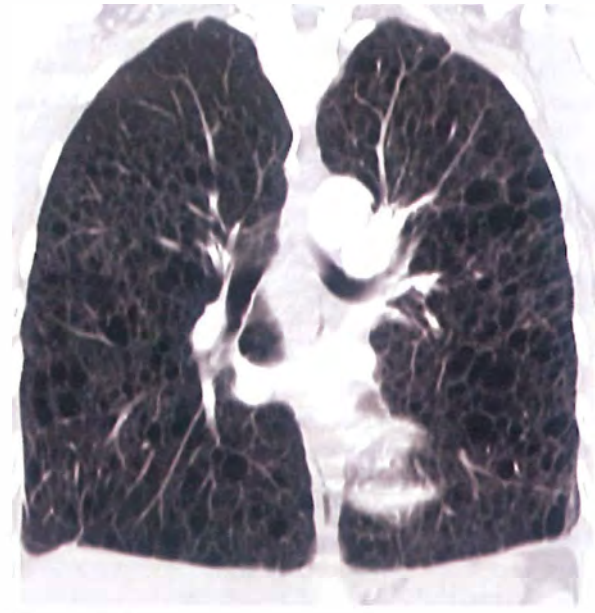


Figure 6-18: Lymphangioleiomyomatosis

Vasculitides that Cause ILD

Granulomatosis with Polyangiitis

Granulomatosis with polyangiitis (GPA) is a vasculitis that involves all of the following:

- **Upper respiratory** tract and paranasal sinus involvement
- **Granulomatous** pulmonary vasculitis with large (sometimes cavitory) nodules
- Necrotizing **glomerulonephritis**

Sometimes, it is limited to just the lungs or the upper airway (limited GPA).

Manifestations of GPA overlap with microscopic polyangiitis, another ANCA-associated vasculitis. The latter does not have granulomatous but rather neutrophilic inflammation, and it does not involve the upper airway.

The **ANCA test** (antineutrophil cytoplasmic antibody—an autoantibody that unleashes a locally destructive immunologic process) is often used as a diagnostic test. It is ~ 90% sensitive and 90% specific. When positive in a patient with GPA, the ANCA test is virtually always **cytoplasmic**, or **c-ANCA** (96%).

ELISA is used to quantitate anti-PR3, the major ANCA autoantibody. In the correct clinical context, a positive ANCA and/or anti-PR3 is often sufficient for diagnosis.

The diagnosis may be confirmed from a biopsy of the involved organ. The nasal membrane has variable sensitivity for diagnosis and the skin is often nonspecific. Biopsy of the kidney usually reveals a pauciimmune glomerulonephritis, and granulomatous infiltration is diagnostic.

The treatment of systemic GPA is **aggressive** because, without treatment, most patients die within 2 years, while

limited forms of the disease may have a more benign prognosis and do not require as aggressive treatment. For patients with active but not severe GPA, MTX and glucocorticoids induce and maintain remission. For those with severe disease, use glucocorticoids combined with cyclophosphamide, MTX, or rituximab. Plasmapheresis is another option. In less severe disease, start with MTX. Prophylaxis against *Pneumocystis pneumonia* is with trimethoprim/sulfamethoxazole (TMP/SMX) until prednisone dose is tapered to ≤ 10 mg per day. Treatment to induce remission is usually for a minimum of 3–6 months.

MTX, rituximab, mycophenolate, or azathioprine are typically used for maintenance therapy.

Again: kidneys, lungs, and sinuses. Consider GPA in any patient who presents with a purulent nasal discharge, epistaxis, and signs of a glomerulonephritis with hematuria. Neuropathy may also be present. The patient is not usually dyspneic and may not have a cough or hemoptysis. They may have thick walled cavitary lung lesions. If you see a similar presentation that is ANCA-negative, think antglomerular basement membrane disease (a.k.a. Goodpasture syndrome).

Lymphomatoid Granulomatosis

Lymphomatoid granulomatosis is a rare EBV-associated, systemic, angi-destructive lymphoproliferative disease. Although characterized by prominent pulmonary involvement, it can also involve extrapulmonary sites. 50% progress to **histiocytic lymphoma**. It is similar to GPA but has **no** upper respiratory lesions and only rarely affects the kidney. Although the principal site is the lung, lymphomatoid granulomatosis less often has **skin**, **CNS**, and peripheral nerve involvement. Biopsy shows a mononuclear angiocentric necrotic vasculitis.

Treatment of affected patients (who are immunocompetent) is with corticosteroids and biologic or chemotherapeutic agents, by experienced practitioners. In patients who are already immunocompromised, reducing immunosuppression can induce remission.

Eosinophilic Granulomatosis with Polyangiitis

Eosinophilic granulomatosis with polyangiitis (EGPA) is a **necrotizing, small- to medium-vessel vasculitis** with **eosinophil** infiltration. It can affect multiple systems but most commonly affects the lungs. It does not affect the sinuses.

Patients typically present with preexisting **asthma** (for about 8–10 years) before vasculitic symptoms appear and have eosinophilia ($> 1,500$ cells/ μ L [1.5×10^9 /L]) and a neuropathy. Biopsy will show perivascular eosinophils. Think about EGPA (and ABPA) when assessing a progressively worsening asthmatic.

EGPA can be unmasked by treating an asthmatic patient with a **leukotriene-receptor modifier** while weaning oral corticosteroids.

The treatment of EGPA is mainly with systemic corticosteroids. Refractory cases are treated with cyclophosphamide,

azathioprine, rituximab, high-dose IV immunoglobulin, and/or plasmapheresis. Once in remission, maintenance is with azathioprine or mepolizumab. Reslizumab and benralizumab are in clinical trials.

Bronchocentric Granulomatosis

Bronchocentric granulomatosis is a destructive granulomatous lesion of the bronchi and bronchioles that is generally believed to represent a nonspecific response to a variety of airway injuries. ~ 50% of all the cases are related to either asthma or ABPA. Because of the lack of a clear clinical syndrome, consider the lesion a nonspecific manifestation of lung disease.

Eosinophilic ILDs

The eosinophilic ILDs are **eosinophilic pneumonia**, **ABPA**, and **EGPA** (discussed earlier). Remember that asthma, hypereosinophilic syndrome, certain parasite infections, and some drugs are non-ILD causes of **peripheral eosinophilia**.

A **hypereosinophilic syndrome** is defined as a persistently elevated eosinophil count in the blood for at least 6 months without any recognizable cause with involvement of either the heart, nervous system, bone marrow, or the lungs.

Eosinophilic Pneumonias

In all types of eosinophilic pneumonia, you must **rule out drugs and parasites** as the cause. Eosinophilic pneumonia consists of 3 types:

- 1) **Löffler syndrome** is typically self-limited and was originally described as a result of the transpulmonary passage of helminthic larvae early in their life cycle. *Ascaris*, *Strongyloides*, and hookworms have all been reported as common causes. However, Löffler syndrome has been reported to occur with fungal infections or as a hypersensitivity response to various medications, such as NSAIDs or sulfonamides. This syndrome describes an acute pulmonary eosinophilia that is transient (usually < 30 days in duration) with blood-tinged sputum containing narrow, elongated Charcot-Leyden crystals from the eosinophil-derived lysophospholipase. It is generally found incidentally, and patients have migratory peripheral infiltrates on chest x-ray. Eosinophils are found in the blood and sputum. Typically, no specific lung treatment is necessary, but if severe, corticosteroids may be prescribed. Anthelmintic therapy (albendazole, mebendazole, or pyrantel pamoate) may also be appropriate.
- 2) **Acute eosinophilic pneumonia** is an acute, febrile pulmonary illness with hypoxemic respiratory failure resembling ARDS. The condition can be idiopathic or caused by inhalational exposures. Rule out infection. BAL shows a large number of eosinophils. This is treated with ventilatory support and systemic glucocorticoids.

- 3) **Chronic eosinophilic pneumonia** is the **most common** eosinophilic pneumonia in the U.S. It usually occurs in middle-aged women. The illness is subacute with cough, wheeze, night sweats, and a low-grade fever. An asthma history is identified in 50% of the patients. The chest x-ray classically shows bilateral, very peripheral infiltrates in a pattern that is the photographic negative of pulmonary edema. However, this pattern is not always present. There is an increased number or percentage of eosinophils in the BAL, but > 1/3 have no peripheral eosinophilia. BAL is often done to exclude infection. A very high ESR is typical. Treat with long-term steroids. The response is usually rapid, with improvement in 24–72 hours. Relapses are common, especially if steroids are tapered too early.

Allergic Bronchopulmonary Aspergillosis

As the term suggests, allergic bronchopulmonary aspergillosis (ABPA) is caused by an **allergic** reaction to *Aspergillus* that results in chronic cough, mucous plugging, and recurrent pulmonary infiltrates with eosinophilia in patients with asthma or CF.

Diagnosis: Think about ABPA in patients with either **asthma** or **CF** who have uncontrolled disease. Look for eosinophilia and *Aspergillus* in the sputum culture. In **asthmatics**, the clinical history is one of recurrent exacerbations that improve with prednisone, with return of wheezing, coughing, and dyspnea shortly after stopping steroids.

Test for ABPA with serum IgG *Aspergillus* precipitins, elevated eosinophils (> 500 cells/ μ L [0.5×10^9 /L]), and/or total IgE (usually > 1,000 IU/mL). Also check an HRCT. Central mucus impaction and bronchiectasis result in a central infiltrate on chest x-ray and HRCT known as the **finger-in-glove** sign. Mucous plugging is common, and sputum can show branching hyphae (nonspecific). If the only finding is lung eosinophilia with peripheral eosinophilia, consider a chronic eosinophilic pneumonia instead.

These antibody levels, plus the clinical history and other lab and x-ray data, can be reviewed in consideration of the major and minor criteria for ABPA (which you do not need to know for the exam).

Treat active ABPA with itraconazole (if not able to tolerate, then voriconazole) and oral steroids. In most patients, the addition of itraconazole reduces the duration of steroids, thus reducing long-term side effects. Treatment with IgE monoclonal antibody (e.g., omalizumab) shows evidence of efficacy. See *Aspergillus* on page 6-74 for additional information.

Idiopathic Pulmonary Hemosiderosis

Idiopathic pulmonary hemosiderosis (IPH) clinically manifests as a triad of:

- 1) hemoptysis,
- 2) diffuse parenchymal infiltrates, and
- 3) iron deficiency anemia.

Patients can have repeated episodes of intraalveolar bleeding that lead to an abnormal accumulation of iron in the form of hemosiderin-laden alveolar macrophages. Subsequently, pulmonary fibrosis from iron deposition and severe anemia can develop. The DLCO can be elevated on PFTs. Remember that pulmonary hemorrhage also occurs in other diseases, such as small-vessel vasculitis and SLE.

One type of IPH has antibasement membrane antibodies. Anti-GBM disease (Goodpasture syndrome) is a similar disease with anti-BM antibodies to the lung and the kidney. Unlike Goodpasture's, IPH does **not** affect the kidneys.

IPH has a chronic course in adults. In children, IPH is extremely rare but more acute and more severe. Treatment is with chronic steroids; immunomodulators have shown limited success.

NONINTERSTITIAL DIFFUSE LUNG DISEASES

ALVEOLAR PROTEINOSIS

PREVIEW | REVIEW

- Which organisms cause chronic pneumonia in patients with pulmonary alveolar proteinosis?

Alveolar proteinosis is usually more alveolar than interstitial. There are defective alveolar macrophages causing a buildup of surfactant phospholipids. It can occur as a primary disease or secondary to dust exposure, granulocyte macrophage colony-stimulating factor (GM-CSF) deficiency, or myeloid dyscrasias.

Chest x-ray looks like pulmonary edema. Consider this with gradual dyspnea, fatigue, low-grade fevers, and occasional productive, gelatinous sputum production. Patients may be hypoxemic from a large right-to-left shunt with secondary polycythemia.

HRCT shows a **ground-glass** appearance with interspersed, thickened, interlobular structures—a pattern called “crazy paving.”

Diagnose with positive GM-CSF antibodies and bronchoscopy with BAL and biopsy showing copious periodic acid-Schiff (PAS) material filling terminal bronchioles with milky effluent. If GM-CSF is negative and BAL evidence is not revealing, perform surgical lung biopsy.

Treatment: If severe, do a whole-lung lavage under general anesthesia with double-lumen endotracheal tube (very experienced specialists only). If the disease is refractory to repeated whole-lung lavage, a trial of inhaled or subcutaneous GM-CSF or rituximab can attempt to restore proper function to the alveolar macrophages. Know that nonresolving pneumonias in these patients are most likely to be caused by *Nocardia*, mycobacteria, *Pneumocystis*, or endemic fungi. If the patient smokes, counsel them to stop. *Nocardia* can also present as a brain abscess from dissemination of pulmonary infection.

ANTI-GBM DISEASE

Anti-GBM disease can present as a pulmonary-renal disease, and a certain subset presents with diffuse pulmonary hemorrhage (Goodpasture syndrome). This is discussed in the [Nephrology](#) section.

HEMOPTYSIS

PREVIEW | REVIEW

- Which autoimmune diseases are associated with pulmonary hemorrhage? Which cardiopulmonary diseases?

Immunologic lung diseases that cause pulmonary hemorrhage:

- Goodpasture syndrome
- SLE
- Granulomatosis with polyangiitis
- Microscopic polyarteritis
- IPH
- Rarely, other vasculitides such as Behçet disease and Takayasu arteritis

Cardiopulmonary diseases that cause pulmonary hemorrhage:

- Pulmonary embolism (infarct usually needed)
- Pulmonary AV malformations
- Aortic aneurysm
- Pulmonary hypertension
- Septic emboli
- Mitral stenosis
- Heart failure

Other causes of hemoptysis, diffuse alveolar hemorrhage, and pulmonary hemorrhage:

- Acute bronchitis (most common cause)
- Bronchiectasis
- Aspergilloma
- Tuberculosis
- Lung abscess
- Severe thrombocytopenia or coagulopathy
- Aspergillosis, mucormycosis, and other acute fungal infections
- Lung cancer
- Bronchial adenoma
- Pulmonary carcinoid
- Endobronchial metastases
- Chemotherapy and bone marrow transplantation
- Drugs (e.g., cocaine)
- Coagulopathy (often with additional pathology present)
- Trauma or instrumentation within lung

Massive hemoptysis is usually defined as > 200 mL of blood coughed up in 24 hours or a rate of bleeding that is sufficient to potentially compromise the airway. Massive hemoptysis is most commonly caused by bleeding from the bronchial (arterial) circulation. Hemoptysis while on an anticoagulant in most cases is still associated with airway or pulmonary pathology.

Assurance of a patent airway and protection of the unaffected lung is important, in some cases requiring intubation and/or selective intubation of the unaffected lung.

Locate the site of bleeding by chest x-ray or CT scan and bronchoscopy—this is important. A temporary balloon can infrequently be used to tamponade an airway, allow clotting in the atelectatic area, and avoid spillover to the unaffected lung. However, more commonly, interventional radiologic embolization is used early to control bleeding once the anatomical location is suggested by imaging and bronchoscopy.

VENOUS THROMBOEMBOLIC DISEASE

PREVIEW | REVIEW

- What is the usual cause of pulmonary embolism (PE) in hospitalized patients?
- Which symptoms and physical exam findings are seen with submassive PE?
- Characterize the clinical findings seen with massive PE.
- What is the 1st step in evaluating a patient with possible PE?
- What happens to the A-a gradient in most patients with a large PE?
- What is the imaging of choice to diagnose PE in the nonpregnant patient with normal renal function and no dye allergy?
- In a low clinical probability scenario, what does a normal ventilation/perfusion (V/Q) scan imply with regard to the probability of PE?
- In a patient with a low clinical probability of venous thromboembolism, what is the significance of a negative D-dimer? A positive one?
- Know perfectly the 3 items under [Putting It All Together – How to Diagnose PE on page 6-43](#).
- In which situations can you use direct oral anticoagulants (DOACs) to treat thromboembolism?
- In which situations do you not use DOACs for treating thromboembolism?
- In which situations do you use low molecular weight heparin (LMWH) to treat thromboembolism? Unfractionated heparin?

- Should aPTT be monitored in patients on LMWH? How are Factor 10a levels used?
- What are the major complications with heparin-induced thrombocytopenia (HIT) Type II? Describe the treatment.
- In which patients is warfarin contraindicated?
- When are thrombolytics used to treat PE?
- What are the indications for a vena cava filter?
- Make sure you thoroughly understand the treatment points under [Putting It All Together – How to Treat PE on page 6-46](#).
- Which medications are the 1st choice for venous thromboembolism prophylaxis in the hospitalized at-risk patient?

OVERVIEW

Venous thromboembolic (VTE) disease is the term that includes both deep venous thrombosis (DVT) and pulmonary embolus (PE). The majority of medically significant PEs originate as DVTs in the lower extremities or pelvic veins. Virtually all are from DVTs above the knee (iliofemoral area). Most calf vein thromboses do not embolize. Remember postoperative surgical risk factors for VTE are higher for orthopedic, colorectal, trauma, and spinal cord injury.

Other sources of PEs are upper extremity, internal jugular, and subclavian thrombi. Typically, the source for the **upper body** thrombi are **IV catheters**, especially PICC lines.

PE is the 3rd most common **cardiovascular** cause of death (after ischemic heart disease and stroke); 11% die within 1 hour of onset of symptoms. Despite medical knowledge of the cause and effect of PE, the **incidence** has **not** declined. In hospitalized patients, inadequate VTE prophylaxis is the usual cause of PE.

This is the sequence of events in medically significant PE:

- 1) Embolic obstruction of a pulmonary artery
- 2) Increased alveolar dead space (ventilated but not perfused)
- 3) Vascular constriction
- 4) Loss of alveolar surfactant with atelectasis (V/Q mismatch + shunt areas)

These events result in an increased resistance to blood flow → increased pulmonary artery pressure → increased right ventricular (RV) work. The pulmonary circulatory system is highly compliant and therefore inherently has high **capacitance**. Consequently, up to **50%** of the lung vasculature can be blocked before the increased workload on the RV becomes significant in a normal individual. Massive PE usually occurs when > 2/3 of the functioning lung pulmonary arterial circulation is compromised.

Note that lung-tissue infarction is rare (< 10% of cases) because the tissue is perfused by **multiple sources**, including both the **bronchial and pulmonary arterial circulations** and **back diffusion** through the pulmonary venous system.

DIAGNOSIS OF PE

We will go over the clinical findings of PE first, then go over all the diagnostic tests, and then have a brief (whew!) discussion on working up PE that brings it all together.

Presentation

Clinical findings are varied and usually nonspecific, but there is a suggestive **set** of signs and symptoms. Sudden onset of dyspnea, pleuritic chest pain, and tachypnea are the most common. Hemoptysis and pleuritic pain, when due to PE, indicate an associated lung **infarction**.

Massive PE is defined by sustained hemodynamic instability (bradycardia, SVT, hypotension) requiring vasoactive support that is attributable to the PE.

PE is divided into risk stratified groups based on hemodynamic stability and sPESI, FAST, and BOVA severity scores. The definitions are important for determining prognosis and for ascertaining treatment strategies for patients:

- 1) **High-risk PE** is defined as cardiac arrest, obstructive shock, or persistent hypotension (systolic BP < 90 mmHg) not attributable to sepsis, hypovolemia, or arrhythmia (ERS 2019 guidelines).
- 2) **Intermediate-risk PE** is usually a patient with hemodynamic stability who has clinical/radiologic/laboratory severity scores that are considered intermediate risk, based on hemodynamics, troponin leak, and RV dysfunction notable on TTE.
- 3) **Low-risk PE** is defined as a hemodynamically stable PE with no clinical, radiologic, or laboratory features that are concerning for RV dysfunction.

The Wells prediction rules or revised Geneva criteria determine the **pretest** probability of PE based on clinical findings and medical history. As discussed later, assessing these (or similar verified pretest probability rules) is the **1st** step of the diagnostic workup of PE ([Table 6-11 on page 6-44](#) and [Table 6-12 on page 6-44](#)).

Malignancy, one of the Wells DVT criteria, is present in 50% of patients with **phlegmasia cerulea dolens** (an unusual type of DVT resulting in additional thrombosis of collateral veins, which causes massive edema, pain, and blue discoloration from arterial insufficiency). Malignancy is also suggested by superficial migratory thrombophlebitis, DVT resistant to anticoagulants, and thrombophlebitis in unusual places, such as the arms and trunk.

Review of Lab and Radiological Tests for PE

Here we discuss 12 tests and how they are used to diagnose PE and determine the patient's prognosis. In the

next topic we put it all together and cover how PE is actually diagnosed.

These are the 12 tests. Know all of them:

- 1) ABGs
- 2) Chest x-ray
- 3) ECG
- 4) CTPA
- 5) Venous ultrasound of lower extremities
- 6) V/Q scan
- 7) Venous studies
- 8) D-dimer
- 9) Pulmonary angiography
- 10) Echocardiography
- 11) Serum troponins
- 12) Serum BNP

Use **ABGs** to look for V/Q mismatch. Hypoxemia and increased A-a gradient are key indicators for V/Q mismatch that occur with large PEs. The V/Q mismatch is initially from decreased perfusion of ventilated areas (dead space). Shunting, from perfusion of poorly ventilated areas, occurs later as a side effect of PE (secondary to bronchoconstrictive mediators and atelectasis). Secondary RV failure can also contribute to the V/Q mismatch.

Chest x-ray helps exclude other causes in the differential (e.g., **pneumonia**, **pneumothorax**). Chest x-rays in patients with PE are most commonly either normal (12%) or nonspecific (e.g., infiltrate, effusion, atelectasis). Even so, PE is suggested by:

- Pulmonary infiltrate with a normal or elevated WBC count on peripheral smear
- Pulmonary consolidation in conjunction with an elevated ipsilateral hemidiaphragm (from atelectasis)
- Hampton hump—a pleural-based, wedge-shaped defect from infarction just above the diaphragm
- Oligemia (Westermarck sign; infrequently seen)—a lack of vascular markings in the area downstream of the embolus
- Large right descending pulmonary artery (Palla sign)

ECG is highly suggestive but **not** sensitive. ECG changes seen with PE are tachycardia and RV strain from acute cor pulmonale. On ECG, acute right heart strain = S1Q3T3. That is, the S wave is large in lead I, the Q wave is large in lead III, and the T wave is inverted in lead III. This is not seen often, but it tends to appear frequently on exams! The most common EKG finding in PE is sinus tachycardia. ECG also helps rule out MI.

CT pulmonary angiography (CTPA; more under **Computed Tomography (CT)** Chest on page 6-1) is as accurate and is less invasive than pulmonary angiography. CTPA is the **gold standard** for primary, noninvasive imaging to diagnose **acute** PE with high sensitivity and specificity. It is

especially helpful when the patient has cardiopulmonary problems that might obscure the results of the V/Q scan.

When assessing for **chronic** pulmonary thromboembolism, the V/Q scan is more sensitive than CTPA.

Ventilation/Perfusion lung scan remains useful in obese patients, in those with **iodine allergy**, and in patients with **chronic kidney disease (CKD)** for whom contrast dye is undesirable. The V/Q scan is the test of choice for the diagnosis of recurrent PEs due to chronic venous thromboembolic disease.

Normal: A normal chest x-ray plus a normal V/Q scan has a **very low risk of PE**. When coupled with a low clinical probability, a normal V/Q scan essentially eliminates the diagnosis of PE.

Low-probability and **moderate-probability** scans are considered indeterminate because these patients have a 14–40% chance of PE.

Moderate-probability scans consist of subsegmental perfusion defects or matched ventilation and perfusion defects. A chest x-ray finding of an infiltrate in the area of perfusion defect indicates the same risk. If clinical suspicion of PE is low, no further testing is necessary. If it is high, consider CTPA, selective pulmonary arteriogram, ultrasound (U/S) of the lower extremities, or empiric anticoagulation.

High-probability scans occur in 2 situations:

- 1) ≥ 2 segmental or larger perfusion defects are present with a normal ventilation study.
- 2) The perfusion defect is much larger than the ventilation defect.

The trouble with V/Q scans is that large numbers come back as low-probability/indeterminate. You greatly improve accuracy of the above scans by factoring in pretest probability of a PE. For instance:

- ~ 30% of patients with a low-probability scan have a PE, but with a low pretest probability, this rate drops to 2%! With a high pretest probability, it jumps to 40%.
- ~ 85% of patients with a high-probability scan have a PE, but with a high clinical probability, this rate jumps to 96%! With a low pretest probability, it plummets to 6%.

Determining the probability for PE (by means of verified criteria such as Wells or revised Geneva) is included as the 1st step of the diagnostic workup.

Venous studies: Determining the existence of DVT of the lower extremities is important in diagnosing and preventing PE.

Treatment of isolated venous thrombosis in the calf with no involvement of the popliteal vein is controversial because the incidence of embolization is 50% less than with proximal thromboses. Some centers use anticoagulation, and some follow with serial ultrasounds if there are no risk factors (i.e., immobility, prior DVT, inpatient status, cancer, elevated D-dimer $> 500 \mu\text{g/L}$ [$0.5 \mu\text{g/mL}$]).

Duplex ultrasonography combines real-time, B-mode ultrasonography, which visualizes the vessel with Doppler flow detection, with looking for **compressibility** of the vessel and **flow**. This test is reliable only in **symptomatic** patients being evaluated for their 1st DVT by an **experienced** operator (operator-dependent). In these patients, the sensitivity is 93% while the specificity is 98%. It is poor for detecting distal DVT (because the vessels are hard to visualize) and abdominopelvic thrombi (from which most cases of PE arise).

D-dimer testing is sensitive and useful. Used with any 1 of the above noninvasive tests, it increases the **negative** predictive value of the test. A **negative** D-dimer in a **low-risk** patient **excludes** DVT/PE as a diagnosis.

Because of the **poor specificity**, the D-dimer has a poor positive predictive value, so do **not** use it to screen for DVT or PE. A positive D-dimer in a low risk individual is not diagnostic of PE.

Pulmonary angiography was the gold standard for the diagnosis of PE. Because pulmonary angiography is an invasive test, it is reserved for cases with inconclusive results from CTPA and/or V/Q scan. It is used in patients who have a high clinical probability of disease but negative results from other studies, such as CTPA and Doppler U/S.

Pulmonary angiography, especially if selective (guided by V/Q or HRCT scan findings), is a relatively safe procedure. Mortality is < 0.1%, although in patients with marked pulmonary hypertension mortality may be higher. Morbidity = 1-2%.

Echocardiography has poor sensitivity and specificity. However, it can be used at the bedside to determine if right heart strain is present in a patient who has a presentation consistent with massive PE. In such fluid-refractory hypotensive cases, when there is acute RV strain, relatively normal LV function, and a clinical picture consistent with PE, urgent thrombolytic therapy can be considered. A transesophageal echocardiogram can sometimes identify a central pulmonary embolus or a clot in transit through the heart.

Echo is also useful for making a prognosis in acute PE. Increased mortality is seen in patients who have normal BP and evidence of RV dysfunction or presence of an RV thrombus.

Troponins I and T are elevated in 30-50% of submassive to massive PEs and are probably the result of right heart failure. They are mainly used to determine the prognosis but are often drawn for cardiac evaluation in the midst of the acute presentation. Elevated levels correlate with increased severity of PE and increased short-term mortality.

BNP elevation can also be used as a marker of increased morbidity and mortality.

Putting It All Together — How to Diagnose PE

So, how is the diagnosis of PE made using these tests?

Know! It is really quite simple:

- 1) Use clinical prediction rules (Wells or revised Geneva are the most commonly cited) to determine probability of DVT and then pretest probability of PE (refer to [Table 6-11 on page 6-44](#) and [Table 6-12 on page 6-44](#)). In patients with low pretest probability, a negative D-dimer indicates a low likelihood of PE and essentially excludes the diagnosis.
- 2) U/S of lower extremities is recommended for patients with intermediate-to-high pretest probability for PE. If there is a high pretest probability for PE and proximal (iliofemoral or higher) thrombi, treat for PE.
- 3) CTPA, V/Q scan, or standard pulmonary angiography is recommended in patients with intermediate or high pretest probability if the lower extremity U/S does not show clotting.

Once the diagnosis of a PE is made, utilizing the Simplified Pulmonary Embolism Severity Index to risk stratify patients by their mortality risk is the next step in triaging their care.

TREATMENT OF PE

Treatment options for PE include:

- Adjunctive treatment (i.e., O₂, hemodynamic support with vasopressors, extracorporeal membrane oxygenation [ECMO])
- Anticoagulants (i.e., heparins, DOACs, warfarin)
- Thrombolytics (i.e., tPA [tissue plasminogen activator])
- Surgery (i.e., vena cava filters, thromboembolectomy)

Adjunctive Treatment for PE

Give oxygen for hypoxia. Many use IVF boluses to treat hypovolemia and raise preload or filling pressure in a dilated, strained RV. If in shock, norepinephrine is the vasopressor of choice. Mechanical ventilation is used in the setting of respiratory failure.

Anticoagulants for PE

The main anticoagulants are **heparins**, **fondaparinux** (Arixtra), **direct oral anticoagulants** (DOACs), and **warfarin**. Achieve adequate anticoagulation ASAP with a heparin or fondaparinux! It is indicated in hemodynamically stable patients in whom PE is **suspected** or confirmed unless there are contraindications.

Table 6-11: Wells Criteria for DVT

Criteria	Score
Active cancer (current Tx or palliation, or Tx within last 6 months)	1
Recent immobilization of lower extremities (e.g., plaster cast, paralysis, paresis)	1
Recently bedridden > 3 days or major surgery with general/regional anesthesia	1
Localized tenderness along the distribution of deep venous system	1
Entire leg swollen	1
Calf swelling 3 cm larger than asymptomatic side (measured 10 cm below tibial tuberosity)	1
Pitting edema confined to the symptomatic leg	1
Collateral nonvaricose superficial veins	1
Alternative diagnosis is at least as likely as DVT.	-2
Score: ≥ 3 = high probability of DVT 1-2 = moderate probability 0 = low probability	
Note: If symptoms are in both legs, use the more symptomatic one.	

Table 6-12: Geneva Criteria for PE

Criteria	Score under Original Version	Score under Simplified Version
Previous DVT/PE	3	1
Heart rate 75-94 beats/minute	3	1
Heart rate ≥ 95 beats/minute	5	2
Surgery or fracture in the previous 4 weeks	2	1
> 65 years of age	1	1
Hemoptysis	2	1
Active cancer	2	1
Unilateral lower-limb pain	3	1
Pain on lower-limb deep venous palpation and unilateral edema	4	1
Three-level score under original version: ≥ 11 = high probability of DVT 4-10 = intermediate probability 0-3 = low probability		
Three-level score under simplified version: ≥ 5 = high probability of DVT 2-4 = intermediate probability 0-1 = low probability		
Two-level score under original version: ≥ 6 likely DVT 0-5 unlikely DVT		
Two-level score under simplified version: ≥ 3 likely DVT 0-2 unlikely DVT		

Anticoagulants are relatively contraindicated in the following:

- Uncorrected major bleeding disorder (e.g., thrombocytopenia, hemophilias, liver failure, renal failure)
- Uncontrolled severe hypertension (systolic BP > 200 mmHg, diastolic BP > 140 mmHg)
- Potential bleeding lesions (e.g., active peptic ulcer, esophageal varices, aneurysm, recent trauma/surgery to the head/orbit/spine, recent stroke, intracranial or intraspinal bleed)
- NSAIDs (increases risk of GI bleeding; if able, stop NSAIDs)
- Repeated falls or unstable gait

Remember warfarin is teratogenic and increases risk of fetal bleeding, so low molecular weight heparin is the preferred agent in pulmonary embolism treatment during pregnancy. (For more information on pulmonary embolism in pregnancy, see the [Women's and Men's Health](#) section.) Contraindications require consideration of an IVC filter or thrombectomy/embolectomy.

Heparins

There are 2 types of heparin, low molecular weight heparin (LMWH) and unfractionated heparin (UFH). LMWH is preferred over UFH for PE.

LMWH: Use subcutaneous full-dose LMWH (dalteparin or enoxaparin) whenever possible to treat PE (inpatients and outpatients) because of the lower risk of major bleeding compared to UFH. Either LMWH or UFH can be used for the initial treatment of PE. Most prefer LMWH, especially if the patient is hemodynamically stable, because LMWH reaches the therapeutic state faster. UFH is used in the setting of dynamic renal dysfunction or when there is need for rapid reversal.

LMWH is made from the depolymerization of heparin, which produces some molecular fragments with 30-50% the weight and more anticoagulant activity. LMWH has no effect on thrombin like UFH does. Rather, it solely inactivates Factor 10a (so aPTT is not sensitive to LMWH anticoagulant effect). Factor 10a levels can be used to monitor therapeutic effect. LMWH causes fewer instances of major bleeding than UFH in DVT, and in any VTE situation anticoagulation is established more quickly than with UFH. LMWH can still cause heparin-induced thrombocytopenia (although less often than UFH), so monitor the platelet count.

LMWH is preferred for treating VTE in pregnant women, cancer patients, and anybody who is treated for an extended period because the risk of osteoporosis is much lower than with UFH. You can monitor activity by assessing activated Factor 10a levels in outpatient settings, but this is usually not necessary as dosing is weight based.

Do not use LMWH in patients with a creatinine clearance < 30 mL/minute. Instead, use UFH because it can be titrated.

For both UFH and LMWH, protamine is the antidote for bleeding, but it is less effective against LMWH.

UFH binds with antithrombin (AT) to make it 1,000–4,000× more effective in inactivating thrombin and Factor 10a. To inactivate thrombin, heparin binds to both AT and thrombin.

UFH is **no longer** the drug of choice for DVT, but it is still used for the initial treatment of PE—especially if the patient is unstable and might require rescue thrombolysis. UFH dosage is determined by means of a **weight-based nomogram** to achieve adequate anticoagulation. Check aPTT levels every 6–8 hours after dosage change to allow time to achieve a steady state.

UFH is more often given to unstable PE patients because subcutaneous LMWH requires good blood pressure and tissue perfusion for optimal delivery, and this situation is not reliable in unstable patients. (Thrombolytics are also used in hypotensive patients with PE; know that you do **not** give tPA to **stable** patients with PE.)

Adjust the dose of IV UFH to keep the **aPTT** at least 1.5× control for 7–10 days. Greater increases than this result in an increased incidence of bleeding. Then continue anticoagulant treatment (minimum **3–6 months**), preferably with either LMWH, DOAC, or warfarin.

Complications: The major problem with UFH use is hemorrhage. Before giving it, be sure the patient has no major bleeding syndromes, no evidence of recent bleeding, and no significant thrombocytopenia.

Patients who are at high risk for bleeding should be given UFH in an infusion so it can be turned off and the effect reversed quickly with protamine if needed.

Heparin antidote: Again, for both UFH and LMWH, **protamine** is the antidote for bleeding. However, it is less effective against LMWH.

Heparin-induced thrombocytopenia (HIT):

- HIT Type **I** develops within 1–2 days of initiating heparins. HIT-I is common and of **no** clinical consequence.
- HIT Type **II** is an immune response where **antibodies** develop against the complex of heparin and platelet Factor 4. The antibodies are named anti-H-PF4. HIT-II starts **4–10** days after initiation of treatment. It occurs in 1–3% of patients receiving UFH and in about 0.5% of patients receiving LMWH. Arterial and venous thromboemboli are the major life-threatening complications.

Always monitor the **platelet count** in patients on heparin; if it drops > 50% and/or thromboembolic symptoms develop, stop using heparin—even heparin flushes. Use the 4 Ts score to determine the likelihood of HIT (see more in the **Hematology** section). Then, start treatment with a direct thrombin inhibitor, such as argatroban. Start DOAC or warfarin when the platelet count recovers to $\geq 100,000/\mu\text{L}$ ($100 \times 10^9/\text{L}$; and continue the thrombin inhibitor) because there is a long-term risk of clots as long as the antibodies are present.

Factor 10a and Direct Thrombin Inhibitors

There are 2 groups of direct oral anticoagulants (DOACs):

- 1) Factor 10a inhibitors: apixaban (Eliquis), rivaroxaban (Xarelto), edoxaban (Savaysa, Lixiana), betrixaban (Bevyxxa)
- 2) Direct thrombin inhibitor (dabigatran [Pradaxa])

They are fixed-dose oral agents that, compared to warfarin, do not require routine laboratory monitoring and have fewer drug-drug interactions. These agents usually reach their peak efficacy within a few hours after ingestion, so bridging therapy with unfractionated or LMWH is not required. Previously, the major disadvantage with these oral agents was the lack of a reversal agent, but in 2018 the FDA approved a reversal agent to dabigatran: idarucizumab (Praxbind), a monoclonal antibody that binds to dabigatran and rapidly neutralizes the anticoagulant effect. There is no safety profile on the use of DOACs in pregnancy. Andexanet alpha (activated factor 10) was approved by the FDA in 2018 for reversal of rivaroxaban and apixaban. In massive bleeding in the presence of direct thrombin or factor 10a inhibitors, also consider 4-factor prothrombin complex concentrate or tranexamic acid.

In 2013, multiple large Phase III trials demonstrated the noninferiority of DOACs compared to UFH or LMWH + vitamin K antagonists (VKA) such as warfarin in acute symptomatic VTE and fatal VTE recurrence with reduced rates of major bleeding. Most of these trials were performed in stable patients and designed as noninferiority trials. Do not use these agents for the initial treatment of a hemodynamically unstable pulmonary embolus since their use can interfere with potential thrombolytic therapy or pulmonary embolectomy if clinically indicated.

Fondaparinux

Fondaparinux is a **Factor 10a inhibitor**. Give it subcutaneously, once daily. It is approved for **DVT prophylaxis** in surgical patients and for treatment of both **DVT** and **PE** as an alternative to UFH and LMWH. Fondaparinux does not cause heparin induced thrombocytopenia (HIT), so it is a useful drug for patients who need anticoagulation or prophylaxis and who have a history of HIT.

Fondaparinux is cleared exclusively by the **kidneys**. Therefore, it is contraindicated in patients with creatinine clearance < 30 mL/minute and probably should be used cautiously when the clearance is between 30 and 80 mL/minute because it accumulates. It does not require Factor 10a level monitoring, and there is **no antidote**. Rate of bleeding is similar to heparins. Fondaparinux and enoxaparin are preferred over UFH in patients receiving parenteral/subcutaneous therapy without hemodynamic stability.

Warfarin

International normalized ratio (INR) is a product of the $PT_{\text{patient}}/PT_{\text{control}}$ ratio multiplied by an international sensitivity index (ISI). The ISI accounts for the sensitivity of the thromboplastin used by the lab, which varies from batch to batch. The formula is $INR = (PT_{\text{patient}}/PT_{\text{control}}) \times ISI$. INR is used to determine proper dosages of warfarin.

Warfarin is adjusted to maintain INR at a goal range of 2.0–3.0 (target 2.5). Initial dosing is usually 5 mg/day, and this is often titrated to patient specific parameters based on things like diet or drug-drug interactions. Note: Warfarin is a vitamin K antagonist that prevents activation of Factors 2, 7, 9, and 10.

Remember: After starting warfarin, Factor 7 is the most rapidly decreasing procoagulant, but protein C (an anticoagulant) also decreases rapidly—so you can (rarely) see an initial net procoagulant effect. This can occur only until the slower-clearing Factor 2 decreases enough to result in a net anticoagulant state. This usually takes ~ 4 days. This potential problem is addressed by starting the warfarin right after heparin is started (within 8 hours) and keeping patients on heparin for at least 4 days. Alternatively, using enoxaparin or fondaparinux (rather than UFH) can decrease hospital stays.

Warfarin necrosis is an idiosyncratic side effect that causes full-thickness skin necrosis requiring skin grafts.

Any decrease in the minimum level of dietary vitamin K results in an increase in the INR. Monitor the INR more frequently if the diet is changed or if the patient is treated with an antibiotic that might kill the gut flora required for proper vitamin K absorption.

Warfarin interacts with many drugs. For a detailed review of warfarin interactions, see the [General Internal Medicine](#) section.

Note: Warfarin can be started at the same time or any time after heparin or fondaparinux is started. The overlap period should be at least 4–5 days (10 days with massive PE) with the INR at a therapeutic level for 2 days before discontinuing the heparin and continuing the warfarin.

Warfarin in pregnancy can cause congenital deformities, especially if given in the 1st trimester. Use LMWH or adjusted-dose UFH instead. For more information on pulmonary embolism in pregnancy, see the [Women's and Men's Health](#) section.

Treat patients who have cancer (with venous thromboembolisms) with LMWH for the entire duration of therapy.

Thrombolytics for PE

tPA is indicated for patients with massive PE with hemodynamic compromise who have “acceptable” risks of bleeding and do not have absolute contraindications.

PE patients with intermediate risk factors for increased mortality can also benefit if they develop hemodynamic instability. Consider the patient's bleeding risk. A multidisciplinary pulmonary embolus response team (PERT) team is recommended in high (and some intermediate) risk cases.

Thrombolytics are not indicated for treatment of low-risk PE.

Vena Cava Filters for PE / VTE

Indications for vena cava filters include recurring VTE with adequate anticoagulation or recurring VTE when anticoagulant treatment is contraindicated.

Retrievable vena cava filters are used when only short-term protection is required and can be removed when the risk for PE has subsided or when anticoagulation can be resumed.

So, what can be used if TPA is not an option?

Surgical thrombectomy/embolectomy is a potential option but has high operative mortality.

Devices allow for mechanical thrombectomy (i.e., catheter extraction, rheolytic thrombectomy using high velocity saline jets) or mechanical disruption (i.e., pigtail catheters, intravascular U/S), but results vary by institutional expertise.

Putting It All Together — How to Treat PE

Know!

First, stabilize the patient: Put on O₂ and give hemodynamic support as needed with IV fluids and vasopressors.

Then, determine which anticoagulant to start. It is usually subcutaneous LMWH—especially if the patient is pregnant, has cancer, or is bedridden with normal renal function. If there is a history of HIT, fondaparinux is a good choice unless the patient has a creatinine clearance < 80 cc/min. In this case, argatroban, a direct thrombin inhibitor, is your only choice. If the patient is unstable without a history of HIT, IV UFH is given (aPTT = 1.5× control) to allow for rescue thrombolytics in the setting of decompensation. If massive PE, consider thrombolytics.

Home treatment with LMWH, DOAC, or warfarin is continued for:

- 3 months for PE due to transient risk factors
- At least 3 months and long term for PE without identifiable risk factors for those with low-to-moderate bleeding risk
- Indefinitely for recurrent PEs or thrombotic tendencies without significant bleeding risk

Periodically evaluate the risk/benefit of long-term anticoagulation.

Some DOACs can be started immediately after UFH is stopped, or they can be started 6–12 hours following the last dose of LMWH. Warfarin alone can be used after UFH when INR is 2.0–3.0 for 2 days.

TREATMENT OF DVT WITHOUT PE

Know that if the patient has a high probability of DVT with a low probability of PE (or if these diagnoses have been confirmed), the treatment is **exactly the same as that for PE** (more under [Treatment of PE on page 6-43](#)).

A patient that has extensive DVT with swelling (resulting in insufficient arterial blood flow in the limb causing pain, cyanosis and paresthesias) would be diagnosed with phlegmasia cerulea dolens and would be considered a surgical emergency, requiring thrombolytics or thrombectomy.

Although few **calf vein thromboses** migrate above the knee, the ones that do are usually **painful**! So, treatment depends on present risk factors or pain. If risk factors or pain exist, treat; if not, perform serial U/S.

RISK AND PROPHYLAXIS OF VTE

Pulmonary embolism is the most common preventable cause of death in hospitalized patients. Prophylaxis for DVT (and therefore PE) is cost effective. Despite the existence of numerous evidence-based guidelines, adequate prophylaxis is still not being offered to many at-risk patients (which makes this topic ripe for exam questions).

VTE Prophylaxis

The American College of Hematology (ACH) issued guidelines in 2018 for VTE prophylaxis, and the recommendations have somewhat simplified things.

Know that the use of either pharmacological prophylaxis **or** mechanical prophylaxis is favored over combined pharmacological and mechanical prophylaxis.

Unless patients are very high risk for bleeding, a drug for VTE prophylaxis is recommended. Types include subcutaneous LMWH, fondaparinux, and UFH. LMWH is preferred over DOACs for acutely ill, hospitalized patients. The ACH does not recommend extended duration post-hospitalization prophylaxis with DOAC over in-hospital prophylaxis. DOACs are typically used in patients who refuse injections or after orthopedic procedures.

For patients at the highest risk for bleeding, use pneumatic compression instead of drugs for VTE prophylaxis (or instead of no VTE prophylaxis).

FAT EMBOLI

Fat emboli cause the triad of **dyspnea**, **confusion**, and **petechiae**—usually in the neck, axilla, and/or conjunctiva. Fat emboli can occur within 72 hours after a **fracture** of

a **large bone** (e.g., femur) or operative manipulation of a large bone, sometimes **after CPR**, and with **sickle cell** bone-occlusive crisis.

Treatment is supportive; corticosteroids have **not** been proven to be helpful.

PULMONARY HYPERTENSION (PH)

PREVIEW | REVIEW

- Which common physical exam findings are seen in pulmonary hypertension (PH)?
- What are the 1st tests you order in the workup of PH? Which follow-up test is done if the 1st tests are suggestive?
- Which test of lung function, when low, indicates a poor prognosis in PH?

OVERVIEW

Definition of PH by the 2019 World Symposium on Pulmonary Hypertension: The **mean** pulmonary artery pressure is ≥ 20 mmHg on a right heart catheterization. Left heart failure as a cause is excluded by demonstrating the pulmonary capillary wedge pressure (PCWP) to be ≤ 15 mmHg and the pulmonary vascular resistance (PVR) to be > 3 Wood units (WU).

The World Health Organization (WHO) categorizes PH into 5 groups based on the **etiology**:

- **Group 1 PAH** (pulmonary **arterial** hypertension) is composed of familial PAH (heterozygous *BMPT2* mutations), idiopathic PAH (IPAH; previously known as primary pulmonary hypertension), **and** associated PAH caused by diseases or toxins that damage small muscular pulmonary arterioles. Examples include collagen vascular diseases, intracardiac shunts, portal hypertension, HIV, appetite suppressants/stimulants, toxic rapeseed oil, pulmonary veno-occlusive disease (PVOD), and pulmonary capillary hemangiomatosis (PCH).
- **Group 2 PH** is due to **left-sided heart** disease (i.e., atrium, ventricle, valve).
- **Group 3 PH** is seen in disorders of the **respiratory system** (e.g., ILD, COPD) or chronic hypoxemia (e.g., OSAHA).
- **Group 4 PH** is caused by **chronic venous thromboembolic** disease.
- **Group 5 PH** has unclear and/or multifactorial causes (i.e., myeloproliferative disorders, metabolic disorders, fibrosing mediastinitis).

Note that Group 1 is pulmonary **arterial** hypertension (PAH). PAH affects the entire vasculature of the lung, including the endothelium, smooth muscle, and even the extracellular matrix. However, it affects the arterioles of the pulmonary vasculature the most. This results in an **obliterative** process in which the pulmonary

vessels become more tortuous and close off with resultant increased resistance. Group 4 definitive treatment is surgery, often with high morbidity, and lifelong anticoagulation. Riociguat (an oral soluble guanylate cyclase stimulant) can be used in inoperable patients.

PHYSICAL FINDINGS OF PH

Symptoms include dyspnea on exertion and fatigue and can be nonspecific, making early diagnosis difficult. Physical exam reveals a loud 2nd heart sound (P_2 component is accentuated), tricuspid regurgitation, and RV heave.

Tricuspid regurgitation is common with PH and is due to the dilation of the RV (holosystolic murmur along the LLSB that increases with inspiration and a parasternal heave). The tricuspid regurgitation and RV failure present as jugular venous distention (JVD) with large v waves, liver pulsations, and lower extremity edema.

DIAGNOSIS OF PH

The chest x-ray can provide clues in an undiagnosed case. Significant PH manifests on the chest x-ray as enlargement of the central pulmonary arteries with attenuation of the peripheral vessels, resulting in oligemic, darker lung fields ("pruning" on chest x-ray). Use V/Q scan to evaluate for chronic thromboembolic disease as a cause of PH; this can be missed on a CT chest with contrast.

The ECG shows a right axis deviation (from right ventricular hypertrophy). The 1st tests to order when you suspect PH are an ECG and an echocardiogram.

The echocardiogram is useful in the workup of PH to evaluate for:

- Elevated pulmonary artery pressure (and to estimate RV systolic pressure)
- Right ventricular hypertrophy and RV dilation/dysfunction
- Right atrial enlargement (RAE) and right atrial size
- Shift of interventricular septum toward the left during systole

It can also rule out congenital cardiac pathology and evaluate for anatomical shunting through a cardiac defect.

If the echocardiogram is suggestive of pulmonary hypertension, right heart catheterization is the next best step. For a positive diagnosis, the mean pulmonary artery pressure is ≥ 20 mmHg and PCWP ≤ 15 mmHg.

An additional finding in the diagnosis of Group 1 PAH is pulmonary vascular resistance > 3 WU.

Remember that most pulmonary function parameters are normal in PH, but the DLCO decreases. Know that a very low DLCO indicates a poor prognosis in patients with PH.

TREATMENT OF PH

Exercise, Diuretics, and Oxygen

Exercise is encouraged based on the individual's symptom limitations and improves quality of life and functional capacity.

Diuretics are recommended for fluid overload.

Oxygen helps symptoms in any WHO group when the patient is hypoxemic. Give oxygen to all who meet the criteria as discussed under [Treatment of Stable COPD on page 6-24](#).

Balloon atrial septostomy, double-lung transplantation, and heart-lung transplantation are considered when symptoms remain Class 3 or 4 despite maximal combined medical therapy for Group 1.

Vasodilators in PH

Note

The recommendations of the 2015 Joint Task Force of the European Society of Cardiology (ESC) and European Respiratory Society are as follows: Pharmacologic agents for reducing PH are intended for Group 1 PAH.

Calcium Channel Blockers

Calcium channel blockers (CCBs) can be used in the small number of patients who have positive vasoreactivity testing.

Vasoactive reactivity testing looks for a response to a CCB during right heart catheterization for a specific subset of Group 1 PAH (idiopathic, hereditary, toxins, and drugs). Amlodipine, nifedipine (for relative bradycardia), and diltiazem (for relative tachycardia) are used, and selection is guided by underlying heart rate. Vasoreactivity is confirmed by a reduction in mean pulmonary artery pressure (mPAP) ≥ 10 mmHg to reach an mPAP of ≤ 40 mmHg, with the same or increased cardiac output, and minimal change in systemic blood pressure. Commonly used agents include inhaled nitric oxide (the preferred agent), epoprostenol, adenosine, and iloprost. Patients without documented vasoreactivity should not be started on a CCB due to risk of syncope and RV failure.

Endothelin Receptor Antagonists

Bosentan (Tracleer), ambrisentan (Letairis) and macitentan (Opsumit) are oral endothelin receptor antagonists. Endothelins are vasoconstricting polypeptides released by an injured endothelium and are elevated in patients with PH and heart failure. Medications in this category tend to be very well tolerated.

Prostanoids

Continuous IV (pump) infusion of epoprostenol (Flolan, Veletri) and treprostinil has been approved and is recommended as 1st line therapy for NYHA Class IV disease.

These medications have been shown to yield good results for functional Class III also, but there are many other agents from which to choose for Class III disease.

Know that patients getting IV epoprostenol or treprostinil exhibit tachyphylaxis and require a slow ramp-up of the dosage over time.

Inhaled vasodilators iloprost (Ventavis) and treprostinil can help reduce the side effects of IV prostanoids, but improvement in survival has not been demonstrated.

Oral medications in this group are selexipag (Uptravi), a prostacyclin receptor agonist, and treprostinil (Orenitram), a prostacyclin analogue.

PDE-5 Inhibitors

Sildenafil (Revatio, Viagra), tadalafil (Adcirca, Cialis), and vardenafil inhibit cyclic guanosine monophosphate (cGMP) phosphodiesterase Type 5 (PDE-5) in smooth muscle of the pulmonary vasculature, where PDE-5 is responsible for the degradation of cGMP. Increased cGMP concentration results in pulmonary vasculature relaxation and vasodilation in the pulmonary bed.

Guanylate Cyclase Stimulators

Guanylate cyclase stimulators are used for chronic thromboembolic pulmonary hypertension (CTEPH) and portopulmonary hypertension. Do not combine this with PDE-5 inhibitors. The 1 drug available so far is riociguat (Adempas).

Prostacyclin Oral Agents

Selexipag is a nonprostanoid, selective oral prostacyclin receptor agonist for the long-term treatment of PAH in adults. Treprostinil is an oral prostacyclin analogue used for long-term treatment of PAH.

Caution: Many of these medications have significant drug interactions. For example, ritonavir, amiodarone, and fluconazole can increase bosentan levels, and bosentan can decrease amiodarone levels. Expert guidance is suggested.

- Which specific tests for *M. tuberculosis* are available to diagnose tuberculosis (TB) using pleural fluid?
- Which diagnostic tests are done for suspected pleural TB?
- What is the definition of hemothorax?
- Define chylous effusion. What causes it?

EXUDATIVE vs. TRANSUDATIVE

Pleural effusions (Figure 6-19) are either transudative or exudative. They are distinguished by comparing total protein and LDH in the effusion to that in the serum. Also, LDH level (in units/L) in the effusion is an independent indicator. One can send labs in 2 stages or, as is more commonly done, send all at once, particularly if the etiology is not clear or if there is concern for infection (i.e. empyema and/or parapneumonic effusion).



Figure 6-19: PA chest—right-side pleural effusion
Source: Vinay Maheshwari, MD

A **transudative effusion** is secondary to **systemic** changes that affect the accumulation and absorption of pleural fluid. The most common causes are LV failure, hypoalbuminemia, cirrhosis, and nephrotic syndrome.

An **exudative effusion** is due to a **local** cause, and the 2 most common are bacterial pneumonia and cancer—but remember PE, even though it is not as common. [Table 6-13 on page 6-50](#) details the results of fluid studies that help determine whether a pleural effusion is a transudate or an exudate. These biochemical measurements and ratios are called Light's criteria. Note that **all 3** conditions must be met for an effusion to be called a transudate—failing any 1 criterion makes it an exudate.

Put another way, only 1 Light's criterion is needed to qualify as exudative effusion.

PLEURAL EFFUSIONS

PREVIEW | REVIEW

- Name the most common causes of transudative pleural effusions.
- Which 3 conditions must be met for an effusion to be called a transudate?
- Which clinical and laboratory features make a pleural effusion complicated?
- What is the definition of empyema?

Table 6-13: Light's Criteria for Pleural Effusions

	Eff:Serum Protein Ratio		LDH in Effusion		Eff:Serum LDH Ratio
Transudative	≤ 0.5	and	≤ 200 U/L (3.34 μkat/L)	and	≤ 0.6
Exudative	> 0.5	or	> 200 U/L (3.34 μkat/L)	or	> 0.6

Concern over using LDH as a parameter twice in Light's criteria has given rise to alternate diagnostic criteria for exudates:

- The 2-test rule: pleural cholesterol > 45 mg/dL (1.17 mmol/L) or pleural LDH > 0.45× the upper limit of your lab's normal for LDH
- The 3-test rule: pleural protein > 2.9 g/dL (29.00 g/L), pleural cholesterol > 45 mg/dL (1.17 mmol/L), or pleural LDH > 0.45× the upper limit of your lab's normal for LDH

Transudative effusions and/or the underlying causes are usually treated with diuresis and sometimes with albumin.

Exudative effusions require further tests of the fluid to establish the cause. For this reason, you want to send several tubes of pleural fluid to the lab. Evaluate the 1st tube, then tell the lab to save the rest. Once you know the type of effusion, you can then decide on the other tests, if your lab will do such 2-stage testing. If not, the tests discussed below can be sent all at once. If there is concern for a parapneumonic effusion, the pertinent labs should be sent at once, including pleural fluid pH, cell count, glucose, LDH, cholesterol, and protein.

Transudative Effusions

Transudative effusions do not need further evaluation.

Know that **LV failure** is the #1 cause, and it is not unusual to see an isolated right-sided effusion. Transudative effusions are common after abdominal surgery and are typically benign.

In patients without obvious heart failure, perform a thoracentesis on unilateral, asymmetric, or diuretic-nonresponsive effusions of significant size.

Generally, do **not** tap bilateral effusions that are equal in size and responsive to diuretics occurring in patients with well-established LV failure, cirrhosis, hypoalbuminemia, or nephrotic. The overwhelming majority of these are transudates.

Relief of dyspnea after therapeutic thoracentesis for an effusion is due to a **decrease** in the intrathoracic volume! This is because most of the volume occupied by a pleural effusion distends or displaces the diaphragm, causing the dyspnea. Only ~ 20% of the volume results from compression of the lung. Know that the

removal of a large amount of pleural fluid can actually be accompanied by a transient fall in the pO₂ during the first 12 hours, until atelectatic alveoli can reexpand and participate in gas exchange. In some cases, with removal of at least 1.4–2 L, reexpansion pulmonary edema may develop.

Exudative Effusions

Once you determine that your fluid is an exudate, tell the lab to do the following studies on the remaining fluid you sent (or, with high suspicion for exudate, malignancy, or infection, obtain all labs at once):

- Glucose and amylase; consider triglyceride level
- Cholesterol
- Cell count with differential
- Gram stain and bacterial culture
- Cytology
- pH
- Marker for tuberculosis (e.g., adenosine deaminase level) if available and if there is suggestive clinical information
- Analyze the serum/pleural fluid albumin ratio.
- If the above studies do not help you with diagnosis, consider CTPA to evaluate for PE.

These studies, plus the clinical history and exam, help you determine the most likely cause, which we will discuss in the next topic. In general, when there is high suspicion for infection (i.e., empyema, parapneumonic effusion), the pleural fluid should be promptly sampled and labs sent all at once to avoid delaying any necessary intervention.

Bacterial pneumonia is the most common cause of an exudative effusion in the U.S. The effusion develops in association with **bacterial** pneumonia or lung abscess. Consider the possibility of effusion every time you consider bacterial pneumonia as a diagnosis for a dense infiltrate on chest x-ray. If clinical evidence of effusion is present in the setting of pneumonia, quantify the size using imaging (decubitus chest x-ray, CT, or U/S). The key is **10 mm**! If there is > 10 mm of fluid from the lung surface to the chest wall, the patient may need a thoracentesis to determine if there is an empyema or complicated parapneumonic effusion.

A **complicated** effusion is diagnosed if any of the following are found on analysis of the therapeutic thoracentesis fluid:

- Loculations on imaging
- pH < 7.20
- Glucose < 60 mg/dL (3.33 mmol/L)
- Positive Gram stain or culture

The treatment of a complicated effusion generally requires chest tube drainage. This removes the bulk of the inflammatory material and organisms to give the

patient the best chance to heal. In some cases, this type of effusion may progress to empyema, which requires tube thoracostomy drainage or, in some cases, surgery.

Transudative effusions can be misclassified as exudates using Light's criteria when a patient with heart failure has been receiving diuretics.

Empyema is the diagnosis when visible frank pus is found in pleural space. Treatment options include tube thoracostomy with IV antibiotics and, if not successful, a brief trial of intrapleural tPA and DNase for persistent loculations to avoid decortication. Otherwise proceed to VATS or open thoracostomy with decortication.

Malignancy is the 2nd most common cause of an exudative effusion. The most common malignant pleural effusions are **lung** cancer (1/3), **breast** cancer (1/4), and **lymphoma** (1/5). (Lung, breast, lymphoma... 1/3, 1/4, 1/5.)

In a pleural-based malignancy, repeated cytologic examination of the effusion fluid has as high a yield as pleural biopsy! 3 effusion samples have a combined yield of > 90%. Larger volumes sent for cytology have greater yield than relatively small samples. Thoracoscopy is done if the repeat cytologies are negative. Closed pleural biopsies are rarely needed anymore to diagnose cancer. The main use for a closed pleural biopsy is to diagnose pleural TB.

Less common (but important!) causes of exudative pleural effusions are mesothelioma, PE, viral infections, and TB.

Mesothelioma: Think about mesothelioma (most often related to asbestos exposure) in patients with dyspnea, chest pain, and a grossly **hemorrhagic** pleural effusion with pleural thickening or mass, most commonly with an occupational history of asbestos exposure.

Pulmonary embolism: Consider this in the dyspneic patient with an exudative effusion showing normal fluid amylase, glucose > 60 mg/dL (3.33 mmol/L), normal or slightly increased cell count and differential, and a Gram stain showing no organisms. These effusions may be hemorrhagic. Pleural effusion caused by PE is often missed clinically! There may be more compelling clinical reasons in the initial evaluation of such a patient that may suggest a PE.

Viral infection: Many viruses cause **self-resolving** pleural effusions. Think of a probable viral cause in someone who improves quickly without intervention.

Tuberculosis: Think of tuberculous effusion in the patient with risk factors for **primary** TB and additional history of fevers and wasting. Pleural fluid cell count is usually **lymphocytic**. AFB smear and culture of the pleural fluid have a low yield (20–30% in HIV negative), so the strategy incorporates mycobacteria-specific tests. For suspected pleural TB, order pleural adenosine deaminase (ADA; if available), serum interferon-γ release assay (IGRA), nucleic acid amplification (NAA) *Mycobacterium tuberculosis* direct (MTD), Xpert MTB/

RIF, or MTBDRplus (detection of TB and determination of rifampin or INH resistance).

If you do not have these special tests available, or the above testing is negative despite a high clinical suspicion, a **pleural biopsy may be done**. Send your tissue for routine pathology with AFB stains and send a sample for AFB smears and culture. Aside from the special mycobacteria-specific tests described above, obtaining pathology + cultures of pleura is the approach with the highest diagnostic yield for TB (between 65 and 90%; higher than any single approach).

In clinical practice, closed pleural biopsies are rarely performed in the U.S. Most of the pleural sampling procedures are done with VATS, which has a high diagnostic yield and can be used for both pleural fluid sampling and pleural biopsy.

Again: To diagnose cancer, use repeated taps and cytology. To diagnose TB on a pleural effusion, use special tests and pleural or VATS biopsy.

And a weird one: Think about **yellow nail syndrome** if the patient has a history of chronic peripheral edema and chronic exudative pleural effusions (often chylothorax). Patients with this genetically transmitted syndrome also have yellow, dystrophic nails.

Some Key Effusion Findings

Some clues to help you remember cell count and differential findings:

- WBCs > 1,000/μL ($1 \times 10^9/L$): Think exudate.
- WBCs > 10,000/μL ($10 \times 10^9/L$): Think complicated parapneumonic effusion.
- WBCs > 100,000/μL ($100 \times 10^9/L$): Think empyema or pus.
- Mesothelial cells normally line the cavity and are occasionally confused with malignant cells. There is a consistent finding that there are very few mesothelial cells with a tuberculous pleural effusion. So, if a high **mesothelial** cell count is reported in the fluid, then TB is highly **unlikely** to be the cause.
- Eosinophils > 10%: Think of pneumothorax, hemothorax, drug reaction, postthoracotomy, TB, paragonimiasis (trematode—fluke) or other parasites, fungal infection, and benign asbestos-related pleural disease.
- Lymphocyte predominance: Think of TB, malignancy, chronic inflammatory (i.e., rheumatoid, sarcoid), yellow nail syndrome, or chylothorax.
- Neutrophil predominance: Think of acute pneumonia, pancreatitis, PE, and peritonitis.
- Know the specific definition of hemothorax: grossly bloody pleural effusion with a hematocrit > 50% of the hematocrit of the peripheral blood. Think of trauma!

For fluid chemistry findings:

- Glucose ~ 80 mg/dL (4.44 mmol/L): Think TB.
- Glucose ~ 60 mg/dL (3.33 mmol/L): Think cancer or empyema.

- Glucose < 30 mg/dL (1.67 mmol/L): Think rheumatoid arthritis or empyema.
- Amylase is increased in pancreatic fistula and esophageal rupture (salivary amylase).
- Adenosine deaminase (ADA) concentrations (especially isoenzyme ADA-2) are elevated in tuberculous pleural effusions. (Conversely, ADA level < 40 U/L [666.68 nkat/L] is rarely TB.) This test is used as a diagnostic aid when a TB effusion is suspected but other tests are negative. Other tests include the IGRA and low-sensitivity, high-specificity PCR to identify TB DNA.

What if the pleural fluid is milky white, but not pus? Chylous effusions are white-colored, exudative effusions with a triglyceride level > 110 mg/dL (1.24 mmol/L; due to fat globules; i.e., chylomicrons). The chylous effusions are due to leakage of thoracic duct lymph. Think **trauma** and **cancer (especially lymphoma)**. Imaging studies of the mediastinum will help define the etiology.

Pseudochylous pleural effusions are caused by chronic inflammatory processes, especially TB and rheumatoid arthritis lung disease. Triglycerides in pseudochylous effusions are < 50 mg/dL (0.56 mmol/L). Total cholesterol is > 65 mg/dL (1.68 mmol/L) because the white color is due to cholesterol, not chylomicrons. Neither the chylous nor pseudochylous specimens clear with centrifugation.

PNEUMOTHORAX

PREVIEW | REVIEW

- Which conditions can result in secondary pneumothorax?

Classically, primary spontaneous pneumothorax (PSP) was thought to most commonly affect tall, slender, often smoking men 20–40 years of age. With high-resolution CT, we know that many of these patients have subpleural emphysematous blebs that rupture, causing spontaneous pneumothorax.

Secondary spontaneous pneumothorax (SSP) can be caused by:

- COPD/Emphysema (the most common cause)
- *Pneumocystis* pneumonia in AIDS patients
- Cystic fibrosis
- Langerhans cell histiocytosis (LCH)—smoking males
- Lymphangioleiomyomatosis (LAM)—exclusively premenopausal women
- Barotrauma—In the past, up to 10–15% of patients on mechanical ventilators developed barotrauma, including pneumothorax, though this has been reduced by the use of lung protective ventilation strategies (i.e., low tidal volumes of 6–8 mL/kg predicted body weight [PBW]).

Presenting symptoms of PSP and SSP are similar and include dyspnea and chest pain. SSP symptoms may be more severe due to underlying lung disease. Physical exam can show decreased breath sounds but often may not be helpful with underlying lung disease. Chest x-ray is the 1st and often only test needed for diagnosis. CT is useful if the diagnosis is still in question. In the ER or ICU, the most rapid and sensitive test for pneumothorax on a ventilator is bedside ultrasound. The ultrasound will also guide the placement of a chest tube, if needed.

Initial treatment: If the pneumothorax is small (< 15–20% or < 2 cm) and the patient is stable, observe and give the patient high-flow O₂. Giving high-flow O₂ may increase the rate of reabsorption (vs. inhalation of room air).

If the pneumothorax is larger (> 2 cm) or the patient is symptomatic or hypoxic, consider placement of a small anterior chest tube. In an emergent setting, this can consist of an IV catheter inserted in the 2nd intercostal space, aspirated, and either put on water seal or connected to low suction. A chest tube is mandatory in pneumothorax patients receiving positive pressure ventilation, regardless of the size of the pneumothorax, due to the risk of tension pneumothorax!

Here's a review of the chest tube drainage system components (Figure 6-20).

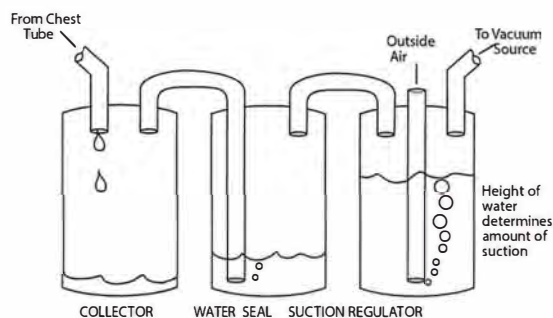


Figure 6-20: Chest tube drainage system

1st chamber (nearest the patient) = **collection chamber**—this is where effluent from the pleural cavity is collected.

2nd chamber (the middle) = **water seal chamber**—this allows air to bubble out from the pleural cavity but does not allow air into the chest. Bubbles in this chamber indicate air is in (or still entering) the pleural space. Or consider a leak in the chest tube itself!

3rd chamber (attached to suction) = **suction regulator**—the height of water determines the amount of suction on the chest tube (when vacuum is applied to the chamber and there is bubbling in the water of the chamber).

A persistent air leak for > 7 days suggests a leak in the chest tube, an alveolar-pleural fistula, or a broncho-pleural fistula, which requires surgical intervention and pleurodesis to prevent recurrences.

Recurrence rate for PSP is 28%, while that for SSP is 43%. Risk of mortality is 1–4% for PSP and up to 17% for SSP.

Recurrence prevention: Pleurodesis decreases the recurrence rate significantly. Pleurodesis is **not** usually done with the 1st episode of SSP, but there is more evidence suggesting that you should do pleurodesis for even the 1st occurrence of PSP due to the recurrence rates. Adjacent parenchymal blebs may influence this decision. Talc is the best and cheapest agent for pleurodesis. Doxycycline and minocycline are next. Often pleural abrasion with gauze accomplishes the pleurodesis effectively.

PNEUMONIAS

OVERVIEW

Pneumonia is categorized in 1 of 3 ways:

- 1) Community-acquired pneumonia (CAP)
- 2) Hospital-acquired pneumonia (HAP)
- 3) Ventilator-associated pneumonia (VAP)

In the 2016 Infectious Diseases Society of America (IDSA) and the American Thoracic Society (ATS) guidelines, the concept of health care-associated pneumonia (HCAP) was removed in favor of HAP and VAP.

COMMUNITY-ACQUIRED PNEUMONIA (CAP)

PREVIEW | REVIEW

- Identify the organisms that cause typical and atypical community-acquired pneumonia (CAP).
- Detail the characteristics that a sputum sample must have to be considered an adequate specimen.
- List the tests that you need to order for patients with severe or unresponsive CAP.
- A patient who works on an animal farm develops pneumonia. Which organism should you think about?
- Which organism should you consider if pneumonia develops in a patient who spent an afternoon in a bat cave in Mississippi?
- Which organism should you think about if pneumonia develops in a patient who drove through an Arizona dust storm?
- Which organism should you consider if a chronic, cavitating pneumonia develops in a male logger from Arkansas?
- Name 2 drugs recommended to treat CAP in outpatients without risk factors for drug-resistant *S. pneumoniae* (DRSP).

- Name 3 regimens recommended to treat inpatient CAP in the non-ICU patient.
- Which antibiotics do you use for empiric treatment of the ICU patient with cavitary pneumonia and risk factors for *P. aeruginosa*?
- What are the diagnostic possibilities for the unresponsive patient with apparent pneumonia?

CAP can be organized into 2 groups based on the organisms that cause disease:

- 1) **Typical** CAPs are due to organisms such as pneumococcus, *H. influenzae*, *Staphylococcus aureus*, gram-negative rods (GNRs), and *Moraxella catarrhalis*.
- 2) **Atypical** CAPs are due to bacteria (i.e., *Mycoplasma*, *Chlamydophila*, *Legionella*), viruses (e.g., flu, adeno, RSV, parainfluenza, rhino), and endemic fungi (e.g., cocci, histo, blasto). Atypical pathogens cannot be identified by Gram stain or routine bacterial culture (require special media) and/or are resistant to β -lactam antibiotics, which are 1st line drugs for empiric treatment of CAP.

The etiology for CAP is determined in about 38% of cases (viruses [*Rhinovirus* leading] detected in 27% and bacteria [*Streptococcus pneumoniae* leading] detected in 14%). There are some risk factors that predispose to certain pathogens (see [Pathogens on page 6-55](#)).

In 2019, the IDSA/ATS came together to issue guidelines for evaluating, diagnosing, and treating CAP. Think about CAP from 2 perspectives:

- 1) **Empiric** treatment (when the organism is not known)
- 2) **Pathogen-directed** treatment (when it is known)

Presentation of CAP

Symptoms are variable (from mild to severe) and include fever, anorexia, sweats, dyspnea, sputum production, cough, and pleurisy. Nausea, vomiting, and diarrhea occur in 20%. **Elderly** patients are also often **confused**.

Exam findings include tachycardia, tachypnea, evidence of consolidation (i.e., increased tactile fremitus, bronchial breath sounds, crackles), and/or parapneumonic effusion (decreased tactile fremitus and percussion).

There is **overlap** in signs and symptoms caused by typical and atypical pathogens—so you cannot reliably use the history of symptoms or the chest x-ray findings to differentiate typical from atypical pathogens.

Diagnosis of CAP

Per the IDSA/ATS 2019 guidelines, the initial workup of CAP is very **limited**. A more **aggressive** workup is recommended for patients:

- with risk factors for severe disease (e.g., underlying structural lung disease or uncontrolled comorbidities),
- with a severe presentation (requiring ICU), or
- who are unresponsive to empiric treatment.

Diagnostic Tests

Chest x-ray is required for diagnosis of CAP. Some confusion in reading the x-ray can result from coexisting HF, COPD, or malignancy. Remember that an infiltrate may not appear in a volume-depleted patient until after the patient is volume resuscitated or in a neutropenic state. For a comparison of lower lobe and middle lobe pneumonia, see [Figure 6-21](#) and [Figure 6-22](#).

Do a **sputum Gram stain and culture** in patients with:

- severe or unresponsive CAP,
- COPD or structural lung disease,
- failed outpatient antibiotic therapy,
- a history of alcohol abuse,
- immune compromised systems,
- illness requiring hospitalization,
- cavitary infiltrates, and/or
- a pleural effusion.

In the intubated patient, send a deep-suction endotracheal aspirate to the lab as soon as possible because targeted antibiotics in the ICU **do** affect outcome for these inpatients, whereas outpatients do just as well with empiric therapy. Add an acid-fast stain if tuberculosis is in your differential based on the presentation and chest x-ray. Do **not** do sputum tests on those patients who do not meet these indications or on outpatients with CAP.

Sputum interpretation: The culture and sensitivity results are accurate only if there are > 25 neutrophils and < 10 epithelial cells per low power field. If more epithelial cells are present, then it is contaminated from the mouth. If the patient gives you a cup with what looks like saliva mixed with a few

mucoid globs, fish out these goobers and send them to the lab (higher yield)!

Order **blood cultures** for patients with:

- sepsis,
- severe or unresponsive CAP,
- illness requiring hospitalization,
- COPD,
- liver disease,
- a history of alcohol abuse,
- cavitary infiltrates,
- asplenia,
- pleural effusion,
- leukopenia, and/or
- a positive pneumococcal urine antigen test.

Do **not** do blood cultures in admitted CAP patients who do not meet these indications or in outpatients.

Other tests: In patients with severe CAP, add urine antigen tests for pneumococcus and *Legionella* to the blood and sputum cultures.

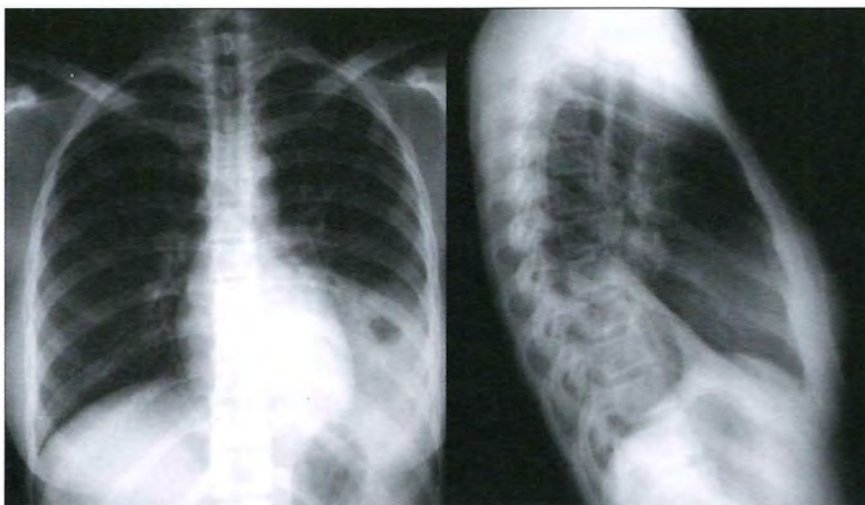


Figure 6-21: LLL pneumonia
Source: Vinay Maheshwari, MD

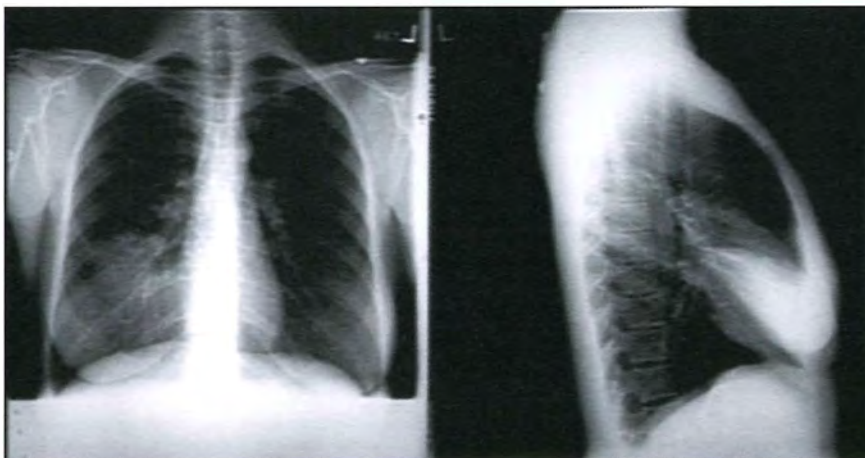


Figure 6-22: RML pneumonia
Source: Vinay Maheshwari, MD

Additional admission tests are CBC, chemistry panel, liver function tests, and O₂ saturation.

Serologic tests are usually **not** helpful in the initial evaluation. DNA probes and nucleic acid amplification are **not** indicated.

Treatment of CAP

Remember to think of CAP from 2 perspectives: **empiric** treatment and **organism-specific** treatment. The following treatment discussion is based on the 2019 IDSA/ATS guidelines. As you read, see the summary in Figure 6-23 on page 6-56.

Empiric Treatment of CAP

Empiric treatment is started before pathogen identification and is based on:

- **Severity** of the illness and need for hospitalization. See the pneumonia severity index (PSI) in Table 6-14.
- **Likelihood** of a specific pathogen based on associated risk factors

What you prescribe empirically is partly determined by whether the patient will be admitted. (Usually, outpatients = oral, and inpatients = parenteral.)

The PSI scoring class can supplement the clinician's decision if the patient needs to be admitted to the hospital based on risk of mortality. Scoring Class 1 is for those < 51 years of age with no comorbidities. For Classes 2–5, comorbidities are a factor in score calculation. Factors such as ability for oral intake, cognitive impairment, or homelessness also play a role in decision-making.

A rapid 5-point scoring system applying to patients ≥ 65 years of age to aid in the decision to admit or not is the CURB-65 (confusion, uremia, respiratory rate, blood pressure, and age ≥ 65 years) scale. Each parameter represents 1 point. If the score sums to > 1 point, then consider hospitalization or close follow-up.

Pathogens

Remember that treating empirically means treating on the basis of an educated guess about the causative organism. The most commonly seen pathogens in CAP are *S. pneumoniae* and viruses. For discussion of specific pathogens, see **Typical Organisms of CAP** on page 6-57 and **Atypical Organisms of CAP** on page 6-60.

In addition, know these **organism-specific** associations:

- COPD or immunoglobulin deficiency (especially IgG): *Moraxella catarrhalis* and *H. influenzae*
- Cattle or sheep exposure: *Coxiella burnetii* (Q fever)
- Bird fanciers: *Chlamydophila psittaci* (psittacosis)
- Hunters: *Francisella tularensis* (tularemia)
- Bat caves, especially in the Mississippi and Ohio River valleys: *Histoplasma capsulatum* (histoplasmosis)

Table 6-14: The Pneumonia Severity Index (PSI)

	Findings	Points Assigned
Demographic Factors	Males	Age (years)
	Females	Age – 10
	Nursing home residents	Age + 10
Comorbid Illnesses	Neoplastic disease	+ 30
	Liver disease	+ 20
	Heart failure	+ 10
	Cerebrovascular disease	+ 10
	Renal disease	+ 10
Physical Exam	Altered mental status	+ 20
	Respiratory rate ≥ 30 bpm	+ 20
	Systolic BP < 90 mmHg	+ 20
	Temp < 95°F (35°C) or ≥ 104°F (40°C)	+ 15
	Pulse ≥ 125 bpm	+ 10
Laboratory	pH < 7.35	+ 30
	BUN ≥ 30 mg/dL	+ 20
	Na ⁺ < 130 mEq/L (130 mmol/L)	+ 20
	Glucose ≥ 250 mg/dL (13.9 mmol/L)	+ 10
	Hct < 30%	+ 10
	P _a O ₂ < 60 mmHg or O ₂ sat < 90%	+ 10
	Pleural effusion	+ 10
Scoring	Points	Mortality (%)
1	0	< 0.1
2	< 70	≥ 0.6
3	71–91	≥ 0.9
4	91–130	≥ 9.3
5	> 130	≥ 27

- Travel to California or Southwest: *Coccidioides immitis* (coccidioidomycosis)
- Living in or travel to the southeast, mid-Atlantic, and central states—especially Illinois and Arkansas, but often associated with hunting or working in wooded areas: *Blastomyces dermatitidis* (blastomycosis)
- Risk factors for HIV/AIDS or other immunocompromise: *Pneumocystis jirovecii* pneumonia (PJP) and TB
- Chronic disease, immunosuppression, and alcoholism: gram-negative organisms
- Diabetes, cancer, kidney disease, HIV/AIDS, or a recent cruise ship or hotel stay in winter or summer: *Legionella*

Empiric Antibiotics

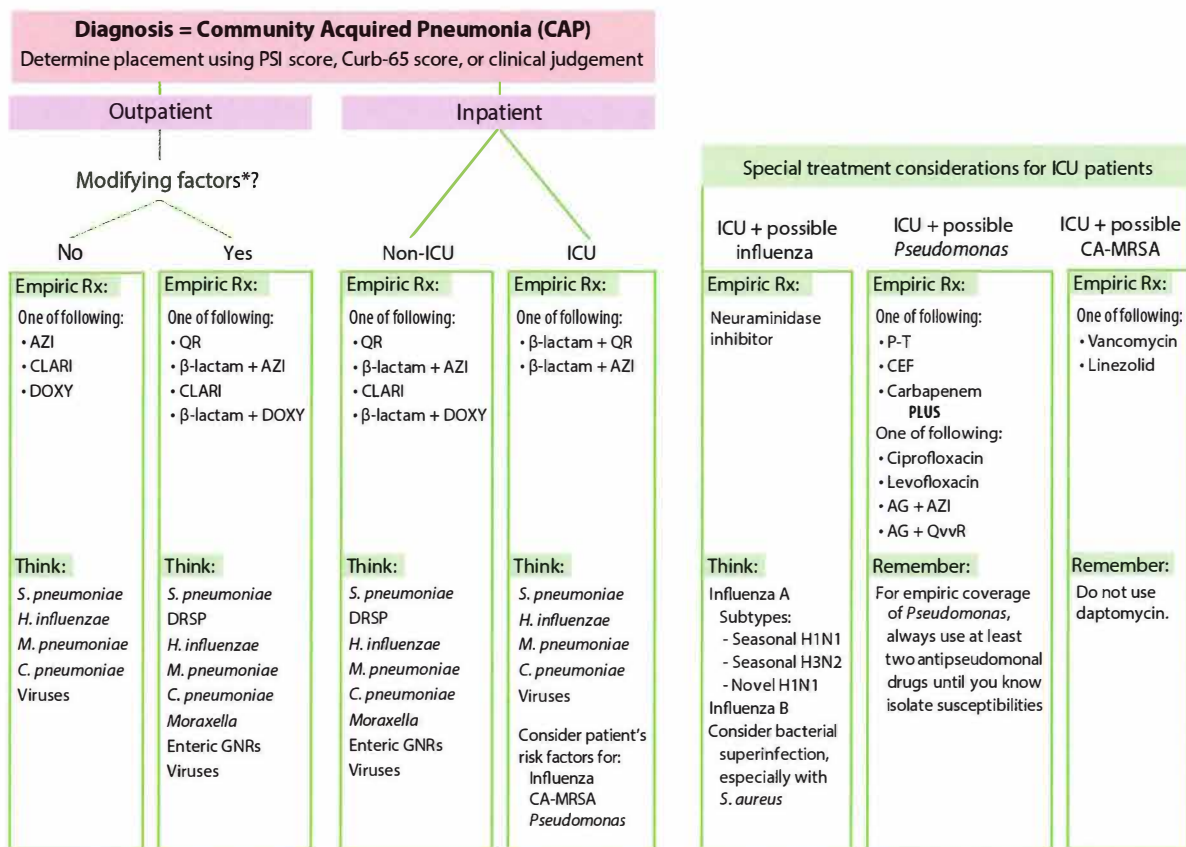
As we go through this discussion for the treatment of CAP, see [Figure 6-23](#). Know that identifying the specific microbial cause of CAP is expensive and difficult (successful < 50% of the time).

Except in ICU cases, no data has shown that targeted treatment of a specific organism is superior to empiric treatment of possible organisms. Therefore, empiric treatment is accepted as appropriate and is initially preferred in guideline-directed therapy rather than attempting to diagnose the specific pathogen. Guideline-directed therapy leads to improved outcomes, with shorter hospital stay, decreased mortality, and more rapid improvement. This is why sputum cultures are done only in special cases.

Outpatients

The majority of patients with CAP are treated as outpatients, based on a severity index indicating low risk, with either macrolides (**azithromycin** or **clarithromycin**) or **doxycycline**. Note that erythromycin is a choice, but GI side effects limit its use, and it is less effective against *H. influenzae* than the advanced macrolides. Azithromycin has antiinflammatory properties and is associated with more ICU-free days in patients with severe sepsis, with pneumonia.

If the patient has risk factors (see *Streptococcus pneumoniae* [Pneumonia](#)) for drug-resistant *S. pneumoniae* (DRSP) or has comorbidities that can affect outcome (i.e., modifying factors), use a respiratory quinolone or high-dose amoxicillin (because the resistance can sometimes be overcome with larger β -lactam doses) plus a macrolide. An alternative is to pick an oral cephalosporin with known activity against DRSP plus a macrolide. Doxycycline can be substituted for



* Modifying factors = Risks for DRSP (age > 65 years, β -lactam Rx within past 3 months, alcoholism, immunosuppression, exposure to child in day care), and/or any of following comorbidities: COPD, diabetes, renal or heart failure, malignancy

β -lactam choices for outpatients (oral): high-dose amoxicillin or amoxicillin/clavulanic acid in patients with risk factors for DRSP; alternatives: cefpodoxime or cefuroxime

β -lactam choices for inpatients (intravenous): cefotaxime or ceftriaxone

AG = aminoglycoside (gentamicin, tobramycin, or amikacin)

AZI = azithromycin

Carbapenem = imipenem or meropenem

CEF = cefepime

CLARI = clarithromycin

DOXY = doxycycline

P-T = piperacillin-tazobactam

QR = respiratory quinolone (levofloxacin, gemifloxacin, or moxifloxacin)

DRSP = Drug-resistant *Streptococcus pneumoniae*

Figure 6-23: Treatment of outpatient and inpatient community-acquired pneumonias

the macrolide. If the patient cannot tolerate a β -lactam or quinolone, lefamulin, a new FDA-approved (2019) antibiotic, can be chosen as monotherapy.

Inpatients

Non-ICU inpatients are treated intravenously with a respiratory fluoroquinolone; **or** cefotaxime, ceftriaxone, or ampicillin-sulbactam; **or** ertapenem **plus** either a macrolide **or** doxycycline **or** ceftaroline. If the patient is at risk for influenza, *Pseudomonas*, or CA-MRSA, refer to Figure 6-23 for empiric antibiotic choices. Start treatment **immediately** once you determine that admission is necessary.

ICU patients (with no risk factors for *Pseudomonas*) are treated with intravenous cefotaxime, ceftriaxone, or ampicillin-sulbactam **plus** a respiratory fluoroquinolone **or** a macrolide.

If the ICU patient has risk factors for *P. aeruginosa*, start:

- piperacillin-tazobactam, or
- cefepime, or
- a carbapenem (imipenem or meropenem)

Plus:

- ciprofloxacin or levofloxacin, or
- an aminoglycoside and a respiratory fluoroquinolone, or
- an aminoglycoside and azithromycin.

If CA-MRSA is suspected based on historical risk factors, add linezolid or vancomycin. Start treatment immediately.

Narrowing Empiric Therapy

By day 3, you know whether your patient is improving, and you might have an organism identified if you sent any specimens for microbiology (i.e., sputum and blood cultures, urine antigen tests).

If the lab identifies an organism, narrow the treatment to focus on that organism. Switch to oral medications if patient is improving with stable BP and PO tolerance.

Treatment varies from 5–7 days depending on the antibiotic selected, but duration may extend to 7 days for HAP or VAP or even longer if the patient is in an immunocompromised state or there is slow clinical improvement. Follow up with a chest x-ray about 4–6 weeks after discharge and consider malignancy in the patient who has persistent lung abnormalities.

If your patient deteriorates over the first 3 days on empiric treatment, think of these possibilities:

- You have the **wrong diagnosis**, and it is not an infectious infiltrate (e.g., PE, HF, collagen vascular disease, hypersensitivity pneumonitis).
- Your empiric regimen is **not covering** the causative organism. Revisit the list of risk factors and associations. What did you miss? If you are giving the right drugs, are you giving the correct doses?

- There is a **new infection** in addition to the original one (e.g., staphylococcal pneumonia in addition to an original viral pneumonia). Think empyema if a parapneumonic effusion was present on admission or even if it was not there initially, since effusions can sometimes develop or enlarge during treatment. Chest x-rays that demonstrate development of pneumatoceles (thin-walled cysts) or lung abscesses over the first few days should make you think pneumococcus, CA-MRSA, and *Pseudomonas*.

TYPICAL ORGANISMS OF CAP

PREVIEW | REVIEW

- Which patients are at increased risk for infection with drug-resistant *S. pneumoniae* (DRSP)?
- Name some potential pulmonary complications of pneumococcal pneumonia.
- Describe the patients who should be vaccinated with PPSV23.
- Name some potential complications of staphylococcal pneumonia.
- Which drug choices are available for targeted treatment of *S. aureus* pneumonia
- The bulging fissure sign is seen with which organism that causes pneumonia?
- Which antibiotics must be added for empiric treatment of pneumonia in the ICU patient with risk factors for *Pseudomonas*?
- Describe the microbiologic characteristics of *Moraxella*.

Now let's talk about the individual organisms that cause CAP. We've briefly covered some of this information before, but it's time for a focused discussion.

It is important to know which organisms are common in your area and what the local antibiotic resistance patterns are when making empiric treatment decisions. This information may be available to you from your hospital microbiology lab in the form of an **antibiogram**.

Streptococcus pneumoniae Pneumonia

Pneumococci live in the nose and throat of up to 40% of healthy children. Any adult who has contact with children, day care centers, and other crowded conditions (e.g., military barracks, dormitories, homeless shelters, prisons) is at risk for becoming colonized and subsequently infected with *S. pneumoniae*.

Children who receive frequent antibiotic prescriptions for viral illnesses are a source of drug-resistant strains because the colonizing organisms mutate under the drug's selective pressure. Upper respiratory inflammation from a cold virus in the colonized patient then sets the stage for bacterial pneumonia and/or sinusitis.

Patients most at risk for pneumococcal disease are > 65 years of age or have comorbidities (e.g., diabetes, alcoholism, and lung, heart, or renal disease). Asplenic patients (e.g., sickle cell) and patients with humoral immunodeficiencies (e.g., AIDS, myeloma, chronic lymphocytic leukemia [CLL], lymphoma) are especially at risk because pneumococci are encapsulated organisms.

DRSP is linked with age ≥ 65 years, recent (within 3 months) β -lactam therapy, alcoholism, immunosuppression, multiple comorbidities, and exposure to a child in day care. DRSP generally refers to resistance against penicillins, macrolides, tetracyclines, cephalosporins, TMP/SMX, and, rarely, fluoroquinolones.

In addition to the generic signs and symptoms of pneumonia, think pneumococcus if your at-risk patient presents with shaking chills, pleuritic chest pain, and rust-colored sputum. CBC reveals a high WBC count. (Leukopenia carries a higher mortality risk.) Chest x-ray often shows lobar consolidation; see Figure 6-24. The diagnosis of *S. pneumoniae* pneumonia is supported when a good-quality sputum Gram stain identifies the lancet-shaped gram-positive diplococci and the organism is grown in sputum culture. A positive blood culture or pneumococcal urinary antigen test is diagnostic. Blood cultures are positive in 25% of hospitalized cases of pneumococcal pneumonia.

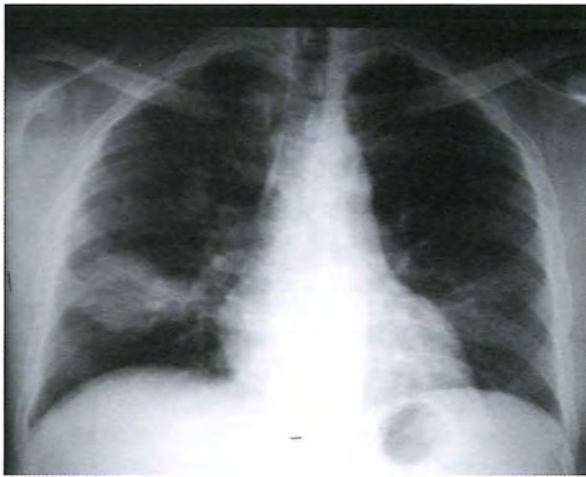


Figure 6-24: Round pneumonia (often seen in pneumococcal pneumonia)

Source: Vinay Maheshwari, MD

Look out for these complications: lung abscess and empyema in the patient with even potential parapneumonic effusion.

Pneumatocoles are thin-walled, air-filled cysts that develop within the lung parenchyma. They are most often the sequela of acute pneumonia, and they can develop secondary to trauma and positive pressure ventilation. The possible etiology of the infectious type is due to the inflammation of the pneumonia that causes a narrowing of the bronchus and partial epithelial sloughing. This leads to the formation of an endobronchial flap or ball valve effect with a one-way airflow, leading to distal dilation of the bronchi and alveoli and occasionally a pneumothorax.

Know that multilobar disease, bacteremia, and peripheral blood WBC $< 6,000/\mu\text{L}$ ($6 \times 10^9/\text{L}$) indicate increased mortality.

Do not forget about the evolving resistance.

DRSP strains are treated with a cephalosporin with known activity against DRSP, a respiratory quinolone, or higher doses of a β -lactam (with hopes of overcoming the resistance—a useful strategy if the infection is not severe).

There are 2 vaccines licensed for pneumococcal disease in the U.S.: the 23-valent polysaccharide vaccine (PPSV23, which contains 23 prevalent serotypes) and the 13-valent protein conjugate vaccine (PCV13, which contains 13 serotypes).

Administrative timing for these vaccines varies depending on whether the patients are > 65 years of age, whether they have been vaccinated before, and which vaccine they received initially. Comorbid conditions also play a role. See the CDC vaccine schedules at cdc.gov/vaccines/schedules.

Haemophilus influenzae Pneumonia

Haemophilus influenzae can be encapsulated or unencapsulated (a.k.a. nontypeable). Due to the widespread use of the Hib vaccination, most *H. influenzae* infections in the U.S. are nontypeable and result from the invasion of these bacteria across the mucous membranes. Pneumonia from nontypeable strains is most often seen in patients with underlying lung disease (i.e., COPD) and AIDS.

Diagnosis: This pneumonia presents generically with fever, cough, and dyspnea. A good sputum sample often demonstrates the organism on Gram stain—pleomorphic gram-negative coccobacilli. Definitive diagnosis is growth of the organism in culture from a normally sterile site (e.g., pleural fluid or blood).

Treatment: Antibiotics effective against *H. influenzae* include amoxicillin/clavulanic acid (ampicillin alone should be avoided due to common resistance, unless susceptibility is demonstrated), 3rd generation cephalosporins, doxycycline, fluoroquinolones, and macrolides. TMP/SMX resistance is 25%.

Staphylococcus aureus Pneumonia

Staphylococcus aureus colonizes the anterior nares and gets distributed to the skin by fingers. Regular *Staphylococcus* strains do not cause problems in immunocompetent patients without skin breaks. However, if the immune system or skin barrier break down, *Staphylococcus* can invade tissues or the blood stream.

There are also particularly virulent strains of *S. aureus*. A Panton-Valentine leukocidin-producing strain (PVL-SA) can cause a virulent necrotizing CA-MRSA infection in immunocompetent patients.

Staphylococcus species can either be susceptible to methicillin (and subsequently to other β -lactams) or resistant to methicillin (MRSA, a surrogate marker for resistance to all β -lactam drugs).

S. aureus CAP is usually seen in patients with a preceding **influenza** infection as a superinfection (although de novo pneumonia due to CA-MRSA occurs). It is also seen in patients with right-sided endocarditis with pulmonary emboli.

Clinical presentation is typical for acute bacterial pneumonia with fever, dyspnea, and cough. However, patients with *Staphylococcus* can have hemoptysis with **salmon-pink** sputum, diffuse lung infiltrates, and pneumatoceles.

Consider a superinfection with *S. aureus* if the history is consistent with a resolving **influenza** infection that worsens with new symptoms of dyspnea and cough.

Think of CA-MRSA in cases of severe pneumonia with pink sputum and pneumatoceles in an immunocompetent patient with poor hygiene or a history of close contact with others.

Diagnosis: As with other pneumonias, diagnosis is supported when gram-positive cocci in clusters are demonstrated on a good sputum sample, followed by the growth of the organism in culture. Blood cultures are helpful if positive, but they are usually negative.

Complications include empyema (frequent), an immune-complex type of glomerulonephritis, and pericarditis.

Treatment: **Methicillin-sensitive** *S. aureus* (MSSA) pneumonia can be treated with a β -lactam. Nafcillin is typically the drug of choice.

Treat **MRSA** pneumonia with vancomycin, telavancin, or linezolid. Daptomycin is **ineffective** for respiratory infections; do **not** use it to treat staphylococcal pneumonia!

CA-MRSA strains often have preserved susceptibility to TMP/SMX, quinolones, and clindamycin. These drugs are fine to use in treating skin infections with CA-MRSA but not lung infections. Use vancomycin or linezolid or telavancin for serious MRSA lung infections.

***Klebsiella pneumoniae* Pneumonia**

A major CAP-causing enteric gram-negative organism is *Klebsiella pneumoniae*. It typically colonizes the oropharynx of those with alcohol use disorder and patients with uncontrolled lung disease or diabetes. It is an uncommon cause of CAP without these risk factors. *Klebsiella* CAP presents with typical features of pneumonia (cough, dyspnea, and fever). As the pneumonia worsens, the lung can become necrotic, and patients get sicker.

Be aware of some buzzwords for this gram-negative pneumonia:

- **Currant jelly** sputum: bloody sputum that resembles jelly
- **Bulging fissure** sign: a lobar consolidation where the affected portion of the lung is overexpanded and causes the abutting fissure to bulge
- **Friedlander** pneumonia: a lobar pneumonia caused by *Klebsiella*

Diagnosis is made by Gram stain and culture of sputum and blood (usually performed because a patient with a gram-negative pneumonia often presents with severe disease and may end up in the ICU).

Treatment: Know that many enteric gram-negatives are either innately resistant to ampicillin or have acquired ampicillin resistance. When you suspect a gram-negative pneumonia, your empiric antibiotic choice should be broad in spectrum (i.e., an extended-spectrum penicillin with a β -lactamase inhibitor, such as piperacillin-tazobactam). This covers most gram-positive organisms until the lab identifies an organism for you. Once cultures identify an organism, you can narrow the treatment based on the susceptibilities. Often, an oral quinolone is adequate to finish therapy.

Pertussis

Adults are the major reservoir for *Bordetella pertussis*. Although pertussis, the disease, is usually self-limited in adults, it can be deadly for infants. Treatment with a macrolide is for 5–7 days. The incubation period is typically 7–10 days. There are 3 stages:

- 1) **Catarrhal stage:** The catarrhal stage presents as a typical, uncomplicated upper respiratory infection lasting 5–12 days. Patients are most infectious during this stage.
- 2) **Paroxysmal stage:** It is not until the paroxysmal stage develops, with its characteristic paroxysms of coughing followed by a “**whoop**,” that pertussis becomes clinically apparent. This lasts 1–2 weeks.
- 3) **Convalescent stage:** An often-prolonged cough occurs (lasting several weeks to months).

To help protect children and infants from acquiring pertussis, it is recommended that all adults receive 1 booster with Tdap. In addition, pregnant women should receive Tdap with each pregnancy.

***Pseudomonas aeruginosa* Pneumonia**

Pseudomonas species grow in **moist** environments. Patients who are infected with this organism have an **underlying illness** that allows their alveoli and airways to remain moist. Most often, the underlying disease process requires either chronic or intermittent antibiotic use. Selective pressure from antibiotics allows colonization of the lung with resistant and hardy gram negatives.

Hence, *Pseudomonas* CAP occurs in patients with underlying lung disease, **especially CF and bronchiectasis**, in patients who use steroids or antibiotics frequently, or in those with HIV infection. The presentation is typical with cough, dyspnea, and fever. The patients with chronic lung disease usually are sicker because *Pseudomonas* CAP aggravates an already-dwindling reserve.

Patients without lung disease who inhale a large amount of steam from **hot tubs** that are heavily contaminated with *Pseudomonas* can also develop pneumonia from this

organism. *Pseudomonas* is not a common cause of CAP. More often, it causes a HAP or VAP.

The diagnosis of *Pseudomonas* CAP is tricky because the organism is **hard to find**. A sputum Gram stain with many polys and a sputum culture that grows the organism suggests infection. Of course, it takes a while for the culture to grow, so you must have a high index of suspicion for this organism and treat it empirically.

Treatment: If you suspect *Pseudomonas* based upon underlying chronic disease or hot tub exposure, empirically treat as outlined in the ISDA guidelines. Once the culture result and susceptibility are available, narrow the regimen.

***Moraxella catarrhalis* Pneumonia**

Moraxella catarrhalis colonizes the mouth and upper airway of both children and adults and is a frequent cause of otitis and sinusitis. However, this organism causes CAP **primarily in patients with underlying lung disease or immunosuppression**, and 45% of patients die from their disease within 3 months of infection.

Moraxella CAP is slightly less acute than disease caused by pneumococcus or *H. influenzae*, and symptoms are less severe. The chest x-ray pattern is variable, ranging from lobar infiltrates to diffuse involvement and even interstitial disease in some cases.

Diagnosis is typically straightforward because a quality sputum sample shows an overwhelming number of **gram-negative diplococci**. It is useful to look at the Gram stain yourself because the organisms line up side-by-side and look like a pair of kidneys (not usually reported by the micro tech on the Gram stain result).

Treatment is also straightforward because the organism is generally susceptible to most drugs used to treat pneumonia: doxycycline, macrolides, cephalosporins, or amoxicillin/clavulanic acid. Penicillin is not a good choice because up to 90% of isolates produce a β -lactamase that breaks down penicillins but not cephalosporins.

ATYPICAL ORGANISMS OF CAP

PREVIEW | REVIEW

- What are the extrapulmonary manifestations of infection with *Mycoplasma pneumoniae*?
- Pneumonia caused by *C. pneumoniae* can be biphasic. What is the characteristic throat symptom in the 1st phase? The 2nd phase?
- Pneumonia in a patient with associated mental status changes and diarrhea should make you think of which organism?
- Which patients were at increased risk of developing severe pneumonia and death from infection with novel H1N1?

- Name the drug options for empiric treatment of influenza A or B.
- Your patient returns from a trip to the southwest U.S. and comes to you with erythema nodosum. Which fungus do you include in your differential?
- Which fungus is endemic to areas of the southern and midwestern U.S.?
- Which endemic fungus causes hilar adenopathy, focal alveolar infiltrates, and multiple lung nodules?
- Describe the microbiologic characteristics of *Blastomyces*.

Recall that atypical organisms of CAP are defined as atypical because they are not identifiable by Gram stain or routine bacterial culture or are resistant to β -lactam antibiotics. These organisms require special culture media (+/- serologic tests, viral panels) to establish the diagnosis.

Bacterial Pneumonias

Mycoplasma pneumoniae

Mycoplasma pneumoniae is a common cause of CAP in **young** patients. It is transmitted by infectious droplets person to person, so outbreaks occur (e.g., college dorms, military barracks). Incubation is 2-3 weeks, and the onset of dyspnea, intractable cough, and fever is typically insidious (although occasionally the presentation can mimic pneumococcal disease). Extrapulmonary manifestations of *Mycoplasma* infection include hemolytic anemia, splenomegaly, erythema nodosum and erythema multiforme (and Stevens-Johnson syndrome), arthritis, myringitis bullosa, pharyngitis, tonsillitis, and neurologic changes (especially **confusion**).

PCR is the diagnostic test of choice. If PCR assay is not available, measure acute and convalescent IgM antibody titers using enzyme immunoassay. If the convalescent titer rises by $\geq 4\times$ the acute titer, you can then make the diagnosis retrospectively with > 95% sensitivity and specificity. Chest x-ray typically shows patchy infiltrates or reticulonodular pattern but are nonspecific.

Patients can develop an autoimmune hemolytic anemia. Cold agglutinin disease is an autoimmune disease characterized by the presence of a high concentration of circulating antibodies (usually IgM) directed against RBCs. It is a specific form of autoimmune hemolytic anemia, one in which the antibodies only bind to the RBCs at low body temperatures. This complication is treated with warming, steroids, and possibly plasmapheresis.

Treatment of *Mycoplasma pneumoniae* is with a macrolide (azithromycin for 5 days is favored) or fluoroquinolone.

Chlamydophila pneumoniae

Chlamydophila pneumoniae (formerly *Chlamydia pneumoniae*) more commonly causes CAP in adults > 65 years of age.

Symptoms and ease of transmission are similar to *Mycoplasma pneumoniae* with the addition of **pharyngitis** and **hoarseness**. Often, there is a biphasic illness. The patient presents with a sore throat that is negative for group A *Streptococcus*; 2–3 weeks later, hoarseness and pneumonia develop. Again: Sore throat → pneumonia + hoarseness = *C. pneumoniae*.

Confirm the diagnosis of pneumonia due to *C. pneumoniae* by PCR of respiratory secretions.

Treatment: Effective antibiotic therapy includes azithromycin for 5 days or fluoroquinolone for 7 days. The postinfectious dry cough can last several weeks.

Legionella pneumophila

Legionella pneumophila causes CAP when the organism is inhaled from contaminated water or soil, typically in the winter and summer months. Epidemics are seen in hotels and on cruise ships, and the organism can also cause HAP when hospital water systems are contaminated. No person-to-person spread has been shown.

Presentation can be similar to, and is often confused with, *Mycoplasma pneumoniae*. The disease begins with headache, GI symptoms (especially diarrhea), and occasionally confusion, then evolves into high fevers and lung-related symptoms of cough and dyspnea. Pleural effusions are not uncommon in *Legionella* pneumonia.

Labs can show hyponatremia, hypophosphatemia, thrombocytopenia, elevated liver function tests, elevated ferritin, and hematuria.

The preferred diagnostic tests for *L. pneumophila* pneumonia are PCR and urinary antigen. The gold standard remains sputum culture on special media (buffered charcoal yeast extract agar (high iron content), but results take > 3 days). The urinary *Legionella* antigen test detects only *L. pneumophila* Serogroup 1, which causes 90% of cases of *Legionella* pneumonia. Consequently, this test has about 80% sensitivity and specificity of 97–100%.

Treatment is with macrolides (especially azithromycin) or quinolones for 5–7 days and up to 10 days for slow clinical responders.

Viral Pneumonias

Influenza

Influenza **A** (common subtypes: H3N2, seasonal H1N1, and 2009 H1N1 [swine flu]) and **B** viruses can cause primary viral pneumonia or can be associated with a secondary bacterial superinfection. Diagnosis can be made by viral culture of respiratory secretions (takes days for results) or with rapid PCR test (takes minutes for results).

Consider **influenza** pneumonia in a patient who has typical influenza symptoms, including myalgias and fever with progressive worsening of cough and dyspnea. Examination is typical for pneumonia, but there is scant sputum production. Hypoxemia is common. In 2009–2010, a pandemic caused by the novel H1N1 swine influenza carried with it an increased morbidity in very young people and in pregnant women.

Consider **secondary bacterial** pneumonia as an influenza complication in the patient whose flu-like illness appears to be improving then suddenly worsens with signs of pneumonia (cough, dyspnea, and a new fever). Think of *S. aureus*, pneumococcus, and *H. influenzae*. Gram stain and culture of sputum usually show the superinfecting organism.

More common than either of the previously described presentations is the **mixed viral and bacterial** pneumonia seen with influenza outbreaks. This is the patient who gets influenza and then eventually gets associated bacterial pneumonia. Time does not lapse between obvious flu and pneumonia. Rather, the clinical picture is one of blended disease. In this situation, the patient coughs up purulent sputum after a few days of influenza illness, then waxes and wanes between improvement and exacerbation. Chest x-rays show areas of consolidation, and sputum shows an abundance of bacteria.

Influenza A and B are diagnosed rapidly with a nasal swab PCR. An assay that distinguishes between influenza A and B is especially recommended. However, the rapid tests are not 100% sensitive, and false negatives are common. Subtyping analysis requires molecular PCR testing, and this is only done at specialized labs.

Treatment: Primary prophylaxis is recommended for exposed individuals in nursing homes and in those with chronic diseases. Empiric treatment of influenza requires the use of **zanamivir** (Relenza), peramivir (Rapivab), **oseltamivir** (Tamiflu), or baloxavir. Since most cases of influenza A have acquired **resistance** to amantadine and rimantadine, they are not recommended for use. (Influenza B is inherently resistant to amantadine and rimantadine.) Some H3N2 and seasonal H1N1 subtypes of influenza A even have resistance to oseltamivir, but novel H1N1 (swine flu) remains susceptible. Treatment within 48 hours of presentation has the most clinical benefit.

Adenovirus

Adenovirus in adults initially causes cold symptoms (sore throat, runny nose, and cough) with eventual development of pneumonia in a small subset. Most cases of adenovirus pneumonia have been observed in the military. Immunodeficient patients can develop life-threatening adenovirus pneumonia.

Diagnostics are typically not done except in immunosuppressed patients (culture of respiratory secretions and PCR testing).

Treatment is supportive.

RSV

Respiratory syncytial virus (RSV) generally causes a cold in most adults, but the elderly and patients with immunosuppression can get pneumonia.

Diagnosis can be made by PCR testing of the respiratory secretions.

Treatment is supportive except in those with bone marrow transplants (then use ribavirin).

Endemic Fungal Pneumonias***Coccidioides immitis***

Coccidioides immitis infection (coccidioidomycosis) is endemic in the southwestern U.S. (especially in Arizona and in California's San Joaquin Valley). It is often referred to as valley fever.

History typically involves travel to an endemic area followed by nonspecific symptoms including fatigue and arthralgias. The resulting illness can be subclinical and self-resolve, or CAP can develop within 2–3 weeks of exposure.

Erythema **nodosum** and erythema **multiforme** are associated skin findings. Chest x-ray findings vary from normal to adenopathy, infiltrates, nodules, and persistent thin-walled cavities.

Disseminated coccidioidomycosis is seen in immunocompromised or HIV-infected individuals. This is a fulminant disease that can involve the brain, skin and bone. Treatment is with an azole or amphotericin B. Relapses are common.

Diagnose by enzyme-linked immunoassay (EIA), culture, immunodiffusion, or complement-fixing antibodies. The finding of coccidioidomycosis from any tissue is evidence of infection as it is never normal flora.

The common form of coccidioidomycosis is **self-limited** and does not require treatment, although it can leave thin-walled lung cavities. The 2016 IDSA guidelines recommend the treatment of patients who have:

- Risk for dissemination
- Persistent fevers for ≥ 1 month
- $> 10\%$ weight loss
- > 3 weeks of night sweats
- Infiltrates in at least 50% of 1 lung (or portions of both lungs)
- Prominent or persistent lymphadenopathy
- High *Coccidioides* antibody titer
- Difficulty working
- > 2 months of symptoms
- Immunocompromise
- Diabetes
- Pregnancy
- Debilitations

Treat Hispanic, African American, and Filipino individuals due to increased risk of extrapulmonary infections.

When treatment is required for coccidioidomycosis, treat with fluconazole or itraconazole for 3–6 months and amphotericin B for severe pneumonia.

See the **Infectious Disease** section for more on coccidioidomycosis.

Histoplasma capsulatum

Histoplasmosis is endemic in areas of the southern and midwestern U.S. It is especially seen in the Mississippi and Ohio River valleys. (Do not confuse this with coccidioidomycosis, a.k.a. San Joaquin Valley fever. Refer to *Coccidioides immitis*.) Remember that the “H” and “Os” in HistOplasmOs is go with the “H” and “Os” in OHio. Or, think of “histoplasMOsis (Mississippi, Ohio).” It is caused by animals living in soil (e.g., chickens) and cave-dwelling animals (e.g., bats).

With acute histoplasmosis, the chest x-ray shows hilar adenopathy and focal alveolar infiltrates. Heavy exposure (epidemic, disseminating form) is suggested by a chest x-ray revealing **multiple nodules** in addition to the hilar adenopathy. The majority of fibrosing mediastinitis cases are from the sequelae of histoplasmosis and can cause obstruction of the superior vena cava, esophagus, and trachea.

Diagnosis of histoplasmosis:

- If there is systemic disease, use the antigen test of the blood, bronchoalveolar lavage (BAL), or urine in addition to fungal culture.
- If there is an acute **pneumonia**, the urinary antigen test can be used. Serologic tests can be used; complement fixation is more sensitive than immunodiffusion.

No treatment is indicated for localized disease, although some recommend itraconazole depending upon the severity of the illness and the state of the host.

Disseminated or severe disease is treated with amphotericin B. The liposomal preparation is preferred because it has better penetration into the lymph nodes, spleen, and marrow (locations where the majority of histoplasmosis replication takes place). HIV patients require chronic suppression with itraconazole.

For more on histoplasmosis, see the **Infectious Disease** section.

Blastomyces dermatitidis

Blastomycosis is uncommon, and the great majority of patients will need treatment with an antifungal agent. It is usually acquired after exposure to soil in the central, southeast, and mid-Atlantic states. (Think of “having a blast” in Chicago.)

Progression can be indolent to severe. The respiratory system is usually the mode of entry, and the condition can present as acute or chronic pneumonia. Hematogenous dissemination to the skin can occur with microabscesses forming along a new verrucous skin lesion.

Chest x-ray can show nodules, alveolar infiltrates or dense mass-like infiltrates.

No skin test is available for the diagnosis of blastomycosis. It is more pyogenic than the other fungi, and patients can cough up purulent sputum that reveals the organism with KOH prep. The buzz phrase for blastomycosis is “broad-based budding yeasts” (Figure 6-25).

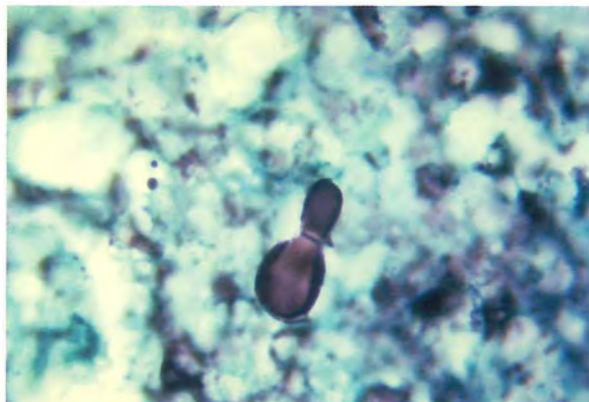


Figure 6-25: Methenamine silver stain of pathology specimen shows the broad-base budding of blasto yeasts
Source: CDC

Treatment of blastomycosis:

- Indolent (uncommon): observation or oral itraconazole
- Mild to moderate: itraconazole for 6 months
- Severe: First use amphotericin B, then switch to itraconazole. HIV patients require chronic suppression with itraconazole, similar to histoplasmosis (refer to *Histoplasma capsulatum*).

For more on blastomycosis, see the [Infectious Disease](#) section.

Mycetoma

Mycetomas are balls of fungus that grow in cavities from prior lung disease (e.g., TB, nontuberculous mycobacteria [NTM], fibrocavitary sarcoid, bronchiectasis, bullae). A ball consists of live and dead fungal hyphae, fibrin, and other debris or fungal elements. Balls are often attached to the lung wall by a stalk, but they are sometimes mobile. *Aspergillus* is by far the most common cause, but rarely other fungi as well as some bacteria (e.g. nocardia) can form a mycetoma.

Mycetomas present as a very indolent disease of the lung, with cough, hemoptysis, and constitutional symptoms. Chest x-ray shows cavities with fluid or fungus balls. The CT scan or occasionally the chest x-ray may show a crescent sign: air in a crescent around the mycetoma. Aside from chronic wasting and necrosis of the surrounding lung, the major complication is life-threatening hemoptysis.

Sometimes patients do not develop typical fungus balls, called aspergillomas, but instead they have chronic infection of prior cavities with *Aspergillus*. This presentation

is simply called **chronic pulmonary aspergillosis**. The galactomannan and β -D-glucan assays, in addition to the culture, can be used to diagnose chronic pulmonary aspergillosis.

For hemoptysizing patients, early antibacterial treatment is recommended due to frequent bacterial superinfection. Embolization by interventional radiology (IR) may be needed once the source of bleeding is localized. Antifungal therapy generally does not work on the mycetoma itself, but it may in some cases be helpful if there is semiinvasive disease associated with the mycetoma. In some cases surgery may be warranted if the patient has had massive hemoptysis and the nature of the lesion allows surgery (i.e., there is no extensive pleural reaction around the area of the mycetoma).

VENTILATOR-ASSOCIATED PNEUMONIA (VAP) AND HOSPITAL-ACQUIRED PNEUMONIA (HAP)

PREVIEW | REVIEW

- Which organisms are the usual causes when a patient requires intubation and then develops pneumonia within the 1st couple of days after admission?
- Characterize the organisms that cause pneumonia in patients who have been in the ICU on the ventilator for > 5 days.

HAP refers to pneumonia not associated with mechanical ventilation. The 2016 IDSA/ATS guidelines state that patients with HAP and patients with VAP should be regarded as 2 distinct groups.

VAE (ventilator-associated event), used as a VAP surveillance tool, occurs when the patient is on a ventilator > 48 hours and develops worsening oxygenation with an increase in F_iO_2 or PEEP (now you have a VAC [ventilator-associated condition]) and/or evidence of infection or inflammation, with leukocytosis or leukopenia, fever, or a new antibiotic started (now you have an IVAC [infection-related ventilator-associated complication]).

VAP is defined as pneumonia that develops > 48 hours after endotracheal intubation.

HAP is defined as pneumonia that develops > 48 hours after admission to the hospital.

These 2 types of pneumonia are more likely than CAP to have multidrug-resistant (MDR) organisms.

VAP

The organisms that cause VAP vary depending on how soon after admission the patients are intubated. VAP in patients intubated within 1–4 days of admission is more likely to be caused by CAP organisms and less likely to be drug resistant. The more time that elapses between

admission and intubation (usually > 5 days), the more likely the patient is to develop pneumonia from **hospital organisms** that have colonized the oropharynx and the upper airways. These organisms are more likely to be **MDR**.

The most commonly encountered VAP MDR infections are:

- MRSA
- *Pseudomonas* species
- *Stenotrophomonas maltophilia*
- *Acinetobacter* species

Suspect pneumonia in any patient who develops new fever or clinical deterioration while on a ventilator. The incidence is highest in the first 5 days of ventilator use. **Malnutrition** in the ICU is an important predisposing condition.

The 2019 IDSA/ATS guidelines recommend noninvasive sampling (endotracheal aspirate of sputum) with semiquantitative cultures to determine the microbiologic etiology of VAP rather than invasive sampling (BAL, protected specimen brush [PSB]); blind bronchial sampling [a.k.a. mini-BAL] with quantitative cultures.

The treatment of VAP is often initially empiric but then guided by the results of **endotracheal (ET) aspirate culture**.

Empiric treatment should be guided by the local antibiogram, providing information about the distribution of organisms and their antibiotic susceptibility profiles. This local information should be as specific as possible for the hospital and ICU where the patient is being treated.

For empiric treatment of VAP:

- It is recommended that coverage for *S. aureus*, *Pseudomonas aeruginosa*, and other gram-negative bacilli be used in any empiric regimen.
- Vancomycin or linezolid should be used to cover for the possibility of MRSA.
- 1 or 2 antipseudomonal agents should be used depending on the patient's risk factors for MDR organisms and/or the local antibiogram. If there are no such risk factors present (i.e., septic shock, ARDS, acute renal replacement therapy), then 1 drug can be used to treat *Pseudomonas* pneumonia.

Deescalation to pathogen-specific treatment is recommended once culture results return and condition allows. A course of 7 days is generally recommended.

Extended-spectrum β -lactamase-producing organisms should be definitively (not empirically) treated according to results of antimicrobial susceptibility testing results.

Acinetobacter treatment is usually with a carbapenem, broad-spectrum cephalosporin, or a combination

ampicillin/sulbactam/ β -lactamase inhibitor or based on antibiotic susceptibility testing results.

Note: If the patient was recently admitted with pneumonia and intubated, treat for CAP organisms per [Figure 6-23 on page 6-56](#) unless MDR organisms are suspected.

Procalcitonin and clinical criteria together may be used to discontinue antibiotics if suspected pneumonia was a false alarm. However, initiation of antibiotic therapy in suspected HAP/VAP should be decided on clinical grounds and not by procalcitonin.

HAP

The approach to HAP is similar to that of VAP. The organisms are often the **same**, except MDR organisms are less frequently involved, and patients are less sick. Empiric antibiotic therapy follows the same principles discussed for VAP. However, treatment for HAP subsequently should be guided by noninvasive **sputum culture** rather than ET aspirate (as in VAP)—i.e., de-escalating from empiric therapy.

ASPIRATION SYNDROMES

PREVIEW | REVIEW

- Describe the presentation of a patient with an aspiration pneumonia.

There are 5 main types of aspiration syndromes:

- 1) Aspiration of gastric acid causing a chemical pneumonitis (a.k.a. Mendelson syndrome)
- 2) Aspiration of bacteria from oral and pharyngeal areas causing an aspiration **pneumonia**
- 3) Aspiration of exogenous and endogenous lipid material resulting in a lipoid or cholesterol pneumonia
- 4) Aspiration of a foreign body
- 5) Aspiration of food or liquid

With aspiration syndromes, infection generally occurs only after a **large amount** of material is aspirated (e.g., after endotracheal intubation or seizures or in a severely intoxicated patient). The infiltrate usually occurs in the right lower lobe (RLL), the right middle lobe (RML), or, in some cases, bilaterally in the lower lobes. If the patient is supine at the time of aspiration, infiltration is most likely to occur in the superior segment of a lower lobe. If the patient is upright, the aspiration can preferentially occur in the RML, but may also occur in the lingula or lower lobes. When a patient aspirates, it is not necessary to start antibiotics immediately because the stomach contents often only cause a chemical pneumonitis. The onset of fever, leukocytosis, change in sputum to thick yellow or green sputum, and persistent

infiltrate suggests aspiration pneumonia, which generally will benefit from treatment with antibiotics.

Observe the patient carefully because cavitating pneumonia and/or empyema may develop. The breath can be extremely malodorous in those with anaerobic infections! The most common infection-causing anaerobic bacteria are *Fusobacterium nucleatum*, *Bacteroides melaninogenicus*, and anaerobic streptococci. However, aspiration pneumonias are often polymicrobial.

Diagnosis is typically clinical, based on the history of aspiration. The radiograph may show an infiltrate, with possible subsequent organization into a cavity (Figure 6-26). Gram stain shows mixed flora. Sputum is unreliable. Changes in the volume, color, and thickness of the sputum, often with persistent fever and leukocytosis, suggest bacterial aspiration pneumonia.

Treatment is with a β -lactam combined with a β -lactamase inhibitor (e.g., amoxicillin/clavulanic acid or ampicillin-sulbactam) or, alternatively, with clindamycin.

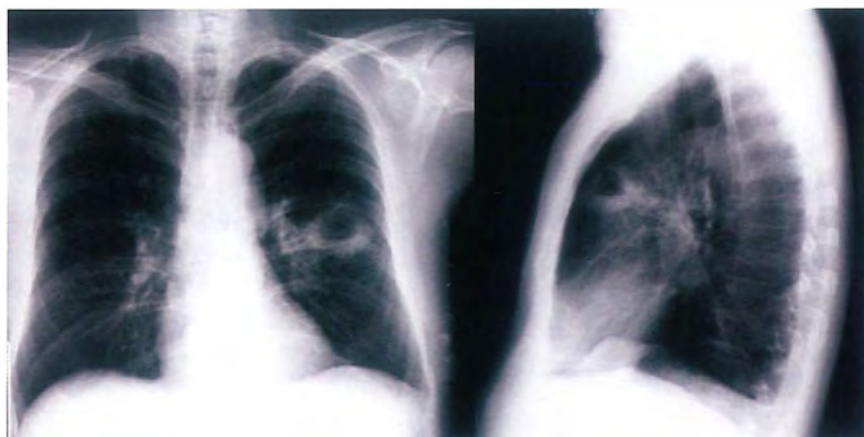


Figure 6-26: Left upper lobe cavitary pneumonia from aspiration
Source: Vinay Maheshwari, MD

lesions (in the upper lobes and the posterior segment of the lower lobes in cases of aspiration). Septic emboli, with or without cavitation, appear as multiple nodules in the mid-to-lower lung zones, in accordance with the circulation.

Diagnosis is usually clinical and relies substantially on the history. There is a need to exclude TB and other organisms that may cause cavitation; anaerobes are particularly difficult to culture.

Treatment: β -lactams or β -lactamase inhibitors are drugs of choice. Once there is clinical improvement, you can switch the patient to oral amoxicillin-clavulanate. Duration of treatment can exceed 3 weeks.

LUNG ABSCESS

PREVIEW | REVIEW

- Describe the presentation of a patient with a lung abscess.

A lung abscess forms after an infection causes a necrotic lung to cavitate. The most common cause is aspiration of organisms from the oropharynx. Risk factors for aspiration include seizures, alcoholism, esophageal abnormalities, and swallowing problems. Typical organisms that live in the mouth are gram-positive bacteria such as *Staphylococcus* and *Streptococcus*, while patients with poor dentition are predisposed to anaerobes. People with alcohol use disorder have a high incidence of gram-negative enterics (e.g., *Klebsiella*).

Lung abscesses as foci of metastatic infection can occur with right-sided staphylococcal endocarditis, in IV drug abusers, and in dialysis and chemotherapy patients who have chronic venous access.

A lung abscess presents with malaise, weight loss, and an indolent cough with progressive purulent, often fetid, sputum (especially in anaerobic infections). Abscesses due to metastatic staphylococcal infection (septic emboli) are more acute. The chest x-ray typically shows cavitary

MYCOBACTERIAL INFECTIONS

PREVIEW | REVIEW

- Describe the differences between primary tuberculosis (TB), latent TB, and reactivation TB.
- How do you make the diagnosis of active pulmonary TB?
- What is the percentage of patients who have active pulmonary TB and nonreactive TB skin tests?
- What do you do differently to read the TB skin test in the patient who has received the bacillus Calmette-Guérin (BCG) vaccine?
- In which direction relative to the arm is the TB skin test read?
- In which groups of patients is a reactive TB skin test of ≥ 5 mm significant? ≥ 10 mm? ≥ 15 mm?
- List some reasons why a patient with true latent TB might have a negative TB skin test.
- What are you going to do for the patient who is high risk for TB disease but has a negative skin test?
- What is the booster effect seen with TB skin testing?

- What is the definition of a new converter?
- Which patients should be screened with IGRA tests?
- Can a patient with a negative TB skin test still have TB? What about with a negative IGRA?
- What is the usual treatment (and for how long) for an asymptomatic, HIV-negative 30-year-old with a positive TB skin test and normal chest x-ray?
- What is the usual treatment for latent TB? (Hint: The patient in the last question has latent TB.)
- What are the 4 drugs used to treat active TB?
- In the 4-drug regimen used to treat active TB, how long is each drug given?
- Which side effects can result from the different antimycobacterial drugs? What is the required screening?
- What is Lady Windermere syndrome?
- What do you do for the healthy patient with a single sputum sample positive for *M. kansasii*?
- A patient returns from a vacation to Mexico with complaints of chronic drainage from a recent tummy tuck incision. What is the likely organism?

TUBERCULOSIS (TB)

TB is one of the top 10 causes of death worldwide, infecting nearly 2 billion people. The countries with the highest incidence are India, Indonesia, China, Nigeria, Pakistan, and South Africa. Although the incidence in the U.S. is considered low, it is still a significant problem, especially in those infected with HIV. Much of the following topic discussion is in accordance with the ATS/IDSA/CDC 2017 guidelines. You can download them from cdc.gov/tb.

You must know TB thoroughly. There is not a lot of yellow highlighting here because you must know this entire topic perfectly!

The TB infection sequence is primary infection → latent infection → reactivation.

Primary TB occurs when aerosolized, contaminated droplets are inhaled and droplet nuclei reach the alveoli. The bacteria multiply locally for a while and then spread to areas of the body with high oxygen tensions (e.g., bone, brain, kidneys, lung apices). Acquired and cell-mediated immunity arrest the dissemination in > 90% of those affected, and further growth of organisms stops during this initial stage (the latency period). Patients who do not have functional cell-mediated immunity can then develop active TB—termed **primary TB**. Disease occurs throughout the lungs and can disseminate (e.g., meningitis, pericarditis), and symptoms may manifest quickly after initial exposure. **Children, AIDS patients, and those on TNF-α inhibitors** are most at risk for primary disease.

Latent TB occurs in the exposed patient with a functional immune system. The organisms are held at bay

by the formation of granulomas, and the patient does not develop a primary infection. In the lung, the granulomas sometimes calcify and can be observed as **Ghon complexes**. Usually, this sensitized person is asymptomatic—but a TB skin test reacts, showing that they are infected with the organisms. A significantly reactive TB skin test in a patient with no evidence of active tuberculosis is called latent tuberculosis infection (**LTBI**). Only assess for latency if treatment will be considered, either by tuberculin skin testing or with interferon-γ release assays.

Reactivation TB occurs when the cell-mediated immune system loses its ability to keep the organisms in check. This loss of ability occurs with aging and the development of comorbidities and may take months, years, or even decades to develop. Reactivation disease tends to be localized to the lung apices, and dissemination is generally uncommon. The risk of reactivation is highest after exposure (5% within the first 2 years and another 5% thereafter; HIV/AIDS patients are an exception and have a 40% risk of reactivation within months).

Common systemic signs of reactivation TB include fever, weakness, night sweats, and weight loss. Pulmonary disease is indicated by cough, pleuritic chest pain, and hemoptysis. Pleural effusions associated with TB may be either a manifestation of reactivation (most common) or primary TB. The pleural effusion is exudative and predominantly lymphocytic, with an elevated protein and LDH and with no or few eosinophils.

The chest x-ray may show an upper lobe infiltrate, hilar lymphadenopathy, and cavitory lesions (Figure 6-27 and Figure 6-28). Patients who develop cavities have the largest burden of organisms.

Most reactivation TB is pulmonary, 15% is extrapulmonary. Consider TB in a patient with indolent, chronic arthritis or chronic meningitis.

Miliary TB is the term given to uncontrolled hematogenous spread. The clinical presentation is variable—from overwhelming disease with multisystem organ failure (in primary infection) to chronic wasting (in reactivation infection). This form of TB is most common among infants and children < 5 years of age, as well as in immunocompromised individuals. The classic chest x-ray shows a faint and diffuse reticulonodular infiltrate (Figure 6-29).

The 2017 CDC-recommended approach to the diagnosis of active pulmonary TB (Figure 6-30 on page 6-68) includes:

- TB skin test or interferon-γ release assay (IGRA)
- Chest x-ray
- Acid-fast smears and cultures of the sputum
- ≥ 1 nucleic acid amplification test (i.e., NAA, PCR)

Acid-fast bacilli (AFB) smears are cheap but are only up to ~ 80% sensitive (false negatives) and have a 50-80% positive predictive value. (The AFB can be NTM—you do not know until you get the organism precisely identified.)



Figure 6-27: RUL pneumonia, consistent with TB (noncavitary)
Source: Vinay Maheshwari, MD

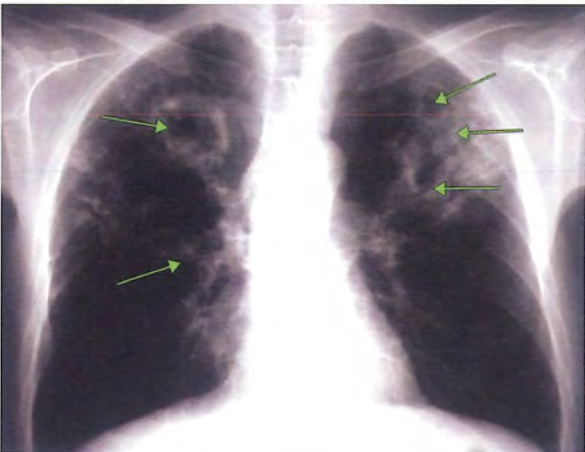


Figure 6-28: Reactivation TB with RUL cavitary lesion

Some of these issues are resolved with mycobacterial cultures, but they take a long time to grow.

NAA tests can be done on both smear-positive and smear-negative sputum samples and improve the sensitivity to ~ 95% because PCR can distinguish between TB and NTM.

Do **not** wait for the test results before treating reactivation TB if your clinical suspicion for disease is high (i.e., positive TB skin test or IGRA with risk factors). Initial treatment is with isoniazid, rifampin, pyrazinamide, and ethambutol. Subsequent treatment is determined by the drug susceptibility results, 2-month culture conversion, and the presence of cavitation on the initial chest radiograph.

Report all persons with current reactivation TB or suspected current reactivation TB to the appropriate state or local health departments.



Figure 6-29: Miliary TB with reticulonodular infiltrates
Source: Vinay Maheshwari, MD

We will cover the treatment of LTBI and active TB after we discuss the screening for LTBI.

Screening for Latent Tuberculosis Infection (LTBI)

Who gets screened?

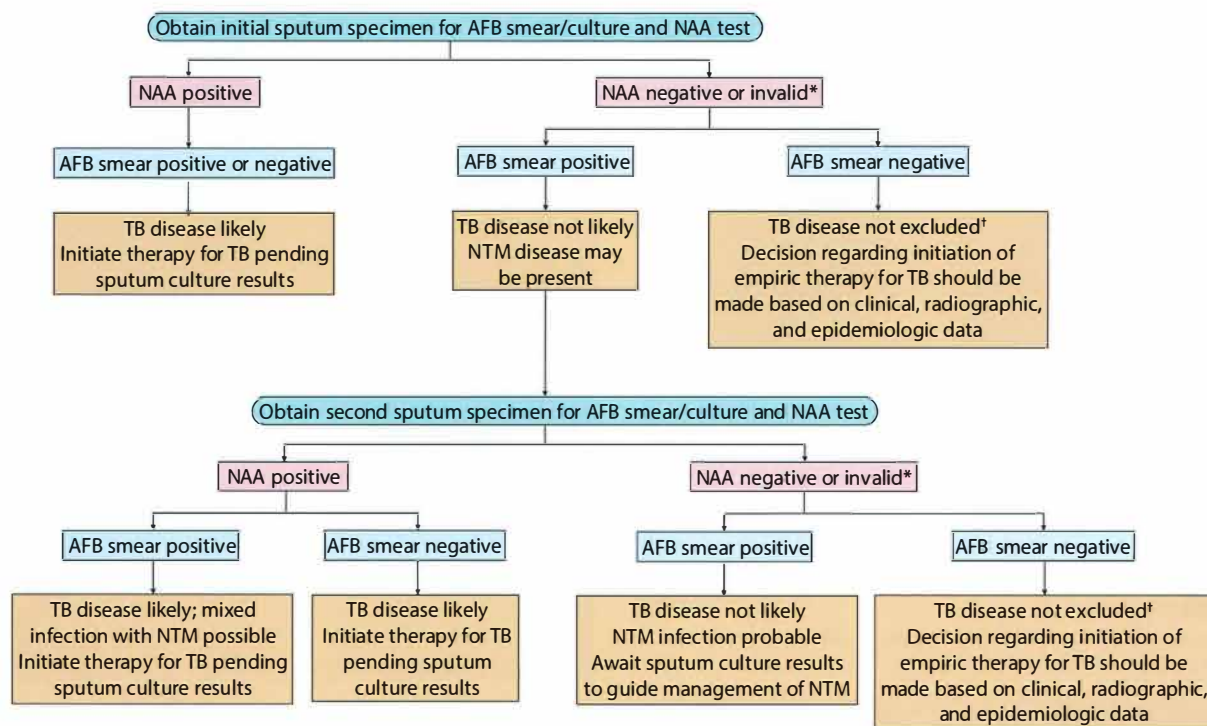
High-risk groups include:

- HIV or those at high risk for HIV
- Close contacts with those with TB
- IV drug abusers
- Low-income, medically underserved populations
- Homeless individuals
- Migrant workers
- Residents of long-term care facilities (e.g., nursing homes, jails)
- Individuals with medical conditions that predispose to the progression to active TB disease (e.g., DM, silicosis, immunosuppression)

How are they screened?

There are 3 methods:

- 1) **Tuberculin skin test** (most widely used)
- 2) **IGRAs**
- 3) Chest x-ray, sputum for AFB, and the IGRA (Use these to screen for active disease in patient populations that are easily **lost to follow-up**; e.g., those in jails and in homeless shelters.)



AFB = acid-fast bacilli; NAA = nucleic acid amplification; TB = tuberculosis; NTM = nontuberculous mycobacteria

* A negative NAA result should be accompanied by a negative test for inhibitors that may limit amplification (if the enhanced amplified *Mycobacterium tuberculosis* direct [E-MTD] assay was used). The Xpert MTB/RIF assay contains a positive control that signals an invalid result if an inhibitor is detected.

An invalid NAA result indicates failure of the assay. An invalid result is usually reported after the test has been repeated using the same specimen. Receipt of an invalid NAA result should prompt a repeat test using a new specimen.

† TB remains possible; the organism burden may be too low to meet the sensitivity threshold for detection via NAA or smear.

Data from:

Lewinsohn, D.M., Leonard, M.K., LoBue, P.A., et al. Official American Thoracic Society/Infectious Diseases Society of America/Centers for Disease Control and Prevention Clinical Practice Guidelines: Diagnosis of Tuberculosis in Adults and Children. *Clin Infect Dis* 2017; 64:e1. World Health Organization. Global Tuberculosis Report, 2016. WHO, Geneva 2016.

Centers for Disease Control and Prevention (CDC). Updated guidelines for the use of nucleic acid amplification tests in the diagnosis of tuberculosis. *MMWR Morb Mortal Wkly Rep* 2009; 58:7.

Figure 6-30: TB disease workup

The tuberculin skin tests react in most **infected** people. That said, know that **25%** of patients with active pulmonary TB have **nonreactive TB skin tests**. So, a negative TB skin test does not exclude TB in patients who have a high pretest probability of disease. The tuberculin skin test is contraindicated **only** if there was a necrotic skin reaction to a previous test.

The TB skin test may be given if the patient has had the bacillus Calmette-Guérin (BCG) vaccine; this is used in some countries as a TB vaccine. Because most of these people were vaccinated as infants and the immune response to these antigens wanes with time, the purified protein derivative (PPD) result will probably be **valid**. Interpret the diameter of induration at 48–72 hours in the **standard** fashion and treat accordingly. Still, the CDC prefers the IGRA over the TB skin test in these patients; it is not affected by the BCG vaccine.

The standard TB skin test uses the Mantoux method of an intradermal injection of 0.1 mL (5 tuberculin units) of PPD tuberculin in the forearm. The injection site is evaluated 48–72 hours after the injection. The reading is based on the diameter of the **indurated/swollen** area—not the erythematous area—measured perpendicular to the long axis of the forearm (Figure 6-31).

The 2017 recommendations from ATS/IDSA/CDC as to what constitutes a significant reading take into account the degree of clinical suspicion of LTBI and the risk group of the patient. A particular diameter of induration may be significant in one group and insignificant in another. As of 2019, once a health care worker's baseline tuberculin skin test is obtained, annual screening does not occur unless known exposure takes place or the health care worker is at high risk for exposure (e.g., pulmonary physicians)

All of the following are considered positive skin tests (i.e., require treatment).



Figure 6-31: Properly reading the TB skin test (indurated area perpendicular to long axis of forearm)

Source: CDC

≥ 5 mm is positive for those in the high-risk groups:

- HIV or major cell-mediated dysfunction
- Fibrotic changes on chest x-ray consistent with prior TB
- Close contact with a documented TB case
- Patients with organ transplants and other immunosuppressed patients (receiving the equivalent of **≥ 15 mg/day** of prednisone for **≥ 1 month**, or receiving TNF-inhibitor, or receiving chemotherapy)

≥ 10 mm is positive for those in the intermediate-risk groups:

- Homeless persons
- Recent immigrants (within 5 years) from high-prevalence countries
- IV drug users who are HIV-negative
- Prisoners and corrections officers
- Health care workers with high exposure risk
- Patients with DM, silicosis, malignancy, and malnutrition
- New converters (see [New Converter and the Booster Effect](#))

≥ 15 mm is positive for the low-risk groups. This includes most people in the community.

The most concise way to remember this:

- HIV, positive chest x-ray, close contacts, severely immunocompromised **≥ 5 mm**
- No risk factors **≥ 15 mm**
- All the rest **≥ 10 mm**

The **negative** TB skin tests can be a true negative or a false negative. Interpretation of the **negative** test requires that you consider the following:

- Was the test placed too soon? It takes up to **10 weeks** to react after an exposure. If a recently exposed patient has a negative TB skin test, then recheck it 10–12 weeks after exposure. Whether you treat this patient in the interim depends on whether you think the patient is really high risk for TB (an individual judgment—not based on specific parameters). This

may be done in infants or in young children or in immunocompromised individuals. A nurse, for example, is more high risk than an accountant, which can also influence the decision in this window period.

- Can the patient actually react to the test? Is the patient possibly anergic? HIV positive patients who initially test negative are not retested until CD4 levels are **> 200** secondary to false-negative results. Consider **anergy** in patients with immunosuppression and sarcoidosis. However, know that control tests are no longer recommended. As we said, up to 25% of people with active disease have a negative PPD, even when the control test is reactive. Therefore, the control test does not help you interpret a nonreactive TB skin test. In fact, this has been a cause for misinterpreting test results in the past!

Here's the bottom line: If you **strongly suspect TB** in a patient (e.g., exposure in a high-risk individual), then **start empirical treatment** even if the patient has a negative TB skin test result. Be aggressive about continuing the workup.

New Converter and the Booster Effect

The term new converter is used to discuss certain patients who are monitored with yearly skin tests (e.g., inmates in correctional facilities and homeless shelters as well as staff with negative baseline skin test screening and known exposure).

The induration that occurs with TB skin testing is a delayed-type hypersensitivity reaction mediated by the memory T-cell response to *M. tuberculosis*, nontuberculous mycobacteria, or BCG. Now, some people's T cells "remember" better than other people's T cells. Most people who have an LTBI have induration within 48–72 hours of a skin test, but the sensitized people who have memory-impaired T cells (often, the elderly) may not respond within 72 hours. Retesting a week later with a 2nd TB skin test often stimulates the memory-impaired T cells to better recall previous antigen exposure and indurate.

Stimulating memory-impaired T cells in this manner is called boosting. Significant induration occurring on the 2nd test following no induration on the 1st test is called the **booster effect**. This booster effect starts at 1 week after the 1st dose and can persist for 1 year after the 1st TB test, so it can be difficult to determine if the new induration on a yearly screening reflects the booster effect (indicating LTBI from an old primary infection) or a new conversion from a recent exposure (in which case the patient is then labeled a **new converter**). A new converter has a **≥ 10-mm increase** in the TB skin test **induration** within **2 years** from the 1st nonreactive test. Treat all new converters and all with a positive booster effect the same as you would for any positive TB skin test!

Here's the classic way that boosting gets confused with new conversion.

A correctional officer who has constant potential exposure to TB gets the 1st annual TB skin test. There is no reaction. One year later, during the required yearly TB screen, there is 10 mm of induration. Is this new induration because an LTBI developed in the last year (and is the patient thus a new converter), or is it due to boosting? You do not know.

Therefore, in patients who are scheduled for annual TB skin tests, a 2-step TB skin test regimen is often employed for the 1st screening. In this 2-step regimen, the patient gets an initial test, and if the initial test is nonreactive, the patient is retested in a week, with the 2nd test establishing the patient's baseline result. If the patient has a negative baseline test but develops significant induration with the following year's test, you can say with certainty that the new induration is from recent exposure and that the patient is a new converter.

Again, understand that 10 mm of induration in a health care worker at high risk merits treatment regardless of whether it is a boosted result or a new conversion.

Interferon-γ Release Assays

Interferon-γ release assays (IGRAs) are used in clinical practice and are endorsed by the CDC to screen for active and latent TB in lieu of the TB skin test. The 2 commercially available, FDA-approved IGRAs are the QuantiFERON-TB Gold In-Tube test and the T-SPOT.TB assay.

IGRAs test for antigen-specific interferon-γ release during TB infection. The tests cannot distinguish active from latent disease, so do not use them to diagnose active TB. Also, false-negative tests in active disease can be a problem. The test results can be known in 1–2 days. There is no booster response. BCG does not cause a false-positive result.

The 2017 CDC recommendations for the use of IGRA include:

- IGRAs are preferred over TB skin testing in noncompliant patients and in those who have been given BCG.
- TB skin testing is preferred in children < 5 years of age.
- All other patients can either get the IGRA or the TB skin test, but not both.

A negative IGRA, like a negative TB skin test, does not exclude infection in patients who have a high pretest probability of disease. Manage indeterminate tests based on the likelihood of having TB.

Positive Purified Protein Derivative (PPD) Considerations

What do you do when a patient has a positive skin test or IGRA?

A positive test indicates that the patient has or has had LTBI but not necessarily active disease. If the patient has had no previous TB workup, perform a workup for active

disease. This includes a full review of systems, a good physical exam, a chest x-ray, sputum for an AFB smear and culture, and at least one PCR test for *M. tuberculosis*.

(Sputum testing is not required if the chest x-ray does not demonstrate abnormalities and the patient's review of systems is inconsistent with active disease.)

If the PPD or IGRA is positive and active disease is present, treat for active tuberculosis (see Treatment of Active TB).

If the PPD or IGRA is positive and no active disease is present, the decision to treat for LTBI is determined by the risk of the patient progressing to active TB vs. the risk of treatment. An 80-year-old with a long-standing positive PPD may have already used up most of his or her lifetime risk. However, if such a patient has a newly positive PPD and is truly a close contact of an active TB patient, their risk is much higher and warrants treatment for LTBI. Care must be given to minimize hepatotoxicity.

Treatment for LTBI

Treatment is provided to eradicate the TB infection before it can develop into active disease. Again, the risk of conversion is 5% within 2 years for the general population and ~ 40% within several months for HIV patients. See Table 6-15.

For treatment of LTBI in HIV-negative adults, the American Thoracic Society, CDC, and Infectious Diseases Society of America (2016) specify 4 main management options:

- INH and rifapentine (RPT) for 3 months
- INH for 9 months
- Rifampin (RIF) for 4 months
- INH and RIF for 3 months

Again, what about negative IGRAs or PPDs?

Patients who have been a close contact of someone with active TB but have a negative TB test can either be observed or treated for LTBI, depending upon their risk (e.g., an HIV-positive patient would probably be treated, whereas a healthy person with no other risks would probably be observed). Children are definitely treated. Retest the negative cases in 10–12 weeks. If treating with INH, add pyridoxine to avoid peripheral neuropathy.

Treatment of Active TB

The emergence of multidrug-resistant strains has changed the treatment of active TB. Let's first define the 4-drug and 3-drug regimens.

The 4-drug regimen:

- 1) RIF
- 2) INH
- 3) Pyrazinamide (PZA)
- 4) Either ethambutol (oral, preferred) or, much less commonly, streptomycin (injection)

Table 6-15: Positive PPD Determination Based on Preexisting Conditions

Treatment of Latent Tuberculosis Infection (LTBI): Certain groups are at high risk of developing TB disease once infected. These people are candidates for treatment regardless of their age—after ensuring active infection is not present. The treatment regimen for patients who are not HIV-positive depends on compliance and comorbidities.

Treat all of the following (all ages):

PPD Result (Induration)	In People with the Following Conditions
≥ 5 mm is positive in these high-risk groups	- Known/Suspected HIV infection - Close contacts (e.g., same household) of active cases - Chest x-ray suggests previous inactive tuberculosis - Organ transplants and other immunosuppressed patients with > 1 month of equivalent prednisone use (>15 mg/day)
≥ 10 mm is positive in these intermediate-risk groups	- Recent immigrants from a country with a high prevalence - IV drug users - Employees and residents of high-risk settings (e.g., prisons, jails, hospitals, homeless shelters, mycobacteriology lab workers) - Patients with certain comorbidities (e.g., silicosis, DM, advanced chronic kidney disease, leukemia, lymphoma, solid tumor malignancies, recent weight loss of > 10% of predicted body weight (PBW), gastrectomy, post-jejunoileal bypass surgery) - Children < 4 years of age and others with high-risk comorbidities
≥ 15 mm is positive in low-risk patients	No known risk factors
PPD negative but high-risk	High-risk (e.g., immunocompromised) contacts of active TB cases

The **3-drug** regimen consists of the first 3 drugs (remember: may the TB patient who doesn't get RIF, INH, and PZA rest in peace). The use of PZA in pregnant patients in the U.S. has been discouraged, but there has been extensive safe use outside of the U.S. in this population.

In the U.S., all patients with active TB are initially treated for **2 months** with the **4-drug therapy**, unless criteria for the 3-drug therapy are met. Give the first 3 drugs for the full 2 months, and the 4th drug may be dropped if the susceptibility testing shows sensitivity to the first 3 drugs. **After** the first 2 months, give **INH and RIF** for an additional **4 months** (i.e., 6 months total).

HIV-infected patients on protease inhibitors (PIs) are usually given rifabutin instead of rifampin, depending upon the antiretroviral therapy used. Consult the CDC's tables of recommendation for treatment modifications when highly active antiretroviral therapy (HAART) is used with TB medications. Early initiation of HAART within the first 2 weeks or so, particularly in those with a low CD4 count, increases survival. Duration of therapy for HIV-infected patients also is 6 months, but this may be increased in patients with CNS or skeletal involvement or with cavitary lung lesions that stay culture positive. If the patient did not complete 2 months of PZA or there is drug-resistant disease, treatment is extended per the CDC recommendations.

Someone must **observe** all patients taking the medication unless compliance is absolutely assured. This directly observed therapy (**DOT**) is supervised by the local health department. Hospitalized patients with known or suspected active TB are monitored through infection control programs. Airborne infection isolation and respiratory protection are used to prevent the nosocomial

transmission of disease. Patients treated in the outpatient setting are recommended to stay home, away from others, particularly those susceptible to TB, during the diagnostic evaluation. N95 masks should be worn by health care workers while the patient is hospitalized. As an outpatient, the patient should wear a mask when seeing visitors or when leaving the home while pulmonary symptoms are present.

When can **3 drugs** be used?

Only if there is a slight chance of drug-resistant infection and **all** the following criteria are met:

- New TB patient and isolate susceptible to both INH and rifampin
- No known exposure to a patient with a drug-resistant infection
- Does not come from a high-prevalence country

Additional notes:

- Give vitamin B₆ (pyridoxine) with INH-containing regimens to prevent peripheral neuropathy and mild CNS effects.
- If the patient cannot take PZA, give INH and RIF for a total of 9 months.
- If the TB is resistant to INH only, stop INH and give the other 3 drugs for 6 months total or RIF and ethambutol for 12 months.
- Multidrug-resistant TB (i.e., to INH and RIF) is difficult to treat. Treatment is based on sensitivities. Consult a specialist.
- Mothers who have untreated (infectious) TB should not breastfeed, but they can provide expressed milk for their infants. Breastfeeding can resume when the mother has been treated for 2 weeks.

- Tuberculous meningitis: Add adjuvant corticosteroids.
- PZA inhibits uric acid excretion, so do not use during acute gouty flares.
- Ethambutol and PZA can cause rash.

Know these side effects:

- INH, RIF, and PZA are all hepatotoxic.
- In all patients on INH, regardless of age, monitor monthly for signs and symptoms of liver toxicity. Laboratory testing is necessary only if signs or symptoms develop or if they are at risk for hepatotoxicity! Such risks largely include older age, pregnancy (see the [Women's and Men's Health](#) section for TB in pregnancy), concomitant hepatotoxic medications, history of viral hepatitis, and IV drug abuse.
- Ethambutol is not hepatotoxic, but it can cause a decrease in visual acuity. Often, decreased color perception is the 1st sign of this deterioration. It is usually reversible if the drug is quickly discontinued. Patients should have an ophthalmologic exam before treatment and have periodic checks thereafter (i.e., Snellen chart, gross confrontation eye exam, pseudo-isochromatic color vision plates, and clinical history). Any inflammatory disease of the eyes is at least a relative contraindication for ethambutol.
- Streptomycin is an older aminoglycoside. It is ototoxic and nephrotoxic.

NONTUBERCULOUS MYCOBACTERIA (NTM)

NTM include mycobacteria species other than *M. tuberculosis* and *M. leprae*. Many NTM species have been found to cause infections in humans, especially in immunocompromised patients and in patients with structural lung disease. Representative common examples include *M. avium* complex (MAC), which includes *M. avium* and *M. intracellulare*; *M. kansasii*; and *M. goodii*. These species are sometimes found incidentally in the sputum of healthy individuals.

Pulmonary Infections with NTM

There are 2 basic groups of NTM clinical lung disease seen in non-HIV patients:

Pattern 1: A middle-aged male with underlying lung disease (e.g., COPD, bronchiectasis) presents with cough, weight loss, and lung infiltration—possibly even cavitory lesions. This presentation is very similar to TB, but the progression is more indolent. Radiographs are often difficult to interpret because of the underlying lung disease.

Pattern 2: A middle-aged, female nonsmoker presents with cough productive of purulent sputum and interstitial infiltrates on radiograph. When the infiltrates are in the right middle lobe or right lingular segment, the presentation is termed **Lady Windermere syndrome**—based on a character from one of Oscar Wilde's plays. Radiographs or CT scans often show bronchiectasis or nodules.

Because the immune response of these 2 patient groups is generally intact, the NTM do **not** spread **outside** of the lungs.

The diagnosis is made using the ATS criteria. They require that a chest x-ray or HRCT scan of the lungs shows specific abnormalities (bronchiectasis and nodules). In addition, the criteria require either ≥ 2 sputum culture-positive samples for the same organism, a lung biopsy showing granulomas, a positive AFB with 1 sputum culture-positive sample, or 1 BAL with growth of NTM. Nucleic acid probes are available to make a rapid diagnosis of MAC on sputum samples.

Know that an isolated sputum sample growing NTM in a healthy person is not diagnostic of disease and does not require treatment! Consider treatment in patients who have pulmonary symptoms and significant nodular or cavitory opacities. Often, clinicians look for signs that these are active or radiologically progressive to distinguish it from residual scarring due to prior disease.

Patients with severe immunodeficiencies (e.g., AIDS with **CD4 counts < 100 cells/ μ L**) are unable to hold the infection at bay in the lung. Instead, they may develop disseminated disease with positive blood cultures and manifestations in the lungs, liver, and bone marrow. Patients present with constitutional symptoms and often diarrhea. Labs indicate systemic disease with leukopenia, anemia, and elevated transaminases—blood cultures for mycobacteria are often positive.

Treatment of NTM is tough and lengthy, usually 1–2 years (at least 12 months and two consecutive negative sputum cultures). Guide treatment by culture results and an assessment of the risk and benefits. With no symptoms and stable chest imaging, observation is an option. Clarithromycin (or azithromycin) with rifampin and ethambutol are given 3 $\times$ /week for most patients with nodular-bronchiectatic disease, while daily therapy with these agents is used for more severe nodular-bronchiectatic, cavitory, and disseminated disease. Rifabutin is an alternative for rifampin in the treatment of the latter conditions. Also consider using an injectable, such as amikacin or streptomycin, for severe disease.

Hospitalized patients with known NTM do **not** require respiratory isolation (unlike patients with known or suspected TB).

Cutaneous Infections with NTM

Know that NTM can cause infections of **surgical sites** in immunocompetent patients. Patients with immune deficiencies can have disseminated disease that starts with a skin infection. If you see the classic history of recent plastic surgery, travel with exposure to sand and water, and an indolent drainage from the surgical site, think about these culprit organisms: *M. abscessus*, *M. fortuitum*, *M. chelonae*, and *M. marinum*.

TB Skin Tests and NTM

Memory T cells that have been stimulated by NTM react to the antigen in the TB skin test, but the reaction is usually not as robust as with true TB sensitization. Still, this reaction to NTM is why we have cut-off measurements for significant reactions with TB skin testing.

This is somewhat useful to know when you are evaluating a patient who has an indurated, but not significant, TB skin test result and AFB+ sputum. (The AFB may possibly end up being identified as NTM in culture.) NAA testing for *M. tuberculosis* is really helpful in this situation to exclude true TB.

IMMUNOSUPPRESSED PATIENTS

PREVIEW | REVIEW

- In developed countries, what are the 2 most common causes of pneumonia in patients with HIV/AIDS?
- What is the preferred regimen for the treatment of *Pneumocystis jiroveci* pneumonia (PJP)?
- How does the preferred regimen for the treatment of PJP differ when the patient has a $P_aO_2 = 60$ mmHg?
- Discuss the various types of *Aspergillus* pulmonary infections.
- What is the recommended treatment of invasive pulmonary aspergillosis (IPA)?

IMMUNE DYSFUNCTION

Note: The following is covered in more depth in the [Infectious Disease](#) and the [Allergy & Immunology](#) sections.

Bacterial pneumonia is the most frequent cause of death in immunodeficient patients. Mortality is 50%.

Humoral dysfunction: B-cell dysfunction or decreased antibodies are seen in most patients with ALL, CLL, and multiple myeloma. These patients are especially susceptible to **encapsulated** organisms, including *S. pneumoniae*, *H. influenzae*, and meningococci.

Patients with hypogammaglobulinemia, asplenia, sickle cell, or abnormal complement also tend to acquire infections caused by the same encapsulated organisms.

Cell-mediated dysfunction: T-cell defects are seen in patients with AIDS, lymphoma, and uremia, post-organ transplant, and after use of steroids or alkylating agents. These patients are susceptible to infections caused by encapsulated bacteria, *Pneumocystis* (PJP), mycobacteria, viruses (CMV and HSV), fungi (*Cryptococcus*), *Legionella*, and *Nocardia*. Although the incidence of PJP has dramatically decreased with the use of prophylactic drugs and HAART, *Pneumocystis* is the 2nd most common cause of pneumonia in AIDS patients in developed countries (the 1st is bacterial pneumonia).

In some developing countries, TB is the most common pulmonary infection in AIDS. A minority of patients with ALL have a T-cell variant, and these patients may have a T-cell deficiency.

Neutrophil dysfunction is seen in AML, CML (the **myelogenous** leukemias), bone marrow transplant, and patients who are otherwise getting ablative chemotherapy. These patients tend to get infections with gram-negative organisms, *Staphylococcus* species, *Corynebacterium jeikeium*, and fungi (*Candida* and *Aspergillus*).

ORGAN TRANSPLANT

Organ transplant patients get the same infections as patients with T-cell defects. Briefly:

- During the **first 30 days**, the immune system is still working, and patients most commonly get the usual nosocomial and surgery-related infections. Common lung infections are **gram-positive and gram-negative** pneumonias.
- During the first **1–6 months**, opportunistic infections start appearing. Lung infections during this period especially include CMV, *Pneumocystis*, *Aspergillus*, and *Cryptococcus*.
- **After 6 months**, infections are more likely to be community acquired.

Think of CMV if there is a mixed bag of “-itises” because patients often get concurrent pneumonitis, hepatitis (generally mild), and adrenalitis, leading to adrenal insufficiency!

Diagnosis: Finding inclusion bodies on BAL **suggests** CMV colonization. Finding inclusion bodies on a tissue sample (lung biopsy) **confirms** invasive CMV disease. Also, use CMV serology and blood PCR to guide management.

Treatment: Ganciclovir. Can consider adding IV CMV immunoglobulin if no response occurs.

See the [Allergy & Immunology](#) section for more on post-transplant infections.

MYELOPROLIFERATIVE DISORDERS

If a patient with a myeloproliferative disorder gets a localized infiltrate, it is typically caused by a **gram-negative bacterial** pneumonia. Treat it empirically.

LUNG PATHOGENS IN THE IMMUNOSUPPRESSED

Bacterial Pneumonia

Bacterial pneumonia, usually due to *S. pneumoniae* or *H. influenzae*, occurs in HIV/AIDS patients with **CD4 counts ~ 300 cells/ μ L** (0.3×10^9 cells/L)—higher than those with PJP. HIV-positive patients have a 6× increased risk of pneumonia and a **100×** increased risk

of bacteremia with pneumococcus compared to HIV-negative individuals. When considering a pneumonia diagnosis in a patient with risk factors for HIV, think about PJP and pneumococcus.

***Pneumocystis jiroveci* Pneumonia (PJP)**

PJP, a.k.a. PCP and *Pneumocystis* pneumonia, is the most common opportunistic infection in AIDS patients. A history of PJP and/or a CD4 count of < 200 cells/ μ L (0.2×10^9 cells/L; or 14% of all T cells by flow cytometry) confers the greatest risk. The incidence of PJP in patients who are adherent to both antiretroviral therapy (ART) and PJP prophylaxis is near zero.

Patients with PJP present with indolent, progressive dyspnea and cough with scanty sputum (+/- fever). Think about PJP in any HIV+ patient with pulmonary symptoms. Oxygen desaturation with or without ambulation may be present. Chest x-ray typically shows diffuse, bilateral, symmetrical interstitial and alveolar infiltrates. CT can be helpful if the diagnosis remains unclear; if CT reveals no findings, diagnosis of PJP is unlikely.

PJP is diagnosed with sputum or BAL examination using dye-based stains, fluorescent antibody stains, or PCR assays.

Treatment: TMP/SMX (by IV or PO) is the preferred 1st line agent. Alternatives include atovaquone, dapsone/TMP, or clindamycin/primaquine and IV pentamidine. The latter 2 can be used in severe disease if unable to use 1st line therapy. A majority of PJP patients improve on the initial course of therapy (usually 3 weeks' duration), but a good number have intolerable side effects from the treatment (e.g., rash and bone marrow suppression with TMP/SMX).

Give steroids to PJP patients with a $P_aO_2 < 70$ mmHg or an A-a gradient > 35 mmHg. Corticosteroids given concomitantly with the initiation of anti-PJP treatment reduce the likelihood of respiratory failure and death in patients with moderate-to-severe pneumonia.

Remember to check for G6PD deficiency if you prescribe dapsone or primaquine.

Mycobacteria

For TB disease in HIV/AIDS, the treatment is largely the same as for any other patient (refer to the discussion of [Treatment for LTBI on page 6-70](#)) except the following: rifabutin may be required for those on specific HAART regimens, intermittent treatment is not recommended, and a weekly rifapentine-based continuation regimen is not recommended. Most AIDS patients with TB come from areas where there is already a high prevalence of TB.

The most effective treatment for NTM (*M. avium* complex [MAC]) is to get the CD4 count > 100 cells/ μ L (0.1×10^9 cells/L; with ART) and to initiate combination

therapy against MAC—typically using clarithromycin or azithromycin with rifabutin and ethambutol.

Fungi

Aspergillus

Aspergillus can cause invasive disease in patients with AML, ALL, Hodgkin disease, heart or bone marrow transplant, chronic corticosteroid use, and granulocytopenia lasting > 25 days (slow growing!). Occasionally, we see this disease in AIDS patients.

Sputum cultures growing *Aspergillus* are usually ignored in patients with competent immune systems because *Aspergillus* is often found incidentally in normal sputum.

The spectrum of *Aspergillus* disease depends on the immune system of the patient and includes aspergilloma, invasive sinusitis, invasive pulmonary aspergillosis (IPA), and hematogenous dissemination to various organs (the most severe manifestation).

IPA once was one of the most-feared complications of treating hematologic malignancies because of a very high mortality rate. Improved antifungal therapy and preventive prophylaxis in high-risk patients have reduced the mortality rate from IPA in this population.

IPA presents as either an acute or an indolent pulmonary syndrome of fever, cough, dyspnea, and occasional hemoptysis in a severely immunocompromised patient. Occasionally, no symptoms are present in marrow transplant patients because they lack any immune response. Chronic necrotizing pulmonary aspergillosis may occur in patients with severe COPD treated with systemic steroids.

Diagnosis of IPA requires quick recognition of the clinical picture, HRCT of the chest (the buzzword is “halo sign,” which is a hemorrhage surrounding a nodule, signifying early evidence of pulmonary infarction), and lab tests. Lung samples can be obtained and cultured—sometimes the organism is visible in path specimens and grows in culture. Galactomannan is a polysaccharide that is a major component of *Aspergillus* cell walls. Because it is a water-soluble carbohydrate, it is found in blood, urine, CSF, and BAL of infected patients. This aids in the diagnosis of aspergillosis. Know that piperacillin/tazobactam contains a significant amount of galactomannan antigen and may cause a false-positive test. β -D-glucan, a component of most fungal cell walls, is also used to diagnose invasive fungal infection by blood test.

Treatment of *Aspergillus* infections depends on the form of disease:

- IPA in the immunosuppressed: IV voriconazole +/- an echinocandin. Liposomal amphotericin B or isavuconazole is an alternate if the patient cannot tolerate voriconazole.

- Chronic pulmonary disease: PO itraconazole or voriconazole
- Rhinosinusitis: surgery + antifungal (lipid amphotericin B, voriconazole, or isavuconazole)

Cryptococcus

Cryptococcal pulmonary disease is linked with Hodgkin lymphoma, corticosteroids, and transplants but **not** with PMN defects or neutropenia. Chest x-ray may show nodules or mass lesions. *C. neoformans* in sputum **indicates** infection (contrary to *Aspergillus*). Needle aspiration and lung biopsy are also an accurate means of diagnosing cryptococcal pneumonia. If found, perform a lumbar puncture to evaluate for CNS infection.

Patients with HIV/AIDS and **CD4 counts < 100 cells/μL** (0.1×10^9 cells/L) are especially susceptible to cryptococcal meningitis.

Coccidioides

Coccidioides immitis is endemic in the southwestern U.S. (particularly California and Arizona). Most immunocompetent patients with infection are asymptomatic or develop a **mild** flu-like illness that is self-limited. Disseminated or chronic infections are most common in patients with myeloproliferative disorders, Hodgkin lymphoma, transplants, and AIDS.

Histoplasma

Disseminated histoplasmosis is common in AIDS patients with CD4 counts < 100 cells/μL (0.1×10^9 cells/L) who live in endemic areas, such as the southern and midwestern U.S. and the Caribbean. It is especially found in the Mississippi and Ohio River valleys.

Nocardia

Nocardia asteroides lung infections are usually seen in T-cell deficient patients (not those with humoral deficiency) and in patients with pulmonary alveolar proteinosis. The pulmonary lesions may cavitate. Brain abscesses and subcutaneous dissemination can occur. This is treated with sulfonamides.

Candida

Candida pneumonia is **very rare and difficult** to diagnose in markedly immunosuppressed patients. *Candida* in the sputum is nonspecific and almost always signifies colonization.

Mucormycosis

Patients with **leukemia** are at especially high risk of pulmonary mucormycosis. It is also seen in uncontrolled **diabetics** with frequent DKA. This infection has a **poor** prognosis.

Reactivation Infections

TB, toxoplasmosis, HSV, cryptococcosis, histoplasmosis, and strongyloidiasis can reactivate in the immunosuppressed.

NONINFECTIOUS INFILTRATES

PREVIEW | REVIEW

- Name some causes of noninfectious pulmonary infiltrates.

Drugs may have cytotoxic or noncytotoxic lung effects:

- Methotrexate is the most common cause of **noncytotoxic** lung reactions and causes a hypersensitivity interstitial pneumonitis.
- Bleomycin is the most common cause of cytotoxic pulmonary toxicity.
- Gold-induced lung disease is reversible—just stop the drug.
- Amiodarone, bleomycin, and the nitrosoureas all cause **dose-related** pulmonary interstitial disease (while almost all other offending drugs have a hypersensitivity or idiosyncratic effect). Amiodarone may also cause an idiosyncratic reaction manifested in the lung. Uremia, supplemental O₂, and radiation therapy exacerbate bleomycin lung toxicity. Lung biopsy is the diagnostic procedure of choice, but it is typically not needed.
- **Crack** cocaine can cause a hypersensitivity pneumonitis, diffuse alveolar hemorrhage, infarctions, and COP.

Hemorrhage is **common** in patients with **AML**—it can be the **sole** cause of pulmonary infiltrates in these patients. But remember: In AML, rule out *Aspergillus* infection as the cause of the hemorrhage. (Also remember, hemorrhage may be caused by idiopathic pulmonary hemosiderosis, Goodpasture's, and SLE and can occur after bone marrow transplantation.)

Leukemic noninfectious pulmonary infiltrates most commonly occur in **ALL**, and they **always** imply a high percentage of blasts. Leukostatic infiltrates (globs of WBCs in the pulmonary **vessels**) occur in myeloid leukemias when the WBC count is > 100,000 cells/μL and can cause dyspnea and hypoxia. 50% of **lymphoma** patients have infiltrates.

Radiation changes in the lung usually present **within 6 months** of treatment. These changes are divided into 2 phases, with **radiation pneumonitis** occurring within 6 weeks. Radiation changes (pneumonitis/fibrosis) have a characteristic chest CT appearance with **sharp boundaries** corresponding to the field of radiation exposure.

CRITICAL CARE

PREVIEW | REVIEW

- Characterize the acute respiratory distress syndrome (ARDS) Network approach to fluid management in patients with ARDS.
- Describe the ventilator-induced lung injury that can happen when treating ARDS.
- What is considered the optimal ventilator setting TV for ARDS?
- Describe the specifics of permissive hypercapnia.
- Discuss the different modes of mechanical ventilation.
- Name the DESAT causes of failure to wean.
- What are the 2 categories of actions to keep in mind when adjusting a ventilator?
- When should you use PEEP?
- A patient with severe chronic obstructive pulmonary disease is placed on the ventilator. She suddenly becomes hypotensive. What steps do you follow to stabilize her?
- What is the best route to provide nutrition for a mechanically ventilated patient?
- What is refeeding syndrome and how is it prevented?
- Discuss the potential complications of pulmonary artery catheters.
- Predict pulmonary artery catheter values in hypovolemic shock and in cardiogenic shock. See [Table 6-16 on page 6-85](#).
- A patient presents with *E. coli* sepsis. Predict cardiac output, wedge pressure, and SVR in relation to normal values. See [Table 6-16 on page 6-85](#).

ACUTE RESPIRATORY DISTRESS SYNDROME (ARDS)

ARDS is hypoxemic acute respiratory failure due to bilateral inflammatory lung injury with bilateral non-cardiogenic pulmonary edema.

ARDS can have a **direct** or **indirect** precipitating event. **Direct** causes include aspiration, pneumonia, and inhalation injuries. **Indirect** events are sepsis, pancreatitis, multiple transfusions, and trauma. Aspiration and sepsis are the most common. Risk of ARDS increases with multiple precipitating events.

Diagnosis

The 2012 Berlin Conference definition of ARDS has replaced the 1994 American European Consensus Conference definition.

The Berlin definition eliminates the acute lung injury (ALI) category and categorizes ARDS as mild, moderate, or severe based upon the ratio of P_aO_2/F_iO_2 and the response to applied positive end-expiratory pressure (PEEP).

The Berlin definition requires that all of the following 4 criteria are met for diagnosis of ARDS:

- 1) Onset of respiratory symptoms within **1 week**
- 2) Chest x-ray or lung CT findings consistent with **(noncardiogenic) pulmonary edema**—not otherwise explainable
- 3) Increased hydrostatic pressure is ruled out (by echocardiogram if needed) so that the respiratory failure cannot be fully explained by increased hydrostatic pressure from fluid overload or cardiac failure.
- 4) Moderate-to-severe hypoxemia—the degree of hypoxemia defines severity. By definition, in a patient on a ventilator with $PEEP \geq 5$ cm H_2O :
 - **Mild ARDS:** $P_aO_2/F_iO_2 > 200$ but ≤ 300
 - **Moderate ARDS:** $P_aO_2/F_iO_2 > 100$ but ≤ 200
 - **Severe ARDS:** $P_aO_2/F_iO_2 \leq 100$

As shown above, P_aO_2/F_iO_2 is the ratio of P_aO_2 in mmHg over F_iO_2 as a decimal (0.21–1.00).

ARDS mnemonic:

- **Acute** onset
- **R**estrictive lung mechanics from pulmonary infiltrates
- **D**iffuse panendothelial inflammatory injury manifested in the lungs—i.e., not due to hydrostatic pressure
- **S**hunt hypoxemia—The degree of hypoxia defines severity of ARDS.

There is typically a **48–72-hour** lag time between the injury and ARDS; it is quicker with neurologic insults and trauma-related lung injury. All of the factors that lead to the leaky lungs in ARDS are still unknown. Injury results in local edema with subsequent fluid accumulation in the interstitium and the alveoli, compounded by the presence of inflammatory cells and their mediators. The inflammation causes chaos and heterogeneous disease in the lungs, from microthrombi clots in local vessels to aggregates of protein, surfactant, and cellular debris that clog up the alveoli in whorls. Inflammatory cells invade the interstitium and alveoli *en masse*, releasing more mediators. Eventually, large sections of lung simply collapse, resulting in massive shunting and hypoxemia. The microthrombotic occlusion of pulmonary vessels leads to nonperfusion of ventilated areas, causing dead space and hypercapnia—in addition to severe hypoxemia ([Figure 6-32](#) and [Figure 6-33](#)).

Patients initially present with symptoms of the underlying cause with dyspnea, increased work of breathing, and eventual respiratory fatigue.



Figure 6-32: Anteroposterior chest showing ARDS
Source: Vinay Maheswari, MD

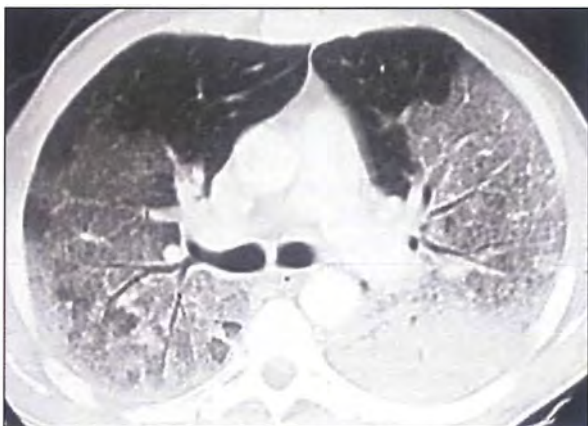


Figure 6-33: CT chest showing ARDS
Source: Vinay Maheswari, MD

With supportive care, patients improve and enter a proliferative phase, during which their lungs repair and organize. Usually, this is when they can be weaned from ventilator support. A few patients go on to develop mild fibrosis as part of healing and remain ventilator- and/or oxygen-dependent for a prolonged period. A restrictive pattern may be detectable on pulmonary function tests (PFTs) even after a year. As yet, there is no prophylaxis for ARDS.

The death rate is 25–58% and has decreased with the use of lung-protective ventilatory support strategies and improved critical care support. The most common cause of death within the first 3 days after the onset of ARDS is the underlying problem! Respiratory failure is not the most common cause of death in ARDS patients after 3 days; it's nosocomial pneumonia and sepsis.

Making the diagnosis of pneumonia in the patient with ARDS is difficult because infiltrates and leukocytosis are common in ARDS. Bronchoscopy is only performed if the diagnosis is uncertain or if a specific diagnosis is

entertained (e.g., controlled mechanical ventilation [CMV] or *Pneumocystis jiroveci* pneumonia [PJP]) and therapy is altered by bronchoscopy results. Give antibiotic therapy as indicated by Gram stain, culture, and sensitivity results.

Treatment

Prevention of pneumonia and other complications of critical illness in a patient with ARDS is important. Adequate hand washing and using sterile technique are mandatory.

Treatment of ARDS: Treat the underlying condition and provide optimized cardiopulmonary support. If the patient has an undrained abscess in the abdomen or elsewhere, encourage surgeons to remove it or use interventional radiology to drain it. Give empiric antibiotics if sepsis is the suspected cause.

Keep patients slightly hypovolemic. **However**, it is very important to provide enough volume to maintain adequate cardiac output and tissue oxygen delivery. The goal is to prevent worsening lactic acidosis and the resultant multiorgan failure.

The ARDS Network FACT trial (data released in 2006) demonstrated that conservative fluid replacement (targeting normal central venous pressure [CVP], pulmonary artery occlusion pressure [PAOP], and hemodynamic function) was better than a liberal strategy; less (fluid) is more (beneficial). It led to decreased ICU and ventilator time and decreased organ dysfunction. Mortality, however, was similar. This trial also concluded that management with CVP is as good as using a pulmonary artery catheter. This fluid algorithm can be found at ardsnet.org/tools.shtml.

Nutrition should be **enteral** rather than parenteral, if possible. This reduces the risk of catheter-induced sepsis and may also prevent the translocation of endotoxin and gram-negative colonic bacteria. Special formulas high in omega-3 fatty acids have not shown benefit in ARDS and septic shock and are discouraged.

Ventilator Support for ARDS

PEEP stands for **positive end-expiratory pressure**. On the ventilator, a valve shuts when the patient is near end-expiration, while there is still positive intrathoracic pressure.

ARDS displays shunt physiology. The best way to improve oxygenation is to recruit, or “pop open,” atelectatic and fluid-filled alveoli. At the same time, you want to avoid barotrauma and oxygen toxicity. To avoid oxygen toxicity, try to get a P_aO_2 of 60 mmHg with $F_iO_2 < 60\%$ ASAP. To pop open alveolar units, use PEEP. To avoid ventilator-induced lung injury (VILI), use **adequate but not excessive** PEEP (i.e., the minimum level of PEEP that allows an adequate mean arterial pressure (MAP) and a safe F_iO_2 of 60%).

When managing ventilators, keep in mind the potential for VILI, which arises from overdistended alveoli (from an increased tidal volume [TV] or an increased end-inspiratory plateau pressure) and the cyclic opening and closing of atelectatic alveoli (recruitment-derecruitment). An adequate level of PEEP prevents repetitive closure and opening of lung units.

Recommendations from 2000 from the NIH ARDS Network (and reconfirmed with a Cochrane analysis in 2013) indicate improved outcome with low TVs = 6 mL/kg and PEEP at adequate levels. (Lung protective ventilatory support strategy is discussed later under this topic.) Initiating low TVs early in the course of the disease appears to be critically important, and 6 mL/kg is considered the optimal TV. Generally, we start worrying about VILI due to excessive plateau pressures at > 30 cm H₂O.

Previously, TVs in the range of 12–15 mL/kg had been used, but this is too high for many patients with ARDS because their TLC is much smaller than normal. There is a trend to lower TVs in all patients on ventilators, whatever the cause (although there is no strong data to support a benefit, as there is in ARDS).

No single ventilator mode has proven better than another for ARDS patients. An assist-control, volume-cycled ventilator mode was used in the ARDS Network trial.

Initial settings:

- $F_iO_2 = 1$ (then follow a P_aO_2 goal as per Figure 6-34)
- TV = Start at 6 mL/kg of the ideal body weight (IBW). Monitor end-inspiratory plateau pressure! Maintain it at ≤ 30 cm H₂O.
- Inspiratory flow = Start at 60 L/minute.
- PEEP: See Figure 6-34. The PEEP is determined using a nomogram of F_iO_2 and achieving the P_aO_2 goal of 55–80 mmHg.
- Some physicians use a PEEP pressure just greater than the lower inflection point on the ventilator pressure-volume (PV) curve. Yet others use an empiric regimen, in which they adjust the PEEP to maintain an adequate S_aO_2 of at least 90% and a low enough F_iO_2 (< 60%). PEEP typically starts at ≤ 5 cm H₂O and usually goes up to 10–20 cm H₂O. For more information, see Positive End-Expiratory Pressure (PEEP) on page 6-82.

Novel therapies (e.g., granulocyte-macrophage colony-stimulating factor [GM-CSF], stem cells, nitric oxide, surfactant, ketoconazole) have not been demonstrated to improve survival.

A meta-analysis demonstrated a survival benefit from prone positioning, a.k.a. proning. The 2013 large PROSEVA multicenter trial demonstrated a survival

benefit with early initiation of prolonged (16 hours) proning. Issues around proning:

- Data supports increasing the P_aO_2/F_iO_2 ratio with prone positioning, which stabilizes the anterior chest wall, causing improved physiology and recruitment of previously unused alveolar units.
- The prone position was found to get the heart off of the left lower lobe and help with expansion.
- The prone position can cause pressure necrosis complications of the face and anterior body surfaces. In fact, if the ICU team is not experienced with prone positioning, bad things can happen (e.g., extubation, venous catheters fall out, blindness, even fractures). Well trained ICU staff is paramount for successful prone positioning success. Specialty beds are not required for successful proning maneuvers.

No clear mortality benefits exist with the empiric use of neuromuscular blockade.

Permissive hypercapnia: The ARDS Network low TV lung-protective ventilatory support protocol is the standard of care for ventilatory support in patients with ARDS. The study results demonstrated a mortality decrease. More specifically, some evidence suggests that respiratory acidosis may decrease lung injury and be protective. Permissive hypercapnia is acceptable in patients with ARDS. However, most nonparalyzed patients with ARDS on assist/control mode maintain a satisfactory minute ventilation.

The goal in a patient with ARDS is to maintain adequate tissue oxygenation—maintaining the $S_aO_2 > 88\%$. Do not worry so much about the P_aCO_2 . Allow hypercapnia to develop. The resultant acidosis can be corrected by any of the following:

- Increasing the respiratory rate (RR)
- Increasing the TV if the end-inspiratory plateau pressure is low
- Using NaHCO₃

Remember: Giving NaHCO₃ typically results in a subsequent increase in CO₂ as $NaHCO_3 + H^+ \leftrightarrow Na^+(Cl^-) + H_2O + CO_2$.

Renal compensation for the respiratory acidosis usually ensues, and typically you do not need to give an alkali or increase the minute ventilation. Permissive hypercapnia is acceptable in severe exacerbations of obstructive lung disease as well. Again, the therapy-determining measurement is the S_aO_2 , not the P_aCO_2 .

Permissive hypercapnia is not recommended in patients with intracranial hypertension or hemodynamic instability.

Trials show no proven survival advantage in the following treatments for ARDS: early high-frequency oscillation, surfactant administration, NSAIDs, antiendotoxin therapy, inhaled nitric oxide, and IV N-acetylcysteine (as an antioxidant).

NIH NHLBI ARDS Clinical Network Mechanical Ventilation Protocol Summary (Part I)

INCLUSION CRITERIA: Acute onset of

1. $P_aO_2/F_iO_2 \leq 300$ (corrected for altitude)
2. Bilateral (patchy, diffuse, or homogeneous) infiltrates consistent with pulmonary edema
3. No clinical evidence of left atrial hypertension

PART I: VENTILATOR SETUP AND ADJUSTMENT

1. Calculate predicted body weight (PBW).
Males = $50 + 2.3 [\text{height (inches)} - 60]$
Females = $45.5 + 2.3 [\text{height (inches)} - 60]$
2. Select any ventilator mode.
3. Set initial TV to 8 mL/kg PBW.
4. Reduce TV by 1 mL/kg at intervals ≤ 2 hours until TV = 6 mL/kg PBW.
5. Set initial rate to approximate baseline minute ventilation (not > 35 bpm).
6. Adjust TV and RR to achieve pH and plateau pressure goals below.

OXYGENATION GOAL: P_aO_2 55–80 mmHg or SpO_2 88–95%

Use incremental F_iO_2 /PEEP combinations below to achieve goal. [Note: Higher PEEP options (lower row) will decrease F_iO_2 and may be preferred in patients with high F_iO_2 who can tolerate higher PEEP (stable blood pressure, no barotrauma). Survival is similar with both PEEP approaches.]

F_iO_2	0.3	0.4	0.4	0.5	0.5	0.6	0.7	0.7
PEEP	5	5	8	8	10	10	10	12
	12–14	14	16	16	18–20	20	20	20

F_iO_2	0.7	0.8	0.9	0.9	0.9	1.0	1.0	1.0
PEEP	14	14	14	16	18	20	22	24
	20	20–22	22	22	22	22	22	24

PLATEAU PRESSURE GOAL: ≤ 30 cm H₂O

Check Pplat (0.5 second inspiratory pause) at least q 4h and after each change in PEEP or TV.

If Pplat > 30 cm H₂O: Decrease TV by 1 mL/kg steps (minimum = 4 mL/kg).

If Pplat < 25 cm H₂O and TV < 6 mL/kg, increase TV by 1 mL/kg until Pplat > 25 cm H₂O or TV = 6 mL/kg.

If Pplat < 30 and breath stacking or dys-synchrony occurs: may increase TV in 1 mL/kg increments to 7 or 8 mL/kg if Pplat remains < 30 cm H₂O.

pH GOAL: 7.30 – 7.45

Acidosis Management: (pH < 7.30)

If pH 7.15–7.30: Increase RR until pH > 7.30 or $P_aCO_2 < 25$ (Maximum RR = 35).

If pH < 7.15 : Increase RR to 35.

- 1) If pH remains < 7.15 , TV may be increased in 1 mL/kg steps until pH > 7.15 (Pplat target may be exceeded).
- 2) May give $NaHCO_3$.

Alkalosis Management: (pH > 7.45)

Decrease vent rate if possible.

Figure 6-34: NIH NHLBI ARDS Clinical Network Mechanical Ventilation Protocol summary

To summarize, when using the ventilator in the treatment of ARDS, avoid VILI and oxygen toxicity by doing the following:

- Start the TV at 6 mL/kg of the IBW. Keep plateau pressure ≤ 30 cm H₂O.
- Start the F_iO_2 at 1 and follow the recommendations set by the ARDS Clinical Network (Figure 6-34).
- Use adequate but not excessive PEEP.
- Use permissive hypercapnia if needed.
- Use the mentioned ARDS Network PEEP dosing tables (on ardsnet.org/tools.shtml and reproduced in Figure 6-34) as guidelines but adjust it as necessary to meet the needs of the individual patient.

Corticosteroids for ARDS

The pendulum has swung away from the use of steroids solely for ARDS inflammation. If steroids are used, start early (first 14 days) in moderate-to-severe ARDS.

SEPSIS

Sepsis, as defined in the 2016 Third International Consensus Definitions for Sepsis and Septic Shock (SEPSIS 3) guidelines, is life-threatening organ dysfunction caused by a dysregulated host response to infection. Sepsis is not a specific illness, it is a constellation of clinical signs and symptoms. As such, there is no gold standard diagnostic test. Sepsis and how it evolves in a patient is shaped by pathogen and host factors and how the host responses are amplified. Comorbidities, age, medications, and interventions influence the host responses and the sepsis syndrome.

Septic shock is defined as hypotension (MAP < 65 mmHg), hyperlactatemia, and the need for a vasopressor despite fluid resuscitation.

The Sequential Organ Failure Assessment (SOFA) Score assesses various organ systems, and in each category a score is created with morbidity implications. A SOFA score of at least 2 in conjunction with septic shock predicts a mortality of 40%. SOFA score items include assessment of:

- P_aO_2/F_iO_2 ratio
- Mechanical ventilation
- Platelets
- MAP
- Vasopressor requirement
- Bilirubin
- Glasgow Coma Scale
- Creatinine

Shock from sepsis confers a higher mortality than from nonsepsis etiologies. Prompt evaluation and potential treatment intervention are indicated. Obtain blood and other cultures, as well as lactate and other labs to help explain the findings.

The 2018 Surviving Sepsis guidelines outline correct sepsis management. They dropped protocolized treatment as well as empiric dual antibiotics for *Pseudomonas*. Initiate fluid resuscitation with 30 mL/kg of IV balanced crystalloid if hypotensive or lactate ≥ 4 mmol/L. The patient may require additional fluid when reassessed for volume responsiveness. If the patient has refractory hypotension, administer vasopressor therapy. Use of central venous pressure (static) measurements or pulmonary artery catheters to guide fluid management are no longer routinely recommended. Dynamic measures of fluid responsiveness such as passive leg raise, pulse pressure variation, and stroke volume variation are recommended instead. Effective fluid resuscitation can improve lactate clearance and can be used as a marker of improvement. Lactate should be obtained on initial evaluation and then 4 hours later if > 2 mmol/L.

Early antibiotic administration is a high priority and should be done preferably within the 1st hour and has shown to decrease hospital mortality in a linear fashion. Optimally, obtain cultures 1st and achieve source control of the sepsis. However, these efforts should not delay early antibiotic administration within the 1st hour of sepsis recognition. Give broad-spectrum empiric antibiotics targeting the likely source and cause of infection, usually vancomycin and gram-negative coverage. These can be tailored and then deescalated as cultures and other studies return and the patient improves.

Vasopressors are used for patients who remain hypotensive despite adequate fluid resuscitation. The 1st line recommended vasopressor is norepinephrine (2–12 mcg/minute, though there's no true ceiling). Epinephrine or vasopressin can be added if fluid and norepinephrine are insufficient to support blood pressure. The target MAP is ≥ 65 mmHg. For persistent hypotension, consider reevaluation for other causes, and an echocardiogram can be helpful. This may indicate whether inotropic support is needed. Steroids may be considered for those with refractory hypotension or those who have had exogenous steroids recently that might lead to adrenal suppression.

Critically ill patients (especially patients with sepsis +/- ARDS) can have a **normal** P_aO_2 and still have **abnormal** O_2 uptake by the tissues. This is thought to be a major contributor to multiple organ failure.

Be careful! **Mixed venous** O_2 may be **misleading** in the septic patient because there is significant peripheral shunting. Lactic acid levels may be misleading as an indicator of tissue hypoxia because an increase can also be caused by the liver's failure to clear it. Nevertheless, the lactic acid measurement and clearance is used in the decision-making of the Surviving Sepsis Campaign.

Always correct the underlying problem. Source control may require surgery or drainage of a focal infection, or removal of a catheter or line, **even if** the patient is **unstable**.

As previously stated, the utility of invasive monitoring in most cases of sepsis is highly questionable. A 2014 multicenter trial by the European Society of Intensive Care

Medicine demonstrated that CVP-guided fluid management is not needed. The use of pulmonary catheters in the medical ICU increases mortality; as a result, routine use has declined precipitously. If a pulmonary catheter is used, remember the following general principles regarding pulmonary capillary wedge pressure (PCWP):

- PCWP reflects left ventricular end diastolic pressure (LVEDP), and LVEDP is an indicator of LV function, reflecting compliance and stroke volume.
- Always read the PCWP at end-expiration.
- Read PCWP in all patients on a graphed wave form (not a digital printout).
- Never take the patient off PEEP to read the PCWP.

LVEDP is **often** determined **directly** during **left** heart catheterization just before contrast ventriculography (rather than during a right heart catheterization in the ICU). It is also checked when patients are being evaluated for causes of pulmonary hypertension.

Read more on PCWP in the [Cardiology](#) section.

INVASIVE MECHANICAL VENTILATION

Inflate the cuff of the endotracheal (ET) tube to the lowest possible effective pressure, ~ 15 mmHg. When the pressure exceeds ~ 25 mmHg, serious damage can occur to the tracheal mucosa.

The timing of a tracheostomy is controversial and takes into account specific patient variables and the likelihood of requiring prolonged ventilatory support. Typically, a tracheostomy is not performed during the 1st week of intubation (barring other indications). Tracheostomy is **not** indicated solely to decrease airway resistance during weaning.

VAP is a frequent complication of mechanical ventilation (see more under [VAP on page 6-63](#)). Here is a quick review: Almost all patients are colonized with gram-negative bacteria in the upper and lower airways within 74–96 hours of endotracheal intubation. It can be very difficult to sort out true pneumonia vs. colonization. Ventilator-associated tracheobronchitis (VAT) has also been described for those without infiltrates. The 2016 Infectious Disease Society of America/American Thoracic Society (IDSA/ATS) guidelines recommend against antibiotic treatment for VAT. For a diagnosis of pneumonia, you should see:

- New or worsening infiltrate
- Leukocytosis
- Purulent sputum or endotracheal secretions
- Fever or hypothermia

Noninvasive sampling is preferred to diagnose VAP. Cover both *Pseudomonas* and methicillin-resistant *Staphylococcus aureus* (MRSA) with empiric antibiotic treatment for VAP. In 2016, the CDC proposed a new definition for ventilator-associated events (VAE) that is used for objective, nonclinical surveillance purposes with events reported to the National Healthcare Safety

Network. A VAE is entered based on changes in oxygen or PEEP, changes in antibiotics secondary to changes in oxygenation requirements, fevers, elevation in white blood count, or purulent secretions.

Modes of Mechanical Ventilation

Continuous Ventilation

CMV has a set rate and a set TV that does not allow spontaneous breathing. Patient-ventilator asynchrony is a big problem. Therefore, this mode is best used in patients who are heavily sedated, under anesthesia, paralyzed with muscle relaxants, or in a deep coma.

Assist/control (AC) is CMV with a set rate and TV, but this mode allows the patient to initiate additional breaths “above the ventilator.” When the machine senses that the patient is attempting to take a breath (the pressure sensor detects a negative pressure inspiratory effort that exceeds a set threshold), it kicks in with a full machine-supported breath at the ordered TV. This is a commonly used mode of ventilation. One caveat: If patients are anxious, hyperventilating, or have obstructive lung disease, they continue to trigger additional full machine breaths, get even more hyperventilated, and are at risk for developing auto-PEEP. This usually occurs when the rate is $\geq$ the high teens to twenties.

Intermittent Ventilation

Intermittent mandatory ventilation (IMV) is similar to AC in that you dial in a set rate and TV, but spontaneous breaths at a patient-determined rate and TV can be taken between the set breaths. Because this spontaneous breath requires a lot of work from the patient to suck in a breath through the ET tube and the ventilator circuit, we often add pressure support ventilation to the IMV mode. Therefore, when the patient takes a spontaneous breath, there is a boost of pressure (you set the amount) to help overcome the resistance of the ET tube and the ventilator circuit. Typically, you use a pressure support of 5–20 cm H₂O, but you need to titrate this pressure for an individual patient after you see what kind of spontaneous TVs the patient can generate.

Note: The above volume-cycled ventilators have a pop-off valve set at a certain inflation pressure to prevent over-pressurization of the lungs.

Pressure Support Ventilation (PSV)

PSV, when used in a spontaneously breathing patient (no set TV or RR), supplies only pressure support, and there is no need for mandatory breaths. This is a very comfortable mode for the patient because he or she determines the rate, inspiratory time, and TV. However, you must have a patient with a stable respiratory drive (i.e., not heavily sedated and not paralyzed). More importantly, remember that there is no guarantee as to what TV will be generated at a specific level of pressure support (this will be influenced by airway resistance

and compliance of the respiratory circuit and system). If your patient is prone to—and develops—acute HF, the lungs may acutely become stiffer, or less compliant, and for a given level of pressure support a smaller TV will be delivered, potentially causing tachypnea and respiratory distress. The inspiratory pressure can be increased while the underlying cause is addressed.

Pressure Control Ventilation (PCV)

PCV is a form of ventilation that is actually a throwback to the first ventilators. In this mode, machine breaths are pressure cycled, not volume cycled. You determine the pressure you want the patient to receive on each breath, inspiratory/expiratory ratio, and the rate at which the breaths are delivered. If the patient attempts a spontaneous breath, they get a machine breath at the pressure you have designated.

This may be helpful in limiting airway pressures in patients with high-end inspiratory plateau pressures in other volume-cycled modes that leave them susceptible to barotrauma. Use of this mode lets you use a low TV and a high PEEP strategy for ARDS, because the peak inspiratory pressure is lower on PCV than on AC for any given achieved TV. As with PSV, the TV varies with airway resistance and respiratory compliance. Hence, this mode must be titrated carefully and monitored at the bedside to determine the proper pressure settings and achieved TV.

Weaning and Failure to Wean

Weaning is best accomplished by using protocols. Generally, weaning is performed as the patient stabilizes ($F_iO_2 \geq 40\%$, minimal vasopressor requirements, adequate mentation) and combines a spontaneous awakening trial (sedation/analgesia is reduced to allow the patient to awaken) with a subsequent spontaneous breathing trial (SBT):

- 1) SBT protocols have the patient breathe at low levels of pressure support for 30–120 minutes to see how the patient tolerates spontaneous breathing with no or minimal assistance from the ventilator. The respiratory frequency and minute ventilation are monitored along with the patient's vital signs, respiratory effort, and pattern. If the patient has a suitable cough to protect their airway and secretions expectorated are deemed to be manageable by the patient, they can be extubated. The rapid shallow breathing index or RSBI (RR per minute/TV in liters) can help predict weaning failure. If the RSBI is > 105 breaths/minute the predicted weaning failure rate is increased. The SBT can also be performed on patients who have a tracheostomy in place.
- 2) Patients who are difficult to wean may be subsequently weaned by using pressure support trials with progressive reduction in the amount of pressure support until they are able to tolerate an SBT.

Possible causes of failure to wean (DESAT) include:

- Drugs (e.g., sedatives). Sedation or altered mental status is one of the most common reasons for failure to wean.
- Endotracheal tube and electrolyte imbalances. Sometimes the intraluminal diameter of the tube is too small. Over time, it is common for ET tubes to decrease in diameter due to secretions and biofilms adhering to the internal lumen. Automatic tube compensation is a ventilatory mode that dynamically compensates for the increased resistance of the ET tube, thereby making the final stages of weaning more predictable. Hypocalcemia, hypophosphatemia, and hypomagnesemia all impair weaning.
- Secretions
- Alkalemia (which decreases the respiratory drive)
- Too high or too low a $P_a\text{CO}_2$ just before extubation (Keep these parameters near the patient's baseline.)

There is potential danger in suddenly switching from positive pressure ventilation in patients with limited cardiac function or occult cardiac ischemia to full spontaneous breathing: stopping positive pressure ventilation → increased venous return → increased cardiac filling pressures → need for increased cardiac output → HF or cardiac ischemia in susceptible patients. These patients are often treated with diuresis and even IV nitroglycerin in order to temporarily lower the preload.

Chronic obstructive pulmonary disease (COPD) patients with chronic respiratory failure are less able to get rid of CO_2 , so intubation with a larger-bore endotracheal tube helps decrease airway resistance, and extubation to NiPPV improves outcomes. Also avoid overventilating a patient with COPD who is at baseline a CO_2 retainer. That is, adjust the minute ventilation ($\text{TV} \times \text{RR}$) to match the baseline $P_a\text{CO}_2$ (estimated or known from a blood gas).

Adjusting a Ventilator

Remember: When we are adjusting a ventilator to improve a patient's ABGs, we have to separate our actions into 2 categories:

- 1) Those that change alveolar or minute ventilation ($\text{TV} \times \text{RR}$) change the patient's $P_a\text{CO}_2$ and pH. Remember alveolar ventilation is inversely proportional to $P_a\text{CO}_2$. Alveolar ventilation = $(\text{TV} - \text{dead space}) \times \text{RR}$.
- 2) Those that alter a patient's oxygenation are F_iO_2 , PEEP, and inspiratory/expiratory ratio.

Positive End-Expiratory Pressure (PEEP)

PEEP is a positive pressure that remains in the chest at the end of exhalation. This can be done purposely to a patient on a ventilator by closing a valve during exhalation and not allowing the pressure in the airways to return to zero.

You dial in a PEEP pressure—the desired end-expiratory pressure—typically 5–15 cm H_2O (you can go higher in ARDS). The purpose of utilizing PEEP in mechanically ventilated patients is to help prevent the alveoli from completely collapsing at the end of expiration. This prevents atelectasis and, more importantly, leads to better matching of V/Q while having less of a shunt fraction. PEEP also prevents atelectrauma, which is damage caused by shearing forces that arise during repeated reexpansion of collapsed lung units.

Use higher levels of PEEP only with diffuse lung disease! It can actually decrease the $P_a\text{O}_2$ if used in focal lung disease. Use PEEP in cases of diffuse lung disease if required to maintain the $\text{F}_i\text{O}_2 < 60\%$, while keeping the $P_a\text{O}_2 > 60 \text{ mmHg}$.

An elevated PEEP can cause:

- Pneumothorax, ventricular failure, and alveolar damage, which can precipitate or worsen pulmonary edema. The PEEP level recommended in ARDS is based on a nomogram, as discussed previously. Some advocate using the lowest level of PEEP required to oxygenate the patient with a safe F_iO_2 (60%).
- Decreased venous return, causing decreased cardiac output and hypotension

Auto-PEEP

Auto-PEEP usually happens when the patients are not fully emptying their lungs during expiration prior to the initiation of the next breath. This is known as stacking breaths or generating auto-PEEP. The problem is the RR is too fast to allow complete emptying.

A patient on a ventilator gets auto-PEEP if the ventilator is set up in a way that does not allow the patient to fully exhale before initiating the next breath. This is particularly worrisome in patients who have exacerbations of COPD or who are in status asthmaticus. The auto-PEEP may become severe enough that the patient can suffer barotrauma, hypotension, or hemodynamic collapse secondary to the inability of venous return of blood to the heart.

Auto-PEEP can also occur in spontaneously breathing patients with obstructive lung disease and is responsible for creating dynamic hyperinflation, with all of the consequences of auto-PEEP combined with the increased work of breathing. On physical examination you hear the next breath come in before the exhalation is complete. You can see the potential for auto-PEEP by observing the flow waveform and noting an expiratory flow that does not return to the zero baseline before the initiation of the next breath.

Auto-PEEP can be measured in mechanically ventilated patients using either of the following 2 methods:

- 1) Insert an end-expiratory pause in the ventilator circuit and observe the airway pressure monitor during the pause.

- 2) Use ventilators that automatically measure this.
The pressure curve on the flat panel display does not return to the set PEEP level.

The treatment of auto-PEEP requires treatment of the underlying obstructive lung disease. More immediately, reduce the RR. The principle is to take action to shorten inspiration and lengthen the expiration. This can include the following interventions:

- 1) Decrease the RR, which is the primary effective intervention when there is significant auto-PEEP. This may require sedation if the patient is breathing over the ventilator.
- 2) Decrease the TV, which has minimal effect.
- 3) Increase the peak inspiratory flow rate (PIFR), which has a slight effect.
- 4) Treat bronchospasm and reduce airway secretions (if they are leading to increased airway resistance).

If a patient with severe airway obstruction has hypotension related to auto-PEEP **after** being placed on mechanical ventilation, perform the following steps:

- 1) Disconnect the patient from the ventilator and slowly bag the patient through the ET tube. Check for tension pneumothorax and mucous plugs and otherwise ensure that the ventilator is functioning properly.
- 2) Return the patient to the ventilator with new settings that allow for a longer expiratory phase, generally a lower RR. Specific changes include lowering the RR, increasing the inspiratory flow rate (shortening the time the patient gets for inspiration and, hence, allowing a longer time for expiration), and reducing the TV.

Note that the patient must be sedated or paralyzed to accurately measure the auto-PEEP.

As a historical reference, **inverse ratio** ventilation is a technique that was employed in patients with ARDS, whereby auto-PEEP was purposely generated as a mechanism for “recruiting” alveoli. It has fallen out of favor because of the significant potential for barotrauma, need for deep sedation, and no improvement in mortality.

NONINVASIVE VENTILATION (NIV)

NIV or NiPPV consists of a mask interface (either full face mask over the nose and mouth or nasal mask) and tubing connected to a device that can provide bilevel positive airway pressure (BiPAP) or continuous positive airway pressure (CPAP). CPAP can be used in pulmonary edema to improve oxygenation when there is no problem with ventilation (CO_2 is not markedly elevated), while BiPAP is used most commonly, because it will ventilate the patient (blow off CO_2) and oxygenate the patient. For BiPAP, both inspiratory pressure (IPAP) and expiratory pressure (EPAP) are ordered. The greater the difference between IPAP and EPAP, the more CO_2 will be blown off. Some devices allow

measurement of the achieved TV for given IPAP and EPAP settings. However, you can empirically start with IPAP of 10 cm H_2O and EPAP of 5 cm H_2O and increase these in order to ventilate more (increase IPAP) or oxygenate more (increase EPAP, but also some effect from IPAP).

NIV is utilized in spontaneously breathing, awake individuals who do not have a compromised airway but who are in respiratory distress. The indications are often COPD exacerbation, pulmonary edema, or other etiologies where the patient is expected to respond to acute therapy for a reversible cause. For some patients, NIV is not sufficient to meet their needs, such as those with severe gas exchange abnormalities, marked distress, developing lethargy, or intolerance for the mask interface. Intubate patients in marked respiratory distress, for whom NIV is not likely to be sufficient, or who have contraindications. Contraindications include vomiting, massive hemoptysis, intractable respiratory secretions, ongoing aspiration, poor respiratory drive, cardiac or respiratory arrest, inability to tolerate face mask or pressure, facial trauma, surgery or burns, esophageal or gastric surgery, or severe respiratory failure.

Support and manage NIV with the direct involvement of respiratory therapy. Adjustments may be needed at frequent intervals, and patients should be closely monitored by vital signs, oximetry, and blood gases. Patients started on NIV for respiratory failure are managed in a higher level of care, such as initially in the emergency department and then ICU. The patient should be monitored for deterioration that can happen rapidly and may require intubation.

NUTRITIONAL SUPPORT

Nutritional support in ICU settings is **extremely important** and often underemphasized. Use the **enteral route of nutrition** whenever possible. After major surgery or the onset of sepsis, metabolic requirements increase dramatically. Requirements peak in 3–5 days. If the patient is unable to eat, start enteral feedings (standard formula for most critically ill patients) **in the first 24–36 hours of ICU admission**. It reduces mortality and hospital length of stay. Even though enteral feeding increases the possibility of aspiration, it is preferred over total parenteral nutrition (TPN) because it tends to maintain the intestinal epithelium and its natural defenses against bacteria. TPN also has an increased risk of bacteremia and fungemia.

With enteral feeding, you can decrease the risk of aspiration and pneumonia by keeping the head of the bed elevated $\geq 30^\circ$. The position of the head is more important than where the feeding tube is placed (e.g., pre- vs. postpyloric). Per the 2016 ASPEN guidelines, do not check for gastric residuals in an asymptomatic patient. Routine supplements (e.g., omega-3 fatty acids, arginine, fiber) are not indicated. Prepyloric feeding is satisfactory; usually place postpyloric tubes in those with high risk of aspiration or intolerance to gastric feeding.

Refeeding syndrome occurs when severely malnourished patients; e.g., those with chronic alcoholism, anorexia nervosa, malignancies are fed high-carbohydrate loads (i.e., enteral tube feeds or IVF with glucose). These patients develop low total body levels of electrolytes, specifically phosphorus, Mg^{2+} , and K^+ .

With refeeding syndrome:

- There is a dramatic increase in circulating insulin levels and a resulting swift cellular uptake of glucose, phosphate, Mg^{2+} , and K^+ , resulting in a precipitous drop of these agents in the serum. The resulting severe **hypophosphatemia** (lack of ATP and 2-3-diphosphoglycerate) causes heart and respiratory failure, rhabdomyolysis, RBC and WBC dysfunction, seizures, and coma. Hypomagnesemia can result in arrhythmias, including torsades des pointes.
- Myocardial atrophy from prior starvation increases the propensity for acute heart failure secondary to Na^+ and water retention.

Prevent refeeding syndrome by starting the feeding of severely malnourished patients slowly and by aggressively replacing phosphate, Mg^{2+} , and K^+ .

SHOCK STATES

Shock is a circulatory systemic deficiency that leads to insufficient delivery of oxygen to tissues and may lead to organ dysfunction. There are different types of shock, including hypovolemic, cardiogenic, distributive, and obstructive. It is important to differentiate these.

Hypovolemic shock is due to loss of blood volume or dehydration. Hemorrhage from the GI tract, trauma, ruptured aortic aneurysm, or ruptured ectopic pregnancy cause hypovolemic shock. In addition, diarrhea, poor po intake, vomiting, polyuria, and excessive losses through sweating are other potential causes. Patients with this form of shock are hypotensive and tachycardic. The skin may be cold or clammy. There is low urine output. Volume resuscitation and transfusion, as well as correction of the underlying cause are indicated.

Cardiogenic shock is caused by failure of the pump function of the heart due to loss of myocardial contractility or loss of structural components of the heart. These include myocardial infarction, myocarditis, cardiomyopathy, valve failure, bradycardia, arrhythmia, or hypertrophic cardiomyopathy.

The patient is hypotensive and heart rate varies depending on the cause but is usually rapid and faint. The skin is cool and mottled, jugular venous pressure (JVP) is elevated, and crackles are present on the lung exam. Peripheral edema may be present.

Chest x-ray typically shows pulmonary edema, and there may be evidence of cardiomegaly. ECG may show acute or evolving ischemic changes or arrhythmia or may be normal. Cardiac enzymes may be elevated.

Echocardiography is essential and may show decreased ejection fraction, structural abnormalities, valvular disease, and other findings. In some cases, pulmonary artery (right heart) catheterization is done and generally shows an elevated PCWP (usually > 15 mmHg) and a reduced cardiac output/index.

Management generally includes diuretics, vasopressors, oxygen, and possible mechanical ventilation. In some cases, inotropic support with dobutamine or milrinone may be used. Short-term mechanical assist devices include intraaortic balloon pumps and LV assist devices. For patients with acute coronary syndrome, management includes aspirin, heparin, β -blocker, statin, and consideration for PCI or CABG. Thrombolytic therapy can be used if revascularization procedures are not done.

Distributive shock is most commonly caused by septic shock but may also result from noninfectious causes (e.g., acute pancreatitis, burns, bowel obstruction), anaphylaxis, drug reactions, transfusion reactions, neurogenic shock, liver failure, and toxic shock syndrome.

Pathophysiologically, there is direct vasodilatation due to circulating bacterial endotoxin, other exogenous substances or toxins, and/or circulating inflammatory mediators. In addition, there is loss of responsiveness of vascular smooth muscle to vasoconstrictors that maintain tone. There is often loss of capillary integrity with 3rd spacing of fluid.

Early in septic shock there is a hyperdynamic phase with tachycardia and hypotension, and skin is often warm and flushed. As shock progresses, there is hypoperfusion and often reduced cardiac contractility and skin is often cool.

Fluid resuscitation is indicated, and, for sepsis, vasopressor support. See [Sepsis on page 6-79](#).

Obstructive shock is due to blocked circulation in the great vessels or the heart, with decreased ventricular preload or increased ventricular afterload. Decreased ventricular preload may be due to increased intrathoracic pressure from tension pneumothorax, mechanical ventilation, or status asthmaticus; decreased cardiac compliance from constrictive pericarditis or cardiac tamponade; and direct venous obstruction from intrathoracic tumor. Increased ventricular afterload may result from acute pulmonary embolism, acute pulmonary hypertension, and aortic dissection.

Physical findings vary depending on the etiology but can include unilaterally decreased breath sounds and tracheal shift with tachycardia for tension pneumothorax. Findings of air trapping may be present. Patients with acute pericarditis and/or cardiac tamponade can have chest pain, fever, pulsus paradoxus (> 20 mmHg decrease in normal inspiratory drop in blood pressure), the Beck triad of JVP elevation, hypotension, and muffled heart sounds. Often the patient feels weak or faint.

A systematic approach to evaluating shock should include consideration of obstructive shock

etiologies and lead to appropriate testing. ECG may show ST-segment elevations in acute pericarditis or low voltage in pericardial effusion. Echocardiogram may show thickened pericardium and/or pericardial effusion with collapsed ventricles.

Treatment includes relief of tension pneumothorax with tube thoracostomy and correction of conditions that led to its development. Pericardiocentesis, removal of tamponade fluid to relieve shock, and analysis of fluid help determine cause. In some cases, creation of a surgical pericardial window is needed for chronic pericardial effusions. Acute pulmonary embolism with hypotension that does not respond to IV fluid is treated with thrombolytic therapy or mechanical removal (e.g., embolectomy, retrieval catheters).

PULMONARY ARTERY CATHETERIZATION

Right heart and pulmonary artery catheterization are done with a balloon-floated (i.e., Swan-Ganz) catheter. These catheters have specialized uses in the diagnosis and evaluation of pulmonary hypertension and in cardiac care and presurgical management. Weigh the risks and benefits carefully for each patient. Systematic reviews and clinical trials found that the use of a pulmonary artery catheter did not alter patient mortality or length of stay in the ICU or hospital, but incurred increased costs, and resulted in significant complications. Consequently, pulmonary artery catheters are not routinely used in the ICU setting but may be employed in very specific settings, such as right heart catheterization for diagnosis and evaluation of pulmonary hypertension or to determine etiology of shock. They may be used in the coronary care unit (CCU) or perioperatively in some cases.

Catheter insertion:

- As the catheter is introduced—typically via the internal jugular vein—pressure readings of the central venous right atrial (normal = 0–8 mmHg), RV (0–8 end-diastolic; 15–30 systolic), and the pulmonary artery (3–12 end-diastolic; 15–30 systolic) are taken.
- When the catheter is flow directed to a small pulmonary artery, the balloon at the tip temporarily obstructs the forward flow and the reading (wedge pressure, a.k.a. pulmonary artery occlusion

pressure) is a reflection of LVEDP. LVEDP is a reflection of the LV preload (assuming the compliance is not changed). The LVEDP indicates the likelihood of left ventricular failure and pulmonary edema.

Thermal-dilution cardiac output (CO) is a test that uses the temperature gradient of injected water to calculate the CO.

Mixed venous oxygen saturation (S_{vO_2}) is the last measurement of the venous blood before it gets oxygenated. Normally, the S_{vO_2} is 78%. This number drops as the global tissue oxygen debt increases. If it gets too low, you must boost delivery of O_2 to the tissues (by increasing the O_2 saturation, in particular the cardiac output, or Hgb concentration—discussed under [Oxygen Delivery to Tissues on page 6-9](#)).

The systemic vascular resistance (SVR) measurement reflects vascular tone (i.e., vasodilated vs. vasoconstricted).

$$SVR = (MAP - CVP) \times 80/CO$$

MAP = mean arterial pressure; CVP = central venous pressure.

Complications of Pulmonary Artery Catheterization

Establishing central venous access can cause unintentional puncture of nearby arteries, bleeding, neuropathy, air embolism, and pneumothorax.

Advancing the catheter can cause dysrhythmias, which are usually transitory but may be persistent. Advancement of the catheter can cause right bundle-branch block and, in a patient with left bundle-branch block, this may result in **complete** heart block.

A catheter residing in the pulmonary artery can cause pulmonary artery rupture (with 53% mortality), venous thrombosis, thrombophlebitis, pulmonary embolism, and pulmonary infarction.

The 2006 Fluids and Catheters Treatment Trial (FACTT) by the ARDS Network found similar outcomes when using CVP vs. pulmonary artery catheter to guide the management of ARDS patients. See treatment of ARDS under [Treatment on page 6-77](#).

Know [Table 6-16](#).

Table 6-16: Catheterization and Shock

Pulmonary Artery Catheters: Hemodynamic Subsets of Shock

Type	CO	Wedge Pressure	SVR	Treatment
Hypovolemic	Low	Very low	High	NS or RL
Cardiogenic	Very low	High	High	Variable: Consider inotrope, cardiac catheter, IABP
Distributive*	High-nl-low	Low	Very low	See sepsis guidelines.
Obstructive†	Low	Low	High	Resolve obstructive cause, +/- temporize with fluids.

CO = cardiac output; IABP = intraaortic balloon pump; nl = normal; NS = normal saline; RL = Ringer lactate; SVR = systemic vascular resistance

* As seen in septic, spinal, and anaphylactic shock; have total loss of SVR

† As in massive PE or tension pneumothorax

From John Morrissey, MD

SLEEP-DISORDERED BREATHING

PREVIEW | REVIEW

- Discuss the risk factors for obstructive sleep apnea-hypopnea syndrome (OSAHS).
- What should be avoided in patients with OSAHS?
- Describe OHS and how it relates to OSAHS.

OVERVIEW

There are various types of abnormal respiratory patterns that can occur during sleep. These vary from apnea (with obstructive and central origins) and hypopnea to respiratory effort-related arousals.

Apnea is defined as the cessation of breathing for ≥ 10 seconds during sleep. It becomes clinically significant at 5–15 episodes per hour, and severe cases may have > 30 /hour. Oxygen saturation usually decreases by $> 4\%$ during the apneic episodes.

The American Academy of Sleep Medicine definition of **hypopnea** is a decrease of $\geq 30\%$ of the baseline airflow for ≥ 10 seconds and oxygen saturations decreased by $\geq 3\%$ from baseline with an arousal or $\geq 4\%$ from baseline.

The 2 main classes of sleep apnea are central and obstructive, although both can coexist in a single patient.

Respiratory effort-related arousals relate to multiple arousals from sleep due to obstructive symptoms that do not qualify for the definition of hypopnea.

Patients may have daytime hypersomnolence. History of snoring or arrested breathing (witnessed apneic events) is often obtained from a sleeping partner. When severe, **pulmonary hypertension/cor pulmonale** (from the chronic hypoxia) and personality changes may develop.

Diagnosis is confirmed by **polysomnography** (sleep study). The patient is hooked up to multiple electronic gadgets (i.e., ECG, EEG, electrooculogram, pressure sensors for flow measurement, EMG, oximeter, tidal CO_2 recorder) during sleep. The presence or absence of an inspiratory effort during the apneic episode differentiates between obstructive and central apnea. The frequency of hypoxic apneic episodes determines the severity of the disease. A normal number is $< 0\text{--}4$ /hour, mild is 5–14/hour, moderate is 15–30/hour, and severe disease is > 30 /hour.

OBSTRUCTIVE SLEEP APNEA-HYPOPNEA SYNDROME (OSAHS)

OSAHS is sleep apnea or hypopnea occurring despite a continuing ventilatory effort. The obstructive episode is usually followed by a loud snore. Patients have daytime hypersomnolence and snoring and may have headaches and weight gain. Using the STOP-BANG questionnaire—which assesses snoring, tiredness, observed apneas, high blood pressure, BMI, age, neck size, and gender—a score

can be obtained to determine if OSAHS is expected. A score of ≥ 3 has an 84% sensitivity for the diagnosis of OSAHS. In North America, it is estimated to occur 2–3× more often in men. OSAHS is diagnosed after an overnight polysomnogram with apnea plus hypopnea-associated desaturation of $\geq 3\text{--}4\%$; the apnea hypopnea index (AHI) is ≥ 15 /hour. OSAHS is also diagnosed if the patient has an AHI of ≥ 5 with daytime hypersomnolence, or ≥ 15 with or without daytime symptoms.

Risk factors for OSAHS are obesity, myxedema, and upper airway abnormalities. Causes of an abnormal airway include tonsillar hypertrophy or lymphoma, micrognathia, acromegaly, goiter, and temporomandibular joint (TMJ) disease. Although various medications may worsen OSAHS and should be avoided in these patients, they have not been shown to cause OSAHS.

Know that OSAHS is associated with several severe diseases, including hypertension, metabolic syndrome, coronary artery disease, stroke, nonalcoholic fatty liver disease, and arrhythmias.

Perioperative complications and motor vehicle accidents (2–3× increased incidence) are also common in these patients. Patients with untreated, severe disease and those who have untreated CHD have decreased survival.

Treatment of OSAHS

Prescribe lifestyle modifications, including weight loss (when appropriate), sleep hygiene, side sleeping, and avoidance of alcohol and sedatives. Treat OSAHS with either CPAP, BPAP, or autotitrating CPAP. With CPAP, the patient receives air at constant pressure (usually 5–15 cm H_2O) via a well-sealed mask. This splints the pharynx open at night. It is **very effective**. BPAP is similar but allows independent adjustment for inspiratory and expiratory pressures. This improves comfort and compliance. Autotitrating CPAP adjusts pressure according to the patient's needs and is increasingly being utilized.

Uvulopalatopharyngoplasty (UPPP) and dental or mandibular advancing devices are alternatives to consider in selected patients based upon the anatomy and level of obstruction. However, their efficacy is highly variable. UPPP and dental devices can be offered especially in patients with mild-to-moderate OSAHS but are often considered only after the patient does not tolerate or respond to noninvasive PAP. Both UPPP and dental devices are sometimes used in severe sleep apnea to decrease the amount of PAP required, but as noted, efficacy is not always predictable.

Very severe OSAHS and obesity hypoventilation syndrome (OHS; see **Obesity Hypoventilation Syndrome (OHS)**) may require tracheostomy in some cases, which is effective.

Modafinil is used in patients with daytime somnolence despite compliance with other appropriate therapies, as discussed previously. Other medications include armodafinil and methylphenidate.

CENTRAL SLEEP APNEA SYNDROME (CSAS)

CSAS occurs in < 5% of sleep apnea patients. Cheyne-Stokes breathing is a type of central apnea and is typically seen with CNS and cardiac disease (mainly HF). Central apneas can occur in healthy persons when they wake up suddenly at night (referred to as postarousal centrals). They can also occur at high altitude.

Treatment of CSAS: Avoid CNS depressants, such as alcohol, sedatives, and hypnotics. Encourage weight loss and avoiding sleep deprivation.

Nasal CPAP or BPAP with a mandatory back-up rate are usually the 1st line therapies and may be particularly useful in patients who also have OSAHS.

CSAS treatment is not standardized and depends upon the specific etiology. Try different therapies. Supplemental nighttime oxygen is helpful for those with hypoxemia due to heart failure. Acetazolamide is often helpful; it causes a metabolic acidosis that stimulates a central compensatory response. Acetazolamide is a diuretic and therefore may be useful in patients with Cheyne-Stokes breathing with HF.

Question: When do nocturnal O₂ desats occur **without** apnea? Answer: COPD/emphysema, kyphoscoliosis, and muscular dystrophy.

OBESITY HYPOVENTILATION SYNDROME (OHS)

OHS, a.k.a. Pickwickian syndrome, is defined as hypoventilation while awake, although **most** also have OSAHS.

Patients with OHS have 2 main findings:

- 1) BMI > 30 kg/m² in most
- 2) pCO₂ > 45 mmHg when awake

If no ABGs are available, look for an elevated HCO₃⁻ on the serum chemistry as a clue (due to metabolic compensation for the chronic respiratory acidosis). However, this may be confounded by patients undergoing diuresis causing a hypochloremic metabolic alkalosis. Screen for hypothyroidism!

Treatment: Aim therapy at decreasing obesity and increasing the ventilatory drive. Patients should lose weight. Treatment for OHS is similar to OSAHS, but BPAP is the 1st line therapy in order to address the hypercapnia.

LUNG CANCER

For information on lung cancer, see the [Oncology](#) section.

SUPERIOR VENA CAVA (SVC) SYNDROME

PREVIEW | REVIEW

- List the causes of superior vena cava syndrome, both malignant and nonmalignant.

SVC syndrome is a medical emergency. 80% of cases are due to malignancy with the majority caused by **small cell or squamous cell** lung cancers (less often by lymphoma and metastatic tumors). Permanent central venous access is an emerging nonmalignant cause. Others include fibrosing mediastinitis secondary to histoplasmosis or tuberculosis as well as goiters.

Presentation includes swelling of the neck and face (especially the periorbital region), shortness of breath, and cough. Examination reveals distended neck veins with visible collaterals, edema across the chest and onto the face, and difficulty breathing. Hypotension may also be present. Pemberton sign is seen when the patient elevates both arms and develops facial congestion and cyanosis as well as respiratory distress.

Diagnosis is usually obvious by looking at the patient and noting the turgid face and neck. Contrast CT is the recommended imaging. If the patient does not already carry a diagnosis of malignancy, and the chest CT does not show one, look for it! Tracheal obstruction is a major concern.

Treat less acute cases with diuretics and elevation of the head. Steroids help reduce tumor size only in certain malignancies such as lymphoma. Endovenous stents and radiation may help NSCLC and other solid tumor metastasis. Chemotherapy helps small cell lung cancers. All these interventions are strictly palliative.

In the case in which the cause of SVC is nonmalignant (e.g., aortic aneurysm; goiter; benign tumors; and infections such as fibrosing mediastinitis secondary to tuberculosis, syphilis or histoplasmosis), surgery can help. If the cause is venous thrombosis due to an indwelling central venous catheter, remove the catheter and initiate systemic anticoagulation.

MEDIASTINAL MASSES

PREVIEW | REVIEW

- What are the most common causes of anterior mediastinal masses? Middle? Posterior?

For an overview of mediastinal masses, see [Table 6-17 on page 6-88](#).

Table 6-17: Mediastinal Masses — Type Based on Location		
Anterior	Middle	Posterior
Thymoma Thyroid tumor Parathyroid tumor Teratoma Lipoma Aortic aneurysm Lymphoma Thymus Other endocrine tumors	Lymphoma Cysts Lymphadenopathy Aortic aneurysm Hernia	Neurogenic tumors Gastroenteric cysts Esophageal lesions Aortic aneurysm Hernia
Of the primary mediastinal tumors: 20% = Cysts 20% = Neurogenic tumors 20% = Thymomas* 10% = Lymphomas 10% = Teratomas 20% = Miscellaneous		
* Note that thymomas are associated with autoimmune diseases, such as myasthenia gravis.		

COUGH

OVERVIEW

Cough is a common and often troublesome respiratory symptom, particularly when it becomes chronic (in adults, ≥ 2 months). Social stigma is often associated with cough, due to concerns about potential contagion, but people also find it annoying (both for the person with cough and those around it). A systematic approach is important to the diagnosis and management of cough.

DIAGNOSIS

The history should include onset, factors around the onset (e.g., illness, exposures, environmental conditions, change of home or work), frequency of cough, time of day, changes with position (e.g., lying down), exacerbating factors, new medications, presence or absence of sinus symptoms, postnasal drip, gastroesophageal reflux disease (GERD), wheezing, sputum production, change in sputum color or consistency, dysphagia, and aspiration. Relevant past medical history includes prior respiratory tract infections, bronchiectasis, conditions that predispose to dysphagia (e.g., neurologic conditions) or GERD, sinus disease, and pulmonary illnesses. The occupational history and social history are important, noting habits such as cigarette and drug use. Note should be taken of new medications—notably ACEIs and potentially β-blockers—and of therapies employed to treat the cough previously, including OTC medications.

In the physical examination, take note of any signs of sinus disease, oropharyngeal disease, wheezes, crackles, or rhonchi.

The differential diagnosis for chronic cough includes allergic or nonallergic rhinitis/sinusitis, airway disease (e.g., asthma, COPD), GERD, eosinophilic bronchitis, pulmonary disease (e.g., pulmonary fibrosis, sarcoidosis, bronchiolitis), bronchiectasis, tuberculosis, dysphagia/chronic aspiration, foreign body, endobronchial tumor, malignancy, pertussis, postinfectious cough (e.g., viral), and psychogenic cough.

TREATMENT

Management is generally directed by the findings of the history and physical. Smoking cessation (including of all inhaled substances) and avoidance of or protection from dusts, fumes, and irritants is recommended.

Upper airway cough syndrome results from postnasal drip from allergic or nonallergic rhinitis/sinusitis and sensation of these draining secretions. This leads to cough and frequent throat clearing. Management includes daily nasal steroid, antihistamine therapy, leukotriene antagonist, sinus rinse, temporary use of ipratropium nasal spray for nonallergic causes, removal of inciting factors, and allergy testing with immunotherapy.

Patients with GERD symptoms are encouraged to avoid caffeine, practice lifestyle modifications (e.g., avoid eating late at night, walk after dinner, prop up head of bed on blocks), and use H₂ blockers or proton pump inhibitors 30 minutes before eating.

Spirometry with and without bronchodilators can be helpful in identifying those with bronchospasm that may be manifesting as cough, such as cough-variant asthma. However, spirometry may be normal in some patients who are not symptomatic at the time of the test. A trial of albuterol and/or inhaled corticosteroids with or without a LABA (depending on the severity and frequency of the cough) may be indicated. If the patient does not respond to these treatments or there is suggestive information in history and physical, diagnostic testing may be pursued, including chest x-ray, CT scan of the chest, methacholine challenge, ENT evaluation, and even bronchoscopy.

For patients with bronchiectasis, pulmonary hygiene, flutter valve to help clear secretions, and a mucolytic can be helpful. Further management is directed by the clinical course and findings of the diagnostic workup.

HEPATOPULMONARY SYNDROME (HPS)

OVERVIEW

HPS consists of liver disease cirrhosis, positional deoxygenation, and intrapulmonary shunting due to pulmonary capillary dilatations and direct AVMs. HPS is associated with a poor overall prognosis, with a high mortality within 1–2 years due to GI bleeding and hemorrhagic shock.

EPIDEMIOLOGY

Estimates of the prevalence of HPS in patients with cirrhosis vary from 4–47%. This wide variation is likely due to different cutoffs for deoxygenation that were used in studies. However, mild liver disease can also be associated with HPS.

PATHOPHYSIOLOGY

The pathophysiology is not well understood. Hypoxia may occur via V/Q mismatch or shunting.

DIAGNOSIS

Patients can present with dyspnea, platypnea (shortness of breath when sitting upright but improved when supine), and orthodeoxia (deoxygenation when upright but improving when supine). Clubbing is a common finding. Spider nevi are often associated with systemic and pulmonary vasodilatations.

TESTING

Supine and upright oximetry may not demonstrate oxygen desaturation, while a decrement in pO_2 of $\geq 5\%$ or of ≥ 4 mmHg when upright is considered orthodeoxia. Contrast echocardiography (bubble echo) can demonstrate shunt. Though it is not very sensitive, it is the 1st test to perform. Shunt fraction is estimated via assessing the P_aO_2 while breathing 100% oxygen; if $> 5\%$, it is abnormal. Technetium scanning can also be used. If no shunt is present, the majority of the injected albumin will be trapped in the lungs, but if shunt is present, the uptake will be found in the kidneys or brain. The amount found in the brain and kidney can be used to determine the degree of shunt present. Platypnea with orthodeoxia and a shunt fraction $> 6\%$ is strongly suggestive of HPS.

TREATMENT

Supplementary O_2 may be useful provided shunt is not severe. Various vasoactive medications and supplements have been tried with varied and inconsistent responses and no significant randomized studies. For patients who have a poor response to O_2 (i.e., have a large shunt) the definitive treatment is liver transplant. For patients who are not a candidates for liver transplantation, consideration of transjugular intrahepatic portosystemic shunts (TIPS) have been reported to improve oxygenation in some cases, though the effect does not appear to be sustained. Oral garlic, which decreases nitric oxide and selective coil embolization, may also be used in refractory cases.

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APPENDIX A

The P_aO_2 is relatively consistent in a group of people in a room. It is the P_aO_2 that varies individually with lung problems. It is the **difference** between these 2 partial pressures, or gradient, that is the key indicator of problems with the alveolar-capillary unit. Again, $D_{A-a}O_2$ is increased in all causes of hypoxemia **except** in hypoventilation and high altitudes. In reality, the $D_{A-a}O_2$ is useful only when evaluated on room air since the gradient increases as the F_iO_2 increases. It is difficult to know the exact F_iO_2 when a patient breathes with a nasal cannula or a poorly fitted face mask.

The $D_{A-a}O_2$ is 5–15 mmHg in healthy, young patients. It increases normally with age and abnormally with lung diseases, causing a V/Q mismatch (i.e., blood flow or diffusion abnormality). Note: A patient with a significant pulmonary embolus invariably has an increased $D_{A-a}O_2$, but if the patient is hyperventilating (which is common), the P_aO_2 can be normal!

As mentioned, $D_{A-a}O_2$ increases with age. The 2 rules of thumb for determining a normal $D_{A-a}O_2$ are:

- 1) Normal $D_{A-a}O_2 \leq 0.3 \times \text{age}$ (years)
- 2) Normal $D_{A-a}O_2 \leq (\text{age}/4) + 4$

To find the $D_{A-a}O_2$, first determine the partial pressure of O_2 in the alveoli (P_AO_2)—discussed under **Respiratory Physiology** on page 6-7:

$$P_AO_2 = [(P_b - P_{H_2O}) \times F_iO_2] - [P_aCO_2/0.8]$$

At standard temperature at sea level,

$$P_AO_2 = [(760 - 47) \times 0.209] - [P_aCO_2/0.8]$$

$$P_AO_2 = [149] - [P_aCO_2/0.8]$$

Or, for an easier mental calculation,

$$P_AO_2 = 149 - 1.25(P_aCO_2)$$

So, getting back to the original formula,

$$D_{A-a}O_2 = P_AO_2 - P_aO_2$$

where the P_aO_2 is obtained from the arterial blood gas. Or, for an easier mental calculation at sea level and breathing room air, the formula is shifted around to:

$$D_{A-a}O_2 = 149 - [P_aO_2 + (1.25 \times P_aCO_2)]$$

Okay, got this? You obtain the P_aO_2 and the P_aCO_2 from the ABG report. If at sea level and inspiring room air, take a **quarter more** than the P_aCO_2 and **add** it to the P_aO_2 , then **subtract** the result from 149.

APPENDIX B — OXYGEN TRANSPORT TO TISSUES

Oxygen **transport** to the tissues (DO_2) is defined by the following equation:

$$DO_2 = \text{cardiac output} \times C_aO_2$$

where C_aO_2 is the oxygen content of arterial blood.

This is calculated by

$$C_aO_2 = (1.34 \times \text{Hgb} \times S_aO_2) + (0.003 \times P_aO_2)$$

where S_aO_2 is the hemoglobin saturation and Hgb is the hemoglobin level.

(In practice, we can ignore the miniscule amount of O_2 dissolved in plasma, $0.003 \times P_aO_2$.)

So, essentially,

$$DO_2 = \text{cardiac output} \times (1.34 \times \text{Hgb} \times S_aO_2)$$

Notice from this equation that oxygen transported to the tissues depends upon **3** factors:

- 1) Cardiac output
- 2) Hemoglobin level
- 3) Hemoglobin saturation. This is why the hemoglobin-oxygen (oxyhemoglobin) dissociation curve and the use of pulse oximetry are so important.

Nephrology

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RENAL TESTS

PREVIEW | REVIEW

- What disease causes a negative urine dipstick for protein, but high urine protein measured by the lab (protein:creatinine ratio or 24-hour urine protein)?
- What diseases cause positive urine dipstick for heme, but few or no RBCs on urine sediment exam?
- Which findings on the urine sediment exam suggest that hematuria is caused by glomerulonephritis?
- What are the causes of a blood urea nitrogen:creatinine ratio of $> 20:1$?

URINALYSIS (U/A)

The U/A is a set of urine tests that provides information about potential renal and urinary tract disease. The U/A is more than just the dipstick:

- **Visual examination** of the urine: Red or brown (“tea-colored”) urine suggests hematuria, hemoglobinuria, myoglobinuria, or ingestion of beets or certain antibiotics. Cloudy urine may indicate urinary tract infection (UTI) or crystalluria (seen with kidney stones).
- **Reagent strip testing (“dipstick”)**: This tests urine pH, protein, glucose, ketones, blood, heme, bilirubin, urobilinogen, nitrites, leukocyte esterase, and specific gravity.
- **Urine sediment examination (microscopy)**: Look for cells (e.g., red blood cells [RBCs], white blood cells [WBCs], renal tubular cells), casts, and crystals.
- Although technically not part of the U/A, in some situations laboratory testing of the urine is useful (e.g., osmolality, electrolytes, protein).

Many kidney diseases cause proteinuria, hematuria, or both on dipstick. A patient with acute kidney injury (AKI) and a normal U/A probably has either prerenal failure or postrenal failure (ureteral or urethral obstruction). See more in [Table 7-2 on page 7-10](#).

Reagent Strip Testing (Dipstick)

The urine **specific gravity** tells you how dilute or concentrated the urine is. In a patient with AKI, a very concentrated urine (i.e., specific gravity ≥ 1.025) suggests prerenal azotemia such as in volume depletion. In acute tubular injury (a.k.a. acute tubular necrosis [ATN]), the urine specific gravity is similar to plasma (i.e., 1.010) because the tubules cannot concentrate or dilute the urine. In a patient with hyponatremia, a low urine specific gravity (< 1.005) suggests primary polydipsia.

The **urine pH** is important when you are assessing kidney stones or metabolic acidosis. Kidney stones with a high urine pH (> 7.0) are typically struvite or calcium phosphate. When the urine pH is low (< 6.0), stones are usually

uric acid or calcium oxalate. In a patient with a normal anion gap metabolic acidosis (NAGMA; a.k.a. non-anion gap metabolic acidosis), a high urine pH should make you think of distal renal tubular acidosis (RTA; discussed in [Type 1 \(Distal\) RTA on page 7-45](#)).

The urine dipstick for **proteinuria** detects albumin; however, it does not detect other proteins. As a result, immunoglobulins such as urinary light chains in multiple myeloma are not detected on urine dipstick. When the urine dipstick is **negative** for protein, but the spot urine protein:creatinine ratio is high, think **multiple myeloma**. Causes of **false-positive** urine protein on dipstick are very alkaline urine (pH > 8.0), gross hematuria, exposure to intravenous iodinated contrast, and very concentrated urine. Use a spot urine protein:creatinine ratio or a 24-hour urine collection to quantify proteinuria in patients with persistently positive dipstick.

Urine dipstick is very sensitive for the presence of **heme** (detects 1–2 RBCs per high-power field; normal range is ≤ 3 RBCs/HPF). Remember: A positive dipstick for heme can result not only from urinary RBCs; it can also result from free hemoglobin or free myoglobin. When there are few RBCs on microscopic analysis but the urine dipstick is positive for blood, think of hemoglobinuria (intravascular hemolysis) or myoglobinuria (rhabdomyolysis).

Urinary **ketones** are positive in patients with ketosis—diabetic, alcoholic, or starvation ketosis. Glycosuria (positive **glucose** on urine dipstick) may occur in pregnancy, in diabetic patients with hyperglycemia, or Fanconi syndrome (more under [Proximal Tubule on page 7-5](#)).

Nitrites and **leukocyte esterase** suggest the presence of urinary tract infection (UTI). Positive leukocyte esterase indicates WBCs in the urine. Nitrite reflects the presence of bacteria that convert urinary nitrate to nitrite. Note some bacterial infections such as *Enterococcus* are nitrite negative.

U/A is useful in patients with urinary symptoms such as dysuria, urinary frequency, and urinary urgency. U/A, in combination with urine culture, can quickly diagnose UTI. See more in the [Geriatric Medicine](#) section.

Urine Sediment

Cellular Elements

Cells in the urine can include RBCs, WBCs, renal tubular epithelial cells, and squamous cells.

RBCs can be monomorphic (normal shape and size) or dysmorphic (disfigured by the trauma of passing through the glomerulus and tubule). Dysmorphic RBCs (as well as RBC casts; A and B in [Figure 7-1 on page 7-2](#)) suggest glomerular hematuria; monomorphic RBCs can be seen with any cause of hematuria (more under [Hematuria on page 7-2](#)).

Urinary **WBCs** are commonly associated with UTI. However, if the urine culture is negative (i.e., sterile pyuria), consider interstitial nephritis, renal tuberculosis, prostatitis, glomerulonephritis (if RBCs also are present), and nephrolithiasis.

Eosinophiluria can be seen in drug-induced interstitial nephritis but is not a sensitive or specific finding. It can also be seen in UTI, prostatitis, and cholesterol athero-embolic disease.

Squamous cells are from urethral and/or skin contamination and have no pathologic significance.

Casts

Casts are cylindrical structures that are formed in the renal tubular lumen.

Red cell casts (B in Figure 7-1) are seen only with glomerular hematuria, usually glomerulonephritis.

White cell casts are typically seen in pyelonephritis or acute interstitial nephritis; occasionally they are seen in glomerulonephritis.

Coarse granular casts (i.e., muddy-brown or dirty brown casts) are seen with acute tubular injury/necrosis (C in Figure 7-1).

Renal tubular epithelial casts, like granular casts, are seen with acute tubular injury.

Waxy casts typically indicate advanced chronic kidney disease (CKD).

Fatty casts (like **oval fat bodies**, described in **Oval Fat Bodies**) are seen in nephrotic syndrome.

Hyaline casts are a normal finding that can be seen in concentrated urine.

Oval Fat Bodies

Oval fat bodies are lipid-laden renal tubular epithelial cells (D in Figure 7-1) that look like “Maltese crosses” under polarized light (E in the same figure). They are seen in nephrotic syndrome.

Crystals

Know the following crystals in urine sediment examination.

Calcium oxalate crystals are envelope, dumbbell, or needle shaped (A in Figure 7-2). These are seen in patients with calcium oxalate kidney stones; however, they also can be a normal finding. In a patient with possible toxic ingestion, high anion gap metabolic acidosis, and AKI, think ethylene glycol poisoning!

Calcium phosphate crystals are rectangular or wedge-shaped prisms (B in Figure 7-2); urine is alkaline (pH > 7.0).

Uric acid crystals are reddish-brown, rectangular, or rhomboid (C in Figure 7-2); urine is acidic (pH < 6.0). Seen in gout, uric acid stones, and tumor lysis syndrome.

Struvite (a.k.a. calcium-magnesium-ammonium pyrophosphate [triple phosphate]) crystals look like coffin lids (D in Figure 7-2); urine is alkaline (pH > 7.0). Seen with chronic UTI with urea-splitting organisms, struvite crystals lead to formation of staghorn calculi.

Cystine crystals are hexagons (E in Figure 7-2) seen in cystinuria, a genetic cause of kidney stones.

Several drugs can crystallize in the urine (sometimes causing crystal-induced nephropathy), including **sulfonamides**, **indinavir**, **acyclovir**, **atazanavir**, **methotrexate**, and **ciprofloxacin**. Drug crystals are typically needle-shaped and do not have unique morphologies—you will need to determine the drug type from the patient history (more under **Kidney Stones** on page 7-35).

Hematuria

Hematuria can be caused by renal or urologic disease (e.g., UTI, kidney stones, renal/uroepithelial cancer).

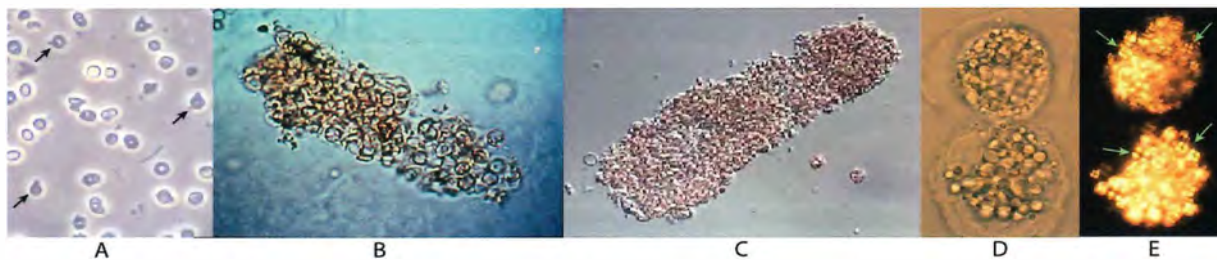


Figure 7-1: Urine sediment: Cellular elements and casts. (A) Dysmorphic red blood cells (RBCs). (B) RBC cast. (C) Coarse (“dirty” brown) granular casts. (D) Oval fat bodies. (E) The same oval fat bodies image under polarized light, showing “Maltese crosses.”

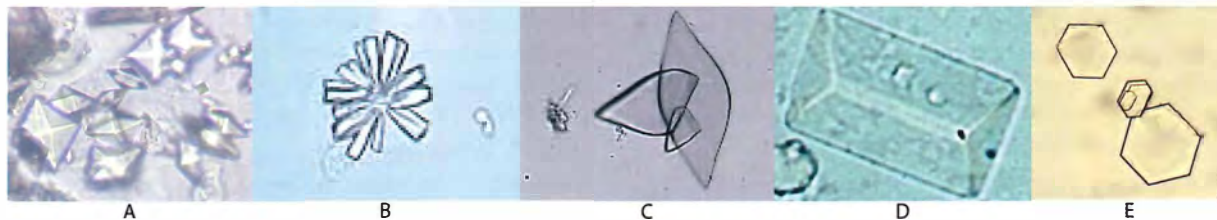


Figure 7-2: Urine sediment: Crystals. (A) Calcium oxalate. (B) Calcium phosphate. (C) Uric acid. (D) Struvite. (E) Cystine.

The 1st step in the evaluation of patients with a positive dipstick for heme or with red or brown urine is to confirm hematuria by urine sediment exam. Microscopic hematuria is defined as ≥ 3 RBCs/HPF. If hematuria is confirmed, check for proteinuria and measure the serum creatinine.

If there is no proteinuria and the serum creatinine is normal, it is **isolated microscopic or gross hematuria**. This is likely to be urologic in origin, and urologic workup should be done first:

- Look for signs of UTI (fever, dysuria, dipstick positive for nitrite and/or leukocyte esterase, or urinary WBCs on sediment exam). If present, do a urine culture.
- Unilateral flank pain suggests nephrolithiasis; evaluate with a noncontrast CT.
- In patients at risk for malignancy (> 40 years of age, smoking history, gross hematuria, pelvic radiation, exposure to cyclophosphamide or occupational exposures), do GU imaging with renal ultrasound, MRI, or CT to exclude renal cell or other GU malignancy.
- Refer to a urologist for cystoscopy if other workup is negative.

Hematuria accompanied by proteinuria is usually renal in origin. If **dysmorphic** RBCs and/or **RBC casts** are present in the urine sediment and renal function is declining, consider urgent evaluation for possible glomerulonephritis.

Glomerular hematuria also can occur in the absence of proteinuria and with normal renal function. This is called **isolated glomerular hematuria**. The most common causes are IgA nephropathy, thin basement membrane nephropathy, and early Alport syndrome. Patients with sickle cell trait or disease also can develop isolated glomerular hematuria.

Strenuous exercise can cause transient hematuria.

Proteinuria

Proteinuria is an important indicator of renal pathology. Normal urine protein excretion is < 150 mg/day. Proteinuria > 1.0 g/day usually indicates glomerular disease. Patients with < 1 g/day are more likely to have tubulointerstitial renal disease. Proteinuria > 3.5 g/day (nephrotic-range proteinuria) is caused by specific glomerular diseases (**Nephrotic Syndromes on page 7-23**).

Transient proteinuria is common with fever or after strenuous exercise. Recheck urine when the acute situation has passed. If the repeat U/A is negative, the condition can be considered benign. With **benign orthostatic proteinuria**, there is abnormal proteinuria only when the patient is upright. This diagnosis usually is seen in adolescents and young adults and is confirmed by a normal urine protein:creatinine ratio on the 1st morning void. No further workup or follow-up is needed, and the proteinuria often goes away over time.

The **24-hour urine protein measurement** is the traditional method for quantifying proteinuria. For this test, the patient collects all urine output over a 24-hour period.

Unfortunately, errors of overcollection or undercollection are common, and the test is cumbersome for the patient.

The **spot urine protein:creatinine ratio** has largely replaced the 24-hour urine protein test for quantification of proteinuria because it is much easier to complete, requiring only a random urine sample. Assuming the patient excretes roughly 1 g/day of creatinine (which is true for a 50-kg woman), the ratio of protein to creatinine equates roughly to the 24-hour urinary protein in grams. For example, a protein:creatinine ratio of 3.5 mg/mg approximates a 24-hour urine protein excretion of 3.5 g/day. This test is used to assess and monitor proteinuria in patients with renal disease. Urine protein:creatinine ratio > 0.15 mg/mg ($\sim > 150$ mg/day) is considered abnormal. Urine protein:creatinine ratio > 1 mg/mg ($\sim > 1$ g/day) usually indicates glomerular pathology. Urine protein:creatinine ratio > 3.0 – 3.5 mg/mg ($\sim > 3.5$ g/day) is considered nephrotic range.

Proteinuria is sometimes quantified by measuring albumin, rather than total protein. **Moderately increased albuminuria** (previously called **microalbuminuria**) is albumin excretion between 30 and 300 mg/day (albumin:creatinine ratio = 0.03–0.3 mg/mg). Moderately increased albuminuria is the earliest indicator of diabetic and hypertensive nephropathy. This small amount of albumin is not detectable by urinary dipstick and can only be diagnosed with a spot urine albumin:creatinine ratio.

ESTIMATING RENAL FUNCTION

Serum Creatinine

The serum creatinine (S_{Cr}) provides a quick, easy estimate of renal function (i.e., glomerular filtration rate). However, the serum creatinine is affected by both renal elimination (creatinine clearance) and creatinine production. The more muscle mass an individual has, the higher the creatinine level. Also, if muscle tissue breaks down (as in rhabdomyolysis or myositis), the creatinine level can rise acutely. An unusually rapid rise (> 1.5 mg/dL [$133 \mu\text{mol/L}$] over 24 hours) suggests rhabdomyolysis-induced renal failure. With aging, there is less muscle mass, and the creatinine may be normal despite reduced renal function.

Trimethoprim and cimetidine **increase** the serum creatinine. These drugs inhibit tubular secretion of creatinine (decreasing creatinine clearance and elevating the S_{Cr}); however, glomerular filtration rate (GFR) is not affected. An elevated ($> 20:1$) ratio indicates either prerenal azotemia (i.e., decreased renal perfusion) or increased protein breakdown. Increased protein breakdown can be due to increased dietary protein intake, GI bleeding, total parenteral nutrition, catabolic states, or steroids that increase protein turnover.

Glomerular Filtration Rate (GFR)

GFR is a measure of overall renal function. Historically, GFR was approximated by measuring creatinine clearance (CrCl) using a 24-hour urine collection. It is now typically

estimated from the serum creatinine and demographic variables. Creatinine-based formulas are quicker and easier, and they often give a more accurate estimated GFR (eGFR) than does the CrCl. Estimation of GFR is essential in staging CKD.

There are 2 main creatinine-based eGFR formulas:

- 1) The **Modification of Diet in Renal Disease (MDRD)** equation estimates GFR from serum creatinine, race, sex, and age. The MDRD equation is less accurate when the eGFR is > 60 mL/minute/1.73 m².
- 2) The **Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI)** equation uses the same variables as the MDRD study and is more accurate in patients with normal or mildly reduced GFR (eGFR > 60 mL/minute/1.73 m²).

Laboratories routinely report eGFR using either the MDRD or CKD-EPI equation. Online calculators also are available. Both formulas are normalized to body surface area. The result is given in units of mL/minute/1.73 m² body surface area.

The **Cockcroft-Gault** formula is another acceptable way to estimate GFR. Although it is less accurate than the MDRD and CKD-EPI equations, it can be calculated from basic variables with just the calculator on your smartphone:

$$\text{CrCl} = \frac{(140 - \text{age}) \times (\text{weight}) \times (0.85 \text{ if female})}{72 \times S_{\text{Cr}}} \quad (\text{Eq. 1})$$

In Eq. 1, CrCl is in mL/minute; age is in years; weight is in kg; and S_{Cr} is in mg/dL.

All these methods for estimating GFR based on the serum creatinine are accurate **only** when the serum creatinine level is in a **steady state** and the patient does not have AKI.

eGFR obtained using these methods is also inaccurate when there is an extreme of age and/or weight and in patients with amputations, cirrhosis, or pregnancy. In these situations, collect a 24-hour urine to estimate GFR by creatinine clearance:

$$\text{CrCl} = \frac{U_{\text{Cr}} \times V}{P_{\text{Cr}}} \quad (\text{Eq. 2})$$

In Eq. 2, U_{Cr} = urine creatinine concentration, V = 24-hour urine volume, and P_{Cr} = plasma (or serum) creatinine concentration.

FE_{Na} AND FE_{Urea}

Fractional excretion of sodium (FE_{Na}) is the percentage of filtered Na⁺ that is excreted in the urine:

$$\text{FE}_{\text{Na}} (\%) = \frac{(S_{\text{Cr}} \times U_{\text{Na}}) \times 100}{S_{\text{Na}} \times U_{\text{Cr}}} \quad (\text{Eq. 3})$$

Where U_{Na} is urinary Na⁺ concentration (mEq/L) and U_{Cr} is urinary creatinine concentration (mg/dL). The FE_{Na} is used to differentiate prerenal azotemia from **ATN** in patients with oliguric AKI:

- Prerenal azotemia: FE_{Na} $< 1\%$
- ATN: FE_{Na} $> 2\%$

FE_{Na} $< 1\%$ also can be seen in contrast-induced nephropathy, cardiorenal syndrome, hepatorenal syndrome, nonoliguric ATN, pigment nephropathy (hemoglobinuria = hemolysis, myoglobinuria = rhabdomyolysis), and acute glomerulonephritis.

FE_{Na} $> 2\%$ can occur in prerenal azotemia with recent diuretic use. In this situation, FE_{Urea} can be used. The fractional excretion of urea (FE_{Urea}) is the percentage of filtered urea (BUN) excreted in the urine:

$$\text{FE}_{\text{Urea}} (\%) = \frac{(S_{\text{Cr}} \times U_{\text{Urea}}) \times 100}{\text{BUN} \times U_{\text{Cr}}} \quad (\text{Eq. 4})$$

FE_{Urea} is more accurate than FE_{Na} in patients receiving diuretics because diuretics increase urinary Na⁺ excretion. FE_{Urea} $< 35\%$ suggests a prerenal state.

RENAL IMAGING

Ultrasound (U/S) and Doppler U/S

U/S is a noninvasive, inexpensive way to diagnose urinary tract obstruction. U/S also can give clues to the presence of CKD: small kidney size (< 8 cm), decreased cortical thickness, and increased cortical echogenicity. These findings sometimes are referred to as “medical renal disease.” U/S also can be used to diagnose and monitor renal cysts, renal masses, and polycystic kidney disease.

Doppler U/S evaluates renal vascular flow. It is used to screen for renal artery stenosis and renal vein thrombosis.

Computed Tomography (CT)

When looking for nephrolithiasis, noncontrast CT is the test of choice and is more sensitive than U/S. CT with contrast is used to evaluate renal masses (e.g., tumors) and complex renal cysts found on U/S. Remember: IV contrast can cause AKI (contrast nephropathy).

Magnetic Resonance Imaging (MRI)

Use MRI as an alternative to CT to evaluate renal masses. MR angiography (MRA) can be used to screen for renovascular hypertension (HTN). Although MRI and MRA avoid the risk of contrast nephropathy, the use of older forms of gadolinium is contraindicated in patients with eGFR < 30 mL/minute/1.73 m² because gadolinium has been linked to nephrogenic systemic fibrosis (more under [Imaging in CKD on page 7-33](#)).

KIDNEY BIOPSY

Indications for kidney biopsy include unexplained AKI, nephrotic syndrome, and suspected glomerulonephritis. In transplant patients with AKI, it is routinely used to distinguish between medication toxicity, acute tubular necrosis, viral infections, and acute rejection.

Bleeding is the major risk of kidney biopsy. Risk factors for major bleeding after kidney biopsy include uncontrolled hypertension, severe uremia (with uremic platelet dysfunction), thrombocytopenia, and anemia. Aspirin, NSAIDs, and antiplatelet agents should be held for at least 5–7 days prior to kidney biopsy. Relative contraindications to kidney biopsy are solitary kidney and a need for chronic anticoagulation.

substances (e.g., H^+ , K^+) are secreted. This allows for the excretion of urine concentrated in uremic toxins and balanced to allow for homeostasis of everything else.

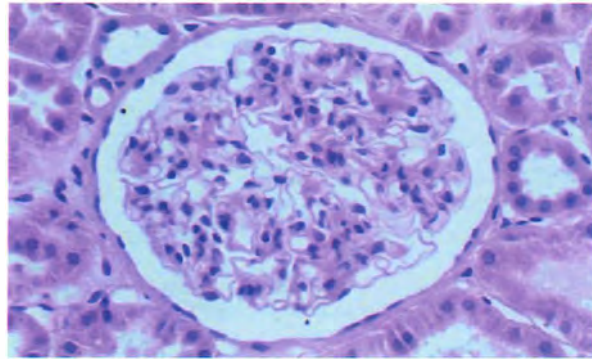


Figure 7-3: Normal glomerulus

Refer to Figure 7-4 and Figure 7-5 on page 7-6 as you go through the functions of the different nephron segments.

RENAL PHYSIOLOGY AND DIURETICS

PREVIEW | REVIEW

- Which nephron segment is responsible for reabsorption of the majority of filtered sodium, chloride, bicarbonate, and water?
- Which portion of the nephron is the most permeable to water?
- Which tubule sets up the osmotic gradient for the thin descending segment in the loop of Henle?
- What toxicity can loop diuretics cause in high intravenous doses?
- Which 2 hormones exert their effects in the collecting duct?
- Which diuretic class can be used to prevent kidney stones?
- Which diuretic is especially important to give to patients with systolic dysfunction and low ejection fraction?

PROXIMAL TUBULE

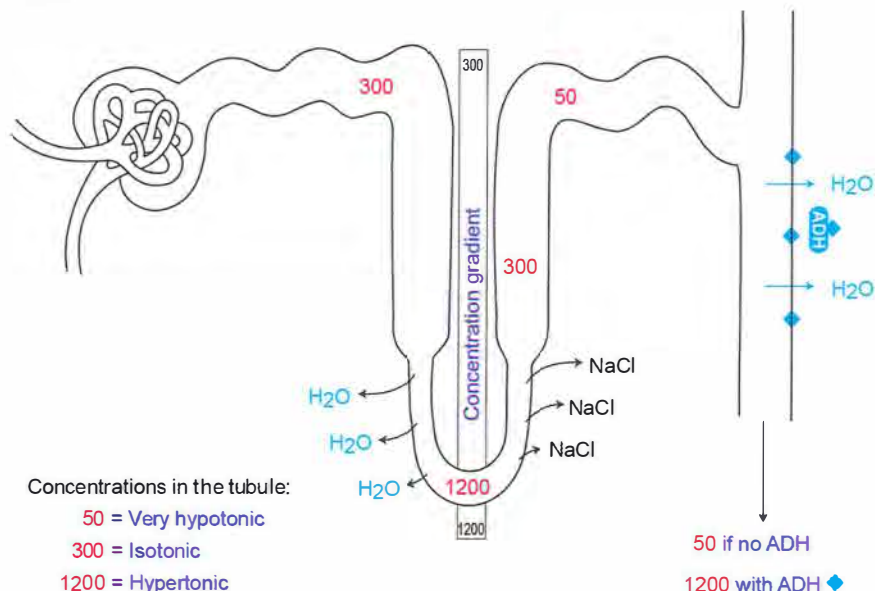
65% of filtered Na^+ , Cl^- , and water is reabsorbed in the proximal tubule. The proximal tubule is very permeable to water, which follows Na^+ and Cl^- reabsorption such that the volume of filtrate is reduced along the tubule but the osmolality and Na^+ concentration remain constant (see Figure 7-4).

Mechanisms of solute reabsorption in the proximal tubule:

- Reabsorption of Na^+ (into the interstitium) is linked to H^+ secretion (into the filtrate) via secondary active transport—stimulated by angiotensin II (AT II) and inhibited by carbonic anhydrase inhibitors.
- Reabsorption of Na^+ (into the interstitium) is linked to K^+ secretion (into the filtrate) via an ATPase transporter—stimulated by AT II.
- Cotransport of Na^+ , Cl^- , K^+ , glucose, and amino acids (into interstitium)
- Paracellular reabsorption of other solutes such as Ca^{2+}

GLOMERULAR FILTRATION

The glomerulus is a specialized capillary plexus surrounded by the Bowman's capsule (Figure 7-3). The capillary endothelium, glomerular basement membrane (GBM), and podocytes together form the glomerular filtration barrier, which allows an ultrafiltrate of the plasma to pass into the Bowman's space. The ultrafiltrate then passes into the tubules, where the “good stuff” (e.g., glucose, water, Na^+ , Cl^- , HCO_3^- , Ca^{2+}) is reabsorbed and excess



90% of filtered HCO_3^- is reabsorbed in the proximal tubule—but the process is indirect and driven by H^+ secretion (1st bullet, above):

- H^+ is secreted into the filtrate and combines with filtered HCO_3^- to form H_2CO_3 (carbonic acid).
- Carbonic anhydrase converts $\text{H}_2\text{CO}_3 \rightarrow \text{H}_2\text{O} + \text{CO}_2$.
- CO_2 passes through the tubular cell membrane and is reabsorbed into the tubular cells.
- CO_2 is converted to HCO_3^- within the tubular cell, again with the help of carbonic anhydrase.
- HCO_3^- is then reabsorbed into the interstitium.

So, for each H^+ that is secreted, 1 HCO_3^- is generated. Figure 7-5 shows the transporters involved.

Carbonic anhydrase inhibitors (CAIs; acetazolamide) disrupt this entire process by reducing the availability of H^+ in the proximal tubular cells and H_2CO_3 in the lumen. When this occurs, the Na^+/H^+ countertransporter does not have substrate, so Na^+ is not reabsorbed and H^+ is not secreted. A mild diuresis ensues, as well as a metabolic acidosis similar to proximal (Type 2) RTA. This makes CAIs useful in patients who are volume overloaded with a metabolic alkalosis.

Know that this Na^+/H^+ countertransporter also is affected by the **K^+ concentration**:

- **Hypokalemia** stimulates H^+ secretion (and thus stimulates HCO_3^- reabsorption) $\rightarrow$ alkalosis. This explains why hypokalemia must be corrected to fix metabolic alkalosis.

- **Hyperkalemia** inhibits H^+ secretion (and thus inhibits HCO_3^- reabsorption) $\rightarrow$ acidosis. Remember that the reverse also is true. Metabolic acidosis causes hyperkalemia (by shifting K^+ out of cells). The 2 can create a vicious cycle!

So, when something goes wrong in the proximal tubules, clinically we can see:

- Failure to reabsorb HCO_3^- = proximal (Type 2) RTA (causing a NAGMA).
- Failure to reabsorb other solutes (Na^+ , Cl^- , K^+ , glucose, amino acids) = Fanconi syndrome +/- hypokalemia.

This is why Fanconi syndrome and proximal RTA often occur together.

LOOP OF HENLE

Follow along in Figure 7-5 as we discuss the physiology of the loop of Henle. Think of the loop as divided into 2 halves with the 1st half (descending) handling reabsorption of water and a little bit of solute and the 2nd half (ascending) handling reabsorption of solutes. The action of the 2nd half of the loop drives the action of the 1st half.

In the descending segment, water moves from the tubular lumen into the interstitium, driven by an osmotic gradient, with maximum concentration at the turn of the loop (i.e., papilla). The renal medulla is very hypertonic—Why? In the thin ascending segment, NaCl passively diffuses into the interstitium, slightly diluting the filtrate. In the

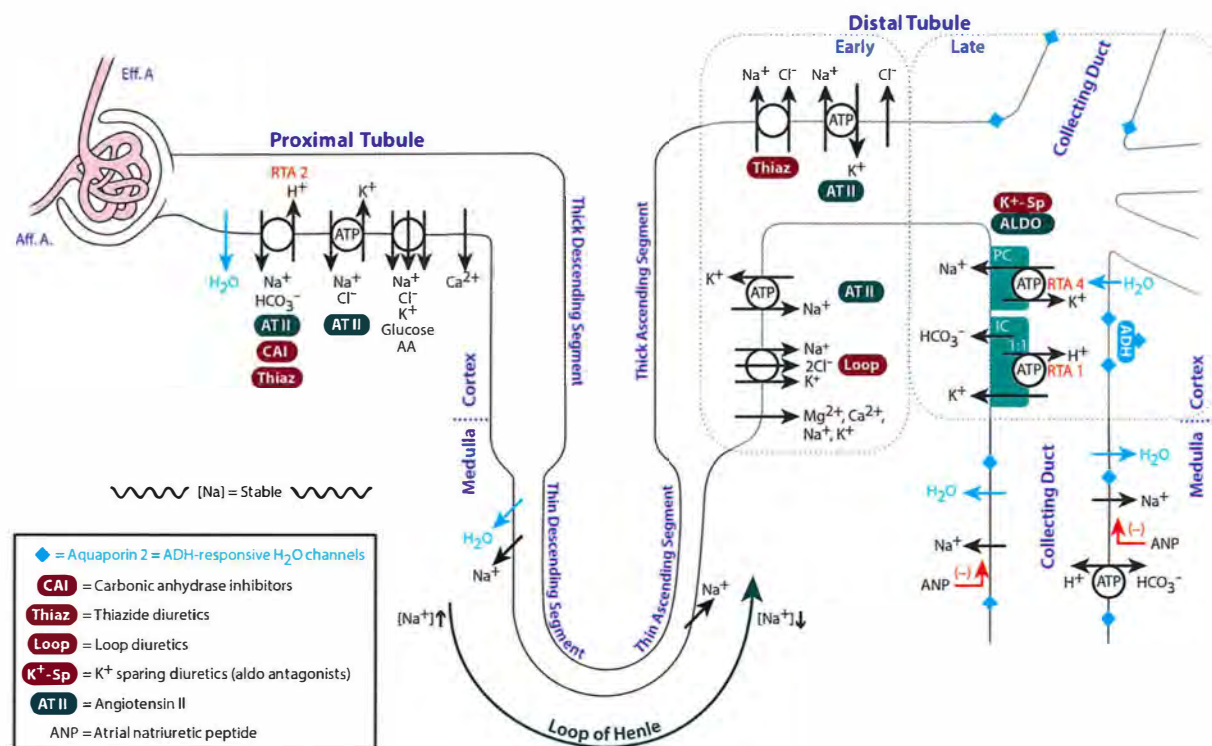


Figure 7-5: The nephron: physiology and diuretic sites of action

thick ascending segment, Na^+ , Cl^- , and K^+ are actively transported from the lumen into the interstitium, increasing the tonicity of the medulla. **That's why!** This active transport is the mechanism that produces hypertonicity in the inner medulla that will later stimulate reabsorption of water when the filtrate gets to the collecting tubule.

In the thick ascending segment, 25% of filtrate solutes are reabsorbed via:

- Countertransport of Na^+ (into the interstitium) and K^+ (into the filtrate) via an ATPase active transport pump; stimulated by AT II
- Cotransport of Na^+ , 2 Cl^- , and K^+ (into the interstitium); **inhibited** by **loop** diuretics
- Paracellular absorption of other solutes such as Mg^{2+} , Ca^{2+} , Na^+ , and K^+ (into the interstitium)

Think about this a minute and look at [Figure 7-5](#); be sure you understand before moving on.

Loop diuretics (furosemide, bumetanide, torsemide, and ethacrynic acid) inhibit the $\text{Na}^+/\text{K}^+/2 \text{Cl}^-$ cotransporter in the thick ascending segment of the loop of Henle. They **remain effective** when GFR is low ($\text{CrCl} < 20 \text{ mL/minute}/1.73 \text{ m}^2$), but you have to increase the dose and/or give IV. Ethacrynic acid is used for patients with sulfa allergies in whom furosemide, bumetanide, and the thiazide diuretics are contraindicated (because these drugs are sulfa derivatives). Know that furosemide and ethacrynic acid can cause permanent ototoxicity at high IV bolus doses.

Loop diuretics cause diuresis by preventing reabsorption of Na^+ in the thick ascending segment—this prevents the development of the interstitial osmotic gradient, relied upon by the thin descending segment for water reabsorption. The net effect is loss of both Na^+ and water. Look at the specific cotransporter that is inhibited by loop diuretics. Notice that K^+ is also reabsorbed with that cotransporter, so now it makes sense that patients taking loop diuretics also develop hypokalemia.

Loop diuretics also increase Ca^{2+} loss in the urine and have been used in the past to treat severe hypercalcemia. Normal saline was infused at a high rate (to replace the volume losses), and a loop diuretic was added. The saline expands the volume and delivers increased flow to the proximal tubule, which prevents paracellular Ca^{2+} reabsorption. The greatly increased Ca^{2+} load is then delivered to the early distal tubule, overwhelming its ability to absorb Ca^{2+} , so calciuresis ensues.

In current clinical practice, saline is still given to volume-depleted patients with hypercalcemia, but loop diuretics are only used if the patient becomes volume overloaded.

Bartter syndrome is an example of a disease that affects the loop of Henle. In Bartter syndrome, there is a defect in the $\text{Na}^+/\text{K}^+/2 \text{Cl}^-$ cotransporter in the thick ascending segment. This leads to hypokalemia and mild volume depletion—as if the patient were taking a loop diuretic.

DISTAL TUBULE

The distal tubule reabsorbs another 5% of remaining solutes with the following clinically relevant processes:

- Cotransport of Na^+ and Cl^- (into the interstitium); inhibited by thiazide diuretics
- Countertransport of Na^+ (into the interstitium) and K^+ (into the filtrate) via an ATPase active transport pump; stimulated by AT II
- Paracellular absorption of Cl^- (into the interstitium)

Thiazide diuretics (e.g., chlorothiazide, hydrochlorothiazide, chlorthalidone, metolazone) inhibit the Na^+/Cl^- cotransporter in the distal tubule.

Like loop diuretics, thiazides cause hypokalemia. Unlike loop diuretics, which increase Ca^{2+} excretion, thiazides **decrease Ca^{2+} excretion**. Remember: Do not prescribe thiazide diuretics to patients with hyperparathyroidism or hypercalcemia of malignancy, as they can worsen hypercalcemia. On the other hand, thiazides can be useful in reducing **urinary Ca^{2+} in patients with kidney stones**.

Gitelman syndrome is an example of a disease that affects the distal tubule. Here, there is a defect in the Na^+/Cl^- cotransporter. Like Bartter syndrome, these patients present with hypokalemia and volume depletion. Distinguish Bartter syndrome from Gitelman syndrome by measuring the urine calcium. It is high in Bartter syndrome, low in Gitelman syndrome.

COLLECTING DUCT

The **collecting duct** is in charge of fine-tuning acid-base, K^+ , and water homeostasis. The actions of this segment are controlled by **aldosterone** and antidiuretic hormone (ADH).

There are 2 important cell types in the **collecting duct**:

- 1) Principal cells (PCs) reabsorb Na^+ (into the interstitium) via an epithelial Na^+ channel. Na^+ reabsorption is linked to K^+ secretion (into the filtrate). This process is stimulated by aldosterone and hyperkalemia and is inhibited by K^+ -sparing diuretics (e.g., amiloride, triamterene, spironolactone, eplerenone).
- 2) Intercalated cells (ICs) secrete H^+ (into the filtrate) via an ATPase active transport pump. For every H^+ secreted, 1 HCO_3^- is reabsorbed. ICs are one of the major regulators of acid-base balance and reabsorb K^+ (to a minor extent).

Water reabsorption in this segment is controlled by **ADH** (i.e., vasopressin). In the absence of ADH, the collecting duct is relatively impermeable to water. When present, ADH leads to insertion of aquaporin-2 into the tubule cell membrane. This makes the collecting tubule permeable to water. In the setting of a hypertonic interstitium in the inner medulla, water is reabsorbed (from filtrate into interstitium) down its osmotic gradient, leading to a concentrated urine. The effect of ADH may be blocked by vasopressin receptor antagonists, conivaptan (IV formulation only), and tolvaptan (oral). These agents are sometimes used to treat hyponatremia.

K⁺-sparing diuretics act at the collecting duct. They include aldosterone antagonists (i.e., spironolactone and eplerenone) and agents that block the epithelial Na⁺ channel that is activated in the presence of aldosterone (i.e., amiloride and triamterene). Although they have different targets, their effects are similar: They block Na⁺ reabsorption, which in the collecting tubule is linked with K⁺ secretion. Hence, they are weak diuretics, but they cause the blood K⁺ to rise.

Diseases that affect the collecting duct:

- 1) Type 1 (distal) RTA is a NAGMA caused by impaired H⁺ ATPase active transport in the intercalated cells, which leads to the inability to secrete acid (and reabsorb HCO₃⁻); urine pH is always > 5.3.
- 2) Type 4 RTA (hypoaldosteronism) is a NAGMA due to aldosterone deficiency or resistance; hyperkalemia is present.
- 3) Diabetes insipidus is due to inadequate ADH (central) or resistance to ADH (nephrogenic). It manifests as polyuria and, if inadequate access to water, hypernatremia.
- 4) Syndrome of inappropriate diuretic hormone secretion (SIADH) is caused by excess ADH hormone and manifests as hyponatremia.

MECHANISM OF ACTION OF DIURETICS

Now that we have reviewed the different tubular segments, we will go over the 4 classes of diuretics:

- 1) **Carbonic anhydrase inhibitors** (acetazolamide):
 - Effect: inhibit Na⁺/H⁺ countertransport in the proximal tubule
 - Complications: acidosis, hypokalemia
- 2) **Loop diuretics** (e.g., furosemide, bumetanide, torsemide):
 - Effects:
 - Inhibit the Na⁺/K⁺/2 Cl⁻ cotransporter in the thick ascending segment
 - Increase Ca²⁺ excretion
 - Diminish the medullary osmotic gradient in inner medulla
 - Used to treat edema
 - Effective at low GFRs but require higher dosing
 - Complications: dehydration, hypokalemia, calcu-
resis, ototoxicity (with high dose IV), and meta-
bolic ("contraction") alkalosis
- 3) **Thiazides** (hydrochlorothiazide, chlorthalidone, metolazone):
 - Effects:
 - Inhibit the Na⁺/Cl⁻ cotransporter in the distal tubule
 - Decrease renal Ca²⁺ excretion
 - Used to treat HTN
 - Less effective at low GFRs; contraindicated in sulfa allergy

- Complications: hypokalemia, hypercalcemia, hyperuricemia, and metabolic alkalosis; thiazides can cause severe hyponatremia and volume depletion in elderly patients.

4) **K⁺-sparing diuretics** (e.g., spironolactone, amiloride):

- Effect: Inhibit the aldosterone-controlled Na⁺ channels (amiloride and triamterene) or block the mineralocorticoid receptor (spironolactone and eplerenone) in the PCs of the collecting duct. The net effect is the same: inhibition of Na⁺ reabsorption and K⁺ secretion in the collecting duct.
- Used to treat HTN, heart failure (HF); used in combination with loop diuretics to minimize hypokalemia
- Complications: hyperkalemia (all K⁺-sparing diuretics) and gynecomastia (spironolactone)

5) **Osmotic diuretics** (mannitol):

- Effect: Diminish Na⁺ and water reabsorption, primarily in the proximal tubule and loop of Henle (It is a nonreabsorbable solute.)
- Rarely used clinically; lose more water than salt
- Complications: hypernatremia; can precipitate pulmonary edema in HF

Table 7-1 provides a summary of the diuretics. Also see [Diuretics on page 7-63](#).

CLINICAL USE OF DIURETICS

Different diuretics have different clinical uses. By far, loop diuretics are the most effective for treating edema from any cause: HF, cirrhosis, nephrotic syndrome, AKI, and CKD. For edema, the other diuretics play important supporting roles. If high-dose loop diuretic is not adequate, add a thiazide diuretic. If hypokalemia develops, add a K⁺-sparing diuretic. If metabolic alkalosis develops, back off or slow down on diuresis; however, if that is not possible or desirable, add a carbonic anhydrase inhibitor.

Thiazide diuretics are a 1st line treatment for HTN; they also are useful in preventing recurrent kidney stones in patients with hypercalciuria, by decreasing urinary Ca²⁺ excretion. In nephrogenic diabetes insipidus, thiazide diuretics decrease polyuria by inducing mild volume depletion and impairing urinary dilution.

Spironolactone has lots of uses! It reduces mortality in patients with systolic dysfunction and a low ejection fraction (see the [Cardiology](#) section). Spironolactone is the 1st line agent for treatment of HTN in primary aldosteronism and for ascites in cirrhosis. The main side effect (aside from hyperkalemia) is gynecomastia; if this happens, use eplerenone instead. Eplerenone is also an aldosterone antagonist but has greater specificity for the mineralocorticoid receptor—and thus has fewer off-target effects.

Table 7-1: Summary of Diuretics

Diuretic	Examples	Site of Action	Clinical Indications
Carbonic anhydrase inhibitors	Acetazolamide	Proximal tubule	Edema + metabolic alkalosis Prevention of acute altitude sickness Glaucoma Hyperkalemic and hypokalemic periodic paralysis
Loop diuretics	Furosemide Torsemide Ethacrynic acid	Ascending limb of the loop of Henle	Edema in: • Nephrotic syndrome • Heart failure • Cirrhosis • AKI • CKD
Thiazide diuretics	Hydrochlorothiazide Chlorthalidone Metolazone	Distal tubule	Hypertension Kidney stones (hypercalciuria) Edema in HF (in combination with loop diuretic) Nephrogenic diabetes insipidus
K ⁺ -sparing diuretics	Spironolactone Eplerenone	Cortical collecting tubule (mineralocorticoid receptor)	Hypertension (especially primary hyperaldosteronism) Heart failure with reduced ejection fraction (spironolactone and eplerenone) Cirrhotic ascites Edema + hypokalemia
	Amiloride Triamterene	Cortical collecting tubule (Na ⁺ channels)	Edema + hypokalemia
Osmotic diuretics	Mannitol	Proximal tubule + loop of Henle	Cerebral edema

ACUTE KIDNEY INJURY (AKI)

PREVIEW | REVIEW

- What is the definition of oliguria? Anuria?
- What is the underlying cause of prerenal kidney injury?
- With postrenal acute kidney injury (AKI), how does the amount of urine produced relate to the degree of obstruction?
- What are the clinical manifestations of emboli caused by vascular manipulation?
- What causes do you consider in a patient with HTN and severe AKI after initiation of an ACEI/ARB?

OVERVIEW

The term “acute renal failure” has been replaced with “acute kidney injury” (AKI) to better represent a wide spectrum of potential kidney damage—not just failure.

A small increase in serum creatinine can indicate a significant decline in GFR. Evaluate AKI by considering prerenal, postrenal, vascular, and intrinsic renal causes.

The Kidney Disease Improving Global Outcomes (KDIGO) 2012 Clinical Practice Guidelines define AKI as any 1 of the following:

- 1) Increase in the serum creatinine by 0.3 mg/dL (26.5 μ mol/L) within 48 hours **or**
- 2) 1.5-fold increase over baseline within the past 7 days **or**
- 3) Oliguria (urine output < 0.5 mL/kg/hour) for at least 6 hours

AKI can be nonoliguric, oliguric (urine output < 0.5 mL/kg/h), or anuric (urine output < 50–100 mL/day).

Anuria is rare. When it does occur, it is usually caused by severe shock, complete bilateral urinary tract obstruction, renal cortical necrosis, bilateral renal arterial occlusion, or rapidly progressive (crescentic) glomerulonephritis.

Refer to Table 7-2 on page 7-10 and Table 7-3 on page 7-10 while reading about AKI.

Prerenal AKI is caused by underperfusion, either from true loss of intravascular volume or decreased effective arterial blood volume.

Intrinsic AKI is caused by disease or damage to the glomeruli, tubules, interstitium, or vascular structures.

Postrenal AKI is caused by obstruction of the urinary tract.

Vascular disease can cause AKI when it leads to ischemia or infarction of both kidneys.

Table 7-2: Acute Kidney Injury Labs and Clues

Category	Causes	Urine Sediment	FE _{Na} [*]	FE _{Urea}	U _{Osm} (mOsm/kg)	U _{Na} (mEq/L)
Prerenal	Volume depletion Heart failure Liver failure NSAIDs ACEI/ARB	Normal ("bland") Granular casts Hyaline casts	< 1%	< 35%	> 400	< 20
Intrinsic renal	ATN	Granular (muddy-brown) casts	> 2%	> 50%	300–350	> 20
	Glomerulonephritis	Dysmorphic RBCs and/or red cell casts	< 1%	(No data)	(No data)	< 20
	AIN	WBCs and/or WBC casts	> 1%	(No data)	(No data)	> 20
Postrenal	Bilateral ureteral obstruction Unilateral ureteral obstruction with solitary kidney Urethral obstruction	RBCs or bland	Varies	Varies	Varies	Varies
Vascular	Atheroembolic	WBCs, eosinophiluria	(No data)	(No data)	(No data)	(No data)
	Renal infarction, renal vein thrombosis	RBCs	(No data)	(No data)	(No data)	(No data)
	Ischemic nephropathy	Normal ("bland")	< 1%	(No data)	(No data)	< 20

^{*} Recent diuretic use can alter the FE_{Na}; in this setting, FE_{Urea} and FE_{Uric acid} are more reliable.

AIN = acute interstitial nephritis
ATN = acute tubular necrosis

FE_{Na} = fractional excretion of sodium
FE_{Urea} = fractional excretion of urea

U_{Na} = urinary sodium concentration
U_{Osm} = urine osmolality

Table 7-3: Types of Acute Kidney Injury and Presenting Findings

Category	Suspect in a Patient with:
Prerenal	Bleeding Heart failure (cardiorenal) Cirrhosis (hepatorenal) Nephrotic syndrome GI fluid loss (nausea/vomiting/diarrhea) NSAID or ACEI/ARB use Diuretic use
Intrinsic renal	Hypotension, shock (ATN) Sepsis (ATN) Drugs (ATN: aminoglycosides, amphotericin, cisplatin, NSAIDs) Contrasts/IV dyes (contrast-induced nephropathy) Drugs (AIN; any antibiotic, pantoprazole) SLE (GN) Vasculitis (GN) Endocarditis (IRGN) Heroin (if nephrotic, think FSGS) Myeloma (cast nephropathy) Malignant HTN
Vascular	Atheroembolic disease, renal infarction, renal vein thrombosis, ischemic nephropathy
Postrenal	Urinary tract symptoms (i.e., older men with hesitancy, weak stream, nocturia) Risk factors for abdominal or pelvic malignancy

AIN = acute interstitial nephritis
ATN = acute tubular necrosis
FSGS = focal segmental glomerulosclerosis
HTN = hypertension
PIGN = postinfectious glomerulonephritis
SLE = systemic lupus erythematosus

In all patients with AKI, look for nephrotoxin and contrast exposure, volume status, and episodes of hypotension. Check orthostatic vital signs, U/A, fractional excretion of Na⁺, and renal U/S.

AKI — EVALUATION AND TREATMENT

For all patients with AKI, evaluate:

- Volume status—especially volume overload (e.g., HF, pulmonary edema)
- Electrolytes—especially look for hyperkalemia, hyperphosphatemia, and hypocalcemia
- Acid-base status—metabolic acidosis
- Uremic symptoms such as decreased mental status and pericarditis

Initial treatment depends on the suspected cause. For example:

- If urinary retention is suspected (e.g., elderly male with bladder distention), place a **urinary catheter**. This can be a diagnostic and therapeutic procedure.
- Treat hyperkalemia with ECG changes (e.g., peaked T waves) with immediate medical therapy (IV calcium gluconate or calcium chloride, insulin + glucose, albuterol, sometimes bicarbonate [HCO₃⁻]). Dialyze if unresponsive. See [Hyperkalemia on page 7-54](#) for more information.
- Treat hyperphosphatemia with dietary phosphate restriction and oral phosphate binders. Treat hyperphosphatemia before giving IV Ca²⁺ to treat hypocalcemia—normalizing phosphate level often corrects the Ca²⁺ level.

- Treat severe metabolic acidosis ($\text{pH} < 7.2$) with IV sodium bicarbonate.
- Treat volume overload (pulmonary edema, severe peripheral edema) with loop diuretics.

Indications for urgent dialysis in AKI:

- Hyperkalemia refractory to medical treatment
- Metabolic acidosis refractory to medical treatment
- Severe volume overload refractory to diuretics
- Severe uremic symptoms, especially uremic pericarditis

PRERENAL AKI

Causes of Prerenal AKI

Prerenal AKI is, by definition, due to a real or “effective” **decrease** in GFR due to hemodynamic changes—most often, decreased renal **perfusion**, as seen in:

- Volume depletion, blood loss, hypotension, or diuretics (common; treated with volume expansion)
- Heart failure (cardiorenal syndrome)
- Drugs that cause vasoconstriction of the afferent arterioles:
 - NSAIDs
 - Calcineurin inhibitors (CNI; cyclosporine, tacrolimus)
- Drugs that cause vasodilation of the efferent arterioles: angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs)
- Hepatorenal syndrome
- Abdominal compartment syndrome

Know: ACEIs/ARBs exacerbate prerenal AKI by blocking AT II-mediated constriction of the efferent arteriole (which maintains GFR in situations of low renal plasma flow), and NSAIDs block the prostaglandins that provide afferent vasodilation. Stop these drugs in any patient with AKI. If the patient has no evidence of hypovolemia on physical exam, consider the other causes listed above—all are associated with reduced glomerular perfusion.

An additional clue to a specific prerenal cause of AKI is NSAIDs in the history. As discussed in **Other Drug-Induced Nephropathies on page 7-28**, NSAIDs cause **constriction** of the **afferent** arteriole and a decrease in GFR in patients who are prostaglandin dependent to maintain GFR, specifically those patients who have comorbidities with preexisting, decreased effective arterial blood volume such as systolic dysfunction or cirrhosis.

Hepatorenal syndrome is a form of prerenal AKI seen in patients with advanced hepatic cirrhosis. Severe vasomotor disturbance caused by splanchnic dilation leads to renal hypoperfusion. There is almost always evidence of **portal HTN** (think ascites, esophageal varices, splenomegaly, leukopenia, thrombocytopenia, anemia) and **jaundice**.

Diagnostic criteria for hepatorenal syndrome, as established by the International Club of Ascites (2015):

- Cirrhosis with ascites and evidence of portal HTN
- A serum creatinine $> 1.5 \text{ mg/dL}$ ($132.6 \text{ } \mu\text{mol/L}$) that progresses over days to weeks
- Lack of improvement in renal function after withdrawal of diuretics and volume expansion with albumin (1 g/kg of body weight per day up to 100 g/day) for at least 2 days
- No evidence of parenchymal kidney disease (i.e., normal U/A, proteinuria $< 500 \text{ mg/day}$, normal renal U/S)
- Absence of any other apparent cause of AKI, including shock, nephrotoxins, and infection (except peritonitis)

Therapy with midodrine and octreotide is aimed at stabilizing patients until they receive a liver transplant.

Abdominal compartment syndrome is a rare cause of prerenal AKI. Abdominal compartment syndrome refers to organ dysfunction caused by intraabdominal HTN (sustained intraabdominal pressure $> 20 \text{ mmHg}$, with or without abdominal perfusion pressure $< 60 \text{ mmHg}$).

Elevated intraabdominal pressure reduces blood flow to the abdominal viscera. Abdominal compartment syndrome can occur with abdominal trauma, massive ascites, intraperitoneal bleeding, acute pancreatitis, and any other condition that raises the intraabdominal pressure. AKI most likely occurs secondary to renal vein compression, which increases venous resistance and impairs venous drainage.

Similar to other causes of prerenal AKI caused by reduced perfusion, the renal indices usually are decreased ($\text{FE}_{\text{Na}} < 1\%$ and $\text{FE}_{\text{Urea}} < 35\%$).

Treat with either surgical decompression (trauma patients) or high-volume paracentesis (in patients with massive ascites).

Prerenal AKI — Labs

BUN:Cr ratio is typically increased to **$> 20:1$** .

Urine is very concentrated with osmolality **$> 400 \text{ mOsm/kg}$** (400 mmol/kg), and often $> 700 \text{ mOsm/kg}$ (700 mmol/kg).

Urine Na^+ is $< 20 \text{ mEq/L}$ (20 mmol/L), indicating normal tubular function (and avid reabsorption of Na^+ reflecting activation of the renin-angiotensin-aldosterone system).

Urine sediment is generally normal but can show granular or hyaline casts.

FE_{Na} is $< 1\%$ in both prerenal AKI and acute GN (see **FE_{Na} and FE_{Urea} on page 7-4**). AKI with an $\text{FE}_{\text{Na}} < 1\%$ and a normal urine sediment $\pm$ a few granular or hyaline casts = **prerenal** azotemia. Dysmorphic red cells, red cell casts, and protein indicate GN.

Patients who are on diuretics can have $FE_{Na} > 1\%$ and still have prerenal AKI. In these situations, FE_{Urea} is more accurate than FE_{Na} . $FE_{Urea} < 35\%$ is suggestive of a prerenal state. You can also use $FE_{Uric\ acid}$ in these situations ($FE_{Uric\ acid} < 12\%$ is suggestive of prerenal AKI). See [Table 7-2 on page 7-10](#).

POSTRENAL AKI

Postrenal AKI (a.k.a. obstructive uropathy) can occur at any point along the urinary tract: the renal papilla and renal pelvis, ureters, bladder, or urethra. Urinary tract obstruction can be either chronic or acute. It can result from external compression (e.g., malignancy) or intraluminal obstruction (e.g., nephrolithiasis). When complete and bilateral (or urethral), urinary tract obstruction can present with anuria. But know that **normal urine output does not rule out obstruction**, particularly when obstruction is chronic and/or partial or intermittent. Obstructed patients can even have increased urine output because of chronic damage to the tubules that impairs their ability to reabsorb water and solutes.

Upper Urinary Tract Obstruction

Obstruction anywhere upstream of the ureterovesical junction is considered upper tract obstruction; most commonly, it occurs at the level of the ureters. Consider unilateral ureteral obstruction if the patient develops AKI and has only 1 kidney. Patients with 2 kidneys generally do not get renal failure from unilateral ureteral obstruction because the 2nd kidney continues to function normally; however, if ureteral obstruction is bilateral, AKI or CKD can ensue.

Ureteral obstruction can be caused by **kidney stones** (more under [Kidney Stones on page 7-35](#)). Acute obstructing nephrolithiasis presents with severe flank pain (i.e., renal colic). Certain **drugs**—especially **methotrexate**, **indinavir**, **acyclovir**, **ganciclovir**, and **sulfa antibiotics**—can cause ureteral obstruction by crystallizing and forming stones.

Intraabdominal **malignancies**, particularly lymphoma and endometrial cancer, can cause upper urinary tract obstruction by compressing the ureters.

Papillary necrosis (the renal papillae are just proximal to the renal pelvis) is rare but can occur in the settings of severe pyelonephritis, chronic analgesic abuse, and sickle cell disease. The sloughed papillae obstruct the urinary tract, often within the kidneys at the level of the renal pyramids and renal pelvis. Patients with papillary necrosis often present with flank pain. U/A shows **sterile pyuria** with or without **WBC casts**.

Retroperitoneal fibrosis is a rare disorder in which there is inflammation and fibrosis in the retroperitoneum that can encase and obstruct the ureters. Often, it is idiopathic. However, it can occur in the setting of IgG4-related disease. For more on IgG4-related disease, see the [Rheumatology](#) section. Retroperitoneal

fibrosis typically presents with back pain and non-specific complaints such as weight loss and fatigue. Ureteral obstruction can be either acute (causing postrenal AKI) or chronic (presenting with atrophic kidneys and advanced CKD). Depending on the etiology, corticosteroids are sometimes used in conjunction with mechanical relief of the obstruction (more under [Obstructive Uropathy — Treatment](#)).

In children, ureteral obstruction is commonly due to **anatomic anomalies** such as stricture at the ureterovesical (ureter-bladder) junction. If undiagnosed or untreated, such children present frequently with advanced CKD in early adulthood, with bilateral renal atrophy.

Ureteral obstruction is usually first diagnosed by U/S, which shows hydronephrosis and/or hydroureter in the absence of bladder distention. CT scan helps determine the site of the obstruction.

Acute Urinary Retention

Acute urinary retention is the sudden onset of lower urinary tract obstruction, occurring at the level of the bladder or urethra. When complete, this can present with anuria and severe renal failure. Patients may have suprapubic pain from the distended bladder. Causes include:

- **Benign prostatic hyperplasia (BPH)**: Patients often (but not always!) report a history of chronic lower urinary tract symptoms, reflecting chronic prostatic hypertrophy. BPH is discussed in the [Women's and Men's Health](#) section.
- **GU malignancy**, especially prostate cancer, bladder cancer, and cervical cancer
- **Kidney stones** that pass through to the bladder also can cause acute urethral obstruction (more under [Kidney Stones on page 7-35](#)).
- **Medications** can cause urinary retention, particularly anticholinergics (e.g., oxybutynin, dicyclomine), sympathomimetics (e.g., phenylephrine, pseudoephedrine), antihistamines (e.g., diphenhydramine), and psychiatric medications (e.g., haloperidol, amitriptyline).
- **Urethral stenosis** also can cause bladder outlet obstruction.

When you suspect acute urinary retention, focus the H&P on eliciting a history of chronic obstructive symptoms, palpating the distended bladder, looking for pelvic masses, performing the prostate exam, and looking for lymphadenopathy. The diagnosis is quickly confirmed or excluded with a bedside bladder ultrasound completed after the patient voids or attempts to void.

Chronic Urinary Retention

Chronic lower urinary tract symptoms are common in aging men and are usually due to **BPH** and consequent

bladder outlet obstruction. However, other etiologies such as **urethral stricture** and **prostate cancer** can sometimes present with chronic symptoms. The same medications that can cause acute urinary retention also can cause chronic problems (more under [Acute Urinary Retention](#)).

Obstructive symptoms include nocturia, urinary frequency, hesitancy, weak stream, and/or incomplete voiding. Renal function (S_{Cr}) should be checked if there is hydronephrosis or high postvoid residual bladder volume. For more information on BPH, see the [Women's and Men's Health](#) section.

Obstructive Uropathy — Diagnosis

Renal insufficiency with elevated creatinine (either acute or chronic) may occur, particularly when obstruction is bilateral, severe, or complete. U/A is typically “bland” (no abnormalities). Chronic obstruction can cause Type 4 RTA (with NAGMA plus **hyperkalemia**).

Lower urinary tract retention can be diagnosed with a bedside bladder ultrasound or postvoid residual measurement. Diagnosis of upper tract obstruction requires a renal U/S or CT scan (if you suspect stones) showing hydronephrosis (dilatation of the renal pelvis; [Figure 7-6](#)) or hydroureter (dilatation of the ureter). Know that hydronephrosis may be absent in ureteral obstruction due to retroperitoneal fibrosis, as the fibrosis can encase the renal pelvis and prevent dilatation.



Figure 7-6: Hydronephrosis from ureteral stones

Obstructive Uropathy — Treatment

Treatment of obstructive uropathy is theoretically simple: Resolve the obstruction. In general, mechanical intervention is indicated acutely, particularly when renal failure is present. For upper tract obstruction, options include placement of percutaneous nephrostomy tubes or ureteral stents. For lower tract obstruction, placement of an indwelling bladder catheter or intermittent bladder catheterization often provides a short-term solution.

Long-term treatment depends on the underlying etiology. Treatment of BPH can include medications (primarily α -blockers such as tamsulosin) and surgical intervention. If malignancy is present, surgery, radiation, and/or chemotherapy may be indicated. Treatment of kidney stones can include lithotripsy and mechanical stone extraction.

VASCULAR AKI

Atheroembolic Disease

Patients who have had vascular manipulation (e.g., cardiac catheterization, angiogram, abdominal aortic aneurism repair) are at risk for atheroembolic disease (a.k.a. cholesterol embolic disease). Unlike contrast-induced nephropathy, this does not cause ATN, but results in delayed kidney injury (after 72 hours) with a gradual deterioration in renal function over weeks to months.

Clinical features include livedo reticularis, eosinophilia, systemic and cutaneous emboli, low serum complement, and a stepwise increase in the creatinine. Hollenhorst plaques also can occur. These are cholesterol emboli in the retinal arterioles appearing as orange-white dots interrupting the circulation. If diagnosis is in doubt, biopsy of 1 of the skin lesions can show a cholesterol embolus.

Treatment of renal disease due to cholesterol emboli is supportive only. Do not anticoagulate.

Renal Infarction

Renal infarction is most often due to thromboembolic disease originating in the heart. Risk factors include atrial fibrillation, mechanical heart valves, and cardiomyopathy. Patients with hypercoagulable states are also at increased risk for renal infarction. Occasionally, renal infarction can occur as a result of a vascular event such as renal artery dissection or aortic dissection involving the renal arteries. Renal infarction must be severe and usually bilateral to cause significant AKI. Septic emboli from infectious endocarditis can sometimes cause renal infarction, though this is seldom severe enough to cause AKI.

Clinical signs of renal infarction include flank pain, hematuria, and elevated LDH. High LDH without other LFT abnormalities? Think renal infarction! Diagnose by CT with contrast (wedge-shaped infarct). Management is usually supportive; however, when infarction is severe and detected early, emergency thrombectomy (by vascular surgery or interventional radiology) may save the kidney. Anticoagulation is usually indicated to prevent recurrent thromboembolic events.

Renal Vein Thrombosis

Thrombosis of the renal vein, like renal infarction, can lead to loss of renal blood flow, ischemia, and AKI. Renal vein thrombosis is most often seen in the setting of hypercoagulable states. Nephrotic syndrome, particularly from membranous nephropathy, is a classic cause of renal vein thrombosis.

Renal vein thrombosis is usually chronic and asymptomatic. Often, it is discovered as an incidental finding on other imaging such as CT to evaluate for pulmonary embolism. However, when renal vein thrombosis is acute and bilateral, flank pain hematuria and acute kidney injury can be seen, resembling renal infarction. If acute complete renal vein thrombosis is suspected, diagnose by CT angiography or MR venography. Kidney ultrasound with Doppler has low sensitivity and can miss the diagnosis. In the absence of AKI or other severe symptoms, treat with anticoagulation alone. Thrombolytics or thrombectomy (by interventional radiology) can be considered if AKI or flank pain are present.

Ischemic Nephropathy

Renovascular disease (i.e., renal artery stenosis) is an important secondary cause of HTN (more under [Renovascular HTN on page 7-61](#)). Renovascular disease is caused by stenosis in one or both renal arteries, either due to atherosclerotic disease or fibromuscular dysplasia. When severe, renovascular disease can lead eventually to chronic renal ischemia and loss of renal function—**ischemic nephropathy**. Ischemic nephropathy usually causes CKD, but occasionally can cause a more rapid deterioration in kidney function (AKI). ACEIs and ARBs can precipitate AKI in patients with bilateral renal artery stenosis. Diagnosis is by kidney ultrasound with doppler (less accurate), CT angiogram, or MR angiogram. Although intervention (e.g., percutaneous angioplasty and stenting) is not usually beneficial for the treatment of the HTN, revascularization can preserve kidney function in patients heading toward renal failure.

INTRINSIC RENAL AKI

The intrinsic causes of AKI require in-depth discussion and are covered under the next 3 main headings:

- 1) **ATN**, discussed first because it is the **most common** cause of **intrinsic renal AKI** (more under [Acute Tubular Necrosis \(ATN\)](#))
- 2) Tubulointerstitial disease (more under [Tubulointerstitial Nephritis on page 7-16](#))
- 3) Glomerular disorders (more under [Glomerular Disorders on page 7-17](#))

ACUTE TUBULAR NECROSIS (ATN)

PREVIEW | REVIEW

- What are some common causes of nephrotoxic (drug-induced) acute tubular necrosis (ATN)?
- What are the lab findings in rhabdomyolysis?
- What are the urine findings in ATN?

OVERVIEW

ATN is the **most common** cause of **intrinsic** AKI—more than interstitial disease or glomerulonephritis. ATN causes ~ 1/2 of the cases of AKI in the hospital.

Tubular dysfunction is the hallmark of ATN. Renal epithelium necrotizes, and the tubules essentially fill up with debris. Failure of tubules to appropriately reabsorb water and solutes leads to activation of tubuloglomerular feedback, leading to a profound decrease in GFR.

ATN follows a 3-phase progression of initiation, maintenance, and recovery:

- 1) **Initiation:** Following the insult, there is an acute and severe decrease in GFR, with associated rapid increases in BUN and serum creatinine.
- 2) **Maintenance:** The severe reduction of GFR usually persists for 1–2 weeks. BUN and creatinine continue to rise.
- 3) **Recovery:** Tubular function returns. Urine volume increases; BUN and creatinine gradually return to normal.

CAUSES OF ATN

Ischemic ATN

Ischemic ATN is the most common form of ATN. It can occur in any form of shock (i.e., hemorrhagic, hypovolemic, cardiogenic, septic) or any condition that causes an **abrupt decrease in renal perfusion**. Frequently, ischemic ATN is seen in ICU settings.

Nephrotoxic ATN

Nephrotoxic ATN has both endogenous and exogenous causes:

- **Endogenous:**
 - Myoglobin (rhabdomyolysis)
 - Free hemoglobin (intravascular hemolysis)
 - Excess uric acid (tumor lysis syndrome)
- **Exogenous:**
 - Contrast-induced nephropathy (iodinated contrast media, used in CT scans and angiography, including cardiac catheterizations); more under [Imaging In CKD on page 7-33](#)
 - Drugs (amphotericin B, **aminoglycosides**, cisplatin, cidofovir, tenofovir, foscarnet, and many others)
 - Osmotic nephropathy (e.g., IVIG with sucrose, mannitol, dextran; patients with CKD are especially vulnerable)
 - Acute phosphate nephropathy (bowel purgatives containing sodium phosphate); more under [Acute Phosphate Nephropathy \(APN\) on page 7-16](#)

Notes on drug-induced nephrotoxic ATN:

- With **amphotericin B**, risk of ATN is based on cumulative dose and is especially likely at > 3 g total dose. Amphotericin B has a direct nephrotoxic effect and

can cause Type 1 or 2 RTA (more under RTAs on page 7-45) and hypomagnesemia. Liposomal forms of amphotericin have a much lower risk of renal toxicity and should always be used if available.

- **Aminoglycosides** cause proximal tubule damage, resulting in a nonoliguric ATN and hypomagnesemia. Correct hypomagnesemia or hypokalemia prior to aminoglycoside treatment to decrease the risk of nephrotoxicity. **Gentamicin** is the most nephrotoxic aminoglycoside. Once-daily dosing of an aminoglycoside is less nephrotoxic than multiple daily doses. Monitor serum levels in all patients getting aminoglycosides for > 72 hours. GFR usually begins to fall 5–7 days after the start of treatment.
- **Cisplatin** is a common chemotherapeutic cause of ATN. It also causes hypomagnesemia.
- **Tenofovir** and **cidofovir** can cause a Fanconi-like syndrome in addition to AKI.
- **Foscarnet** is used to treat ganciclovir-resistant CMV infection. Renal toxicity and hypocalcemia are common; risk is reduced by pretreatment with IV fluids.
- Note: Contrast nephropathy, rhabdomyolysis, and intravascular hemolysis can cause profound renal vasoconstriction with Na^+ retention that can present with a low urine Na^+ and consequent $\text{FE}_{\text{Na}} < 1\%$. This contrasts with other types of ATN, which typically have $\text{FE}_{\text{Na}} > 2\%$.

Heme Pigment–Induced AKI

Hemoglobin and myoglobin are heme pigments that can cause acute tubular injury when present in the circulation at high levels.

AKI from myoglobin can occur in the setting of severe **rhabdomyolysis**. Rhabdomyolysis occurs when muscle damage results in the release of creatine kinase (CK), myoglobin, and electrolytes into the bloodstream. All the following are causes:

- Crush injuries (compartment syndromes), coma, or prolonged immobilization
- Prolonged surgeries
- Strenuous exercise
- Generalized seizures
- Heat stroke
- Severe volume contraction
- Ethanol
- Drugs—cocaine, amphetamines, statins, colchicine, anesthetics causing malignant hyperthermia, neuroleptic malignant syndrome
- Infections—usually viral, especially influenza A and B
- Endocrinopathies—diabetic ketoacidosis, hypothyroidism, hyperthyroidism, and pheochromocytoma
- Electrolyte abnormalities—severe hypokalemia, hypophosphatemia (e.g., in alcoholics during refeeding)

Patients present as a result of the underlying cause and/or with muscle tenderness and cola-colored urine. Labs show increased CK > 100,000 U/L with increases in AST and ALT. It is important to be sure that there is no component of prerenal azotemia contributing to the AKI. Creatinine is typically elevated. Hyperkalemia, hyperphosphatemia, increased uric acid, and hypocalcemia are common complications. U/A shows muddy-brown casts consistent with ATN. The urine is colored brown due to myoglobin pigment. The urine test strip is positive for blood, but no RBCs are visible in the sediment on microscopy.

Early in rhabdomyolysis, hypocalcemia is common, caused by deposition of calcium phosphate in damaged muscle and other tissues.

In recovery, patients can have significant hypercalcemia from mobilization of Ca^{2+} tissue deposits formed during the acute phase. To minimize risk of late hypercalcemia, do not treat early hypocalcemia with calcium replacement unless it is severe or the patient is symptomatic.

Treat as soon as possible with aggressive isotonic fluid resuscitation (1–2 L/hour for the first few hours). After initial resuscitation, continue IV fluids unless/until the patient shows signs of volume overload. Consider using isotonic IV sodium bicarbonate instead of isotonic saline: Alkalinization of the urine may prevent myoglobin-induced tubular damage, though clinical evidence is limited. However, do not use sodium bicarbonate if hypocalcemia is present (it can precipitate seizures) or if the patient is already alkalotic (arterial pH > 7.5 and/or serum bicarb > 30 mEq/L [30 mmol/L]). Watch out for hyperkalemia. Use loop diuretics only to treat volume overload. Dialysis is used in severe cases.

Hemoglobinuria has urine findings similar to those seen in rhabdomyolysis (dipstick positive for heme, but few or absent RBCs on microscopic exam of the urine sediment). Hemoglobin can be released from severe intravascular hemolysis. It also can cause ATN—not due to toxicity, but rather mechanical obstruction from heme pigment casts. Treatment is the same as for rhabdomyolysis.

Contrast-Induced Nephropathy

Contrast-induced nephropathy is defined as acute kidney injury 24–48 hours of contrast exposure. Typically, it resolves spontaneously over days to weeks.

The best way to prevent contrast-induced nephropathy is by avoiding the use of contrast agents, especially in high-risk patients. Use noncontrast CT, MRI, or U/S.

If contrast must be used:

- Avoid volume depletion.
- Administer IV normal saline before and after contrast exposure.
- Randomized trials have failed to demonstrate a benefit of *N*-acetylcysteine (NAC), although some providers still use it in high-risk patients.

- Use the lowest possible volume of contrast.
- Use a low-osmol or isoosmolar contrast agent.
- Avoid NSAIDs.
- Avoid gadolinium (used in MRIs) in patients with estimated GFR < 30 mL/minute/1.73 m². Although it does not cause AKI, it can cause systemic nephrogenic fibrosis in CKD and end-stage renal disease (ESRD) patients.

Acute Phosphate Nephropathy (APN)

APN is a form of AKI that occurs after the use of bowel purgatives containing sodium phosphate. Transient hyperphosphatemia after ingestion or enema containing sodium phosphate leads to an increased intratubular phosphate concentration. This precipitation and tissue deposition of calcium phosphate salts in turn leads to luminal obstruction and direct tubular epithelial injury.

Risk factors for developing APN include underlying kidney dysfunction (GFR < 60 mL/minute/1.73 m²), advanced age, volume depletion, HTN, diabetes, and use of ACEIs or ARBs.

The diagnosis of APN is suggested by AKI with a recent history of receiving bowel purgatives that contain **sodium phosphate**. Confirm the diagnosis by the presence of hyperphosphatemia out of proportion to the degree of kidney injury (or preceding kidney injury).

Prevention: Avoid use of bowel purgatives that contain **sodium phosphate** in high-risk patients.

LABS IN ATN

BUN and Cr rise rapidly early in ATN. BUN:Cr ratio remains normal at 10:1 to 15:1 (> 20:1 suggests prerenal disease). Urine osmolality is usually < 350 mOsm/kg (< 350 mmol/kg) because tubules cannot concentrate the urine. Urine Na⁺ is > 40 mEq/L (40 mmol/L). FE_{Na} is typically > 2%. However, FE_{Na} can be low in contrast-induced nephropathy, severe rhabdomyolysis, and hemoglobinuria. Granular casts in the urine are a hallmark finding of ATN: **muddy-brown, "dirty" granular casts** (C in Figure 7-1 on page 7-2) and renal tubular epithelial cell casts. Sometimes, tubular epithelial cells are seen.

If severe volume depletion is the cause for ATN, then labs can be consistent with a prerenal picture (high BUN:Cr ratio, low urine Na⁺, and low FE_{Na}).

MANAGEMENT OF ATN

Initial management of ATN includes treating the precipitating cause and any accompanying hyperkalemia or metabolic acidosis. Maintain normovolemia, adequate blood pressure, and nutritional support (which decreases catabolism). Discontinue nephrotoxins, including ACEIs/ARBs and NSAIDs. Avoid contrast exposure.

Oliguric ATN usually resolves in 1–4 weeks. Note that oliguria is **not** required for the diagnosis of ATN. However, patients with oliguric ATN are more prone to hyperkalemia and volume overload, so dialysis is often needed earlier.

TUBULOINTERSTITIAL NEPHRITIS

PREVIEW | REVIEW

- Characterize the clinical presentation of acute interstitial nephritis (AIN).
- What glomerular pathologic lesion is seen in patients with NSAID-induced AIN?

OVERVIEW

Interstitial nephritis is characterized by inflammation of the interstitium. Tubular and interstitial diseases have only low-grade proteinuria (< 1–1.5 g/day), and they can cause a NAGMA.

ACUTE INTERSTITIAL NEPHRITIS

Acute (or allergic) interstitial nephritis (AIN) is most often a drug-induced **hypersensitivity** reaction that can cause fever, eosinophilia, and rash. Only 10% of patients have all 3. More often, presentation is unexplained AKI.

The drugs most frequently implicated in AIN include NSAIDs, antibiotics, proton pump inhibitors (e.g., pantoprazole), thiazides, allopurinol, and cimetidine. AIN is an idiosyncratic response to the drug and generally is not related to cumulative dose.

These are the most common antibiotic culprits:

- β -lactams (especially nafcillin or oxacillin)
- Trimethoprim/sulfamethoxazole (TMP/SMX)
- Rifampin
- Ciprofloxacin and, less often, other fluoroquinolones

Remember: Proton pump inhibitors are a major cause of interstitial nephritis.

AIN also can be caused by sarcoidosis, systemic lupus erythematosus (SLE), Sjögren syndrome, transplant rejection, and infection (e.g., pyelonephritis, *Legionella*, streptococci).

The urine sediment in AIN contains few RBCs, WBCs, +/- WBC casts. There is mild proteinuria (< 1 g/day, if quantified). RBC casts are generally not seen. Urinary eosinophils may be present, but this finding is nonspecific; routine testing for urinary eosinophils is no longer recommended. Peripheral blood eosinophilia is sometimes observed in severe cases. FE_{Na} is typically > 1%. NAGMA and Fanconi syndrome can occur if there is proximal tubular damage. Diagnosis of AIN is by renal biopsy, but often patients are treated empirically.

NSAID-induced AIN is different in that the NSAIDs are typically ingested for **months** before symptoms occur. Rash, fever, and eosinophilia are frequently absent. **Contrary** to all other types of AIN, NSAID-induced AIN commonly causes **nephrotic-range proteinuria**, and biopsy shows glomerular changes of **minimal change disease**.

Treatment includes discontinuing the offending drug and observing the patient. Consider steroids in severe cases (usually after biopsy confirmation). Steroids are beneficial if started within the first 2 weeks of the injury.

TINU syndrome (a.k.a. acute tubulointestinal nephritis and uveitis) was first described in 1975. Younger females are usually affected. An elevated modified C-reactive protein (mCRP) and renal biopsy help with the diagnosis. Treat with systemic steroids.

CHRONIC INTERSTITIAL NEPHRITIS

Chronic interstitial nephritis is caused by:

- Drugs—analgesics, cyclosporine, tacrolimus, lithium, cisplatin, proton pump inhibitors, and aristolochic acid
- Heavy metals—especially lead and cadmium
- Chronic obstruction
- Infections—chronic pyelonephritis, reflux nephropathy, tuberculosis
- Sarcoidosis
- Autoimmune diseases—systemic lupus erythematosus, Sjögren syndrome
- Sickle cell disease
- Multiple myeloma

Historically, chronic use of analgesic combinations containing phenacetin (a prodrug of acetaminophen), aspirin (acetylsalicylic acid), and caffeine or codeine was an important cause of chronic interstitial nephritis, papillary necrosis, and CKD—a syndrome called analgesic nephropathy. The incidence of analgesic nephropathy fell dramatically after phenacetin was withdrawn from the market and combination analgesics were restricted to prescription use. Avoid long-term use of analgesic combinations containing acetaminophen, aspirin, and/or caffeine or codeine.

Whether chronic use of individual analgesics (acetaminophen or NSAIDs) can cause CKD in previously healthy individuals is controversial. However, chronic use of NSAIDs may worsen renal function (both acutely and chronically) in patients with underlying CKD and should be avoided in these patients.

Rarely, patients may be exposed to lead via their **occupation** (working with batteries, solder, cabling, ceramics, tin, mining; construction workers may be exposed to lead-based paint), drinking **moonshine** (lead in moonshine is very rare), taking alternative **herbal medications** from India and China, using **lead-glazed plates** or **cookware**, and smoking **marijuana**. Nephropathy usually develops after years of chronic lead exposure and presents as azotemia, a tiny bit of proteinuria, hyperuricemia, and a bland

urine sediment. ~ 50% of patients develop gouty arthritis, termed “**saturnine gout**.” The serum lead level is often normal in this condition; lead chelation testing (e.g., with EDTA) is required to establish the diagnosis.

Remember: Lithium can cause both chronic interstitial nephritis and nephrogenic diabetes insipidus (DI). Sometimes, both are seen in the same patient!

Herbs containing **aristolochic acid**, ingested as weight-loss agents, can also cause kidney failure from chronic interstitial nephritis.

GLOMERULAR DISORDERS

PREVIEW | REVIEW

- What are the systemic manifestations of nephrotic syndrome?
- Rapidly progressive glomerulonephritis (RPGN) has which hallmark finding on renal biopsy?
- What are the 3 major causes of RPGN?
- What is the empiric treatment for RPGN?
- In addition to anti-glomerular basement membrane (anti-GBM) antibodies, which pathologic feature defines Goodpasture syndrome?
- What are the most common sites of primary infection in patients with poststreptococcal glomerulonephritis (GN)?
- How long after the original infection does renal failure from poststreptococcal GN start?
- What are the complement levels in patients with infection-related GN?
- Which infections are associated with development of immune complex-mediated membranoproliferative glomerulonephritis?
- What are the findings on renal biopsy in patients with IgA nephropathy?
- What are the 3 key features of nephrotic syndrome?
- What drugs and diseases are associated with minimal change disease (MCD)?
- Under polarized light, “Maltese crosses” are seen in the urine sediment of patients with which syndrome?
- What is the treatment of MCD?
- What racial group has the highest incidence of focal segmental glomerulosclerosis (FSGS)?
- What is the treatment of primary FSGS?
- Solid tumors are associated with which glomerular disease?
- Which renal tubular acidosis is associated with diabetic nephropathy?
- What is the classic finding seen on kidney biopsy in a patient with diabetic nephropathy?

OVERVIEW

Glomerular diseases can be divided into 2 categories, based on clinical presentation and mechanism of disease:

- 1) **Glomerulonephritis (GN)** is an **inflammatory process** that presents with proteinuria (commonly < 2 g/day) and an active urine sediment: always RBCs (often dysmorphic RBCs; A in [Figure 7-1 on page 7-2](#)), with or without WBCs, **RBC casts** (B in [Figure 7-1 on page 7-2](#)), and WBC casts. Disease can be mild and indolent (hematuria and proteinuria with normal or slowly decreasing renal function) or acute and severe (rapidly progressive renal failure, HTN, and edema).
- 2) **Nephrotic syndrome** is a noninflammatory process that presents with heavy proteinuria (> 3.5 g/day) and edema. The glomerulus is leaky to both protein and fat, and urine fat appears in the form of fatty casts or oval fat bodies (D and E in [Figure 7-1 on page 7-2](#)), which appear as Maltese crosses under polarized light. Hematuria is usually absent; renal function may be normal or decreased. Hypoalbuminemia, edema, hypercholesterolemia, and hypercoagulability are classic features of nephrotic syndrome.

Know that some glomerular diseases (e.g., antineutrophil cytoplasmic antibody [ANCA]-associated vasculitis) usually cause GN, while others (e.g., minimal change disease) usually cause nephrotic syndrome. However, some glomerular diseases (e.g., SLE, membranoproliferative glomerulonephritis [MPGN]) can have either presentation.

The causes of glomerular disease can be either primary renal (usually idiopathic) or secondary to a systemic disease.

For patients with suspected glomerular disease, start with a good H&P and targeted serologic workup. Renal biopsy is required for definitive diagnosis of most glomerular diseases except diabetic nephropathy, which is usually diagnosed clinically.

A strategy that helps classify the glomerular diseases:

- 1) Is the clinical picture suggestive of **glomerulonephritis** or **nephrotic syndrome**?
- 2) If you suspect glomerulonephritis, are the complement levels **low** or **normal**?
- 3) Does the patient have **systemic** findings by history and physical exam, or is the presentation limited to the **kidneys**? (Note: Edema and HTN are kidney, not systemic, manifestations.)

As soon as you see a **nephritic** picture, do serologic testing. Serologies for GN should always include complements (C3 and C4). Even if the patient presents with a history of classic infection-related GN, measure complement levels! Depending on the patient's age, gender, and other features on H&P, other useful serologic tests may include ANA, anti-double-stranded DNA (anti-dsDNA), ASO, ANCA, anti-GBM antibody, HBV, HCV, and HIV testing.

Refer to [Table 7-4](#), [Table 7-5](#), and [Table 7-6 on page 7-24](#) as you go through the glomerular disorders.

GLOMERULONEPHRITIS (GN)

Rapidly Progressive GN (RPGN)

The most aggressive syndrome of acute GN is RPGN. RPGN is a **clinical syndrome of acute GN** with rapidly worsening eGFR (over days to weeks). Kidney biopsy usually shows glomerular **crescents** (**extracapillary proliferation**) inside Bowman capsule ([Figure 7-7 on page 7-20](#)).

Table 7-4: Classification of Glomerulonephritis According to Complement Levels

Complement Level	Renal-Limited GN	Systemic Causes of GN
Low	Complement-mediated MPGN	Immune complex-mediated MPGN Lupus nephritis Infection-related GN (including endocarditis) Cryoglobulinemia
Normal	Renal-limited vasculitis (usually ANCA+)	ANCA-associated vasculitis (3 systemic forms): • Granulomatosis with polyangiitis • Microscopic polyangiitis • Eosinophilic granulomatosis with polyangiitis
	Renal-limited anti-GBM disease	Systemic anti-GBM disease ("Goodpasture syndrome")
	IgA nephropathy	IgA vasculitis
	Alport syndrome (can occur without ear and eye manifestations)	Alport syndrome (with sensorineural hearing loss, anterior lenticonus)

ANCA = antineutrophil cytoplasmic antibody
GBM = glomerular basement membrane
MPGN = membranoproliferative glomerulonephritis

Table 7-5: Glomerulonephritis — Detailed Summary

Classification	Complement Level	Cause	Presentation	Treatment	Notes
Renal-limited presentation	Low	Complement-mediated MPGN	Hematuria, proteinuria (sometimes nephrotic-range), and progressive renal insufficiency	Not well established; plasma exchange, rituximab, and cyclophosphamide have been used	Complements stay low > 3 months. Types include dense deposit disease, C3 glomerulopathy, and C4 glomerulopathy.
	Normal	Renal-limited vasculitis	RPGN HTN	High-dose steroids + cyclophosphamide or rituximab Plasmapheresis if renal failure is severe	Pathology is identical to GPA and MPA (crescentic GN with negative IF). Usually ANCA+
		Anti-GBM disease (renal-limited)	RPGN HTN	Plasmapheresis + high-dose steroids + cyclophosphamide	30–50% of patients with anti-GBM disease have no pulmonary manifestations.
		IgA nephropathy	Gross hematuria after viral illness (no latent period) or persistent microscopic hematuria	ACEIs/ARBs if proteinuria is present Steroids if proteinuria is heavy Cyclophosphamide if RPGN and crescents on biopsy	Best prognosis for patients with intermittent hematuria; may progress in patients with proteinuria
		Alport syndrome	Hematuria Hearing loss Lens abnormalities Family history of kidney disease	ACEIs/ARBs	X-linked (recessive) is most common
Systemic presentation	Low	Immune complex-mediated MPGN (e.g., due to hepatitis C or monoclonal gammopathy) Lupus nephritis Cryoglobulinemia	Systemic features, including fever, skin lesions, arthritis Presents with variable proteinuria—sometimes in nephrotic range	Varies by underlying cause Treat any underlying infection, autoimmune, or lymphoproliferative disorder. Proliferative lupus nephritis treated with cyclophosphamide or mycophenolate + steroids	Serologic testing can help determine etiology: HCV/ HBV, SPEP/UPEP (to identify a monoclonal gammopathy), ANA and anti-dsDNA (for SLE), ASO and blood cultures (for endocarditis), cryoglobulins. Immune complex deposits seen on kidney biopsy (EM)
		IRGN	Abrupt onset weeks after strep or staph infection (especially skin or oropharynx) Insidious onset in the setting of endocarditis or other chronic infections.	Treat the infection, supportive care	Latent period between infection and symptoms Check for antibodies of antecedent strep infection.
	Normal	ANCA-associated vasculitis (MPA, GPA, and eosinophilic granulomatosis with polyangiitis)	RPGN Constitutional symptoms Sinusitis Cough Dyspnea Hemoptysis Purpura	High-dose steroids + cyclophosphamide or rituximab + Plasmapheresis if severe renal failure or pulmonary hemorrhage is present	Requires urgent renal biopsy: crescentic GN with negative IF
		Anti-GBM antibody disease (Goodpasture syndrome)	RPGN and pulmonary hemorrhage (shortness of breath, cough, hemoptysis) Severe respiratory failure and death can occur.	Plasmapheresis + high-dose steroids + cyclophosphamide	Requires urgent renal biopsy: crescentic GN with linear staining on IF

ANCA = antineutrophil cytoplasmic antibody
ASO = antistreptolysin O
C3, C4 = complements
dsDNA = double-stranded DNA
EM = electron microscope
GBM = glomerular basement membrane

GN = glomerulonephritis
GPA = granulomatosis with polyangiitis
HTN = hypertension
IF = immunofluorescence
IRGN = infection-related glomerulonephritis
MPA = microscopic polyangiitis

MPGN = membranoproliferative glomerulonephritis
RPGN = rapidly progressive glomerulonephritis
S_C = serum creatinine
SPEP = serum protein electrophoresis
UPEP = urine protein electrophoresis

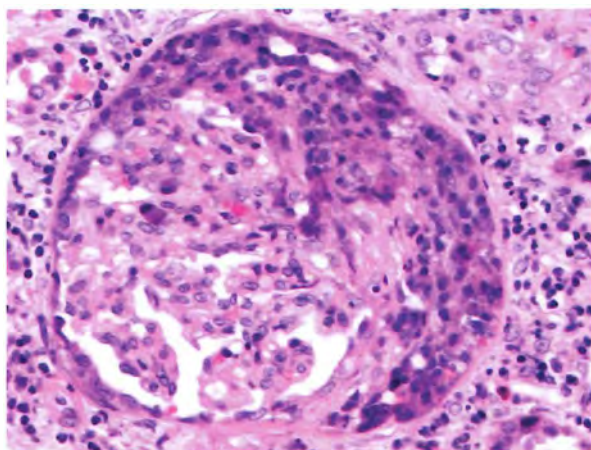


Figure 7-7: Crescentic glomerulonephritis: Bowman space filled with inflammatory cells and fibrosis

In RPGN, creatinine is typically > 3 mg/dL. The urine has protein, red cells, and sometimes RBC casts. Other findings depend on the underlying disease causing the RPGN. There are 3 major causes of RPGN:

- 1) Anti-GBM antibody disease (Goodpasture syndrome)
- 2) ANCA-associated glomerulonephritis
- 3) Immune complex-mediated GN such as IgA nephropathy, lupus nephritis, immune complex-mediated MPGN (e.g., due to cryoglobulinemia in hepatitis C infection), and infection-related GN

Note that while anti-GBM antibody disease and ANCA-associated GN typically present with RPGN (including crescents on biopsy), the diseases that cause immune complex-mediated GN usually **do not** cause RPGN or glomerular crescents. More commonly, these diseases cause a more slowly progressive form of GN without crescents.

Always consider RPGN if a patient presents with severe and progressive renal failure of recent onset with an active urinary sediment. If RPGN is suspected, quickly obtain kidney biopsy and do serologic testing, including ANCA, anti-GBM antibodies, and complements.

Treat suspected RPGN empirically with high-dose IV methylprednisolone while waiting for results of the kidney biopsy and serologic testing. Once the diagnosis is confirmed, add specific therapy based on the underlying disease (e.g., cyclophosphamide + plasmapheresis for anti-GBM disease).

Summary of RPGN: **rapidly progressive** renal failure with **active** urine sediment; renal biopsy shows **crescents**; most common causes are anti-GBM antibody disease and ANCA-associated GN; treat empirically with steroids then focus treatment on underlying disease once diagnosis is confirmed.

Anti-Glomerular Basement Membrane (Anti-GBM) Antibody Disease

Anti-GBM antibody disease causes crescentic RPGN with positive anti-GBM antibodies in the serum, with or without pulmonary hemorrhage. When **pulmonary**

hemorrhage is present (50–70% of patients), the disease is called **Goodpasture syndrome**. Patients with Goodpasture syndrome present with an **active** urine sediment and **hemoptysis with dyspnea**. Younger male patients are more likely to present with Goodpasture syndrome and older females with renal-limited anti-GBM disease.

In anti-GBM disease, antibodies formed in response to an unknown stimulus attack the glomerular (and sometimes pulmonary) basement membrane(s).

Diagnosis is by renal biopsy, which shows crescentic GN (Figure 7-7) and linear IgG deposits along the GBM on immunofluorescence (IF). Linear IgG, along with positive serologic testing for anti-GBM antibodies, distinguishes anti-GBM disease from ANCA-associated vasculitis (where the IF is negative).

Treatment of anti-GBM disease, whether renal-limited or with pulmonary hemorrhage, is urgent plasma-pheresis (to remove the antibodies) and aggressive immunosuppression (steroids + cyclophosphamide). Prognosis depends on the severity of disease at presentation.

Antineutrophil Cytoplasmic Antibody (ANCA)-Associated Vasculitis

ANCA-associated vasculitis can cause crescentic RPGN. Subtypes include:

- Granulomatosis with polyangiitis (GPA)—distinguishing feature: granulomas. Clinical features include:
 - **Upper respiratory disease** (e.g., sinusitis, epistaxis)
 - Lower respiratory disease (e.g., hemoptysis, infiltrates, cavitary lesions, diffuse alveolar hemorrhage [DAH])
 - Usually proteinase-3 (PR3)-ANCA+
- Microscopic polyangiitis (MPA)—necrotizing vasculitis but no granulomas. Clinical features include:
 - DAH
 - **Mononeuritis multiplex**
 - Cutaneous small-vessel vasculitis (palpable purpura)
 - Usually myeloperoxidase (MPO)-ANCA+
- Eosinophilic granulomatosis with polyangiitis. These are variously discussed in the **Rheumatology** section and the **Pulmonary Medicine** section:
 - Asthma/Atopy
 - **Eosinophilia**
 - Crescentic GN/RPGN is less common.

Signs and symptoms of ANCA-associated vasculitis depend on the organs affected. With GPA and MPA, there is usually RPGN (hematuria, proteinuria, rapid deterioration in eGFR), along with the extrarenal findings listed above. Laboratory testing shows normal complements and positive ANCA (either PR3 or MPO). (See the **Rheumatology** section for a discussion of types of ANCAs.) Diagnosis is by kidney biopsy, which shows crescentic GN on light microscopy, but negative immunofluorescence.

Treat ANCA-associated glomerulonephritis aggressively and urgently with pulse intravenous solumedrol, and either cyclophosphamide or rituximab. Early treatment is critical to prevent irreversible loss of kidney function. When the diagnosis is suspected clinically, treatment with IV solumedrol should be started even before the kidney biopsy and ANCA results are available! Plasmapheresis is beneficial in severe disease (pulmonary hemorrhage or severe renal failure).

Infection-Related GN

The most common form of infection-related GN (IRGN; formerly known as postinfectious glomerulonephritis [PIGN]) is seen after Group A β -hemolytic streptococcal infection of the skin or throat. This entity had been called “poststreptococcal GN.” On renal pathology, there is an immune-complex GN. Other organisms such as *Staphylococcus* and sites (e.g., infectious endocarditis, atrioventricular shunt infection) also cause IRGN.

Signs and symptoms of IRGN include hematuria (gross or microscopic), elevated serum creatinine, HTN, and/or edema. With poststreptococcal GN, renal injury is seen 1–6 weeks after the initial illness (average 10 days after throat infections, 2–4 weeks after skin infections). The **latency period** is a diagnostic clue and differs from IgA nephropathy, which is **synpharyngitic**; that is, within 3 days of the pharyngitis episode. Throat cultures may grow β -hemolytic streptococci. Urine is often described as the color of cola. With other forms of IRGN (e.g., caused by endocarditis), the infection may be diagnosed at the same times that the renal injury is identified.

Antistreptolysin O (ASO) antibodies are usually elevated in IRGN due to *Streptococcus* and can be diagnostically useful.

Know that an ASO titer generally remains elevated for **several weeks** after a streptococcal infection. Again, complement levels remain low for 6–8 weeks.

IRGN is caused by an antibody-antigen reaction, with the source of the antigen being the infecting agent. Renal biopsy confirms the diagnosis and shows the presence of immune complexes in the glomerulus. In children, renal biopsies are rarely performed because the diagnosis typically can be made via the clinical history + measurement of complement levels and antistreptococcal antibodies. IRGN is less common in adults, so an adult with suspected IRGN usually gets a renal biopsy.

IRGN can cause severe renal failure, but most patients eventually improve with supportive care and treatment of the underlying infection with antibiotics. Most children recover completely in 6–8 weeks; however, adults may not have complete recovery.

Summary of IRGN: gross and/or microscopic hematuria, proteinuria, renal insufficiency, and low complements. With poststreptococcal GN, renal failure

occurs 1–6 weeks after infection. There is **low complement** for 6–8 weeks, variably positive **antistreptococcal antibody titers** (with group A strep infection), and subendothelial and subepithelial immune “humps” on renal biopsy. Most patients show good response to treatment of the infection.

Membranoproliferative Glomerulonephritis (MPGN)

Complement-Mediated MPGN

MPGN (a biopsy diagnosis) is classified based on etiology into 2 major types: complement-mediated MPGN and immune complex-mediated MPGN. These 2 types are distinguished by kidney biopsy. In complement-mediated MPGN, immune fluorescence is positive for complement but negative for immunoglobulin components (IgG, IgA, IgM, kappa, and lambda light chains); this is because no immune complexes are deposited—only complement. In immune complex-mediated MPGN, immune fluorescence is positive for complement (C3), but also 1 or more of the immunoglobulin components listed above.

Complement-mediated MPGN is due to dysregulation of the alternative pathway. The disease is caused by either a genetic mutation in, or autoantibodies to, complement regulatory proteins. This results in overactivity of the alternative complement pathway and complement deposition in the glomeruli. Regulatory proteins affected by gene mutations include Factors H, I, and B. In antibody-mediated disease, the antibodies can simply be against these same proteins or can be against C3 convertase (the autoantibody to C3 convertase is called C3 nephritic factor).

Low C3 and normal C4 levels are common in complement-mediated MPGN. The low C3 stays **low indefinitely**. This is useful: If you initially suspected IRGN but C3 stays low for > 3 months, suspect MPGN instead, and get a renal biopsy! If biopsy shows complement-mediated MPGN, test for genetic mutations and autoantibodies to alternative complement pathway proteins.

Treatment of complement-mediated MPGN is controversial. For antibody-mediated disease, plasma exchange, immunosuppression, and eculizumab have been used. For disease due to a genetic deficiency, intermittent infusions of fresh frozen plasma to replace the missing factor have been used.

Remember: MPGN is 1 of the diseases that can present with either a nephritic or nephrotic clinical picture.

Immune Complex-Mediated MPGN

Immune complex-mediated MPGN usually is due to an underlying systemic disease.

Immune complex-mediated MPGN is caused by immune complexes deposited within or adjacent to the glomerular basement membrane. Immune complexes form in chronic infections (e.g., **hepatitis B and hepatitis C**, shunt nephritis, abscess), autoimmune disease

(e.g., SLE, Sjögren syndrome), or monoclonal gammopathy. Low complement levels are common in immune complex-mediated MPGN.

Hepatitis C is the most common cause of immune complex-mediated MPGN. It is treated with antiviral therapy. For more on hepatitis C, see the [Gastroenterology](#) section.

If cryoglobulinemia and other severe features are present (i.e., progressive loss of renal function, systemic vasculitis), treat with steroids + plasmapheresis, rituximab, or cyclophosphamide.

Lupus Nephritis

Lupus nephritis is glomerular disease caused by SLE. It is divided into 6 patterns of glomerular injury:

- Class 1—normal/minimal mesangial
- Class 2—mesangial proliferative
- Class 3—focal proliferative (< 50% of glomeruli involved)
- Class 4—diffuse proliferative (> 50% of glomeruli involved)
- Class 5—membranous
- Class 6—advanced-stage lupus nephritis (> 90% global glomerulosclerosis)

Clinically, the most important categories of lupus nephritis are Classes 3, 4, and 5. Classes 3 and 4 typically present with a decline in renal function (can be chronic, subacute, or acute) and glomerulonephritis (i.e., active sediment, low-grade proteinuria). Class 5 can present similarly or with a more nephrotic picture (bland sediment, heavy proteinuria, edema). Sometimes, there are pathologic features of both Class 5 and Class 3 or 4. Complements are usually low, and ANA and anti-dsDNA titers are elevated. Commonly, patients have other clinical symptoms of lupus at the time of renal disease diagnosis; occasionally, renal disease is the only presenting symptom. Perform a renal biopsy on all lupus patients with active urine sediment, regardless of GFR.

Without treatment, lupus nephritis can quickly progress to ESRD. Treat Classes 3, 4, and 5 aggressively with steroids + either mycophenolate mofetil or cyclophosphamide. Use maintenance therapy with mycophenolate or azathioprine to prevent relapses. Classes 1 and 2 are not usually biopsied, have a good prognosis, and immunosuppressive therapy is not needed unless they evolve into Class 3, 4, or 5 (suspect this if there is worsening renal function or worsening proteinuria). Class 6 is end-stage disease, and treatment is not recommended.

For more information on lupus nephritis during pregnancy, see the [Women's and Men's Health](#) section.

IgA Nephropathy

IgA nephropathy is the most common GN worldwide. It is more common in Asians and males 20–40 years of age.

IgA nephropathy has a wide range of presentations, including gross hematuria, microscopic hematuria with or without proteinuria (the most common presentation), and RPGN (more under [Rapidly Progressive GN \(RPGN\)](#) on page 7-18). Gross hematuria in IgA nephropathy commonly occurs either during or immediately following an upper respiratory infection or after strenuous exercise. Unlike infection-related GN, there is no latent period between infection and appearance of hematuria. This is an important distinguishing feature!

In IgA nephropathy, there is immune complex deposition of IgA and C3 in the glomerular mesangium. Although C3 is deposited, serum complement levels are normal.

Diagnosis is with renal biopsy, which shows mesangial proliferation on light microscopy (crescents in severe disease), and deposits of IgA and complement in the mesangium and in the glomerular capillaries on immunofluorescence staining ([Figure 7-8](#)).

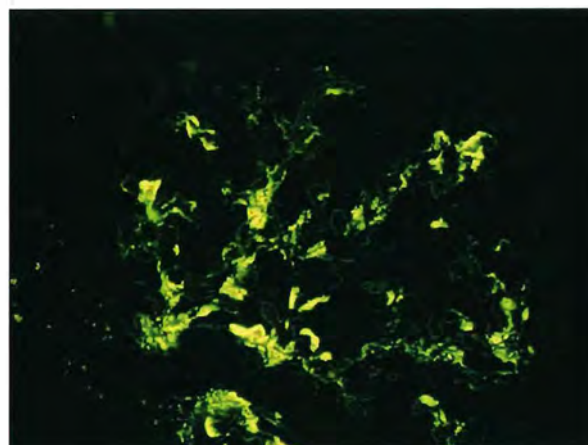


Figure 7-8: IgA nephropathy: mesangial IgA deposits on immunofluorescence

Source: Sriram S. Narsipur, MD

Some illnesses are associated with mesangial IgA deposition but without obvious glomerular injury (e.g., HIV/AIDS, celiac disease, end-stage liver disease). These presentations are called **secondary** IgA nephropathy.

Prognosis for IgA nephropathy is tied to serum creatinine, blood pressure, and amount of proteinuria. Prognosis is good if these values are normal. Prognosis is much worse if any of these are elevated. Up to 50% of patients with proteinuria > 1 g/day may progress to ESRD. Patients with recurrent gross hematuria without proteinuria are at low risk for progression.

Observe patients who maintain normal renal function with no proteinuria. Use ACEIs/ARBs for proteinuria (> 0.5 g/day). Corticosteroid therapy is sometimes used for persistent proteinuria (> 1 g/day) despite 6 months on an ACEI/ARB, or a progressive decline in eGFR. However, the 2015 STOP-IgAN trial showed no improvement in rate of eGFR decline, and an increased risk of adverse events, with immunosuppression. Data are inconclusive on the benefit of statins and fish oil for the treatment of IgA nephropathy.

IgA vasculitis is a systemic vasculitis due to IgA deposition in the kidneys, skin, and other organs. IgA vasculitis is seen mostly in children; however, it can occur in adults. Patients present with abdominal pain, joint pain, lower extremity palpable purpura, and hematuria. Renal insufficiency (elevated creatinine) sometimes occurs. As with IgA nephropathy, complement levels are usually normal. Diagnosis is clinical, or by kidney or skin biopsy which shows IgA deposition in the mesangium (kidney) or venules (skin; leukocytoclastic vasculitis). The disease typically resolves spontaneously; treatment is supportive.

NEPHROTIC SYNDROMES

Nephrotic urine reflects defects in the selectivity of the glomerular filtration barrier, in the absence of inflammation. **Nephrotic-range proteinuria** is defined as urine protein excretion > 3.5 g/day. **Nephrotic syndrome** is nephrotic-range proteinuria, plus hypoalbuminemia and edema. Frequently, hyperlipidemia also is present. Nephrotic syndrome of any type causes urinary loss of immunoglobulins and antithrombin III. This results in both an increased risk of infections (particularly with encapsulated organisms such as *Haemophilus influenzae* and *Streptococcus pneumoniae*) and a hypercoagulable state. Loss of thyroid and iron-binding globulins also occurs (so, low total thyroxine and iron levels).

Table 7-6 on page 7-24 describes the most important causes of nephrotic syndrome.

Nephrotic syndrome is classified according to the pathologic pattern seen on kidney biopsy. These pathologic patterns can be primary (idiopathic), or secondary to a systemic illness. Pathologic patterns in nephrotic syndrome include:

- Minimal change disease
- Focal segmental glomerulosclerosis
- Membranous nephropathy

For each of these 3 main pathologic patterns, disease can be primary (idiopathic), or secondary to a systemic disease (e.g., SLE Class 5 = membranous lupus). Amyloidosis and diabetes mellitus are systemic diseases which cause nephrotic syndrome and produce unique changes on kidney biopsy that do not fit into these 3 classic pathologic patterns. We will discuss these 5 categories of nephrotic syndrome in detail next.

Minimal Change Disease (MCD)

MCD is the most common cause of primary nephrotic syndrome in children and is the cause of 10–15% of nephrotic syndrome in adults. The pathogenesis of MCD is not yet known. It appears to be related to T-cell dysfunction. Pathologically, there is fusion or effacement of the podocyte foot processes in the glomerular capillary walls. This makes for a leaky glomerular filtration barrier and heavy proteinuria.

The **vast majority** of MCD is **idiopathic**, but it is sometimes caused by drugs or systemic diseases.

Know these secondary causes of MCD:

- **Drugs**—NSAIDs; rarely other drugs such as lithium
- **Lymphoma**—both Hodgkin lymphoma and non-Hodgkin lymphoma

Patients present with **anasarca** or severe peripheral **edema** that develops over days to weeks usually **without** HTN. Adults can have renal failure that usually improves with treatment.

As with any cause of nephrotic syndrome, urine sediment may show fatty casts or oval fat bodies (see D and E in Figure 7-1 on page 7-2), which appear as Maltese crosses under polarized light.

MCD diagnosis is made by renal biopsy, which shows **normal** histology on light microscopy and absence of immune deposits on immunofluorescence. Electron microscopy shows fusion or effacement of epithelial (podocyte) foot processes.

Treat MCD initially with steroids. Remission typically occurs within 3–4 months. Steroid-dependent and steroid-resistant disease may be treated with cyclophosphamide or cyclosporine.

The prognosis of MCD is very good; however, relapses are common.

Summary of MCD: **nephrotic-range** proteinuria, fusion of podocyte foot processes, fatty casts or oval fat bodies; secondary causes are **NSAIDs** and **lymphoma**; treat with steroids; **generally very good** prognosis.

Focal Segmental Glomerulosclerosis (FSGS)

FSGS has become the most common cause of idiopathic nephrotic syndrome in African Americans and is the most common primary glomerular disease causing ESRD in the U.S. Although FSGS is most often a primary (idiopathic) disease, it can be familial or secondary. Therefore, consider secondary FSGS if there is a history of HIV/AIDS, heroin use, obesity, sickle cell disease, reduced renal mass, or chronic vesicoureteral reflux.

The hallmark pathology in FSGS is glomerulosclerosis (glomerular scarring) that is **focal** (< 50% of glomeruli are affected) and **segmental** (for affected glomeruli, < 50% of the tuft is involved). This is different from global glomerulosclerosis (100% of the tuft is sclerosed), which is nonspecific scarring that is the end stage of many forms of kidney disease. Like MCD, FSGS has diffuse **foot process fusion** on EM. Unlike MCD, these patients often present as hypertensive as well as nephrotic.

50% have a reduction in kidney function at diagnosis. These patients have slowly progressive renal failure. Those **not** responding to treatment **require dialysis** within ~ 5–10 years. Those with severe proteinuria and reduction in GFR at diagnosis have a worse prognosis.

Table 7-6: Nephrotic Syndrome — Detailed Summary

Pathologic Pattern	Etiology	Presentation	Treatment	Notes
Minimal change disease: Fusion of podocyte foot processes; otherwise, path is normal! Secondary to: • NSAIDs • Hodgkin lymphoma • Lithium	Primary (idiopathic)	Sudden onset of severe nephrotic syndrome	Primary: • Steroids = 1 st line • CNI or cyclophosphamide = 2 nd line	10–15% of nephrotic syndrome in adults
	Look for clues to secondary causes.	Treat the underlying cause.		
Focal segmental glomerulosclerosis Secondary to: • HIV/AIDS • Reflux nephropathy • Obesity	Primary: • Idiopathic (common in African Americans) • Familial	Can be similar to MCD or have more gradual onset	ACEIs/ARBs Steroids +/- CNI (Patients who respond to steroids have the best prognosis.)	Associated with the APOL1 gene variant in African Americans Can recur after kidney transplantation
	Look for clues to secondary causes.	Treat the underlying cause.	FSGS due to HIV is usually with untreated/uncontrolled disease.	
Membranous: Thickening of glomerular basement membrane; subepithelial deposits on EM Secondary to: • Malignancy (especially solid tumors) • SLE ("Class 5") • Drugs (e.g., NSAIDs) • HBV and other chronic infections	Idiopathic: anti-PLA2R antibodies	Acute or subacute onset of nephrotic syndrome Hematuria is sometimes present.	Mild cases: ACEIs/ARBs Persistent and/or severe proteinuria: steroids + cyclophosphamide or rituximab	Anti-PLA2R antibodies are present in 70% of cases.
	Clues are often present on history and physical examination.	Treat the underlying cause.	Look for malignancy, especially in older adults. Screen for lupus, hepatitis B, and hepatitis C.	
Diabetic nephropathy: Nodular glomerulosclerosis	Type 1 or Type 2 diabetes mellitus (usually after 15+ years of disease)	Long-term Type 1 or Type 2 diabetes mellitus Begins with moderately increased albuminuria, with gradual progression to overt proteinuria and chronic kidney disease	ACEIs/ARBs Control of blood glucose, blood pressure, and lipids	Most common cause of nephrotic syndrome Retinopathy typically precedes kidney disease.
Amyloidosis: Apple-green birefringence with Congo-red stain; 8- to 12-nm fibrils on EM	AL amyloidosis: deposition of immunoglobulin light chain fragments Multiple myeloma (most common) Waldenström macroglobulinemia Non-Hodgkin lymphoma	Proteinuria (often, though not always, nephrotic-range) +/- progressive renal insufficiency	Treat underlying hematologic malignancy.	Look for clues to myeloma (low anion gap, hypercalcemia, anemia).
	AA amyloidosis: chronic inflammatory disorders Can be seen in rheumatoid arthritis and chronic infections	Nephrotic syndrome +/- cardiomyopathy	Treat underlying infection or inflammatory process.	Check SPEP, UPEP, and serum free light chains.

Nephrotic syndrome definition is heavy proteinuria (> 3.5 g/day), hypoalbuminemia (< 3.0 g/dL), edema, and hypercholesterolemia. Lipiduria (i.e., oval fat droplets or fatty casts) and a hypercoagulable state may occur.

Complications: DVT and bacterial infections

AA amyloidosis = amyloid A amyloidosis
 AL amyloidosis = immunoglobulin light-chain amyloidosis
 APOL1 = apolipoprotein L1 gene
 CNI = calcineurin inhibitor (cyclosporine, tacrolimus)
 EM = electron microscopy

FSGS = focal segmental glomerulosclerosis
 MCD = minimal change disease
 PLA2R = phospholipase A2 receptor
 SPEP = serum protein electrophoresis
 UPEP = urine protein electrophoresis

It is important to distinguish between primary and secondary FSGS because the treatment differs. Treat primary FSGS with steroids. For secondary FSGS, treat the underlying disease.

Initial treatment of primary FSGS includes ACEIs/ARBs and high-dose steroids for up to 6 months to induce remission. Patients without remission have a poorer prognosis. Treatment can improve prognosis and prevent or delay progression to ESRD.

Treat secondary FSGS with ACEIs/ARBs and therapy directed at the underlying cause, if possible. Initiate antiretroviral therapy in all patients with HIV-associated nephropathy, regardless of CD4 count, because treatment can lead to regression of the renal disease.

HIV patients with nephrotic syndrome usually have the collapsing variant of FSGS, also known as **HIV-associated nephropathy (HIVAN)**. Untreated, HIVAN progresses rapidly to ESRD. Be sure to consider **tenofovir** nephrotoxicity (which causes ATN, not nephrotic syndrome or FSGS) in patients with HIV and renal failure.

Summary of FSGS: **nephrotic-range** proteinuria, **African Americans**, hypertensive; secondary causes are **HIV/AIDS** (the collapsing variant), **reflux nephropathy**, obesity; treat primary disease with steroids.

Membranous Nephropathy

Idiopathic (primary) membranous nephropathy is a common cause of nephrotic syndrome in adults, especially in Caucasian males > 40 years of age. The most important secondary cause of membranous nephropathy is malignancy, particularly solid tumors such as breast, colon, lung, prostate, and bladder cancer. The cancer is usually obvious at the time of renal presentation, but if not, do age-appropriate malignancy screening. **Other secondary** causes include:

- Chronic **infections** (primarily chronic HBV, but also malaria)
- **Drugs**
- **Autoimmune** diseases (e.g., thyroiditis, rheumatoid arthritis, SLE [consider if membranous nephropathy presents in a young female])

Patients with membranous nephropathy present with subacute onset of nephrotic syndrome, and 50% of patients have red cells in the urinary sediment (without RBC casts). Most patients have normal blood pressure and renal function at diagnosis.

Renal biopsies should be done in all cases of nephrotic syndrome when the underlying cause is not obvious (e.g., diabetic nephropathy). In membranous nephropathy, renal biopsy shows thickened capillary walls and GBM "spikes" on **light microscopy** and granular IgG and C3 deposits on **immunofluorescence**. Electron microscopy shows subepithelial electron-dense deposits. The GBM is thickened because new matrix is laid down between the subepithelial deposits.

The majority (70%) of patients with **primary** membranous nephropathy have positive antiphospholipase A2 receptor (**anti-PLA2R**) antibodies. This test can be useful in distinguishing primary from secondary membranous nephropathy, which can guide therapy.

Up to 30% of patients spontaneously improve over a period of 3–5 years, while others improve partially or completely with treatment. ~ 15% of patients progress to ESRD despite treatment. Patients with more severe proteinuria and/or reduced GFR have a worse prognosis, as do men > 50 years old.

Secondary membranous nephropathy often improves with treatment of the underlying disease or discontinuation of any offending drugs.

Because some patients with idiopathic membranous nephropathy can have spontaneous remission, not all patients need to be treated immediately. Aggressively treat only those who have persistent high-grade proteinuria (> 4 g/day) despite at least 6 months of conservative management with ACEI or ARB and HTN control. Treatment is with corticosteroids + either cyclophosphamide or rituximab.

Membranous nephropathy has the highest prevalence of renal vein thrombosis compared with other causes of nephrotic syndrome. If a patient with known membranous nephropathy develops flank pain, hematuria, and high LDH, think about renal infarction secondary to renal vein thrombosis.

Summary of membranous nephropathy: **nephrotic-range** proteinuria; secondary causes are **HBV**, gold, penicillamine, **solid tumors**, **SLE**; aggressively treat primary form with corticosteroids + a cytotoxic agent if proteinuria is > 4 g/day and not responsive to conservative treatment; prognosis is worse in older men.

Diabetic Nephropathy

Diabetic nephropathy is the most common cause of ESRD in the U.S. and worldwide. It is also the most common systemic cause of nephrotic syndrome in adults. Diabetes mellitus also can cause **Type 4 RTA** (i.e., hyporeninemic hypoaldosteronism). The risk of diabetic nephropathy is the same, regardless of whether patients have Type 1 or 2 diabetes mellitus. In most cases, **retinopathy precedes nephropathy** (weaker association in Type 2 diabetes mellitus).

Not all patients with diabetes develop diabetic nephropathy. Know the following risk factors:

- Family history of ESRD
- African American, Hispanic, Pima Native American
- Uncontrolled HTN (systolic blood pressure > 140 mmHg)
- GFR (hyperfiltration in the first 5 years after diagnosis = higher risk)
- Poor glycemic control
- Obesity
- Smoking

The diagnostic finding on renal biopsy is glomerular enlargement, mesangial sclerosis, and nodular accumulations of mesangial matrix (**Kimmelstiel-Wilson nodules**). However, if the clinical picture is “classic” (i.e., proteinuria and slowly rising serum creatinine in the setting of long-standing diabetes mellitus with retinopathy and neuropathy), kidney biopsy is not usually necessary. In patients with atypical presentations, kidney biopsy is sometimes done to exclude other glomerular causes of nephrotic syndrome.

Diabetic nephropathy occurs in 2 phases. In the **silent, or preclinical, phase**, the only detectable abnormality is **moderately increased albuminuria**, which is urinary albumin between 30 and 300 mg/day—an amount often too low to be detected on dipstick. It can be detected by measuring a random urine albumin:creatinine ratio; > 30 mg albumin/g creatinine (or > 0.03 mg/mg) represents moderately increased albuminuria. Test all diabetic patients yearly for albuminuria using the spot albumin:creatinine ratio. Albuminuria screening should start 5 years after diagnosis of Type 1 diabetes mellitus and at the time of diagnosis of Type 2 diabetes mellitus. If moderately increased albuminuria is found, treat with an ACEI or ARB **even if normotensive**.

The **clinical phase** (overt diabetic nephropathy) is characterized by overt proteinuria (> 300 mg/day), HTN, and progressive loss of kidney function.

Control of **HTN** (to $< 130/80$ mmHg, per the 2017 American College of Cardiology/American Heart Association Guidelines for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults, with ACEI/ARB as the 1st line drug) and **hyperglycemia** (HbA1c target $< 7\%$) **slow** the rate of progression of diabetic nephropathy. ACEI/ARB use has been shown in randomized controlled trials to reduce progression from moderately increased albuminuria to overt diabetic nephropathy, and to delay loss of renal function in patients with overt diabetic nephropathy, in both Type 1 and Type 2 diabetes mellitus. However, avoid using ACEIs and ARBs together, as the combination use can increase risk of AKI and hyperkalemia. The sodium glucose cotransporter 2 (SGLT2) inhibitors (e.g., canagliflozin) slow progression of diabetic nephropathy and are recommended by the American Diabetes Association (ADA) guidelines in patients with albumin:creatinine ratio > 300 mg/g and eGFR > 30 mL/minute/1.73 m². However, SGLT2 inhibitors should not be used in patients with eGFR < 30 mL/minute/1.73 m².

Weight reduction and treatment of hyperlipidemia also appear to decrease risk. The ADA guidelines recommend dietary protein intake of 0.8 g/kg body weight/day (the recommended daily allowance) in patients with diabetic CKD who are not yet on dialysis. Very-low-protein diet (< 0.6 g/kg/day) is not recommended, either in diabetic or nondiabetic CKD.

Know: As renal function decreases, insulin requirements decrease (secondary to decreased metabolism by the kidneys).

Multiple Myeloma and Amyloidosis

Multiple myeloma can cause several different renal lesions:

- **Cast nephropathy** (myeloma kidney) is the most common renal lesion with multiple myeloma. Immunoglobulin light chains precipitate in the tubules, leading to acute kidney injury. A **clue** to myeloma cast nephropathy is **negative urinary dipstick for protein** but abnormal **proteinuria on lab quantification** (urine protein:creatinine ratio, 24-hour urine protein, and urine protein electrophoresis). This occurs because the dipstick reacts to albumin but not to the nonalbumin light chains.
- **Hypercalcemia**, which can cause AKI and nephrogenic DI
- **Primary amyloidosis** (a.k.a. immunoglobulin light-chain [AL] amyloidosis) is a multisystem disease that can include nephrotic syndrome and renal failure (**Figure 7-9**; Congo red stain shows deposits with apple-green birefringence under polarized light). AL amyloidosis can occur alone or with multiple myeloma.
- **Mixed immunoglobulin deposition disease (MIDD)** presents with a nephritic picture. On renal biopsy, monoclonal immunoglobulin light chains or heavy chains (or both) are deposited in the glomeruli.

Secondary amyloidosis (a.k.a. amyloid A [AA] amyloidosis) is seen in chronic inflammatory states such as rheumatoid arthritis and familial Mediterranean fever. AA amyloid nephropathy also can be caused by recurrent skin and soft tissue infections such as those caused by chronic injection drug use. Clues to amyloidosis include carpal tunnel syndrome and new-onset HF associated with nephrotic syndrome. AA amyloidosis in the kidney causes nephrotic syndrome.

Enlarged kidney size, as seen on imaging studies, can be caused by **multiple myeloma**, **amyloidosis**, and **HIV-associated nephropathy**.

Secondary Causes of Nephrotic Syndrome

To review, secondary/systemic causes of nephrotic syndrome include:

- **Drugs:** Lithium and NSAIDs can cause MCD. NSAIDs, penicillamine, gold, and anti-TNF agents (e.g. infliximab) can cause membranous nephropathy. Bisphosphonates, anabolic steroids, and interferon can cause FSGS.
- **Malignancy:** Hodgkin lymphoma and non-Hodgkin lymphoma can cause MCD. Solid tumors can cause membranous nephropathy.
- **Infections:** HIV/AIDS can cause collapsing FSGS. HVB, HCV, and syphilis can cause membranous nephropathy.
- **Autoimmune:** SLE (Class 5) and IgG4-related disease can cause membranous nephropathy.
- **Miscellaneous:** Obesity, vesicoureteral reflux, sickle cell anemia, and reduced renal mass can cause FSGS.

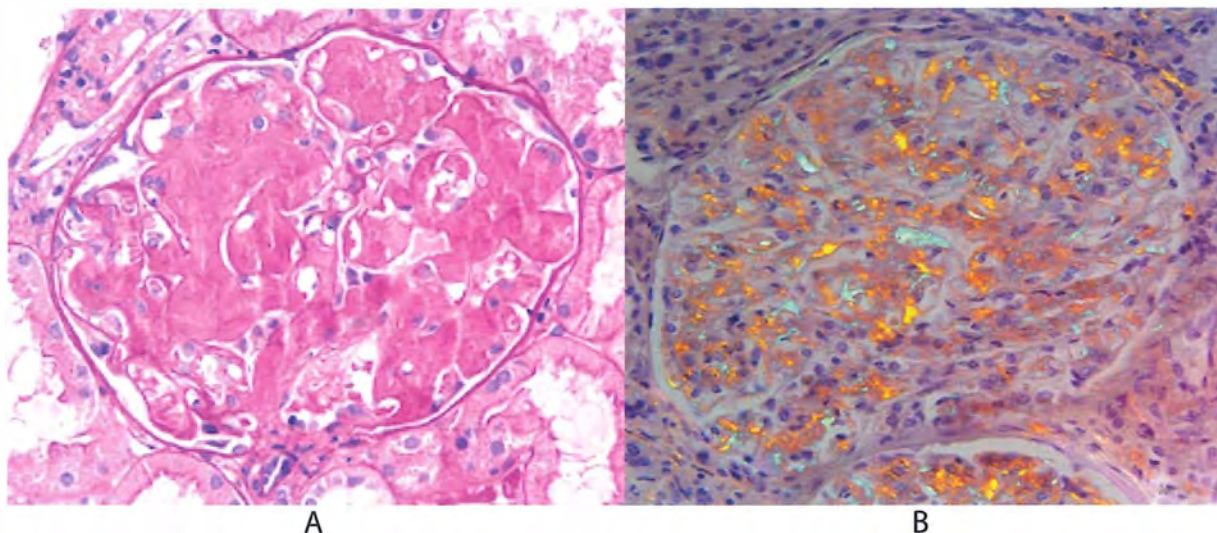


Figure 7-9: Renal pathology in amyloidosis. (A) PAS stain shows mesangial expansion with amorphous, pale, eosinophilic material. (B) Congo red stain and polarized light show apple-green birefringence.

Treatment of Nephrotic Syndrome

General principles: Treat any underlying systemic disease. Use ACEIs/ARBs to decrease intraglomerular pressure and reduce proteinuria. Diuretics, usually loop diuretics, are needed because edema can be severe. Note that immunosuppression (glucocorticoids +/- cyclophosphamide, calcineurin inhibitors, or rituximab) are used in most primary causes of nephrotic syndrome and nephrotic syndrome due to autoimmune disease (e.g., SLE), but not in nephrotic syndrome secondary to most systemic diseases (e.g., amyloidosis, diabetes, obesity, infection). Consider anticoagulation if there is a significant risk of thrombosis, particularly in severe hypoalbuminemia in membranous nephropathy. Be cognizant of the significantly increased rate of infections and vaccinate accordingly.

THROMBOTIC MICROANGIOPATHIES

Thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS) are forms of thrombotic microangiopathy (TMA). TMA is a pathologic pattern of microvascular thrombosis of the arterioles and capillaries. Clinically, you see microangiopathic hemolytic anemia (anemia, high LDH, low haptoglobin, high indirect bilirubin, and schistocytes on the peripheral blood smear), and thrombocytopenia. TMA can be caused by TTP (acquired or genetic), drugs, Shiga toxin, and complement disorders.

Acquired TTP is caused by a severe deficiency of the ADAMTS13 enzyme (defined as activity < 10%), which leads to large von Willebrand factor multimers and platelet aggregation. TTP usually has mild or no renal dysfunction. Often, the only renal manifestation is a U/A dipstick positive for heme but with no RBCs on the urine sediment exam—this is due to hemoglobinuria from the hemolysis. Patients present with progressive weakness,

fatigue, and purpura. This syndrome is often suspected only after the discovery of anemia and thrombocytopenia. ~ 2/3 of patients have some neurological involvement. Diagnose TTP by measuring the ADAMTS13 level; however, do not wait for the result to start treatment if your suspicion is high! TTP is a medical emergency—untreated, mortality approaches 100%. Diagnosis and treatment with plasmapheresis should occur within hours of suspecting the diagnosis.

Certain drugs can cause TMA, with the classic findings of microangiopathic hemolytic anemia and thrombocytopenia, with or without renal failure. Drugs known to cause TMA include quinine (present in tonic water), calcineurin inhibitors (i.e., cyclosporine, tacrolimus), gemcitabine, and VEGF inhibitors (e.g., bevacizumab).

Shiga toxin-mediated hemolytic uremic syndrome (ST-HUS) initially presents with abdominal pain, nausea, vomiting, and bloody diarrhea, followed by AKI, microangiopathic hemolytic anemia, and low platelets. Treatment for ST-HUS is supportive; plasmapheresis is sometimes used.

Complement-mediated HUS (i.e., atypical HUS) is due to complement dysregulation. It can be caused by complement gene mutations or by antibodies to complement proteins (especially complement Factor H). Note that in complement-mediated HUS, low C3 levels are common (though not universal). Patients typically present with microangiopathic hemolytic anemia, low platelets, and renal failure. Kidney biopsy reveals a thrombotic microangiopathy (identical to TTP). ADAMTS13 levels are normal. Genetic testing is not yet widely available, so often the diagnosis is by exclusion of other causes of TMA. Treat with eculizumab.

TTP and HUS also are discussed in the Hematology section.

OTHER DRUG-INDUCED NEPHROPATHIES

NSAIDs have several potentially adverse effects on the kidneys. Renal effects of NSAIDs are seen equally with both nonselective NSAIDs (e.g., ibuprofen, ketorolac, naproxen) and COX-2 inhibitors (e.g., celecoxib).

NSAIDs inhibit prostaglandin (PG) production. This prevents PG-induced **dilation** of the **afferent** arterioles, which is needed to maintain GFR in patients with decreased renal perfusion. By this mechanism, NSAIDs can lead to or exacerbate **acute prerenal failure** in patients with low effective circulating volume (e.g., low cardiac output, hypovolemia). Note that ACEIs/ARBs have a similar effect (exacerbation of acute prerenal failure), in this case due to blockade of AT II-mediated constriction of the efferent arteriole.

NSAIDs can cause Na^+ retention, HTN, and hyperkalemia. Additionally, they can cause acute or chronic interstitial nephritis, with nephrotic-range proteinuria (common) and papillary necrosis (rare).

Chronic injection-drug (e.g., heroin) users are at risk for several types of kidney problems:

- Acute bacterial endocarditis can cause **IRGN** (with low complement).
- Endocarditis can cause septic **emboli** that can result in renal infarction and hematuria.
- Injection drug users are at risk for **HIV** infection and subsequent HIV-associated nephropathy (collapsing FSGS).

KIDNEY INJURY IN CANCER

Renal disease secondary to cancer can be grouped into several categories:

- **Direct infiltration** by lymphoma, leukemia, or myeloma
- **Extrinsic obstruction** at the level of the ureters or urethra, particularly from pelvic and abdominal tumors
- **Intrinsic obstruction** by intratubular precipitation of uric acid (seen in tumor lysis syndrome), methotrexate crystals, or immunoglobulin light chains (i.e., myeloma cast nephropathy)
- **Glomerular disease**—minimal change disease (from Hodgkin lymphoma), membranous GN (from solid tumors), amyloidosis (from multiple myeloma), glomerulonephritis (e.g., mixed immunoglobulin deposition disease, seen in monoclonal gammopathies)
- **Chemotherapy drug toxicity**—including mitomycin C-induced **hemolytic uremic syndrome**; cisplatin and ifosfamide-induced acute tubular injury;

bevacizumab-induced thrombotic microangiopathy; and checkpoint inhibitor-induced interstitial nephritis (e.g., due to pembrolizumab)

- **Hypercalcemia** of malignancy (can lead to AKI due to vasoconstriction and hypovolemia)

Patients with very high WBCs (e.g., acute monocytic leukemia, acute lymphoblastic leukemia) and lymphoma with high tumor burden being treated with antimetabolites are at high risk for tumor lysis syndrome (acute urate nephropathy). Give prophylaxis with aggressive IV fluid hydration (hypotonic or isotonic saline) and either **allopurinol** or **rasburicase**. Alkalinization of the urine is no longer recommended; HCO_3^- is given only in the setting of metabolic acidosis. Watch for hyperphosphatemia and hyperkalemia. For more on tumor lysis syndrome, see the **Oncology** section.

Rasburicase is an enzyme that catalyzes the oxidation of uric acid and is highly effective for both prevention and treatment of hyperuricemia. Know that rasburicase is contraindicated in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency.

Aside from nephrotoxicity due to chemotherapy, treat cancer-associated kidney disease by treating the underlying malignancy.

HEREDITARY AND CYSTIC KIDNEY DISEASES

PREVIEW | REVIEW

- What are the common presenting symptoms of polycystic kidney disease?
- When are renal cysts considered benign?

POLYCYSTIC KIDNEY DISEASE (PKD)

Autosomal dominant PKD is the most common genetic disease of the kidney. Affected patients get cysts in the kidneys, liver, and pancreas, and eventually develop ESRD (**Figure 7-10**). Autosomal recessive PKD is much less common, and usually presents with renal failure and hepatic fibrosis in infancy or early childhood.

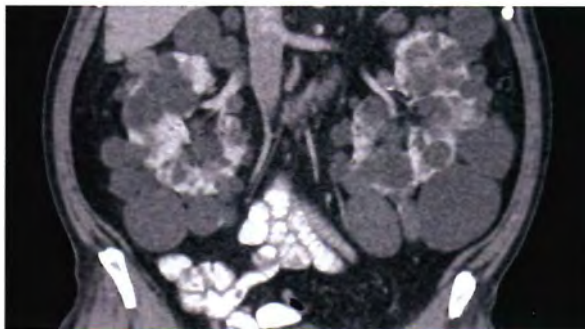


Figure 7-10: Autosomal dominant polycystic kidney disease

Gross hematuria is the most common presenting symptom, while microscopic hematuria is a common laboratory finding. Patients also can present with flank pain, chronic kidney disease, HTN, and cyst infections. Progressive renal failure and HTN are the norm. Associated liver cysts cause hepatomegaly but rarely liver dysfunction.

Cerebral aneurysms occur in 1–5% of patients. Screening for aneurysms is recommended only if the patient with PKD has a family history of subarachnoid hemorrhage or a known cerebral aneurysm. Some experts also recommend that patients with PKD be screened if they have an occupation that places their own life or the lives of others at risk should the patient lose consciousness (e.g., airplane pilots, railroad engineers). Screen for cerebral aneurysms with an MRA.

The diagnosis of autosomal dominant PKD is generally established when polycystic kidneys are identified by imaging (U/S or CT). Renal U/S is used for screening in patients > 18 years of age with a family history of PKD. Genetic testing is available when the diagnosis is in question.

Treatment of PKD is generally supportive. Tight blood pressure control delays loss of renal function. Tolvaptan (a vasopressin antagonist) is used to slow renal function decline in adults with PKD; LFTs must be monitored with this drug as fulminant hepatitis can occur with long-term use.

MEDULLARY DISEASE

There are 2 main inherited medullary kidney diseases:

- 1) **Medullary sponge kidney** is a generally benign disease; however, it is associated with nephrolithiasis and urinary tract infections.
- 2) **Medullary cystic disease** can cause renal failure and presents in childhood. This is 1 of the few chronic kidney diseases in which U/A is usually normal.

ALPORT SYNDROME

Alport syndrome (a.k.a. hereditary nephritis) can be either X-linked (most cases), autosomal recessive (15%), or autosomal dominant (5%) with variable expression. For X-linked disease, men are affected much more severely than women. For autosomal recessive and autosomal dominant disease, severity is the same in men and women.

Alport syndrome results from a mutation in genes encoding Type 4 collagen, affecting the basement membrane (the same target area attacked by the Goodpasture's anti-GBM antibodies) in the glomerulus, cochlea, and lens. Hearing loss is common. The female X-linked carriers have microscopic hematuria only. The affected males usually have renal failure by the time they are adults.

Consider Alport syndrome in any patient with persistent microscopic hematuria (onset at birth) that worsens after an infection (i.e., include this in the differential

diagnosis of infection-related GN and IgA nephropathy). Additionally, especially consider Alport syndrome in a woman with microscopic hematuria when there is a family history of males with advanced kidney disease. Diagnose with a kidney biopsy in both men and women. The hallmark finding is splitting (lamination) of the GBM, visible on EM. Genetic testing detects mutations in the COL4A3, COL4A4, and COL4A5 genes. Thinning of the GBM occurs in both early Alport syndrome and the related (though benign) thin basement membrane disease, which typically presents with isolated microscopic hematuria.

Treat Alport syndrome with an ACEI or ARB. Transplant is the optimal treatment, but patients with Alport syndrome who get a kidney transplant can develop anti-GBM disease in the transplanted kidney because their immune system has not been exposed previously to normal Type 4 collagen.

RENAL CYSTS

Renal cysts are very common. 50% of people > 50 years of age have them. They are considered benign if they are simple on U/S and the patient is asymptomatic. Simple cysts have well-defined margins, dense (compressed) surrounding tissues, and no solid component. Complex cysts (thickened walls, septa, calcifications, or solid component) have malignant potential. Management of complex cysts may include periodic imaging, fine needle aspiration, or surgical excision (partial or radical nephrectomy).

CHRONIC KIDNEY DISEASE (CKD)

PREVIEW | REVIEW

- What is the definition of chronic kidney disease (CKD), and what are its stages?
- How is osteitis fibrosa cystica different from adynamic bone disease?
- List 4 signs or symptoms of uremia.
- How is anemia of CKD treated?
- What rare complication can occur after gadolinium in patients with end-stage renal disease?

OVERVIEW

CKD is defined as either of the following:

- Kidney damage for > 3 months, with or without decreased GFR. Kidney damage can include any of the following: albuminuria, active urine sediment, abnormal imaging (cystic kidneys, hydronephrosis), or abnormal pathology.
- Estimated glomerular filtration rate (eGFR) < 60 mL/minute/1.73 m² for > 3 months, with or without kidney damage

CKD is divided into stages:

- Stage 1—GFR > 90 mL/minute/1.73 m² with evidence of kidney damage (e.g., proteinuria, hematuria, cystic kidney disease)
- Stage 2—GFR 60–89 mL/minute/1.73 m²
- Stage 3—GFR 45–59 mL/minute/1.73 m²
- Stage 3b—GFR 30–44 mL/minute/1.73 m²
- Stage 4—GFR 15–29 mL/minute/1.73 m²
- Stage 5—GFR < 15 mL/minute/1.73 m² or on dialysis

These stages provide a framework for managing the expected complications of anemia, bone disease, HTN, salt and water retention, and uremia. The Kidney Disease Outcomes Quality Initiative (KDOQI) and Kidney Disease: Improving Global Outcomes (KDIGO) provide the best evidence-based guidelines for diagnosis and management of CKD and its complications.

While CKD can be multifactorial, the most common causes of ESRD (CKD Stage 5) are diabetes mellitus and HTN.

Patients with CKD have an increased risk of heart disease because of their comorbidities and because CKD itself is an independent risk factor. Heart disease is the number 1 cause of death.

All patients with CKD should be screened for hepatitis C infection. If positive, they should be evaluated for antiviral therapy per the 2018 KDIGO guidelines. It is particularly important to diagnose and treat hepatitis C infection prior to kidney transplantation.

SMOKING CESSATION

Smoking accelerates the progression of CKD and increases risk of cardiovascular events. Counsel patients regarding smoking cessation and offer resources to aid in their efforts.

BLOOD PRESSURE CONTROL

Hypertension is both a cause and a consequence of CKD. It is present in the majority of patients with CKD, and blood pressure control is 1 of the most important modifiable risk factors for CKD progression.

Rigorous blood pressure control slows the progression of CKD. The American College of Cardiology/American Heart Association (ACA/AHA) guidelines recommend a blood pressure treatment goal of < 130/80 mmHg in patients with CKD.

ACEIs and ARBs decrease proteinuria. In patients with proteinuria, ACEIs/ARBs slow progression of CKD above and beyond their antihypertensive effect. Keep in mind that although they provide long-term improvement in renal outcomes, ACEIs/ARBs can cause hyperkalemia and an acute decrease in eGFR. Monitor for this by checking labs after adding or increasing the dosage of these medications.

GLYCEMIC CONTROL

Diabetes mellitus remains the number 1 cause of ESRD. Chronic hyperglycemia leads to diabetic nephropathy, and good glycemic control can prevent or slow progression of diabetic nephropathy.

The 2020 American Diabetes Association (ADA) guidelines recommend:

- Optimize glycemic control (HbA1c < 7% in most nonpregnant adults).
- Screen for albuminuria annually.
- Treat HTN and albuminuria (urine albumin:creatinine ratio > 30 mg/g) with an ACEI or ARB.
- Consider use of an SGLT2 inhibitor in patients with an eGFR ≥ 30 mL/min/1.73 m² and urinary albumin > 30 mg/g Cr, particularly in those with urinary albumin > 300 mg/g Cr, to reduce risk of CKD progression, CV events, or both (more under [Diabetic Nephropathy](#) on page 7-25).

TREATMENT OF DYSLIPIDEMIA

Lowering lipids appears to slow progression of renal failure. Remember: Dyslipidemia also leads to an increase in cardiovascular mortality in patients with CKD.

The 2013 KDIGO Guidelines for Lipid Management in Chronic Kidney Disease suggest the following:

- Screen all adults with CKD with a lipid panel.
- Treat adults > 50 years of age with eGFR < 60 mL/minute/1.73 m² with a statin or statin/ezetimibe combination.
- Treat adults 18–49 years of age with CKD and another cardiovascular risk factor (i.e., known coronary artery disease, diabetes, prior stroke, or estimated 10-year cardiovascular disease risk > 10%) with a statin.
- Do not initiate statins in patients with ESRD who are on dialysis (large, randomized, controlled trials have failed to show a benefit of statins in this population).
- In patients with CKD and high triglycerides, treat with lifestyle modification.

The KDIGO guidelines, like the 2018 ACC/AHA Guidelines on the Management of Blood Cholesterol, do not specify a particular LDL treatment target.

Fibrates lower triglycerides, but because there is risk of rhabdomyolysis, they should not be used in patients with eGFR < 30 mL/minute/1.73 m².

DIETARY MODIFICATIONS

Moderately restricting dietary protein intake may slow loss of renal function in patients with CKD. The KDIGO and ADA guidelines recommend lowering protein intake for adults with CKD to 0.8 g/kg/day. A moderately low protein diet also may improve uremic symptoms in patients with advanced (Stage 5) CKD not yet on dialysis. A very low protein diet (< 0.6 g/kg/day) is not recommended; it can lead to malnutrition.

Na⁺ restriction improves blood pressure and volume overload (edema), and it may improve cardiovascular outcomes and slow CKD progression. Limiting dietary Na⁺ intake to < 2 g/day is recommended by the 2013 KDIGO CKD Guidelines.

PROGRESSION OF CKD

In patients with CKD, the ultimate result of progressive loss of kidney function (eGFR) is ESRD, which usually requires dialysis or kidney transplant. Strategies to prevent progression of CKD include:

- Smoking cessation
- Blood pressure control (goal < 130/80 mmHg)
- ACEIs or ARBs (in diabetics and patients with proteinuria)
- Glycemic control and use of SGLT-2 inhibitors (in diabetics)
- Treatment of hyperlipidemia
- Avoiding nephrotoxins (e.g., iodinated contrast, NSAIDs, aminoglycosides)
- Treatment of metabolic acidosis with oral sodium bicarbonate

CKD — MINERAL AND BONE DISORDERS (MBDs)

Pathogenesis

Advanced kidney disease causes abnormalities in Ca²⁺ and phosphate homeostasis, which result in a spectrum of adverse consequences. The term “chronic kidney disease-mineral and bone disorder” (CKD-MBD) was adapted to reflect these abnormalities.

Phosphate, Ca²⁺, calcitriol, and parathyroid hormone (PTH) are tightly interdependent. As you read the following, make sure you understand each concept as you encounter it.

Secondary hyperparathyroidism is 1 of the earliest findings in CKD-MBD. PTH release is stimulated by:

- Hyperphosphatemia
- Hypocalcemia
- Low calcitriol (i.e., 1,25-(OH)₂-D, the active form of vitamin D)

These 3 changes develop with decreasing GFR by the following mechanisms:

- High phosphate
 - Lower GFR = less phosphate excreted in the urine
- Low Ca²⁺
 - Low calcitriol
 - Excess phosphate complexes with free Ca²⁺
- Low calcitriol
 - Dietary (25-OH-D) vitamin D deficiency (usually in diet and sunlight; deficiency = common in CKD patients)

- Decreased conversion 25-OH-D (the storage form) to 1,25-(OH)₂-D (calcitriol, the active form) by the kidneys

Management of CKD-MBD

The following recommendations are based on the 2017 KDIGO CKD-MBD guidelines. The goals of therapy are to maintain Ca²⁺ and phosphate levels at or close to the normal range to avoid severe secondary hyperparathyroidism.

Screen all CKD patients for nutritional vitamin D (25-OH-D) deficiency, and supplement as needed (e.g., with ergocalciferol or cholecalciferol) to maintain normal levels.

Serum phosphate levels remain normal until ~ **Stage 3-4** CKD, after which hyperphosphatemia develops. As the phosphate levels rise, treat with low-phosphate diet and phosphate binders.

Phosphate binders are either **Ca²⁺ based** (e.g., calcium carbonate, calcium acetate) or **non-Ca²⁺ based** (e.g., sevelamer, lanthanum). Iron-based phosphate binders (sucroferric oxyhydroxide and ferric citrate) are also available. Use of Ca²⁺-containing phosphate binders should be avoided, especially in patients with hypercalcemia. They may contribute to vascular calcification. Aluminum-containing phosphate binders cause dementia and other toxicity; they should not be used.

Monitor intact PTH (iPTH) levels regularly. Correction of hyperphosphatemia with dietary phosphate restriction and phosphate binders, and correction of 25-OH-D deficiency (if present), usually leads to a fall in the iPTH. If there is severe and progressive secondary hyperparathyroidism, consider adding 1,25-(OH)₂-D (calcitriol) or an active vitamin D analog (e.g., doxercalciferol, paricalcitol). However, do **not** lower the PTH all the way to the normal range because adynamic bone disease can result. The optimal PTH level is not known, but in patients with ESRD on dialysis, the KDIGO guidelines recommend targeting iPTH to 2-9× the upper limit of normal.

Calcimimetics (e.g., cinacalcet) increase PTH receptor sensitivity to Ca²⁺ and reduce PTH levels, while decreasing serum Ca²⁺ levels. Use of calcimimetics should be limited to patients with ESRD on dialysis due to lack of data and the risk of hypocalcemia in patients with CKD who are not yet on dialysis.

Putting it all together, prevention and treatment of CKD-MBD includes controlling iPTH, Ca²⁺, and phosphate levels using the following strategies:

- Low phosphate diet and phosphate binders
- 25-(OH)-D (ergocalciferol, cholecalciferol) if deficient

If hyperparathyroidism is severe and progressive despite these measures, consider:

- 1,25-(OH)₂-D (calcitriol) or vitamin D analogs (e.g., paricalcitol, doxercalciferol)
- Calcimimetics (cinacalcet)—only in patients with ESRD

Renal Osteodystrophy

Renal osteodystrophy refers to the **skeletal** complications caused by CKD that can result in bone pain or fractures.

Patients with CKD can have 3 types of bone disorders:

- 1) **Osteitis fibrosa cystica** due to secondary **hyperparathyroidism** (**high** bone-turnover disorder)
- 2) **Adynamic bone** disease due to oversuppression of PTH release (**low** bone-turnover disorder); often a result of overtreatment of secondary hyperparathyroidism
- 3) **Osteomalacia** (**low** bone-turnover disorder associated with unmineralized bone)

Osteitis Fibrosa Cystica

Osteitis fibrosa cystica is **high-turnover bone disease** resulting from persistent secondary hyperparathyroidism.

Clinical findings of osteitis fibrosa cystica: It is usually asymptomatic but can develop bone pain and fractures. Alkaline phosphatase levels are high. Radiographs classically show subperiosteal bone resorption especially in the distal clavicle and the phalanges (Figure 7-11).

Treat osteitis fibrosa cystica by maintaining serum Ca^{2+} and phosphate levels in the normal range and treating severe, persistent secondary hyperparathyroidism, using the strategies summarized in [Management of CKD-MBD on page 7-31](#).

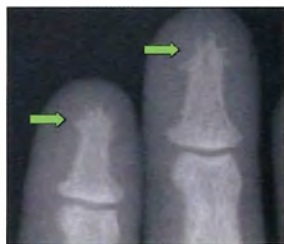


Figure 7-11: Osteitis fibrosa cystica

Adynamic Bone Disease

Adynamic bone disease is a **low bone-turnover state** with reduced bone formation. The cause is **oversuppression of PTH** by overzealous treatment of secondary hyperparathyroidism. For this reason, closely follow iPTH levels in CKD and ESRD patients, and do not lower PTH levels to the normal range.

Consider adynamic bone disease in a CKD patient with persistently low iPTH (< 100 pg/mL). Most affected patients are asymptomatic, but they can have fractures and **hypercalcemia** (especially if on vitamin D analogs and Ca^{2+} -based binders).

Bone biopsy is the gold standard for diagnosis of adynamic bone disease but is rarely indicated. Alkaline phosphatase levels are usually normal.

Treat by reducing or stopping active vitamin D, vitamin D analogs, and Ca^{2+} -based phosphate binders (i.e., substituting with non- Ca^{2+} -based binders). Adynamic bone disease can be exacerbated by the use of bisphosphonates, which inhibit resorption of bone by osteoclasts.

Osteomalacia

Osteomalacia is now uncommon in CKD. Historically, it was due to the use of aluminum-containing phosphate binders that caused aluminum toxicity. Osteomalacia can still occur from vitamin D deficiency.

UREMIA IN CKD

Uremia is a constellation of signs and symptoms associated with a $\text{GFR} < 15$ mL/minute/1.73 m^2 and can include:

- Anorexia, weight loss
- Nausea/Vomiting
- Pericardial and pleural effusions
- Pericarditis
- Platelet dysfunction, bleeding
- Pruritus
- Sensory neuropathies
- Cognitive dysfunction (e.g., confusion, difficulty concentrating, encephalopathy, coma)

The presence of uremic symptoms is an indication for dialysis.

ENDOCRINE PROBLEMS IN CKD

CKD can cause decreased glucose tolerance, decreased gonadal hormone production (with impotence or amenorrhea/infertility), and a low T_3 with a normal thyroid-stimulating hormone.

ANEMIA OF CKD

Advanced CKD causes a **normochromic, normocytic anemia** due to decreased kidney production of erythropoietin. When a CKD patient develops anemia, first exclude other causes of anemia, especially iron deficiency (common in patients with CKD). If iron, B_{12} , and folate stores are adequate and there are no other apparent causes, the anemia can be attributed to CKD.

Anemia of CKD responds dramatically to erythropoiesis-stimulating agents (ESAs).

A trial of PO or IV iron should be given before starting ESAs if there is evidence of iron deficiency (transferrin saturation $< 30\%$ and ferritin < 500 ng/mL).

ESAs can increase risk of cancer progression and stroke, so use of these agents is usually avoided in patients with active malignancy. Use only with caution in patients with a history of malignancy or stroke.

The 2012 KDIGO guidelines explain:

- In **dialysis** patients, initiate ESA when Hgb is 9–10 g/dL (100 g/L).
- For patients with CKD not yet on dialysis, do not start ESAs if Hgb is ≥ 10 g/dL.
- For patients with CKD not yet on dialysis and Hgb < 10 g/dL (100 g/L), the decision to start ESAs should be individualized based upon presence of symptoms,

the rate of fall in Hgb concentration, prior response to iron therapy, risk of needing a transfusion, and the risks related to ESA therapy.

- For both dialysis and nondialysis patients, do not use ESAs to achieve a Hgb > 13 g/dL.

The target Hgb in most patients with anemia of CKD treated with ESAs is 10–11 g/dL.

GOUT IN CKD

CKD is a major risk factor for gout. Glucocorticoids (e.g., prednisone) are the treatment of choice for acute gout in most patients with CKD. Colchicine and NSAIDs are usually avoided whenever possible in patients with significant renal dysfunction. For gout affecting a single joint, treat with an intraarticular steroid injection.

Use allopurinol or febuxostat to prevent recurrent gout flares in patients with CKD and hyperuricemia. These medications decrease the production of uric acid; chronic use often is necessary. Probenecid is **contraindicated** in patients with uric acid stones and is unlikely to be effective in patients with advanced CKD because it works by increasing renal excretion of uric acid.

DRUG METABOLISM IN CKD

Decreased renal function increases the half-lives of many drugs.

As renal function deteriorates, many drugs require dosing reductions, including:

- Vancomycin
- Gentamicin
- Digoxin
- Glyburide
- Procainamide
- Colchicine
- Low-molecular-weight heparin (LMWH)
- Gabapentin
- Insulin

Many antibiotics are cleared by dialysis; therefore, they should be dosed (or redosed) after each dialysis. The common ones include:

- Vancomycin
- Aminoglycosides
- Most β -lactams
- Daptomycin
- Metronidazole
- Ciprofloxacin
- Levofloxacin

IMAGING IN CKD

Avoid older forms of gadolinium contrast (e.g., gadodiamide) in patients with CKD Stages 4 and 5, especially those especially those with ESRD on dialysis.

Gadolinium, a contrast material used in MRIs, can cause **nephrogenic systemic fibrosis (NSF)** in patients with advanced CKD and ESRD.

NSF presents as a thickening of the skin with symmetrical plaques, papules, or nodules. Systemic involvement can include pulmonary fibrosis, myocardial fibrosis, and joint contractures.

Diagnosis of NSF is based upon histopathologic examination of a biopsy (deep incisional or punch biopsy) of an involved site. The course is progressive, sometimes **fulminant**. NSF has not been reported with newer forms of gadolinium (e.g., gadobutrol), so these are considered safe to use in patients with advanced CKD and ESRD (2020 American College of Radiology Manual on Contrast Media).

IV **iodinated** contrast such as that utilized for CT studies and angiograms (including cardiac catheterization) can cause **contrast-induced nephropathy** (more under **AKI – Evaluation and Treatment** on page 7-10).

RENAL REPLACEMENT THERAPY

PREVIEW | REVIEW

- What are the indications for dialysis initiation in CKD?
- What is the most common cause of death in dialysis patients?
- Which organisms are the most common pathogens in peritoneal dialysis peritonitis?
- Which immunosuppressive agents are used in renal transplant patients?

When CKD progresses to ESRD, typically at an eGFR of 8–10 mL/min/1.73 m², renal replacement therapy is usually needed. Forms of renal replacement therapy include:

- Hemodialysis—in-center and home
- Peritoneal dialysis
- Kidney transplantation—deceased donor and living donor

Conservative care of ESRD is an alternative to renal replacement therapy in which supportive care is provided without dialysis or transplant. Conservative care is an option that should be offered to all patients and is preferred in some patients with severe comorbidities or poor functional status (e.g., terminal cancer, advanced HF) in whom dialysis is unlikely to provide benefit. Dialysis in these high-morbidity patients, especially those of advanced age, is associated with loss of functional status, increase in hospitalizations, high burden on patients and families of the dialysis procedure, and a high mortality rate. Conservative care may include:

- Medical management of CKD, including diuretics, anemia management, blood pressure management, and interventions to slow decline in eGFR (more under **Chronic Kidney Disease (CKD)** on page 7-29)

- Psychosocial and spiritual support
- Management of uremic symptoms such as anorexia, fatigue, pruritus
- Pain management, if needed, often with a palliative approach
- Advanced care planning (more in the [General Internal Medicine](#) section)

DIALYSIS

Dialysis: When to start? Answer: When the patient has CKD Stage 5 (eGFR < 15 mL/min/1.73m²) and **symptoms of uremia** (more under [Uremia in CKD on page 7-32](#)). Starting at a specific BUN or creatinine value is of **no** proven benefit.

Other indications for the initiation of dialysis in a CKD (or AKI) patient:

- Refractory metabolic acidosis
- Refractory hyperkalemia
- Fluid overload that is resistant to diuretics

Note: Acute toxin ingestion (e.g., methanol, ethylene glycol, salicylates, lithium) also can be an indication for dialysis, sometimes even when renal function is intact.

Hemodialysis: An upper extremity arteriovenous (AV) fistula lasts the longest but needs to be created at least 3 months before dialysis initiation; otherwise, a tunneled dialysis catheter or AV graft is needed. Refer patients when they develop Stage 4 CKD (eGFR < 30 mL/minute/1.73 m²).

Know that the most common cause of **death** in dialysis patients is **cardiovascular** disease. Infection is next.

Dialysis patients frequently have anemia, high triglycerides, and a low HDL. They usually have a metabolic acidosis just before dialysis and a respiratory alkalosis just after dialysis.

Maintaining **adequate nutrition** in these patients is one of the key factors in reducing morbidity and mortality. Vitamin supplements are important, especially the water-soluble ones. These vitamins are not stored in fat; they must be replenished each day. The main water-soluble vitamins are B-complex, C, and folate.

Peritoneal dialysis: Patients do **not** need AV access, but instead require a tunneled peritoneal dialysis catheter and the ability to manage their dialysis at home. Pay close attention to nutritional status—a **high protein intake** is necessary. Fluid shifts are more gradual, so peritoneal dialysis causes less strain on the heart than hemodialysis.

Many patients receive their peritoneal dialysis exchanges at night using an automated cyclor.

Peritonitis is the main complication of peritoneal dialysis. Presenting symptoms include cloudy fluid, abdominal pain, and fever. It is usually caused by gram-positive skin flora (e.g., *Staphylococcus epidermidis*, *Staphylococcus aureus*), or gram-negative organisms.

Initiate empiric antibiotics while awaiting confirmatory testing with agents effective against both these classes of organisms. The diagnosis of peritonitis is confirmed by a peritoneal dialysis fluid WBC count > 100 WBCs/μL with > 50% PMNs, or a positive culture. Intraperitoneal antibiotics are preferred; use PO or IV only when the IP route is not available, such as where the catheter has been removed. Other complications include hernias, hydrothorax, high protein loss (12 g/day), and loss of water-soluble vitamins (especially folic acid).

KIDNEY TRANSPLANT

Kidney transplant can improve quality of life and life expectancy in ESRD patients, as compared to dialysis. Renal transplant reverses the platelet dysfunction, renal osteodystrophy, and sensory/cognitive dysfunction of CKD. Sometimes, transplant can even reverse late manifestations of small-vessel calcification and motor neuropathy of advanced CKD. The main downside to kidney transplantation is the need for life-long immunosuppression to prevent acute and chronic rejection.

Some kidney diseases tend to recur after transplant in the transplanted kidney: FSGS, MPGN, IgA nephropathy, and even diabetes. The main cause of death after kidney transplant is **cardiovascular disease**.

Before Transplant

There are 2 ways to get a kidney transplant: via a living donor (usually a family member, spouse, or friend) or a deceased donor (usually requiring years on a waiting list). Generally, donor and recipient must have compatible ABO blood types. Some centers are now doing ABO-incompatible kidney transplants.

Major contraindications to kidney transplantation are active and recurrent infections, recent or active malignancy, severe cardiovascular disease (untreated coronary artery disease, cerebrovascular disease, or clinical HF), and history of noncompliance.

Controlled HTN and diabetes are not contraindications, nor is age alone.

In appropriate candidates, a preemptive transplant can be performed before dialysis is initiated.

After Transplant

Kidney Rejection

Anytime renal function deteriorates in a patient with a kidney transplant, think of the AKI in the usual terms. Is it prerenal, intrinsic renal, or postrenal? Intrinsic causes include acute rejection, drug toxicity (calcineurin inhibitor toxicity, AIN), infection (cytomegalovirus or BK virus), and recurrence of the primary disease (primary FSGS can recur almost immediately).

Acute rejection should always be considered, as this is a common cause of AKI in transplant recipients. It is most

likely to occur **in the first 6 months** after transplant and can be either cellular, vascular, or antibody mediated. Renal biopsy is needed to establish the diagnosis.

Hyperacute rejection of the transplanted kidney is now exceedingly rare, due to the widespread use of cross-match testing prior to transplant. This rejection is caused by preformed donor antibodies that acutely damage the kidney, and it occurs within minutes to hours of transplant. Cellular rejection is mediated by T-cells and is treated with high dose intravenous steroids. Antibody-mediated rejection is caused by antibodies to the allograft ("donor-specific antibodies"); treatment can include IV steroids, plasmapheresis, intravenous immunoglobulin, and/or rituximab.

Start workup by checking the transplant using U/S with doppler (to rule out obstruction or venous/arterial thrombosis), FE_{Na} (to assess for prerenal failure), and levels of **immunosuppressant** drugs (e.g., **cyclosporine**, **tacrolimus**, **sirolimus**). Screen for CMV and BK virus. If these are normal and the patient's renal function is not improving with empiric IV fluids, renal biopsy is indicated.

Immunosuppressive Therapy

Immunosuppression in transplant recipients consists of induction therapy followed by maintenance therapy. Induction therapy is intensive immunosuppression early after kidney transplant, when the risk of acute rejection is greatest. Maintenance therapy is long-term, less intensive immunosuppression to prevent acute and chronic rejection.

Induction typically consists of antibodies to lymphocytes (e.g., antithymocyte globulin) or the IL-2 receptor (e.g. basiliximab) and high-dose, IV steroids. Maintenance therapy (started immediately after transplant) usually includes:

- 1) a calcineurin inhibitor (e.g., cyclosporine, tacrolimus),
- 2) mycophenolate mofetil or mycophenolic acid, and
- 3) corticosteroids.

Sometimes, sirolimus is also used.

Cyclosporine and **tacrolimus** are calcineurin inhibitors with a similar mechanism of action. They decrease T-cell proliferation (but **not** function!) **without** affecting the bone marrow. **Sirolimus** (a.k.a. rapamycin) is an mTOR (mechanistic target of rapamycin) kinase inhibitor and has T-cell antiproliferative properties.

All 3 drugs are metabolized by the cytochrome P450 system, so **blood levels** of all 3 are **increased** by erythromycin, ketoconazole, voriconazole, and diltiazem and **decreased** by phenytoin, caspofungin, carbamazepine, rifampin, and phenobarbital.

All 3 drugs cause dose-related nephrotoxicity and carry FDA black box warnings for increased risk of death from infections. Side effects of cyclosporine include tremors,

hepatotoxicity, CNS toxicity, and gum hypertrophy. Tacrolimus is the most diabetogenic. Sirolimus is associated with wound dehiscence/impaired healing and development of lymphoma and hyperlipidemia.

Mycophenolic acid and **mycophenolate mofetil** are "antimetabolites." They have largely **replaced** a similar, older agent, **azathioprine**. Main side effects are nausea, vomiting, diarrhea, and bone marrow suppression, and there may be increased risk for lymphoproliferative disorders. **Know that allopurinol increases serum levels of azathioprine but not mycophenolate mofetil or mycophenolic acid.**

Prednisone is the 3rd component of maintenance immunosuppression. Doses are high immediately after transplant but are tapered rapidly and maintained at a low dose long-term in most patients. Toxicities of long-term steroid use include impaired wound healing, osteoporosis, and hyperlipidemia. Glucocorticoids also can make worse glycemic control in patients with diabetes. To avoid these side effects, strategies to withdraw or completely avoid glucocorticoids after kidney transplant have been explored. Outcomes have been mixed, with a small but significant increase in acute rejection and chronic allograft nephropathy in patients treated with early steroid withdrawal. Most transplant centers continue to use long-term low-dose prednisone as part of their standard immunosuppressive regimen.

Immunosuppression increases susceptibility to urinary tract infections, pneumonia, and sepsis. These are common events after renal transplant. Patients are given primary prophylaxis against *Pneumocystis* and CMV in the early posttransplant period.

KIDNEY STONES

PREVIEW | REVIEW

- Name the factors that promote Ca^{2+} stone formation.
- What systemic diseases are associated with Ca^{2+} stones?
- Which bacteria cause staghorn calculi?
- Which antiretroviral drug causes renal stones?
- Name 1 of the most important general recommendations for patients with kidney stones, regardless of the type of stones.

OVERVIEW

Kidney stones are common: 10–15% of people have at least 1 symptomatic kidney stone during their lifetime.

2/3 of renal stones are calcium phosphate or calcium oxalate; the other 1/3 are struvite or uric acid. Multiple crystal types can coexist in the same stone in a single patient.

Kidney stones are usually asymptomatic until they pass from the renal pelvis into the ureter. Classic symptoms of kidney stone passage are renal “colic” (severe, acute flank pain) with or without gross hematuria. Workup of acute renal colic includes:

- **Renal imaging:** CT of abdomen and pelvis without contrast is the test of choice. Renal ultrasound is an alternative which can exclude obstruction and is 1st choice in pregnant women (for more information on renal stones during pregnancy, see the [Women's and Men's Health](#) section). Abdominal plain film is less sensitive, missing uric acid stones (which are radiolucent) and smaller calcium stones. Imaging confirms the diagnosis, excludes obstruction, and stone size helps predict the likelihood of spontaneous passage. Stones > 1 cm are unlikely to pass spontaneously and usually require urologic intervention.
- **Labs:** Check electrolytes, BUN, and creatinine to exclude acute kidney injury from obstruction.
- **Pain control:** NSAIDs are 1st line; use opioids if needed.

Most stones pass spontaneously, and most patients with acute renal colic from stones can be managed as outpatients. Hospitalization and urgent urologic intervention are indicated if there is evidence of infection (fever, leukocytosis), obstruction (hydronephrosis on imaging), or acute kidney injury. Patients should strain their urine, as laboratory analysis of the stone can guide future preventive strategies. Hydration with oral fluids and α -blockers (e.g., tamsulosin) can facilitate stone passage.

If the stone is > 1 cm or the stone does not pass on its own after a trial of conservative management, refer to a urologist for intervention. Options for mechanical stone removal include:

- Ureteroscopy (middle and distal ureteral stones)
- Percutaneous nephrostolithotomy (best for large or staghorn stones)
- Extracorporeal shock wave lithotripsy (best for smaller stones)

In the remainder of this topic, we discuss evaluation and management of patients with kidney stones after the episode of acute renal colic has resolved (stone passage).

DIAGNOSIS

Workup following the 1st kidney stone includes:

- Imaging, if not previously done
- Measure serum Ca^{2+} and, if hypercalcemia is present, iPTH (exclude hyperparathyroidism).
- Measure serum electrolytes and urine pH (exclude Type 1 [distal] RTA).
- U/A and urine culture (Exclude stone-forming urinary pathogens such as *Proteus*; clue = urine pH > 7.5.)
- Chemical analysis of the stone (when available)

If the above results are normal, no specific treatment is needed aside from encouraging fluid intake (high fluid intake reduces recurrence risk for all stone types).

Although some patients only have a single episode, 50% of patients develop recurrent kidney stones. For **recurrent stones**, perform 24-hour urine collection, measuring urine volume, Ca^{2+} , Na^+ , urea, uric acid, citrate, oxalate, cystine, and creatinine.

The 24-hour urine stone profile has 2 purposes. First, it helps to determine the likely stone type in patients without a stone available for analysis (these are most patients). Second, it identifies individual risk factors for stone formation, which helps to guide targeted prevention of recurrent stones.

Several factors **inhibit** or **promote** stone formation. Urinary citrate, Mg^{2+} , and pyrophosphate inhibit Ca^{2+} stone formation.

Promoters of stone formation:

- Crystals (e.g., uric acid, calcium oxalate), which act as a nidus for stone formation
- Hypercalciuria
- Hypocitraturia
- Metabolic acidosis (causes hypocitraturia and also leaches Ca^{2+} from the bones, resulting in hypercalciuria)
- Hyperoxaluria
- Concentrated urine (low urine volume)
- Hyperuricosuria (high urinary uric acid)

Ca^{2+} stones are composed of calcium oxalate (most common), calcium phosphate, or a combination of the 2.

Almost all patients with **calcium phosphate** kidney stones have hypercalciuria. Hypercalciuria may be idiopathic (50%) or caused by excess vitamin D, Type 1 (distal) RTA, sarcoidosis, primary hyperparathyroidism, or medullary sponge kidney.

High urinary **oxalate** is the most important factor in **calcium oxalate** stone formation. (See A in [Figure 7-2 on page 7-2](#) for calcium oxalate crystals in the urine.) **Vitamin C** is an oxalate precursor and can cause stones if taken in large amounts.

Steatorrhea (e.g., patients with gastric bypass, short bowel syndrome, Crohn disease) also can lead to calcium oxalate stones, in a condition called enteric hyperoxaluria. Unabsorbed free fatty acids in the bowel chelate Ca^{2+} . This prevents Ca^{2+} from binding to oxalate, allowing the oxalate to be absorbed and then excreted in the urine.

High urinary uric acid is a predisposing factor for oxalate stones because **uric acid crystals** can act as a nidus for calcium oxalate stone formation.

TREATMENT

Prevent recurrent Ca^{2+} stones by **pushing fluids** (urine output should be > 2 L/day) and **decreasing dietary protein and Na^+ intake**. If dietary modification and increased fluid intake fail to prevent recurrent stones, options depend on the results of the 24-hour stone profile. Give **potassium citrate** to patients with low urinary citrate or low urinary pH. Treat patients with hypercalciuria with a **thiazide diuretic** (which reduces urinary Ca^{2+} excretion). Treat patients with hyperuricemia

and high urinary uric acid excretion with **allopurinol** or another uric acid-lowering drug. Remember: Uric acid can act as a nidus for Ca^{2+} stone formation!

Note: Do **not** instruct patients to reduce dietary Ca^{2+} intake; this only **increases** oxaluria! In fact, increasing dietary Ca^{2+} (e.g., dairy products) can reduce stone formation by decreasing oxalate absorption in the gut, hence decreasing urinary oxalate. However, Ca^{2+} supplements should be avoided.

Uric acid stones are radiolucent and are not seen on plain film x-ray. (See C in [Figure 7-2 on page 7-2](#) for uric acid crystals in the urine.) Uric acid stones are usually seen in patients with acidic urine ($\text{pH} < 5.5$) and/or high serum uric acid (sometimes with gout). Myeloproliferative syndromes, chemotherapy, and Lesch-Nyhan syndrome can cause a hyperuricosuria in which there is stone formation even at normal urine pH. Treat with urinary alkalinization (e.g., potassium citrate) +/- allopurinol.

Struvite stones are also called “triple-phosphate,” as they are composed of calcium, ammonium, and magnesium phosphates. Struvite stones grow quickly from struvite crystals (D in [Figure 7-2 on page 7-2](#)) and often become **staghorn calculi** ([Figure 7-12](#)). Think chronic UTI when you see staghorn calculi. The **ammonium** needed to make these stones forms only when **urease** breaks down the urea. The most common urease producers are *Proteus* and *Klebsiella*. Treatment consists of removal of the stone(s), acidification of the urine (this and calcium phosphate are the only stones that are **more likely** with alkaline urine), and antibiotics. If the stones cannot be surgically removed, patients require antibiotics indefinitely.



Figure 7-12: Staghorn calculi

Cystine stones are rare and only seen in patients with cystinuria. This is an autosomal recessive disorder usually diagnosed in childhood. Look for clear, **hexagonal** crystals in the urine (E in [Figure 7-2 on page 7-2](#)). Treat by **increasing fluid intake** and **alkalinizing** the urine (like uric acid, cystine solubility increases at high urine pH).

Some **medications** can cause kidney stones and crystal-induced nephropathy. HIV/AIDS patients on indinavir as part of an antiretroviral regimen can get **indinavir** stones. Sulfa drugs and ciprofloxacin can cause stones via crystallization in the urine. Loop diuretics and carbonic anhydrase inhibitors (e.g., acetazolamide) can increase the risk of Ca^{2+} stone formation.

Keypoints to remember about kidney stone management:

- All kidney stone patients should increase oral fluid intake to produce at least **2 L/day** of urine, regardless of stone type.
- Urinary **alkalinization** is appropriate for all stone-formers **except** in struvite and calcium phosphate stones. Potassium citrate, given orally, both alkalinizes the urine and increases urinary citrate (which decreases calcium oxalate stone formation).
- Remember the difference between cystine and citrate: **Cystine** is an amino acid that precipitates into stones; **citrate** chelates Ca^{2+} in the urine, thereby preventing stones.

INTERSTITIAL CYSTITIS

Interstitial cystitis is a chronic pain syndrome that presents with bladder pain but no identifiable infection or other pathology. Diagnosis of interstitial cystitis is based on symptoms of bladder pain, usually relieved by voiding, and exclusion of UTI and bladder dysfunction. U/A, urine culture, and postvoid residual are usually normal. As with other chronic pain syndromes, treatment is challenging. Behavior modification including education, symptom management, fluid management, identification and avoidance of dietary triggers, and bladder training may help. Use of analgesics should be limited to short-term rescue therapy.

ACID-BASE DISORDERS

PREVIEW | REVIEW

- What are the common causes of a normal anion gap metabolic acidosis (NAGMA)? High anion gap metabolic acidosis (HAGMA)?
- How is the osmol gap (OG) calculated?
- Which poisonings cause an increased OG and a normal anion gap (AG)?
- Which poisonings cause both an increased AG and an increased OG?
- Why is isopropyl alcohol different from the other toxic alcohols?
- What is the 4-step method for solving acid-base disorders?
- List the 4 primary acid-base disorders and explain the expected compensatory response of each one.
- What are the causes of HAGMA?
- What urine abnormality is seen in patients who have ingested ethylene glycol?
- What are the classic symptoms in a patient who has ingested methanol?

- What is the treatment for methanol and ethylene glycol ingestions?
- What is the most common cause of NAGMA?
- Which cause of NAGMA also causes hyperkalemia?
- What are 2 causes of NAGMA and hypokalemia?
- Which renal tubular acidosis (RTA) can cause renal stones?
- Multiple myeloma is associated with which RTA?
- What is the serum K^+ level in Type 4 RTA?
- Diabetic nephropathy causes which RTA?
- Answer all of the RTA questions associated with Table 7-10 on page 7-47.

RESPIRATORY vs. METABOLIC DISORDERS

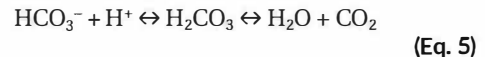
First, let's go over some definitions of terms we use over and over again when discussing acid-base disorders:

- Acidemia is an arterial pH < 7.35; alkalemia is a pH > 7.45.
- Acidosis is a disorder that decreases the pH of extracellular fluid (ECF); alkalosis is a disorder that increases ECF pH. Either of these disorders can be respiratory or metabolic in origin:
 - Respiratory acid-base disorders either retain CO_2 (increasing pCO_2 and decreasing pH) or blow it off (decreasing pCO_2 and increasing pH).
 - Metabolic acid-base disorders are due to an increase of acids or bases in the body, causing a decrease or increase in HCO_3^- and a respective decrease or increase of pH.
- Primary disorder: In a **simple** acid-base disorder, there is an initial shift in acid-base balance that is caused by the "primary" disorder.
- Compensatory response: The change in pH caused by the primary disorder is decreased by a compensatory response of the other system. Metabolic compensatory responses are slow (12–24 hours). Pulmonary responses are immediate:
 - Metabolic acidosis immediately induces a respiratory alkalosis; metabolic alkalosis immediately induces a compensatory respiratory acidosis.
 - Respiratory acidosis slowly induces a metabolic alkalosis; respiratory alkalosis slowly induces a compensatory metabolic acidosis.
- Simple acid-base disorders are, as the ones discussed above, a primary disorder with an opposing compensatory response. Mixed disorders are more than one primary disorder occurring concurrently. The classic example is salicylate poisoning, where there is a metabolic acidosis with a respiratory alkalosis.

In this topic, we use pCO_2 for P_aCO_2 . We also drop the brackets to indicate concentration of a substance. For instance, we use HCO_3^- instead of $[HCO_3^-]$. We use **AG** for serum anion gap, **UAG** for urine anion gap, and **OG** for osmol gap.

MECHANISMS

Understanding acid-base disorders depends on understanding the relationship between bicarbonate (HCO_3^-), carbonic acid (H_2CO_3), and carbon dioxide (CO_2). These substances are in equilibrium with each other and form the **bicarbonate buffer system**:



Eq. 5 is used to derive the Henderson-Hasselbalch (H-H) equation:

$$pH = 6.10 + \log (HCO_3^- / (0.03 \times pCO_2)) \quad (\text{Eq. 6})$$

The H-H equation illustrates the 2 ways the body controls the serum pH:

- 1) Regulation of the respiratory rate and tidal volume, which controls the pCO_2 **or**
- 2) Regulation of the kidney's reabsorption of HCO_3^- or excretion of acids/acid equivalents (phosphoric, sulfuric, and ammonium)

Note that it is the ratio of HCO_3^- to pCO_2 —not the absolute levels—that determines pH.

Also note that you can plug pH and pCO_2 values into the H-H equation and calculate the HCO_3^- . This is how the lab calculates the HCO_3^- for an arterial blood gas (ABG) report.

Soon, we will go over a very cool method of assessing acid-base status, but first let's discuss anion gaps and osmol gap.

ANION GAPS

Serum Anion Gap (AG)

Note: We call serum anion gap, simply, anion gap (AG). We always call urine anion gap (UAG) by its name.

Always calculate the AG when there is any possibility of a metabolic acidosis. To see why, let's first see how AG is calculated:

$$AG = Na^+ - (HCO_3^- + Cl^-) \quad (\text{Eq. 7a})$$

Alternatively, you can use:

$$AG = Na^+ - HCO_3^- - Cl^- \quad (\text{Eq. 7b})$$

These are the **same** formula. Regardless of which way you use it, be very certain about your order of operations so you get the correct value. Note that K^+ is usually left out. This is because it does not change enough to significantly affect the gap.

You are probably wondering why the H^+ cations are not included in this equation. Most of the H^+ cations are buffered out. It only takes a very tiny fraction to change the pH and this tiny bit would not add significantly to the Na^+ level. But the anions do stay around and affect the Cl^- and HCO_3^- levels. Which is what AG is all about.

Normal AG is 3–11 mEq/L (3–11 mmol/L), with an average of 6 mEq/L. We use these values in this section.

Note that a few clinical labs do use K^+ in their AG formula. This boosts their reference range up by ~ 4 mEq/L. In your calculations, always take into account the reference range used by your lab.

The AG is an estimate of the number of anions other than HCO_3^- and Cl^- . These are called the **unmeasured anions** and calculating the AG helps us determine the cause of a metabolic acidosis:

- If the AG is normal, the acidosis is being caused by a process that either decreases HCO_3^- (usually severe **diarrhea**) or increases H^+ (**CKD**, **RTA**; large infusions of **normal saline** given during surgery or when treating diabetic ketoacidosis [DKA] with subsequent removal of Na^+ by the kidney). There is a 1:1 increase in Cl^- with the decrease in HCO_3^- . This is termed a normal AG metabolic acidosis (NAGMA).
- If the AG is elevated but the Cl^- is normal, the required increase in anions (again, the ECF is always neutral) is due to the unmeasured anions. This is called a high AG metabolic acidosis (**HAGMA**) and is caused by **ketoacids** (DKA or alcoholic ketoacidosis), **lactic acid** (from impaired tissue oxygenation), and salicylic acid or metabolites of **ethylene glycol** or **methanol** (poisoning). There is normally a 1:1 increase in AG with the decrease in HCO_3^- except with lactic acidosis where it is 1.5:1.

Under normal conditions, negatively charged albumin is the main contributor to the AG. Therefore, **hypoalbuminemia** results in a lower AG. To correct this falsely low AG, add 2.5 mEq/L to the AG for each 1 g/dL decrease in albumin. The converse is also true; correct the AG downward for patients with an elevated serum albumin.

You can tell a lot from a glance at the electrolyte results after examining a patient. Is Na^+ normal? Great! Then look at HCO_3^- . If it is low, think metabolic acidosis and check the Cl^- . If Cl^- is elevated, bang! it is a probably a NAGMA. If Cl^- is normal, zing! it is probably a HAGMA. Remember the causes! And with a metabolic acidosis, expect somewhat faster or deeper breathing, indicating respiratory compensation. Don't be fooled. With a high-normal Na^+

and low-normal HCO_3^- , you can have a high anion gap! If all this doesn't make perfect sense, review this topic. Read even more on AG in **Metabolic Acidosis** on page 7-43.

Urine AG (UAG)

The **UAG** is used to evaluate the cause of a NAGMA. The UAG can help differentiate between gastrointestinal (GI) loss of HCO_3^- (diarrhea) and renal tubular acidosis (RTA; see RTAs on page 7-45). In the setting of NAGMA due to extrarenal (e.g., GI) HCO_3^- losses, renal H^+ excretion is increased, and this H^+ is excreted in the form of ammonium (NH_4^+). In RTA, there is a renal defect in H^+ excretion, so urine NH_4^+ is low. We do not measure urine NH_4^+ directly; we estimate it indirectly using the UAG.

UAG is calculated from the measured ions in the urine: Na^+ , K^+ , and Cl^- , expressed in mEq/L:

$$UAG = Na^+ + K^+ - Cl^- \quad (\text{Eq. 8})$$

UAG is an estimate of the unmeasured anions in the urine. NH_4^+ is a cation (not an anion), so when the urine NH_4^+ is high (as in metabolic acidosis due to GI losses of bicarbonate), the UAG will be **negative**. A **positive** UAG means there is not much NH_4^+ in the urine. In the setting of a NAGMA, a positive UAG usually indicates an RTA.

Note: K^+ is used in calculating UAG but not serum AG.

In summary:

- A normal/positive UAG value suggests low urinary NH_4^+ (e.g., **RTA Type 4**).
- A negative UAG value suggests high renal excretion of H^+ in the form of NH_4^+ (seen in NAGMA due to HCO_3^- loss from **diarrhea**). Remember **neGUTive** UAG in cases of diarrhea (i.e., **GUT**).

OSMOL GAP (OG)

The osmolality of the blood is normally determined mainly by concentrations of sodium ($[Na^+]$), glucose, and urea.

The OG is elevated when there are unmeasured osmotically active substances (particles or osmoles) in the blood (and possibly causing an acidosis). The OG is the difference between the measured serum osmolality (from the lab) and a calculated estimation of what the osmolality ought to be—if the only effective osmoles present are the normal ones (Na^+ , glucose, and urea). Use the following formula to calculate the serum osmolality:

$$Osm_{calc} = 2[Na^+] + (BUN/2.8) + (glucose/18) \quad (\text{Eq. 9})$$

Subtract this value from the lab-measured serum osmolality to get the OG:

$$\text{OG} = \text{Osm}_{\text{meas}} - \text{Osm}_{\text{calc}} \quad (\text{Eq. 10})$$

$$\text{OG} = \text{Osm}_{\text{meas}} - (2[\text{Na}^+] + \text{BUN}/2.8 + \text{glucose}/18) \quad (\text{Eq. 11})$$

A normal OG is < 10 mOsm/kg.

The main use of the OG is in the workup of an obtunded patient with possible toxic alcohol ingestion. An **extremely high OG** (> 25 mOsm/kg) is almost always due to toxic alcohol poisoning from:

- methanol,
- ethylene glycol,
- propylene glycol, or
- isopropyl alcohol.

Chronic kidney disease, lactic acidosis, and ketoacidosis cause a high OG from retention of small solutes.

Nontoxic causes of a high OG and a **normal AG** are mannitol, sorbitol, and glycerol ingestion.

Toxic causes of a high OG and **normal AG** are isopropyl alcohol, ethanol, and acetone ingestion. These are not metabolized to acids; hence, metabolic acidosis is not usually seen.

Toxic causes of both a high OG and a **high AG**:

- Ethylene glycol, a common ingredient in radiator **anti-freeze** solutions. Toxic acid metabolite = glycolic acid.
- Methanol, a common ingredient in **paint thinners** and **deicing** solutions (e.g., windshield washer fluids). Rarely, methanol is an inadvertent contaminant of **moonshine**. Toxic acid metabolite = formic acid.
- Propylene glycol (rarely; low toxicity). Toxic acid metabolite = lactic acid.

These 3 toxic alcohols directly increase the plasma osmolality, causing a high OG. Toxic alcohols are metabolized by **alcohol dehydrogenase** to their toxic acid metabolites; the OG falls and the HAGMA develops. So, early after ingestion, the elevated OG dominates and later the OG resolves as the HAGMA worsens.

In low doses, **propylene glycol** is generally considered safe and is even an approved food additive. But propylene glycol is metabolized to lactic acid, and excessive absorption can cause lactic acidosis. It is a solvent used in IV lorazepam, and a few cases of severe lactic acidosis have resulted from lorazepam given as a continuous infusion.

Isopropyl alcohol is metabolized to acetone, which, unlike the others, is not an acid and is less toxic than the original alcohol. Hence, isopropyl alcohol intoxication does not cause metabolic acidosis. Still, about 8 oz of isopropyl alcohol can be fatal.

Patients with toxic alcohol poisoning can develop stupor, coma, and hypotension (for more treatment details, see

HAGMA on page 7-43). Treat with dialysis +/- fomepizole, folate, and supportive care, including ventilatory support, IV fluids, and vasopressors.

Table 7-7 lists disorders that cause a high or normal AG and OG.

Table 7-7: Anion Gap (AG) and Osmol Gap (OG) in the Obtunded Patient

AG	OG	Consider...
High	High-very high	Methanol and ethylene glycol Ketoacidosis and lactic acidosis Chronic kidney disease Propylene glycol
	Normal	Salicylate poisoning Methanol or ethylene glycol ingestion after substrates have been converted to acid metabolites
Normal	High	Isopropyl alcohol, acetone, or ethanol ingestion
	Normal	Carbon monoxide poisoning—before lactic acidosis develops

ANALYSIS OF ACID-BASE PROBLEMS

Introduction

The goal of acid-base analysis is to identify simple and mixed acid-base disorder(s) based on labs alone (i.e., ABGs and electrolytes). Here we give you a good method to quickly crank out accurate acid-base diagnoses—even mixed ones.

The MedStudy 4-Step Method of Acid-Base Analysis

Overview of the Method

The process is simple and quick. This method can easily handle multiple, concurrent acid-base disorders. Always remember to take into account the patient's clinical presentation while interpreting the ABG results.

The information required to determine exactly what the acid-base status is:

- From ABGs: pH and pCO₂
- From electrolyte panel: Na⁺, HCO₃⁻, and Cl⁻

The 4 Steps

Prepare: Get the ABG and electrolytes results. Write down: pH, pCO₂, and HCO₃⁻.

Step 1: Check pH. Does the patient have acidemia (pH < 7.35) or alkalemia (pH > 7.45)?

Step 2: Check pCO₂ and HCO₃⁻ to see what disorder is causing the acidemia/alkalemia. The body never fully compensates for the primary disorder. So with an acidemia, the primary disorder must be a metabolic or respiratory acidosis; with an alkalemia, the primary disorder must be a metabolic or respiratory alkalosis.

If patient has acidemia (**low pH**), the primary disorder can **only** be an acidosis caused by:

- metabolic acidosis if HCO_3^- is **low** or
- respiratory acidosis if pCO_2 is **high**.

If patient has alkalemia (**high pH**), the primary disorder can **only** be an alkalosis caused by:

- metabolic alkalosis if HCO_3^- is **high** or
- respiratory alkalosis if pCO_2 is **low**.

Use this very common-sense way to figure out the initial disorder. With a little practice, you'll see some interesting correlations. One very cool and commonly taught one is, if the direction of the HCO_3^- follows the pH (i.e., high pH, high HCO_3^- ; low pH, low HCO_3^-), the primary disorder is metabolic. If pCO_2 follows the pH, the primary disorder is respiratory. But remember the logic as presented above, so if you get confused with the high/high, low/low and what follows what, you can still easily figure out the primary disorder.

Step 3: Now you know which of the 4 disorders is primary. What we do now is calculate the body's automatic compensatory response to this primary disorder using accepted formulas as listed in Table 16.1 of Brenner and Rector's *The Kidney 11th Ed. 2020*. A metabolic primary disorder automatically initiates a respiratory response to move the pH back toward normal, and vice-versa for a pulmonary primary disorder. We illustrate these 2 physiologic reactions in Figure 7-13 and Figure 7-14.

Resp ($1^\circ = \text{pCO}_2$): pH **pCO_2** HCO_3^- 

Figure 7-13: Acid-base equation (respiratory primary disorder)

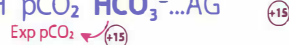
Metab ($1^\circ = \text{HCO}_3^-$): pH pCO_2 **HCO_3^-** ...AG 

Figure 7-14: Acid-base equation (metabolic primary disorder)

In Figure 7-13, the pCO_2 is in bold, showing that we have a respiratory primary disorder and the change in pCO_2 is driving the compensatory response (indicated by the red arrow). Beside the red arrow is the magic [1,2,4,5] square you use to calculate how much HCO_3^- will be changing based on the initial change in the pCO_2 . Remember that one mEq/L change in HCO_3^- occurs per 10 mmHg change in pCO_2 . Because it takes kidneys awhile to respond, the square is divided into acute and chronic values (acute = 1,2; chronic_{1-3days} = 4,5). Also, the kidney response is not quite as high for respiratory acidosis vs. alkalosis (1 vs. 2 acute; 4 vs. 5 chronic).

In Figure 7-14, the HCO_3^- is in bold, showing that we have a metabolic primary disorder and the change in HCO_3^- is driving the compensatory response (indicated by the red arrow). Beside the red arrow is the magic (+15) circle that reminds you of the simplified Winter's formula (expected $\text{pCO}_2 = \text{HCO}_3^- + 15$) that can be used to determine the respiratory response for both metabolic acidosis and alkalosis! When the HCO_3^- is < 10, you must use the complete Winter's formula (expected $\text{pCO}_2 = 1.5 \times \text{HCO}_3^- + 8$; think bicarb + half bicarb + 8).

You'll probably need to dredge up this info immediately after you've figured out the primary disorder. Let's restate it in that context. Here are the 4 primary disorders, along with how to calculate their expected compensatory responses:

- **Metabolic acidosis:** The body's response is to **immediately** hyperventilate (blow off CO_2), causing a compensatory respiratory alkalosis. The expected $\text{pCO}_2 = \text{HCO}_3^- + 15$. Remember (+15) from the magic circle. Again, if HCO_3^- is < 10, use the full Winter's formula (expected $\text{pCO}_2 = \text{bicarb} + \text{half bicarb} + 8$).
- **Metabolic alkalosis:** The body's response is to **immediately** hypoventilate (retain CO_2), causing a compensatory respiratory acidosis. The expected $\text{pCO}_2 = \text{HCO}_3^- + 15$. Remember (+15) from the magic circle. Note: Several other formulas can be used. This is the easiest one and it is used for metabolic acidosis, too. So, really easy to remember!
- **Respiratory acidosis:** The body's response is to retain HCO_3^- in the kidney, **slowly** causing a compensatory metabolic alkalosis. Remember [1 and 4] from the magic square. The expected $\text{HCO}_3^- = \text{change in } \text{pCO}_2 / 10 \times 1$ (if acute) or $\times 4$ (if chronic).
- **Respiratory alkalosis:** The body's response is to excrete HCO_3^- in the kidney, **slowly** causing a compensatory metabolic acidosis. Remember [2 and 5] from the magic square. The expected $\text{HCO}_3^- = \text{change in } \text{pCO}_2 / 10 \times 2$ (if acute) or $\times 5$ (if chronic).

Simple vs. mixed: So you've determined the primary disorder and its expected compensation. If the expected response is pretty close to the actual value, the patient has a simple acid-base disorder and you are done. If not, the patient has a mixed disorder. If the pCO_2 is higher than expected, there is an additional respiratory acidosis. If lower, a respiratory alkalosis. If the HCO_3^- is higher than expected, there is an additional metabolic alkalosis. If lower, a metabolic acidosis. Hey, easier than you thought it would be, right?

Step 4: If there is a metabolic acidosis, even if it is part of a mixed disorder, calculate the anion gap to see if the patient has a HAGMA or NAGMA. $\text{AG} = \text{Na}^+ - (\text{Cl}^- + \text{HCO}_3^-)$; see Eq. 7a and **Serum Anion Gap (AG)** on page 7-38.

That's all there is to the analysis, but you also need all the data gained from a thorough evaluation of the patient to make the proper diagnosis.

Caveats

Key points to keep in mind:

- ABGs and chemistries must be drawn at the same time.
- Always be sure the diagnosis makes sense given the clinical history.
- Again, remember that **"+15" does not work** in determining expected pCO_2 when $\text{HCO}_3^- < 10 \text{ mEq/L}$; use the **full** Winter's formula instead: $1.5 \times (\text{HCO}_3^-) + 8$ (bicarb + half bicarb + 8)

- For primary **metabolic alkalosis**, there is another accepted and more accurate alternative: Expected $p\text{CO}_2$ increases by ~ 0.7 mmHg for every 1 mEq/L increase in the HCO_3^- . It's just not as friendly for bedside calculations.
- Regarding the AG: Although low HCO_3^- with a high Cl^- signals a probable NAGMA, and a low HCO_3^- with a low Cl^- suggests a HAGMA, the Na^+ has a wide normal variation, so you can be fooled. Always do the actual calculation!
- If hypoalbuminemia is present, be sure to use the corrected AG: AG decreases by 2.5 mEq/L for every 1 g/dL decrease in albumin (from 4 g/dL).
- Few patients tolerate a $p\text{CO}_2 > 55$ mmHg in response to a metabolic acidosis. Also, in response to a severe metabolic acidosis, only young healthy patients can blow off CO_2 to a $p\text{CO}_2$ of 10 mmHg; weaker, older patients have a lower limit of 20+ mmHg. When patients reach this limit of respiratory compensation and the serum HCO_3^- keeps dropping, the pH drops at a much faster rate.

METABOLIC ALKALOSIS

Metabolic alkalosis always involves a generation phase (initial H^+ loss or HCO_3^- gain) and maintenance phase (failure of the kidney to excrete HCO_3^- to correct the alkalosis). The most common cause of metabolic alkalosis is **volume contraction** caused by diuretics or vomiting/nasogastric suction.

Generation Phase

Metabolic alkalosis is generated when H^+ is lost or excess HCO_3^- is administered or generated. Clinical situations where this occurs include:

- With vomiting and nasogastric (NG) suction, H^+ (and Cl^-) is lost via **gastric** secretions.
- With primary aldosteronism, there is acid loss (as NH_4^+) via the **kidneys**.
- With diuretic-induced “contraction” alkalosis, there is **renal loss of bicarb-free fluid**, which increases the relative concentration of extracellular HCO_3^- . The volume contraction prevents the excess HCO_3^- from being excreted by the kidneys.

Remember: H^+ loss leads to an increase in the serum HCO_3^- concentration (see Eq. 5 under **Mechanisms** on page 7-38).

Maintenance Phase

Normally, patients with good renal function and normal volume status rapidly excrete excess HCO_3^- in the urine, avoiding the development of metabolic alkalosis. An alkalosis persists only when there is failure of the kidney to excrete the excess HCO_3^- (maintenance phase). The most common cause of inability of the kidneys to excrete HCO_3^- is **volume depletion**.

This makes intuitive sense: HCO_3^- cannot be excreted alone; it must be accompanied by a cation (+), and the options for the kidney are Na^+ and K^+ . If the patient is volume depleted, the kidney will “want” to hold on to Na^+ , as Na^+ loss will worsen volume depletion. If the patient is also hypokalemic (as they often are), the kidneys similarly will “want” to hold on to K^+ . The cost of holding on to Na^+ and K^+ is persistent metabolic alkalosis—an inability to excrete all the excess HCO_3^- . This is a small price to pay, as metabolic alkalosis is much less dangerous than hypovolemic shock or severe hypokalemia.

Here is why this happens mechanistically. With volume depletion, there is:

- Decreased distal Cl^- delivery
- High aldosterone levels

Aldosterone enhances distal Na^+ reabsorption and H^+/K^+ excretion by activating distal tubular Na^+/H^+ and Na^+/K^+ pumps, thereby leading to H^+ loss (alkalosis) and K^+ loss (hypokalemia). This can result in **paradoxical aciduria**, a low urine pH in the setting of metabolic alkalosis. Metabolic alkalosis often is seen together with hypokalemia. This occurs because high aldosterone causes renal loss of K^+ , in addition to H^+ . Also in alkalemia, H^+ shifts from the intracellular space to the extracellular space in exchange for K^+ , thus exacerbating hypokalemia.

Types of Metabolic Alkalosis

The 2 types of metabolic alkalosis are **Cl^- -responsive** and **Cl^- -resistant**. Cl^- -responsive metabolic alkalosis is maintained by volume depletion. With Cl^- -resistant metabolic alkalosis, there is some other defect at play (usually high aldosterone). These 2 types are distinguished based on the urinary Cl^- measurement (Figure 7-15). The urine Na^+ concentration and fractional excretion of Na^+ can be elevated during metabolic alkalosis, even with volume depletion, because urinary HCO_3^- excretion (some is excreted, just not enough) must be accompanied by Na^+ excretion. In volume depletion, urinary Cl^- is < 10 mEq/L (10 mmol/L) because NaCl is avidly reabsorbed to maintain intravascular volume.

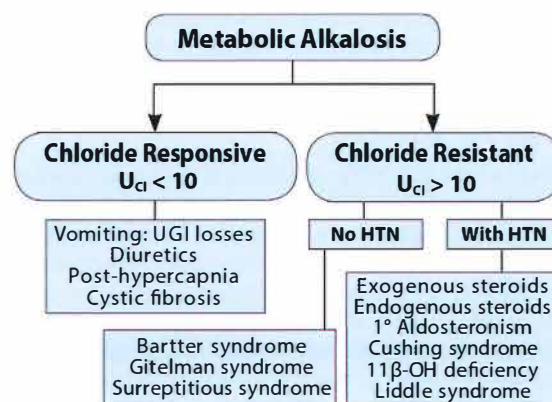


Figure 7-15: Causes of metabolic alkalosis

If urinary Cl^- is $> 10 \text{ mEq/L}$, you have a Cl^- -resistant alkalosis. The 1 exception to this rule is active diuretic use, which is a Cl^- -responsive alkalosis with a high urinary Cl^- due to the direct effect of the diuretic to increase urinary chloride. Bartter syndrome, Gitelman syndrome, severe hypokalemia, surreptitious use of diuretics, and increased intake of HCO_3^- (i.e., milk-alkali syndrome) present with normal blood pressure (BP).

In Cl^- -responsive alkalosis (when urinary $\text{Cl}^- < 10 \text{ mEq/L}$), aim treatment at **restoration of intravascular volume** with IV fluids (with NaCl and/or KCl). Volume resuscitation restores the kidney's ability to excrete HCO_3^- and correct the alkalosis. **K^+ correction** is integral to resolving the alkalosis, as well. Both interventions will lower aldosterone production.

The carbonic anhydrase inhibitor acetazolamide increases sodium bicarbonate excretion and can be used to treat metabolic alkalosis in the setting of volume overload (e.g., edematous states, such as decompensated HF).

Remember: Significant alkalemia of any etiology can cause the diffuse paresthesias/numbness and muscle spasms typically associated with acute hyperventilation; the high pH increases the fraction of bound Ca^{2+} . The resulting decrease in ionized Ca^{2+} produces these symptoms of hypocalcemia. There is no change in total serum Ca^{2+} (ionized + bound). This effect can also be induced by rapid infusion of IV HCO_3^- or citrate (massive blood transfusion).

On the other hand, patients with both metabolic acidosis and hypocalcemia are protected from the hypocalcemia because acidosis decreases the fraction of bound Ca^{2+} and increases the ionized Ca^{2+} . In this situation, **always correct the hypocalcemia before giving bicarbonate to treat the metabolic acidosis!** Correction of acidosis before correction of hypocalcemia removes the protective effect of the acidosis and can precipitate seizures.

METABOLIC ACIDOSIS

Etiology

Metabolic acidosis is divided into 2 categories:

- High anion gap metabolic acidosis (**HAGMA**); caused by 1 of the following:
 - Overproduction of lactic acid or ketoacids
 - Ingestion of agents that are acids (e.g., salicylates) or are metabolized to acids (e.g., methanol, ethylene glycol, propylene glycol, propofol) or cause a lactic/ketoacidosis (e.g., salicylates, isoniazid, metformin, cyanide, iron)
 - Renal failure
- Normal anion (a.k.a. non-AG) metabolic acidosis (**NAGMA**); caused by one of the following:
 - HCO_3^- losses by the kidney: proximal (Type 2) RTA
 - HCO_3^- losses by the gut: diarrhea

- Large infusions of **normal saline** given during surgery or when treating DKA with subsequent removal of Na^+ by the kidney
- Increased organic acids: Total parenteral nutrition can increase the generation of NH_4^+ as a breakdown product of amino acids.
- Inability of the kidney to excrete H^+ : CKD, renal failure, distal (Type 1) RTA, Type 4 RTA

HAGMA

With HAGMA, the fall in HCO_3^- is matched by an increase in unmeasured anions. There is no change in $[\text{Cl}^-]$.

Perform these tests immediately on a patient with unexplained HAGMA:

- Serum glucose
- Urine and serum ketones
- Lactic acid level
- Serum osmolality with calculation of the OG (high in methanol and ethylene glycol ingestions)
- Toxicology screen (if OG is elevated and/or toxic ingestion is suspected clinically)
- U/A to assess for calcium oxalate crystals (seen in ethylene glycol ingestion)

Table 7-8 on page 7-44 lists the causes of HAGMA. The 4 common categories of HAGMA include:

- 1) **Ketoacidosis**: There are 3 main causes of ketoacidosis—uncontrolled Type 1 diabetes, alcohol intoxication, and starvation. Check β -hydroxybutyrate and urine ketones:
 - Diabetic ketoacidosis (DKA): Classic findings include volume depletion, a normal Cl^- , hyperglycemia, and HAGMA in a known diabetic patient. DKA responds to restoration of intravascular volume, replacement of electrolytes, and IV insulin. Note that DKA with normal blood sugar has been reported with SGLT2 inhibitors (e.g., canagliflozin). DKA is discussed in the **Endocrinology** section.
 - Alcoholic ketoacidosis: A key clue is an alcoholic who presents with HAGMA. Classic findings include HAGMA, high OG (from ethanol and acetone, not from the ketones), and hyper- or hypoglycemia in a patient with alcohol use disorder. Alcoholic ketoacidosis responds well to dextrose infusion but be sure to treat any hypophosphatemia first and watch for development of hypophosphatemia during the dextrose infusion!
 - Starvation ketosis typically causes only mild metabolic acidosis. Consider this in a patient with ketoacidosis, normal blood sugar, and no history of alcohol use.

2) **Lactic acidosis:** Lactic acid has 2 isomers—L-lactate and D-lactate. Lactic acidosis presents with a **HAGMA** and can also cause a high OG:

- **L-lactic acidosis:**
 - Type A is due to impairment in tissue oxygenation during shock, cardiac failure, or sepsis. This is a medical emergency that requires immediate treatment.
 - Type B has no impaired tissue oxygenation and can be caused by drug-induced mitochondrial dysfunction (e.g., zidovudine, metformin, propofol), tumors (e.g., leukemia, lymphomas), and alcoholism. It can also be seen in hereditary metabolic myopathies, including glycogen storage diseases.
- **D-lactic acidosis:**
 - Can occur in patients with short bowel syndrome and other malabsorption disorders. They present with typical neurologic abnormalities, from slurred speech to obtundation.
 - The D-lactate isomer is not physiologically active and takes much longer to break down; it therefore accumulates more quickly and persists longer than L-lactate.
 - These patients have HAGMA with a **normal** lactate level because standard lab assays measure only L-lactate, not D-lactate.

3) **Uremia** causes an accumulation of anions (including **sulfate**, **phosphate**, and **urate**), resulting in a HAGMA. Check BUN and creatinine.

4) **Toxins:** Ethylene glycol, methanol, propofol, and propylene glycol are the classic toxic alcohols that present with a HAGMA and a high OG. Salicylate overdose and chronic acetaminophen are causes of HAGMA with a normal OG. Here are some facts on each:

- **Ethylene glycol**—key clues are a **HAGMA** and **calcium oxalate crystals** in the urine. Ethylene glycol metabolizes to toxic acids (1st to glycolic acid, and then to oxalic acid).
- **Methanol**—key clues are a **HAGMA** and **visual symptoms**. Methanol metabolizes to formic acid, a very toxic substance. Patients present with nausea, vomiting, and abdominal pain, and they can have visual complaints described as “walking through a snowstorm.” Formic acid, a metabolite, is directly toxic to the optic nerve.
- **Propofol-related infusion syndrome**—propofol is an IV sedative/hypnotic used for general anesthesia induction. If given in high doses for > 48 hours, it can cause a Type B lactic acidosis and a syndrome featuring renal failure, rhabdomyolysis, hyperlipidemia, J-point elevation on ECG, refractory bradycardia, and various arrhythmias.

- **Propylene glycol**—propylene glycol is used as a solvent for **IV lorazepam** (and numerous other drugs), and it is an FDA-approved food sweetener (!). Propylene glycol is metabolized to L- and D-lactate. Continuous infusion or repeated large IV doses of lorazepam or sustained intestinal absorption of propylene glycol can cause **severe lactic acidosis**. Patients have a HAGMA and a high OG.
- **Salicylate overdose**—key clue is **HAGMA** plus a **respiratory alkalosis**. Salicylate intoxication causes nausea, vomiting, diaphoresis, and **tinnitus**. Respiratory alkalosis is the first effect, followed by the HAGMA. Especially suspect this in elderly patients with these symptoms who are taking OTC medications for arthritis.
- **Chronic acetaminophen use**—at risk are malnourished women who chronically ingest acetaminophen. HAGMA due to chronic acetaminophen use occurs at therapeutic doses rather than in the setting of an overdose. This disorder is distinct from acute acetaminophen overdose, treated with *N*-acetylcysteine (NAC), which blocks the hepatotoxic effects caused by acetaminophen. The accumulating acid is **pyroglutamic acid** (also called 5-oxoproline).

Table 7-8: Common Causes of HAGMAs and NAGMAs

HAGMA: Remember GOLDMARK

- **Glycols:** propylene glycol, ethylene glycol
- **Oxoproline:** acetaminophen
- **L-lactic acidosis:** shock, tissue ischemia
- **D-lactic acidosis:** short gut, malabsorption syndromes
- **Methanol**
- **Aspirin (salicylates)**
- **Renal failure (uremia):** sulfates, phosphates, urate
- **Ketoacidosis:** diabetes, alcohol, starvation

NAGMA

- **Chronic kidney disease**
- **Renal tubular acidosis**
- **Diarrhea**
- **Large infusions of normal saline** given during surgery or when treating DKA with subsequent removal of Na⁺ by the kidney
- **Drugs:** carbonic anhydrase inhibitors (e.g., acetazolamide), amphotericin, toluene

Treatment notes on toxins:

- **Methanol** and **ethylene glycol** are toxic because of their metabolites, formic acid and oxalic acid. Like ethanol, methanol and ethylene glycol are metabolized by alcohol dehydrogenase. Fomepizole inhibits alcohol dehydrogenase and prevents this reaction. Fomepizole + dialysis is the standard of care for both of these ingestions. IV folate, which accelerates the metabolism of formic acid (the toxic metabolite of methanol), should also be given.

- Treat **propofol**-related infusion syndrome by stopping the propofol. Use hemodialysis if there is AKI or severe acidosis.
- Treat **salicylate** poisoning with aggressive IV sodium bicarbonate: Alkalemia prevents salicylate from entering the CNS, and alkalinization of the urine promotes salicylate excretion by the kidneys. Do **not** use acetazolamide to alkalinize the urine—it lowers blood pH, promotes movement of salicylate into the CNS, and worsens neurotoxicity.
- Treat **DKA** with HCO_3^- only if the pH is < 7.0 or there is hemodynamic instability (severe acidemia impairs cardiac contractility).
- Treat **lactic acidosis** with HCO_3^- only if the pH is < 7.1 .

NAGMA

NAGMA (a.k.a. **hyperchloremic acidosis**) has a commensurate increase in Cl^- with the decrease in HCO_3^- . The Cl^- is increased to maintain electrical neutrality.

Table 7-8 summarizes common causes of NAGMAs and HAGMAs. The most common cause of NAGMA is chronic kidney disease, so check the S_{Cr} first. If CKD Stage 3 or higher is present, no further workup is needed.

If renal function is normal, the most likely cause is either GI losses of HCO_3^- or renal tubular acidosis (RTA). The K^+ can be very helpful:

- For NAGMA plus **hyperkalemia**, think Type 4 RTA (hypoaldosteronism).
- NAGMA plus **hypokalemia** is caused by either:
 - GI loss, or
 - RTA Types 1 (distal) and 2 (proximal). See RTAs.

When RTA is suspected, calculate the UAG (see **Urine AG (UAG)** on page 7-39):

- UAG is **positive** with NAGMA due to **RTA**.
 - UAG is **negative** with NAGMA due to **GI** losses.
- Remember, **neGUT**ive—negative UAG with GI loss.

Toluene, a solvent in glues and paints, can cause NAGMA. Suspect toluene exposure in patients with a history of glue sniffing, use of oil-based paints, and use of varnishes in a poorly ventilated area. Other drugs that can cause NAGMA include **acetazolamide** (which inhibits proximal tubular HCO_3^- reabsorption, thus causing a proximal RTA) and **amphotericin** (which causes proximal tubular toxicity).

Treat NAGMA with replacement of HCO_3^- losses, whether due to GI losses or RTA. Depending on the clinical situation and presence of other electrolyte abnormalities, replace with sodium bicarbonate IV fluid or sodium bicarbonate tablets.

RTAs

All renal tubular acidoses (RTAs) are NAGMAs caused by specific defects in tubular acid-base handling. Remember

that NAGMAs have a normal AG (i.e., are **hyperchloremic acidoses**). RTAs are categorized as distal (Type 1), proximal (Type 2), and hypoaldosteronism (Type 4). (Type 3 RTA was originally described in the 1960s but is no longer observed or considered an important clinical syndrome.) Refer to Table 7-9 on page 7-46 as you read through this topic.

Type 1 (Distal) RTA

Type 1 (distal) RTA is a problem in the H^+ ATPase of the intercalated cells in the late distal tubule and cortical collecting duct that results in failure to acidify the urine. It causes **hypokalemia** (mechanism not completely understood) and hypercalciuria +/- nephrocalcinosis and kidney stones. Urine is alkaline.

The most common causes of Type 1 RTA:

- Autoimmune disease (e.g., Sjögren's, SLE, RA)—most common cause in adults
- Genetic (+/- hearing loss)—most common cause in children
- Hereditary hypercalciuria
- Drugs (commonly amphotericin B and lithium)

Treatment is alkali therapy (i.e., sodium bicarbonate—low doses are usually sufficient), K^+ replacement, and addressing the cause.

Type 2 (Proximal) RTA

The proximal tubule is the nephron segment where most HCO_3^- is reabsorbed. Type 2 RTA occurs when there is impaired proximal tubular HCO_3^- reabsorption (review **Proximal Tubule** on page 7-5), resulting in **HCO_3^- wasting**.

In Type 2 RTA, there are 2 proximal tubule defects:

- HCO_3^- reabsorption
- Reabsorption of Na^+ with glucose, amino acids, Cl^- , and K^+

Most common causes of Type 2 RTA:

- Monoclonal gammopathy (i.e., multiple myeloma [MM]) with accumulation of light chains that damage the tubular cells (Note that MM can sometimes also cause a **low** AG.)
- Carbonic anhydrase inhibitors (e.g., acetazolamide)

Type 2 RTA is often seen together with **Fanconi syndrome** (glucosuria, aminoaciduria, and wasting of other solutes, including Mg^{2+} , uric acid, and phosphorus). Urine pH varies. In untreated Type 2 RTA, the urine pH may be acidic (pH < 5.5) because distal acidification is intact. When Type 2 RTA is being treated (with sodium bicarbonate), the urine pH is basic (pH > 5.5) because the exogenous HCO_3^- is being dumped in the urine.

Treatment is HCO_3^- (often very large doses are needed), K^+ replacement, and vitamin D supplementation.

Table 7-9: Renal Tubular Acidosis — Diagnostic Features

	Urine pH	Serum K ⁺	Mechanism	Clinical Features	Main Causes
Type 1 Distal RTA	> 5.5	Low-normal	Decreased H ⁺ secretion by late distal tubule and cortical collecting duct	Stones Hypercalciuria +/- nephrocalcinosis Hearing loss	Autoimmune (SLE, Sjögren's, RA) Hereditary hypercalciuria Drugs (amphotericin B, lithium) In children: Type 1 RTA is usually a primary genetic disorder.
Type 2 Proximal RTA	< 5.5 when untreated > 5.5 when treated with bicarb	Low-normal	Decreased resorption of HCO ₃ ⁻ by proximal tubule	Fanconi syndrome (glucosuria, phosphaturia, aminoaciduria)	Multiple myeloma Acetazolamide, topiramate Heavy metals Amyloidosis
Type 4 RTA (Hypoaldosteronism)	Varies	High	Decreased Na ⁺ /K ⁺ exchange in late distal tubule and cortical collecting duct; reduced NH ₃ generation and NH ₄ ⁺ excretion	Hyperkalemia	Diabetic nephropathy Obstructive uropathy Chronic interstitial nephritis Drugs (NSAIDs, ACEIs/ARBs) Spironolactone Acute glomerulonephritis

Type 4 RTA

Type 4 RTA (hypoaldosteronism) is a result of **low renin**, **reduced aldosterone production**, or **aldosterone resistance** in the principal cells of the late distal tubule and cortical collecting duct. These cause decreased Na⁺ reabsorption with some Na⁺ loss and significant K⁺ retention. Other factors (norepinephrine and angiotensin II) minimize the Na⁺ loss. Because of either insufficient aldosterone or resistance to aldosterone, the epithelial Na⁺ channels do not open. Type 4 RTA causes **hyperkalemia** and a mild NAGMA.

The most common cause of Type 4 RTA is diabetic nephropathy.

Causes of reduced aldosterone **production**:

- With low renin:
 - Diabetic nephropathy
 - Chronic kidney disease
 - Obstructive uropathy
 - Acute glomerulonephritis
 - Drugs: NSAIDs, cyclosporine, tacrolimus
- Primary adrenal insufficiency (decreased cortisol and aldosterone)
- Severe illness
- Drugs: heparin, ACEIs/ARBs

Causes of aldosterone **resistance**:

- K⁺-sparing diuretics (e.g., spironolactone)
- Antibiotics (trimethoprim, pentamidine)

Treatment for Type 4 RTA is usually indicated based on the degree of hyperkalemia. Primary therapy should always be a low-K⁺ diet, often the administration of HCO₃⁻ therapy, and, if necessary, furosemide. Fludrocortisone (a synthetic adrenal corticosteroid with very potent mineralocorticoid effects) can be considered in patients with refractory hyperkalemia, but this therapy often causes HTN and edema.

Review of RTAs

Clues to analyzing possible RTA:

- All types of RTA cause a NAGMA.
- Positive UAG is seen primarily in those with impaired distal acidification: distal (Type 2) and Type 4 RTA.
- **Proximal (Type 1)** RTA can cause **hypercalciuria** +/- nephrocalcinosis or stones; always elevated urine pH; and **hypokalemia**.
- **Distal (Type 2)** is characterized by HCO₃⁻ wasting. Especially consider **MM** and **Fanconi** syndrome. With Fanconi syndrome, the patient can present with metabolic acidosis, hypoglycemia, hypophosphatemia, hypokalemia, and **hyperchloremia**.
- **Type 4** is caused by **aldosterone deficiency** or **resistance** and is marked by mild acidosis and **hyperkalemia**. Consider causes of hyporeninemic hypoaldosteronism (chronic obstructive uropathy, diabetic nephropathy, and NSAIDs).

Exam questions concerning RTA may not even mention the term "RTA." For example, a question presents a patient with a history of nephrocalcinosis, diabetes, or signs/symptoms suggestive of myeloma; you then are asked to select the most likely serum and urine chemistry or the best treatment based on your interpretation of the given labs.

RTA Questions

Okay, now is a great time to do some review. We've gone over the causes of metabolic acidosis. Let's look at some sets of lab results and figure out the cause of each. After reviewing [Table 7-9](#), try to analyze the chemistry profiles presented in [Table 7-10](#). Let's get started!

Table 7-10: Metabolic Acidosis Problems

Scenario	Serum				Urine		
	Na ⁺ (mEq/L)	K ⁺ (mEq/L)	Cl ⁻ (mEq/L)	HCO ₃ ⁻ (mEq/L)	pH	K ⁺ (mEq/L)	Na ⁺ (mEq/L)
Normal	135–145	3.5–5	95–105	22–30	Variable	25–100	100–260
A	140	3.0	113	17	7.9	50	100
B	140	5.5	117	13	6	50	100
C	140	2.9	115	15	6	50	100
D	140	4.0	105	15	6	50	100
E	140	3.3	115	15	6	10	10

Match each chemistry profile (A through E in Table 7-10) with the most likely clinical scenario:

- Patient with DKA
- Patient with diabetes and chronic kidney disease
- Patient with myeloma
- Woman with nephrolithiasis
- Patient with chronic diarrhea

If you're not sure where to start, here is one approach to decoding this table:

- 1) First, look at the HCO₃⁻. All of these are low, so they are all metabolic acidoses.
- 2) Calculate the AG for each scenario, and label the ones with an increased AG as "HAGMA" and the others as "NAGMA." AGs = 10, 10, 10, 20, 10. Only D is a HAGMA; the rest are NAGMAs. The only diagnosis on the list that causes a HAGMA is DKA.
- 3) Look at the NAGMAs to see if any have an alkaline urine (pH > 6.0), despite the low HCO₃⁻. Check to see if the serum K⁺ is also low to normal. If yes, you've found a Type 1 (distal) RTA. Hmm. That's A. Of the diagnoses listed, nephrolithiasis is the one associated with distal RTA.
- 4) Look for a NAGMA with high serum K⁺, and label it "hyperkalemic RTA (Type 4)." Looks like that is B. Type 4 RTA is associated with diabetes and chronic kidney disease.
- 5) A NAGMA with a low urine Na⁺ is probably diarrhea-induced volume contraction—E. You might also be given the urine Cl⁻, in which case you should calculate the urine AG. The urine AG is negative in diarrhea-induced NAGMA but is positive in RTA.
- 6) Proximal (Type 2) RTA, in this case, is the answer of exclusion—the last NAGMA with low K⁺ left on the list—C. Proximal RTA is associated with MM from the diagnosis list.
- 7) And what if you see a low AG? This usually means that either albumin (an anion) is low or immunoglobulins (cations) are high (e.g., MM, Type 2 RTA).

Correct matches:

- A: Woman with nephrolithiasis—distal (Type 1) RTA
 B: Patient with diabetes and chronic kidney disease—Type 4 RTA
 C: Patient with myeloma—proximal (Type 2) RTA
 D: Patient with DKA—HAGMA
 E: Patient with chronic diarrhea—NAGMA due to GI loss
- Questions may ask what disease each scenario could represent, so go over the causes of each type of metabolic acidosis.

Clinical Pearl

Look at the AG formula $AG = Na^+ - (HCO_3^- + Cl^-)$. Usually a HAGMA has a normal Cl⁻ and a NAGMA has a high Cl⁻. This gives you quick way to tell at a glance at the electrolytes **1**) if the patient has a metabolic acidosis (i.e., low HCO₃⁻) and **2**) if it is a NAGMA (i.e., high Cl⁻) or HAGMA (normal Cl⁻). Cool, huh?

DISORDERS OF WATER BALANCE

PREVIEW | REVIEW

- What are the most important regulators of antidiuretic hormone secretion from the posterior pituitary?
- Name 2 causes of hypertonic hyponatremia.
- How do you correct the serum Na⁺ in severe hyperglycemia?
- What causes hypovolemic hyponatremia?
- What causes hypervolemic hyponatremia?
- Which drugs cause the syndrome of inappropriate antidiuretic hormone secretion?
- Which endocrinopathies must be ruled out in all patients with hyponatremia?
- What is the suggested rate of correction for severe hyponatremia?

- When is osmotic demyelination syndrome most likely to occur?
- What is the most common cause of hyponatremia?
- What is the typical serum Na^+ in a patient with diabetes insipidus who has access to water?

OSMOLALITY AND VOLUME STATUS

Osmolality (mOsm/kg) is the number of particles per unit mass of solution (water). Osmolarity (mOsm/L) is the number of particles per unit volume of solution. For water, 1 kg = 1 liter, so osmolality and osmolarity are essentially equivalent. Here, we will use osmolality (mOsm/kg), but you may see osmolality around—there is essentially no difference between the 2. Also, 1 mOsm is equivalent to 1 mmol. Both osmoles and moles are the number of particles; osmolality is the total number of all different types of particles and can be used to predict how water will move across semipermeable membranes. Water will always want to move from an area of low osmolality to an area of high osmolality. In the body, osmolality is important because it affects fluid shifts between the intracellular and extracellular spaces.

Normal serum osmolality is 275–290 mOsm/kg H_2O . Osmolality is maintained within the normal range by changes in water intake (thirst) and renal water excretion. Renal water excretion is regulated by antidiuretic hormone (ADH). Tonicity is a measure of effective osmolality, and it is what is actually sensed by the body's osmoreceptors. The biggest difference between tonicity and osmolality—urea (BUN) does not count toward tonicity, because it can freely cross cell membranes.

ADH is the common term for arginine vasopressin (AVP), sometimes simply called vasopressin. ADH is the primary regulator of renal water excretion. It is a hormone, secreted by the posterior pituitary, that acts on the late distal tubule and cortical collecting duct to increase water permeability. This allows water reabsorption (from the collecting duct back into the circulation) and formation of a concentrated urine.

ADH release is regulated by several mechanisms. The 2 most important are:

- 1) **Osmoreceptors** in the hypothalamus—high osmolality triggers ADH release.
- 2) **Volume (stretch) receptors** in the left atrium (and possibly in the pulmonary veins) and blood vessels—low effective circulating volume triggers ADH release.

The **strongest** stimulant for ADH release is significant **volume loss** resulting in hypotension (e.g., hemorrhagic shock). This stimulates both the stretch receptors and baroreceptors. High serum osmolality is a weaker but more sensitive stimulus for ADH release. More on ADH is in the **Endocrinology** section.

The volume status of the patient with a Na^+ abnormality is **critical** in determining the diagnosis and treatment. In general, if the patient is **edematous**, there is volume **overload**. If the patient has the clinical signs of **volume loss**, there is volume **depletion**. If there is neither of these, the patient is considered euvolemic.

Remember these clinical clues to **hypovolemia**: history of decreased oral intake and/or GI losses (i.e., diarrhea), dry mucous membranes, decreased skin turgor, tachycardia, narrowed pulse pressure, orthostatic hypotension, and resting tachycardia with hypotension. Central venous pressure is low.

Edematous states can sometimes cause ADH release due to decreased effective circulating volume, even though the patient has total body fluid overload. This is seen in severe HF and severe hepatic cirrhosis.

ADH secretion can also be stimulated by nausea, vomiting, pain, medications, or pathology in the brain or lungs. This is called the syndrome of inappropriate ADH (SIADH) and causes euvolemic hyponatremia.

HYPONATREMIA

The clinical presentation of hyponatremia depends on several factors, including rate of onset (acute vs. chronic), underlying cause, and volume status. Begin with a detailed history, including fluid intake, recent illness, and medications. Initial lab evaluation includes serum and urine osmolality, urine Na^+ , and thyroid-stimulating hormone.

Isotonic and Hypertonic Hyponatremia

Hyponatremia is defined as a low serum Na^+ . Hyponatremia usually indicates low serum tonicity and osmolality, reflecting high total body water content relative to total body sodium content.

Usually, a patient with a low serum Na^+ can be assumed to have **hypotonic** hyponatremia and measuring the plasma osmolality (a surrogate for tonicity) is not necessary. But in some situations, the serum Na^+ is low, but the tonicity (and osmolality) is normal or high. Suspect **isotonic** or **hypertonic** hyponatremia (and measure the plasma osmolality) in the following situations:

- Severe hyperglycemia
- Recent transection of the prostate or hysterectomy (procedures that use mannitol)
- Recent exposure to hypertonic iodinated contrast
- Recent exposure to mannitol, glycerol, or IVIG

Hypertonic hyponatremia—both **hyperglycemia** and **mannitol** cause hypertonicity, leading to an osmotic shift of water out of cells. This dilutes serum Na^+ resulting in hypertonic hyponatremia. Remember: For each 100-mg/dL (5.55-mmol/L) increase in glucose over 100 mg/dL, the Na^+ concentration decreases by 1.6 mEq/L (1.6 mmol/L).

Isotonic hyponatremia—this is an artifactual decrease in the serum Na^+ caused by older lab instruments that miscalculated Na^+ in settings of high protein (e.g., myeloma) or lipid content of the blood. Modern laboratories use ion-specific electrodes; thus, this diagnosis is of historical interest only.

Hypotonic Hyponatremia

Classification by Volume Status

Most patients with hyponatremia have true hypotonicity. From here on out, we'll drop the “hypotonic” and refer to hypotonic hyponatremia as simply “hyponatremia.” Refer to [Figure 7-16](#) as you read along.

The low serum osmolality causes water movement into cells, leading to **intracellular swelling**, which can result in cerebral edema, neuromuscular excitability, seizures, and coma—usually when the Na^+ falls **acutely** and severely ($< 120 \text{ mEq/L}$ [120 mmol/L]). If the Na^+ level decreases slowly, the cells equilibrate and do not swell enough to cause these symptoms. Hypotonic hyponatremia is subdivided by **volume status**: hypovolemic, euvolemic, and hypervolemic.

Always think of the serum Na^+ concentration as the ratio of total body Na^+ (TBNa) to water, with increased total body water content (relative to the amount of sodium) as the key disorder in most cases of hyponatremia. In other words, hypotonic hyponatremia is caused by excess **water**, not insufficient sodium. Whenever the serum Na^+ is low, it means the patient has more water relative to TBNa , from either loss of Na^+ , true water excess, or TBNa excess that is exceeded by water excess.

In the patient with hypotonic hyponatremia, the **first** thing to do is to assess the volume status, which is done clinically (using history and physical exam). Volume status essentially reflects TBNa content.

Hypovolemic Hyponatremia

Hypovolemic patients have lost both water and Na^+ but more Na^+ than water. This has several causes:

- Diuretics
- GI losses (vomiting and diarrhea)
- 3rd spacing of fluid
- Primary adrenal insufficiency (Addison disease)
- Cerebral salt wasting (CSW)
- Inadequate solute intake

In primary adrenal insufficiency, both cortisol and aldosterone are deficient. The low aldosterone causes renal Na^+ wasting and decreased K^+ and H^+ excretion, resulting in hypovolemia (sometimes with hypotension), **hyperkalemia**, and **metabolic acidosis**. The low cortisol and the hypovolemia stimulate ADH production, resulting in hyponatremia. More information on hyponatremia is in the [Endocrinology](#) section.

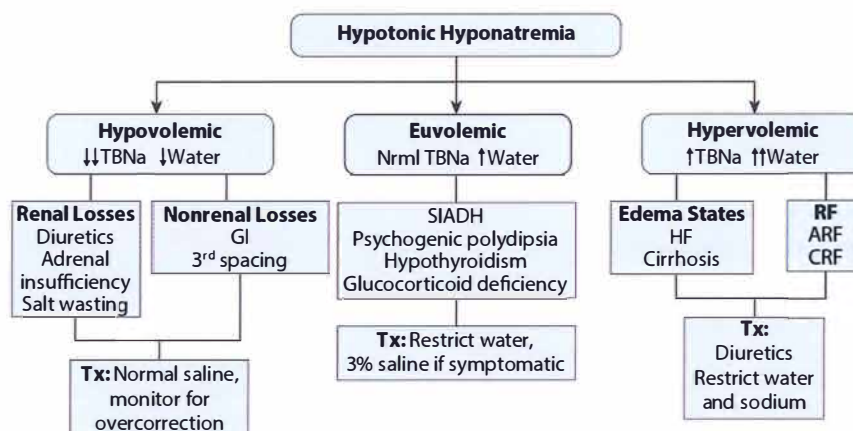
CSW is typically seen in patients with CNS disease, particularly subarachnoid hemorrhage, and is characterized by significant urinary Na^+ losses. This must be differentiated from SIADH because both disorders cause hyponatremia in the setting of CNS insults and result in high urinary Na^+ concentration and low serum uric acid. Patients with CSW have hypovolemia (low extracellular fluid volume) and may have elevated fractional excretion of phosphate.

Hypervolemic Hyponatremia

Hypervolemic hyponatremia reflects increased total body sodium content and increased total body water content, but water excess exceeds Na^+ excess. These patients have **edema** and **jugular venous distention**.

Causes of hypervolemic hyponatremia:

- Edema-forming states: HF, cirrhosis
- Renal failure: acute or chronic



ARF = acute renal failure
CRF = chronic renal failure
HF = heart failure
RF = renal failure
TBNa = total body sodium

Figure 7-16: Causes of hypotonic hyponatremia

Treatment is restriction of **water** and **Na⁺** intake, and loop diuretics. **Avoid thiazide** diuretics because they impair urinary-diluting ability, worsening hyponatremia. **Loop** diuretics work by eradicating the interstitial hypertonicity in the renal medulla, which is the driving force for water reabsorption in the presence of ADH. With loop diuretics, the kidneys are no longer able to make a concentrated urine, so free water excretion increases, even if ADH levels are high.

Vasopressin antagonists (e.g., tolvaptan) are approved for the treatment of hypervolemic hyponatremia when other treatments have failed. However, because these agents are expensive and can cause liver toxicity, do not use them chronically.

Euvolemic Hyponatremia

Euvolemic patients usually have the syndrome of inappropriate antidiuretic hormone (SIADH) or are taking drugs that either mimic ADH or cause ADH release.

Again, recall that pain and nausea are potent natural stimulators of ADH release.

Euvolemic hyponatremia can also be caused by primary polydipsia. But keep in mind—in a patient with normal renal function and solute intake, it takes over 15 L/day of water intake to produce hyponatremia! Hypothyroidism, isolated glucocorticoid deficiency can also cause euvolemic hyponatremia.

SIADH

Causes of SIADH:

- CNS disease
- Lung disease (e.g., cavitary pneumonia)
- Neoplasms (especially small cell lung cancer)
- Intense exercise, pain, nausea
- Drugs, most commonly:
 - NSAIDs
 - SSRIs
 - Carbamazepine and oxcarbazepine
 - Psychotropic drugs: haloperidol, amitriptyline
 - IV cyclophosphamide
 - Vincristine/Vinblastine
 - Cisplatin
 - Chlorpropamide (rarely used)
 - Methylenedioxymethamphetamine (MDMA; Ecstasy)

Diagnose SIADH by a high urine osmolality with a high urine **Na⁺** (> 40 mEq/L) in a patient with euvolemic hyponatremia. A low serum uric acid level also supports the diagnosis of SIADH. The **normal** response to hyponatremia is to excrete free water in the urine (i.e., make a dilute urine, with an osmolality < 100 mOsm/kg). In SIADH, however, the urine is inappropriately concentrated (> 250 mOsm/kg) despite the presence of hyponatremia. Remember: This occurs because ADH

acts on the collecting duct to make it permeable to water, allowing water to be reabsorbed into the hypertonic medullary interstitium (and subsequently into the circulation). Patients cannot excrete free water, so the serum osmolality stays low and the hyponatremia persists and worsens.

Exercise-induced hyponatremia can occur in marathon and other endurance exercise participants. This is caused by both nonosmotic production of ADH and excessive intake of hypotonic fluids.

Primary Polydipsia

Primary polydipsia is a psychiatric disorder in which patients consume tremendous amounts of water (as much as 1 L/hour). If the urine is appropriately dilute (urine Osm < 100 mOsm/kg), it takes a huge amount of water (> 15 L/day) to cause hyponatremia. However, in some patients with polydipsia, plasma ADH may not be fully suppressed, and the patients are unable to fully dilute their urine and efficiently excrete the water. These patients can develop hyponatremia with more modest amounts of water intake. They have a urine osmolality that is lowish, but not maximally diluted (100–300 mOsm/kg).

Endocrinologic Causes

The mechanism for ADH release in moderate-to-severe hypothyroidism is decreased cardiac output, which stimulates the carotid baroreceptors. Rule out hypothyroidism and glucocorticoid deficiency before making a diagnosis of SIADH because both can have low serum osmolalities and high urine osmolalities—mimicking SIADH.

Thiazide Diuretics

Thiazides can also cause euvolemic hyponatremia. This occurs via at least 2 possible mechanisms: **1)** mild volume depletion directly stimulates ADH release; and **2)** thiazides impair urinary dilution in the early **distal** tubule, so the patient cannot maximally dilute their urine. Elderly patients are highly susceptible to this effect of thiazides.

Treatment of Hyponatremia

Only **hypotonic hyponatremia** (hyponatremia with low plasma osmolality) requires treatment. **Hypertonic** hyponatremia (e.g. due to hyperglycemia) resolves with treatment of the underlying process (e.g., insulin and IV fluids for DKA). **Isotonic** hyponatremia is a lab artifact and does not require any treatment. Treat hyponatremia due to hypothyroidism or adrenal insufficiency with appropriate hormone replacement. All other causes of hypotonic hyponatremia should be treated according to the recommendations that follow.

First, determine if the patient is **symptomatic** or **asymptomatic**.

If there are moderate or severe **symptoms** of hyponatremia—such as lethargy, confusion, coma, seizures—treat urgently with 3% saline. The goal is to increase the serum Na^+ concentration by 4–6 mEq/L (within 6 hours) to prevent neurologic deterioration and brain herniation from cerebral edema. Correction of hyponatremia should **never exceed 8 mEq/L over the first 24 hours** due to the risk of osmotic demyelination syndrome (see below).

For **severe** symptoms (seizure, coma), give a 100-mL bolus of 3% saline. If severe symptoms persist, up to 2 more boluses (100 mL each) can be given in 10-minute intervals. This should usually be followed by a hypertonic saline infusion. For **moderate** symptoms (e.g., confusion, lethargy), use either a 100-mL hypertonic saline bolus, or a hypertonic saline infusion. Hypertonic saline infusion should start at a rate of 0.5–1.0 mL/kg lean body weight/hour. Check the serum Na^+ frequently (every 4 hours) and adjust the rate to achieve the target correction of no more than 8 mEq/L over 24 hours. Watch for a water diuresis (high urine output, dilute urine), which can cause the serum Na^+ concentration to rise faster than expected. This is most common in patients with primary polydipsia, hypovolemic hyponatremia, and hyponatremia due to thiazide diuretics. If water diuresis with overcorrection occurs, treat with desmopressin (DDAVP).

Exercise-induced hyponatremia (e.g., in marathon runners) can cause cerebral edema with brain herniation, so promptly treat with 3% hypertonic saline when this disorder is suspected.

ADH antagonists (discussed below) are not recommended for **symptomatic** hyponatremia.

Remember: Isotonic saline worsens hyponatremia in patients with SIADH.

Treat **asymptomatic** hyponatremia (no neurologic symptoms) based on etiology:

- **Hypovolemic** hyponatremia—normal saline to replenish volume deficit (watch for a water diuresis, which can lead to overly rapid correction of hyponatremia!)
- **Hypervolemic** hyponatremia—oral fluid restriction (1.0–1.2 liters/day) +/- loop diuretics
- **Euvolemic** hyponatremia—this is usually caused by SIADH. The first line treatment is fluid restriction (1.0–1.2 liters/day). Salt tablets or urea and loop diuretics can be added if fluid restriction alone is not effective.

Refractory asymptomatic hypervolemic or euvolemic hyponatremia can be treated with an ADH receptor antagonist, such as conivaptan or tolvaptan. However, these agents are expensive, and can cause liver injury with chronic use. ADH antagonists can also cause overly rapid correction of hyponatremia, placing the patient at risk for osmotic demyelination syndrome, so monitor serum Na^+ very carefully.

Osmotic demyelination syndrome (ODS) is a rare but devastating neurologic complication that can occur with

rapid correction of chronic hyponatremia. When the plasma Na^+ concentration rises, the extracellular osmolality is transiently higher than the intracellular osmolality. Osmotic forces cause water to move out of cells into the extracellular fluid space, and the cells shrink. In the brain, this can cause permanent neurologic damage. ODS is more likely to occur in the patient with chronic, severe hyponatremia ($\text{Na}^+ < 115$ mEq/L [115 mmol/L] for > 2 days) whose Na^+ is corrected rapidly (> 10 mEq/L over 24 hours). Symptoms first occur 2–6 days after the rise in the Na^+ concentration and are usually irreversible. Symptoms include speech and swallowing difficulties, weakness or paralysis, cognitive deficits, and coma.

HYPERNATREMIA

Severe hypernatremia **always** represents a **water deficit**. It only occurs when the patient has decreased access to water (i.e., patient is debilitated or H_2O is unavailable) or the thirst mechanism is defective. Unlike hyponatremia, these patients are **always hypertonic**. The appropriate diagnosis and management of hypernatremia require the following steps (refer to [Figure 7-17 on page 7-52](#)):

- 1) Determine if the patient has had inadequate water intake. Determine why the patient has inadequate water intake. For example, does the patient have dementia with impaired thirst mechanism? Is the patient intubated and sedated?
- 2) Determine the volume status. Is the patient hypovolemic, euvolemic, or hypervolemic?
- 3) Assess the urine output. If there is polyuria, consider the possibility of diabetes insipidus (DI). Confirm the diagnosis by measuring the urine osmolality. A low urine osmolality ($\text{UOsm} < 200$ mOsm/kg) in a patient with hypernatremia is diagnostic of DI.

Hypovolemic Hypernatremia

Hypovolemic hypernatremia is the most common form of hypernatremia and is caused by unreplaced losses of water and Na^+ . These patients have both a water deficit and a total body Na^+ deficit, but they have lost more water than Na^+ .

Treat severe **hypovolemic hypernatremia** with **normal saline** first to correct the volume deficit and **then** with hypotonic fluids (e.g., oral water, IV D5W) to further replace the water deficit. Remember: Even normal saline has a lower osmolality than serum in a patient with hypernatremia.

The amount of free water needed in a hypernatremic patient is calculated by multiplying the total body water (60% of weight in kg) by the fractional difference between a patient's Na^+ and normal Na^+ :

$$\text{Vol}_{\text{water}} = (\text{total body water}) \times [(\text{Na}^+_{\text{serum}} - 140) / 140] \quad (\text{Eq. 12})$$

$$\text{Vol}_{\text{water}} = 0.6 \times (\text{body weight}) \times [(\text{Na}^+_{\text{serum}} - 140) / 140] \quad (\text{Eq. 13})$$

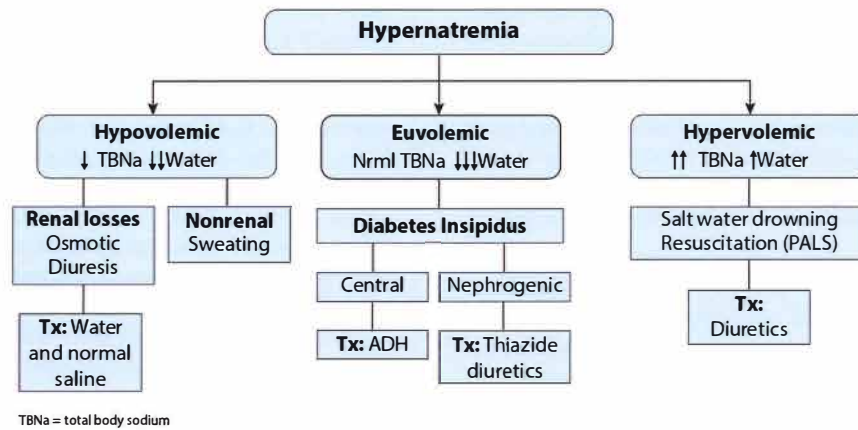


Figure 7-17: Causes of hypernatremia

If a 100-kg patient has a serum Na^+ of 156 mEq/L, the amount of free water needed to fully correct the hypernatremia is 6.9 L. This is usually given over 1–2 days to decrease the Na^+ concentration at a rate of 0.5 mEq/L/hour or 10–12 mEq/L/day.

Cellular swelling can occur from rapid correction of any severe hypertonic state, such as hypernatremia, nonketotic hyperglycemic coma, and severe uremia. (You may recognize these variables— Na^+ , glucose, and BUN—from the equation for calculated serum osmolality.) Cellular swelling can cause cerebral edema, seizures, and coma. So, be careful with the rate of correction, and measure serum Na^+ frequently.

Euvolemic Hypernatremia

Euvolemic hypernatremia occurs when there is unreplaced loss of water, but overall volume status is maintained. Euvolemic hyponatremia is sometimes seen in patients with DI and reduced access to water (who thus become hypernatremic) but have not yet developed frank volume depletion. DI is a disorder in which the kidneys cannot appropriately concentrate the urine, due to either a lack of ADH (central DI) or renal resistance to the effects of ADH (nephrogenic DI). The distinguishing feature of DI is polyuria with a low urine osmolality. Typical DI patients with normal access to water do not develop severe hypernatremia—they have **normal or borderline-high** serum Na^+ levels. This is because their thirst mechanism is intact, so they are constantly drinking water (mild hypernatremia causes thirst, leading to increased water intake, preventing severe hypernatremia). Their primary complaint is usually polyuria and polydipsia.

However, when access to free water is restricted in a DI patient (e.g., when the patient is NPO due to surgery), patients can rapidly develop severe hypernatremia.

A low urine osmolality in a patient with hypernatremia is consistent with DI. DI can be either central or nephrogenic. Diagnosis and determination of the type of DI

are done with the water restriction test. See more on DI in the [Endocrinology](#) section for a discussion on how to interpret results from water restriction testing. Central DI is treated with vasopressin (DDAVP). Nephrogenic DI is difficult to treat—a low-sodium diet, thiazide diuretics, and NSAIDs are sometimes used.

Hypervolemic Hypernatremia

Hypervolemic hypernatremia is uncommon. It most often occurs with administration of sodium bicarbonate during advanced cardiac life support. Treat with loop diuretics and then free water if needed.

POTASSIUM DISORDERS

PREVIEW | REVIEW

- Which K^+ derangement can be seen in Cushing syndrome (hypercortisolism)?
- Which K^+ derangement can be seen in Addison disease (primary adrenal insufficiency)?
- Discuss the effects of nonsteroidal antiinflammatory drugs on serum K^+ .
- How does the acid-base status affect K^+ levels?
- Which electrocardiogram changes are seen with hyperkalemia?
- What is special about the treatment of hyperkalemia in patients taking digoxin?
- What urine test can help distinguish between Bartter and Gitelman syndromes?
- When hypokalemia occurs with hypertension and alkalosis, what is the probable cause?
- What are the differences between Bartter and Gitelman syndromes?

OVERVIEW

The potassium disorders are hyperkalemia and hypokalemia, diagnosed by a high or low serum K^+ level. Potassium disorders are caused by changes in potassium intake, excretion (by the kidneys or gut) or shifts between the intracellular and extracellular spaces. First, we will review the mechanisms of potassium balance, and then we will discuss each potassium disorder in depth.

ALDOSTERONE

Aldosterone regulates the K^+ level by increasing renal K^+ excretion. Recall from [Distal Tubule on page 7-7](#), K^+ secretion occurs in the late distal tubule and cortical collecting duct under the influence of aldosterone, linked with Na^+ reabsorption.

Any situation that increases aldosterone release (or mimics aldosterone) **lowers** the serum K^+ . These include:

- Increased renin as a result of decreased effective arterial blood volume:
 - Volume depletion (e.g., GI losses, diuretic therapy)
 - Decreased renal perfusion (e.g., HF, renovascular HTN)
- Increased renin as a result of inappropriate release:
 - Renin-secreting renal tumors
- Increased aldosterone as a result of inappropriate overproduction by the adrenal gland:
 - Bilateral adrenal hyperplasia
 - Aldosterone-producing adrenal adenoma
- Increased excretion of hormone with aldosterone-like effects:
 - Cushing syndrome (hypercortisolism)

Conversely, any situation that inhibits aldosterone release or aldosterone action **increases** the serum K^+ :

- Type 4 RTA (hyporeninemic hypoaldosteronism): seen in chronic interstitial nephritis and diabetic nephropathy, exacerbated by NSAIDs
- **Primary adrenal insufficiency (Addison's)** affects both the zona glomerulosa (outer layer; site of aldosterone production) and the zona fasciculata (middle layer; site of cortisol production)—but not secondary adrenal insufficiency because lack of adrenocorticotrophic hormone affects **only** the zona fasciculata.
- Drugs that block aldosterone production or action:
 - K^+ -sparing diuretics (Remember: Spironolactone blocks the aldosterone receptor; amiloride blocks aldosterone-sensitive Na^+ channel.)
 - ACEIs and angiotensin receptor antagonists
 - NSAIDs
 - Heparins (Both unfractionated and low molecular weight heparins can be toxic to the zona glomerulosa.)

Know: NSAIDs decrease renin, so they can make K^+ go up—but generally only if the patient has another factor predisposing to hyperkalemia (e.g., CKD, ACEI use). Basically, NSAIDs make hyporeninemic states worse than they already are—see [Other Drug-Induced Nephropathies on page 7-28](#) for more explanation.

CELLULAR SHIFTS

Shifts between the intracellular and extracellular spaces can also affect serum K^+ level:

- Alkalosis, β -agonists, and insulin increase K^+ uptake into cells → **hypokalemia**
- Acidosis, α -agonists, and β -blockers decrease K^+ uptake into cells → **hyperkalemia**

The relationship between alkalosis/acidosis and hypokalemia/hyperkalemia can get confusing. Keeping it simple:

- Metabolic alkalosis → hypokalemia. Mechanism: K^+ shifts into cells in exchange for H^+ .
- Metabolic acidosis → hyperkalemia. Mechanism: K^+ shifts out of cells in exchange for H^+ .
- Hypokalemia → metabolic alkalosis. Mechanism: Low K^+ stimulates renal H^+ secretion; see [Proximal Tubule on page 7-5](#).
- Hyperkalemia → metabolic acidosis. Mechanism: High K^+ inhibits renal H^+ secretion.

OTHER FACTORS AFFECTING K^+ LEVEL

K^+ excretion by the kidney is stimulated by increased tubular flow, increased distal Na^+ delivery, aldosterone, the presence of nonresorbable anions in the tubules, and metabolic alkalosis. The following factors also affect serum K^+ and are important to know:

- Increased cell turnover causes **hyperkalemia** (e.g., tumor lysis syndrome, rhabdomyolysis, intravascular hemolysis, acute leukemia).
- Trimethoprim in TMP/SMX interferes with K^+ secretion in the principal cells of the late distal tubule and cortical collecting duct, especially in patients with preexisting renal disease, causing **hyperkalemia**.
- Both Type 1 (distal) RTA and Type 2 (proximal) RTA can cause **hypokalemia** for complex reasons.
- Loop and thiazide diuretics block reabsorption of solutes and water. Thiazides increase distal delivery of Na^+ and Cl^- and cause mild hypovolemia, activating the renin-angiotensin-aldosterone system. The combination of high distal Na^+ delivery and high aldosterone leads to increased Na^+ reabsorption and K^+ secretion in the collecting tubule, causing **hypokalemia**.
- The penicillins, including piperacillin, act as nonresorbable anions and increase K^+ excretion. Cisplatin nephrotoxicity can result in K^+ wasting.
- There are 3 genetic syndromes associated with **hypokalemia**: Liddle's, Bartter's, and Gitelman's. We'll discuss these under [Causes of Hypokalemia on page 7-55](#).

HYPERKALEMIA

Causes of Hyperkalemia

"Spurious" hyperkalemia (a.k.a. pseudohyperkalemia) occurs in a hemolyzed specimen or when there is thrombocytosis $> 400,000/\mu\text{L}$ or leukocytosis $> 100,000/\mu\text{L}$. Always retest if an unexpected lab result is found.

There are 3 main mechanisms of hyperkalemia:

- 1) Transcellular shifts (from cells to the extracellular space)
- 2) Decreased renal K^+ excretion
- 3) Excess K^+ ingestion or administration

Transcellular shifts can be caused by rhabdomyolysis, hemolysis, metabolic acidosis, and drugs (e.g., β -blockers, α -agonists).

Decreased renal K^+ excretion can be seen in AKI, advanced CKD, primary adrenal insufficiency (Addison disease), and Type 4 RTA (hyporeninemic hypoaldosteronism). Several drugs can decrease renal K^+ excretion, including K^+ -sparing diuretics (e.g., spironolactone, amiloride), NSAIDs, ACEIs/ARBs, direct renin inhibitors, calcineurin inhibitors (e.g., cyclosporine, tacrolimus), and heparins (which reduce adrenal aldosterone production).

Excess K^+ ingestion or administration usually does not cause hyperkalemia if renal function is intact, unless the amount of K^+ given is extraordinarily high. Hyperkalemia can result when there is acute or chronic renal failure, which reduces the kidney's ability to excrete a K^+ load.

Hyperkalemia Manifestations

Most patients have no symptoms if the increase in the K^+ has been chronic, even with a level near 7 mEq/L. Symptoms can occur at lower serum levels when the increase is acute. Presentation can include weakness or paralysis, cardiac conduction abnormalities, or arrhythmias. Typically, if a patient is experiencing weakness, they also have ECG changes, although the opposite is not necessarily true.

Know the sequence of ECG changes that occur with progressive hyperkalemia (Figure 7-18):

- 1) Peaked T wave and short QT interval
- 2) Progressive lengthening of PR and QRS intervals
- 3) Loss of P wave and QRS widening into sine waves
- 4) Ventricular fibrillation or cardiac standstill

Hyperkalemia Treatment

Treatment is aimed at decreasing the serum K^+ concentration and stabilizing cardiac membranes. Most acute treatments work by shifting K^+ from the extracellular space to the intracellular space. Loop diuretics, dialysis, and GI cation exchangers (e.g., sodium polystyrene sulfonate, patiomer) are the only treatments that actually remove K^+ from the body.

Treatment of severe hyperkalemia with ECG changes:

- Note: Hypercalcemia worsens the cardiac toxicity of digoxin. If a patient with severe hyperkalemia is on digoxin and requires IV calcium, it needs to be given very slowly to avoid hypercalcemia.

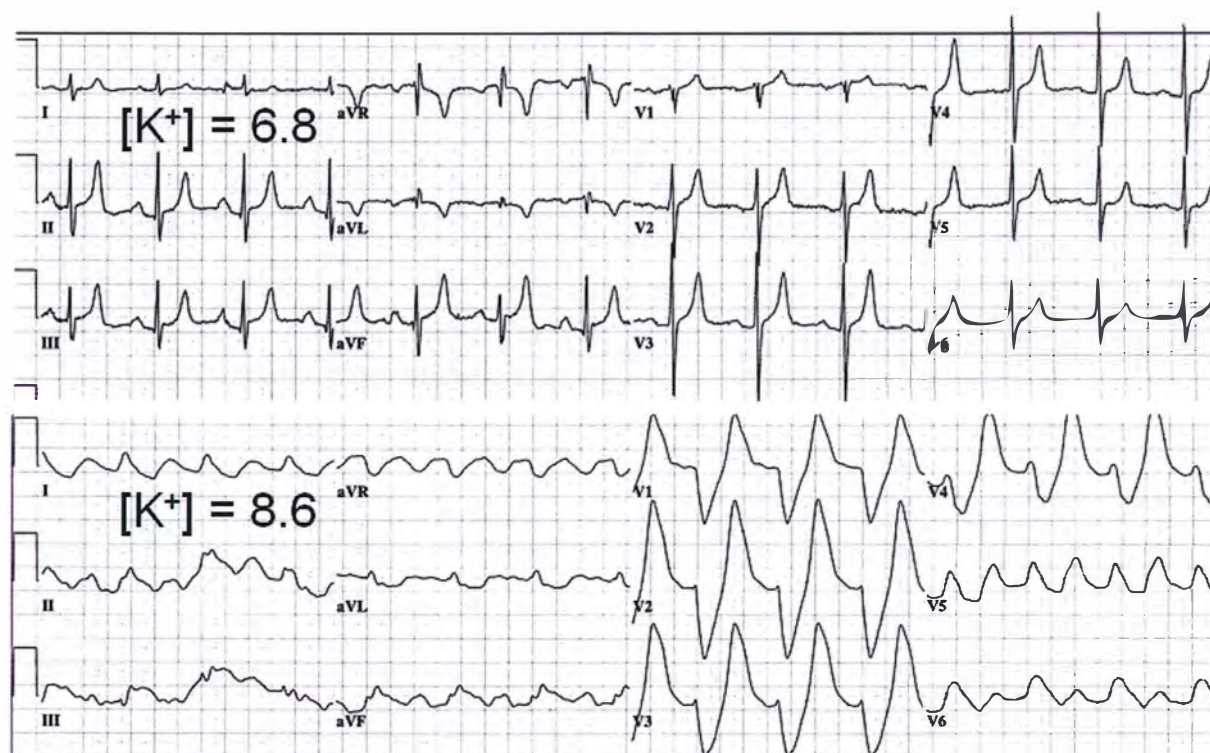


Figure 7-18: ECGs with moderate and severe hyperkalemia

- **IV calcium gluconate** (okay for peripheral injection) or IV calcium chloride (requires central access)
- **Insulin with glucose infusion** (effect in minutes)
- **Sodium bicarbonate** injection or infusion, if acidosis is present (30 minutes for effect; minimal response in patients without acidosis). Avoid sodium bicarbonate in patients with HF or volume overload.
- **Albuterol** nebulization (90 minutes for effect) or injection (30 minutes for effect). Be careful in patients with heart disease.
- **Loop diuretics** (in patients who make urine) with IVF to maintain euolemia
- **Dialysis** (in patients with kidney failure or those who do not respond to the above therapies)

Sodium polystyrene sulfonate (SPS) is a cation-exchange resin given orally or as an enema that exchanges Na^+ for K^+ across the gut wall and induces an osmotic diarrhea full of K^+ . Know that SPS, especially SPS in sorbitol (the most common preparation), can cause colon necrosis. Risk is highest in patients who have had surgery within 1 week and in patients with ileus, large or small bowel obstruction, or underlying bowel disease (e.g., inflammatory bowel disease). Avoid SPS unless the patient has severe, life-threatening hyperkalemia that is refractory to other therapies and when dialysis and patiomer are not available.

Patiomer, like SPS, binds K^+ in the GI tract but does **not** cause intestinal necrosis. Patiomer is available as oral therapy and is most commonly used to treat chronic hyperkalemia in patients with CKD. If available, patiomer is a reasonable treatment option in patients with acute hyperkalemia when used in conjunction with other treatments.

Patients with hyperkalemia in the setting of severe CKD or ESRD may be treated as described above, but they may also need immediate dialysis.

Treat $\text{K}^+ \geq 6.5$ mEq/L without symptoms or ECG changes with insulin + glucose, β -agonists, and sodium bicarbonate (if acidosis), followed by loop diuretics, patiomer, or dialysis. $\text{K}^+ \leq 6.5$ mEq/L can be treated with loop diuretics and dietary restriction.

Know that sodium bicarbonate infusions can cause edema and may precipitate pulmonary edema in patients with HF.

Make sure you check the patient's medication list and discontinue all drugs that cause hyperkalemia, such as ACEIs/ARBs, K^+ -sparing diuretics, β -blockers, heparin, NSAIDs, and TMP/SMX.

HYPOKALEMIA

Causes of Hypokalemia

To determine the cause of hypokalemia, first look to the history and physical exam to see if there are obvious causes (e.g., vomiting, diarrhea, diuretic use).

Usually the cause is obvious, but if it is not, assess urinary K^+ excretion to determine if there is renal K^+ wasting (Figure 7-19 on page 7-56). This can be done with a 24-hour urine K^+ measurement or a spot urine potassium:creatinine (K:Cr) ratio. If urinary K^+ excretion is low (< 20 mEq/day or spot urine K:Cr ratio < 1 mEq/g), the kidney is responding appropriately: Look again for GI sources of K^+ loss (e.g., surreptitious vomiting, laxative use) or a reason for transcellular shifts (e.g., hypokalemic periodic paralysis). If urinary K^+ is high (> 20 mEq/day or spot urine K:Cr ratio > 1 mEq/g), this indicates renal K^+ wasting. In this case, the acid-base status and the BP can guide you to the correct diagnosis. See Figure 7-19 on page 7-56.

Bartter and **Gitelman** syndromes are genetic causes of hypokalemia where there is impaired Na^+ reabsorption in the thick ascending limb of the loop of Henle (Bartter's) and the distal tubule (Gitelman's).

In **Bartter syndrome**, Na^+ reabsorption in the loop of Henle is impaired, and patients look like they are taking a **loop diuretic**. In **Gitelman syndrome**, the defect is in the Na^+/Cl^- cotransporter in the distal tubule, and patients look like they are taking a **thiazide diuretic**. Characteristics of Bartter's and Gitelman's are summarized in Table 7-11.

Table 7-11: Comparison of Bartter and Gitelman Syndromes

	Bartter Syndrome	Gitelman Syndrome
Age of Onset	Infants, children	Early adults
Hypokalemia	+	+
Metabolic Alkalosis	+	+
Hypomagnesemia	+	+
Urinary Ca^{2+}	High	Low
Chondrocalcinosis	–	+
Site of Defect	Loop of Henle	Distal tubule
Looks like patient is taking a...	Loop diuretic	Thiazide diuretic

The easiest way to distinguish Bartter from Gitelman syndrome: Patients with Bartter's have hypercalciuria, and patients with Gitelman's have hypocalciuria. This is easy to remember if you recall loop diuretics are sometimes used to treat hypercalcemia (increase urinary Ca^{2+} excretion), and thiazide diuretics are sometimes used to treat Ca^{2+} -containing kidney stones (decrease urinary Ca^{2+} excretion).

Major causes of hypokalemia:

- Hypokalemia with **metabolic alkalosis** and **normal or low BP**:
 - Volume contraction: vomiting, NG suction, bleeding, or diuretics (thiazides and loops)
 - Bartter syndrome, Gitelman syndrome (See Table 7-11.)

- Hypokalemia with **metabolic alkalosis** and high BP:
 - Primary aldosteronism
 - Secondary aldosteronism: renovascular disease (i.e., renal artery stenosis, fibromuscular dysplasia), HF with diuretic use, cirrhosis
 - Renin-secreting tumor
 - Cushing syndrome
 - Liddle syndrome
- Hypokalemia with **metabolic acidosis**:
 - Distal (Type 1) and proximal (Type 2) RTA
 - Diarrhea
- Hypokalemia due to **shifting** of K^+ into cells:
 - β -agonists
 - Insulin
 - Metabolic alkalosis
 - Hypokalemic periodic paralysis
- Other causes of renal K^+ wasting:
 - Penicillins
 - Cisplatin
 - Mg^{2+} deficiency

Hypokalemia Manifestations

Symptoms generally begin when the serum K^+ level is ≤ 3.0 mEq/L and include muscle weakness, fatigue, and palpitations. Severe hypokalemia (< 2.5 mEq/L) can cause U waves on the ECG (Figure 7-20), decreased deep tendon reflexes, and rhabdomyolysis. Serum K^+ does not decrease to below normal until there is a net loss of 200–300 mEq of K^+ from the body. The consequence of this is that large amounts of KCl are usually required for replacement.



Figure 7-20: U wave in hypokalemia

Hypokalemia Treatment

Try to identify the underlying cause, and treat contributing factors, such as volume depletion and/or metabolic alkalosis. Replace K^+ orally when possible. Poor response generally means the deficit is large and the patient merely requires more K^+ . Comorbid Mg^{2+} deficiency causes renal K^+ wasting, so always check and replenish Mg^{2+} stores.

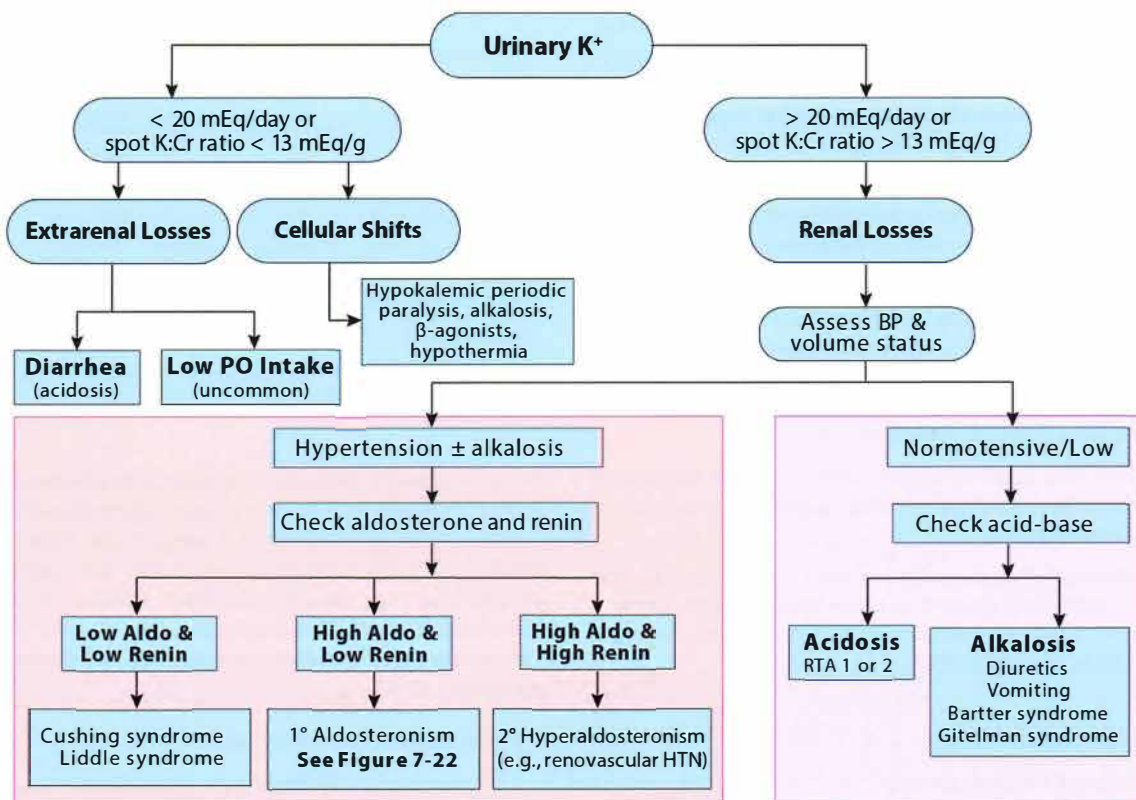


Figure 7-19: Evaluation of hypokalemia

CALCIUM, PHOSPHORUS, AND MAGNESIUM DISORDERS

PREVIEW | REVIEW

- What are the common causes of hypercalcemia?
- What are the effects of **hypomagnesemia** and **hypermagnesemia** on serum Ca^{2+} level?
- In addition to its effect on Ca^{2+} levels, **hypomagnesemia** causes which other electrolyte abnormality?
- What is refeeding hypophosphatemia?

CALCIUM

Ca^{2+} balance is regulated by PTH and active vitamin D (i.e., calcitriol or $1,25\text{-(OH)}_2\text{-D}$), which affect Ca^{2+} reabsorption by the kidneys, Ca^{2+} absorption by the gut, and Ca^{2+} exchange with the bones. Ca^{2+} derangements are discussed extensively in the [Endocrinology](#) section.

The measured serum Ca^{2+} concentration is a total of free/ionized Ca^{2+} (iCa^{2+} , about 45% of total calcium), Ca^{2+} bound to albumin (~40%), and Ca^{2+} bound to other substances (~15%). iCa^{2+} is the state available for immediate use by the body and correlates with symptoms of hyper- or hypocalcemia. Measure iCa^{2+} directly to get the most reliable assessment of a patient's Ca^{2+} status.

Routinely, however, we measure the total serum Ca^{2+} . If serum albumin is low, the measured total serum Ca^{2+} decreases, but the iCa^{2+} may be normal. In this case, either measure the iCa^{2+} directly, or correct the total serum Ca^{2+} for hypoalbuminemia: For each 1-g/dL (10-g/L) decrease in albumin, add 0.8 mg/dL (0.2 mmol/L) to the measured total serum Ca^{2+} .

In pregnancy, Ca^{2+} absorption and excretion are increased because the active form of vitamin D, $1,25\text{-(OH)}_2\text{-D}$, is $> 2\times$ normal.

Know:

- Acidosis: $\downarrow$ fraction of bound $\text{Ca}^{2+} \rightarrow \uparrow \text{iCa}^{2+}$
- Alkalosis: $\uparrow$ fraction of bound $\text{Ca}^{2+} \rightarrow \downarrow \text{iCa}^{2+}$

Hypercalcemia

These are common causes of **hypercalcemia**:

- **Malignancy**: multiple myeloma, solid tumors with bone metastases, or paraneoplastic (PTH-related protein mediated)
- **Primary hyperparathyroidism**: Neck irradiation is a risk factor.
- **Granulomatous diseases**: sarcoidosis, tuberculosis
- **Medications**: thiazide diuretics (most common), theophylline, lithium
- **Excess vitamin D**, vitamin A, or calcium carbonate (milk-alkali syndrome)
- **Endocrine disorders**: adrenal insufficiency, thyrotoxicosis

Mild hypercalcemia is asymptomatic. Severe or acute hypercalcemia can cause confusion, nausea, anorexia, polyuria/polydipsia, volume depletion, and acute kidney injury. ECG shows shortened QT intervals. Moderately high chronic hypercalcemia (e.g., from primary hyperparathyroidism) can lead to kidney stones, HTN, and chronic kidney disease.

Severe hypercalcemia ($\text{Ca}^{2+} > 14 \text{ mg/dL}$ [3.5 mmol/L]) is most often caused by malignancy. It requires urgent treatment with aggressive volume replacement (most are volume depleted) with IV normal saline or other isotonic fluid. Use calcitonin and bisphosphates when hypercalcemia is persistent or severe. Use loop diuretics only if overt volume overload (peripheral or pulmonary edema) develops.

Hypocalcemia

Common causes of **hypocalcemia**:

- Vitamin D deficiency
- Severe pancreatitis
- Rhabdomyolysis
- Sepsis
- Hypomagnesemia and hypermagnesemia (Always check Mg^{2+} level!)

Less common causes:

- Hungry bone syndrome following parathyroidectomy
- Hypoparathyroidism
- Pseudohypoparathyroidism (PTH resistance)
- Citrate (in blood products; citrate binds calcium, causing low iCa^{2+} with normal total Ca^{2+})
- Advanced CKD (from low $1,25\text{-(OH)}_2\text{-D}$ and high PO_4^-)

Mild hypocalcemia is asymptomatic. Severe or acute hypocalcemia causes paresthesias, muscle twitching, tetany, seizures, and prolonged QT interval. Workup begins with ECG and labs, including albumin, PTH, vitamin D, phosphorus, and Mg^{2+} . Treat symptomatic hypocalcemia with Ca^{2+} replacement (PO or IV). Mild, asymptomatic hypocalcemia does not require treatment. Never give IV Ca^{2+} to a patient with hyperphosphatemia: Calcium phosphate can precipitate in blood vessels and organs! Replace Mg^{2+} and vitamin D if levels are low.

More information on hypercalcemia and hypocalcemia can be found in the [Endocrinology](#) section.

MAGNESIUM

Hypomagnesemia

Hypomagnesemia is **very common**. Causes are:

- Small bowel disease, resection, or bypass (malabsorption)
- Chronic diarrhea
- Acute pancreatitis
- Diuretics: kidney loss
- Recovery phase of AKI (ATN or obstruction)

- Bartter and Gitelman syndromes
- Nephrotoxic drugs (aminoglycosides, amphotericin B, cisplatin, pentamidine, cyclosporine, tacrolimus)
- Miscellaneous causes: proton pump inhibitors (impaired GI Mg^{2+} absorption)
- Hungry bone syndrome (after parathyroidectomy)
- **Alcohol abuse**
- Postsurgical state
- Foscanet (due to chelation)
- Hypercalcemia (causes renal Mg^{2+} loss)

The relationship between Ca^{2+} , Mg^{2+} , and K^{+} can be difficult to remember. Here's the quick synopsis:

- **Hypercalcemia** causes **hypomagnesemia**.
- Both hyper- and hypomagnesemia cause **hypocalcemia**.
- **Hypomagnesemia** causes **hypokalemia**.

Always check Mg^{2+} in patients presenting with hypocalcemia and/or hypokalemia because Mg^{2+} deficiency leads to renal Ca^{2+} and K^{+} wasting, so they are not correctable until Mg^{2+} stores are replenished!

Clinical manifestations of hypomagnesemia most often occur concurrently with other electrolyte and/or mineral derangements, such as hypokalemia or hypocalcemia. Muscle weakness, spasms, and tetany are the more common neuromuscular manifestations. ECG abnormalities precede cardiac manifestations (wide QRS and peaked T waves). Refractory **cardiac arrhythmias** are more likely with depleted Mg^{2+} stores (even with a **normal** serum level).

Replace Mg^{2+} orally in patients without symptoms, using a sustained release preparation (e.g., magnesium chloride, magnesium lactate)—appreciating that the deficit is usually huge if the serum Mg^{2+} level is low. Treat severe or symptomatic hypomagnesemia with 1–2 g magnesium sulfate as a single IV dose, followed by a continuous infusion of 4–8 g magnesium sulfate over 8–24 hours. Note: Each gram of magnesium sulfate ($MgSO_4$) has 8.12 mEq (4.06 mmol) of Mg^{2+} .

Hypermagnesemia

Hypermagnesemia, on the other hand, is **rare** and occurs due to:

- The use of Mg^{2+} -containing laxatives, antacids, or enemas in patients with advanced CKD (All are contraindicated in this group of patients.)
- $MgSO_4$ infusion during preeclampsia treatment
- Less common, but noteworthy, causes: tumor lysis syndrome, milk-alkali syndrome, lithium overdose, and Epsom salts ingestion (even as a gargle)

Symptoms begin when the Mg^{2+} level is $> 4\text{--}6$ mEq/L (2 mmol/L). There is initial nausea, followed by sedation, muscle **weakness**, and a loss of deep tendon reflexes, progressing to paralysis (including heart and respiratory muscles).

Treat acute symptoms according to renal function:

- Normal renal function—stop Mg^{2+} -containing products. Use normal saline and loop diuretics if needed.
- Moderate renal impairment—use the same treatment as above but start treatment with normal saline and loop diuretics.
- Severe renal impairment—start hemodialysis. In addition to above, use IV Ca^{2+} as a Mg^{2+} antagonist.

Do not forget to look for hypocalcemia, which can develop as a result of increased Mg^{2+} concentrations.

PHOSPHATE

Hyperphosphatemia

Acute increase in serum phosphate can be from:

- AKI (especially in rhabdomyolysis)
- Rapid cell turnover (tumor lysis or acute leukemia)
- Phosphate-containing laxatives (especially in CKD patients)

Chronic hyperphosphatemia is seen in:

- CKD
- Hypoparathyroidism
- Vitamin D toxicity (with hypercalcemia)

Hyperphosphatemia is usually asymptomatic, but severe acute hyperphosphatemia can cause acute renal failure (acute phosphate nephropathy). Treat acute hyperphosphatemia with volume expansion (IV normal saline), keeping an eye on the Ca^{2+} . For a discussion of the treatment of chronic hyperphosphatemia in CKD (the most common situation), see [CKD – Mineral and Bone Disorders \(MBDs\)](#) on page 7-31.

Hypophosphatemia

Clinical manifestations of hypophosphatemia include irritability, muscle weakness, seizures, coma, and death. Severe hypophosphatemia ($PO_4^{3-} < 1$ mg/dL) can cause rhabdomyolysis (as can low K^{+}), cardiomyopathy, respiratory failure, and nervous system dysfunction.

Refeeding syndrome is an important cause of severe hypophosphatemia in patients with malnutrition and/or alcoholism. Refeeding of malnourished patients can cause severe hypophosphatemia by redistribution of phosphate into cells. Even if a malnourished patient has a normal phosphate level on admission, the patient can become severely hypophosphatemic a few days after a normal diet, tube feeding, or parenteral nutrition is established. This is due to the muscle cells becoming anabolic and taking up phosphate as the glycogen level returns to normal. Similarly, in the ICU, when a malnourished patient is started on TPN, the glucose load causes phosphate uptake by cells, resulting in severe hypophosphatemia. This form of refeeding hypophosphatemia is a common clinical scenario.

Alcoholic patients with hepatic encephalopathy often have a respiratory **alkalosis** and may receive **glucose** solutions, both of which cause phosphate to enter cells. This, in turn, causes severe **hypophosphatemia**, which can precipitate acute rhabdomyolysis.

A malnourished alcoholic presenting with **alcoholic ketoacidosis** is often treated glucose-containing IV fluids. This can result in severe hypophosphatemia and, subsequently, rhabdomyolysis.

Do not forget about the renal-wasting causes of hypophosphatemia:

- **Primary hyperparathyroidism** (causes renal phosphaturia)
- **Fanconi syndrome** (proximal tubular losses of phosphate, glucose, amino acids, and HCO_3^-)
- **Tumor-induced osteomalacia** (a.k.a. oncogenic osteomalacia)

Treatment of hypophosphatemia: Treat underlying cause of low phosphate, especially in renal phosphate wasting syndromes.

Give supplemental phosphate to patients with DKA or those having alcohol withdrawal; include it in hyperalimentation fluid.

Be cautious replacing phosphate in patients with CKD: They cannot excrete it, and aggressive phosphate supplementation can cause severe hyperphosphatemia.

VOLUME DEPLETION

Volume depletion is diagnosed based on history (see below) and physical exam findings of orthostatic hypotension, tachycardia, dry mucous membranes, and decreased skin turgor. The cause of volume depletion is usually evident from a history of:

- **Vomiting** can cause volume depletion with:
 - Metabolic **alkalosis**
 - Low serum Cl^- (losing stomach HCl in the emesis—makes sense)
 - Hypokalemia (from renal K^+ wasting mediated by aldosterone)
- **Diarrhea** can cause:
 - Metabolic **acidosis** (NAGMA; HCO_3^- is lost in the stool.)
 - An appropriately high serum Cl^- (Cl^- is avidly reabsorbed to increase intravascular volume.)
- **Loop diuretics and thiazide diuretics** can cause:
 - Metabolic **alkalosis** with low serum Cl^- (like vomiting)
 - Hypokalemia
 - These are both due to high distal Na^+ delivery in the setting of a high aldosterone state. Aldosterone stimulates Na^+ reabsorption, which is linked to H^+ and K^+ secretion.
 - High urinary Cl^- if the patient is actively taking the drug (unlike vomiting)

- **Osmotic diuresis** (e.g., hyperglycemia) can cause:
 - High urine output
 - Urine osmolality same as plasma (250–300 mOsm/kg)

These causes are summarized in Table 7-12. See the discussion of thiazides under **Thiazide-Type Diuretics** on page 7-63. Some diuretic-resistant patients with HF are on both loop and thiazide diuretics. This combination has the potential to cause severe volume depletion with prerenal AKI, so patients on both these drugs need to be monitored carefully. Treat volume depletion with isotonic IV fluids (e.g., normal saline, lactated Ringer's). Patients with metabolic acidosis due to diarrhea may benefit from HCO_3^- replacement.

Table 7-12: Causes of Volume Depletion

	Serum		Urine	
	Cl^-	HCO_3^-	Cl^- (mEq/L)	Osm (mOsm/kg)
Prolonged Vomiting	Low	High	Low (< 10)	High (> 300)
Prolonged Diarrhea	High	Low	Low (< 10)	High
Thiazides	Low	High	High	High
Osmotic Diuresis (hyperglycemia, mannitol)	Normal	Normal	High	250–350 (but high volume)

HYPERTENSION (HTN)

PREVIEW | REVIEW

- In which age groups does newly diagnosed hypertension (HTN) suggest that the cause might be secondary?
- What is the main cause of renovascular HTN in men > 50 years old?
- What is the main cause of renovascular HTN in women < 40 years old?
- What does the combination of a continuous abdominal bruit imply in a hypertensive patient?
- How do you confirm the diagnosis of primary aldosteronism?
- Which types of diuretics are the 1st line agents for the treatment of HTN?
- Angiotensin-converting enzyme inhibitors/angiotensin receptor blockers are absolutely contraindicated in which patients?
- Why are β -blockers not recommended as 1st line drugs for HTN?
- What is the goal for blood pressure reduction in patients who present with hypertensive crisis?

NOTE

Our recommendations for diagnosis and treatment of HTN are based on the 2017 American College of Cardiology and American Heart Association (ACC/AHA) Hypertension Guidelines.

CLASSIFICATION

HTN is diagnosed by the average of 2 or more office BP measurements. Out-of-office BP measurements (ambulatory BP monitors or home BP monitoring) are recommended to confirm the diagnosis of HTN.

HTN definitions, according to the 2017 ACC/AHA Guidelines:

- Normal: < 120/< 80 mmHg
- Elevated: 120–129/< 80 mmHg
- HTN Stage 1: 130–139/80–89 mmHg
- HTN Stage 2: > 140/> 90 mmHg

EVALUATION OF HTN

The following is the standard evaluation for newly diagnosed HTN. Initially, look for cardiovascular disease risk factors and consider **secondary causes** in patients with resistant HTN and those with indications for further screening (see [Secondary HTN](#) and [Table 7-13](#)).

History: Ask about personal and family history or symptoms of CVD (cardiovascular disease), peripheral vascular disease (PVD), cerebrovascular disease, renal disease, DM, and lipid problems. Ask about the use of alcohol, smoking, street drugs, prescribed medications, diet, and psychosocial history. Also ask about symptoms of sleep apnea, including daytime somnolence.

Perform a full physical exam, including:

- BP: Use the correct size cuff; measure at least twice, with patient seated after at least 5 minutes of rest; the arm should be resting with the cuff at the level of the heart.
- General: height, weight (for BMI calculation), and waist circumference (to evaluation for possible metabolic syndrome)
- HEENT: fundoscopic exam for hypertensive changes
- Neck: bruits, enlarged thyroid
- Lungs: rales, wheezes
- Heart: rate, rhythm, murmurs, extra heart sounds, and evaluation of the PMI (point of maximal impulse)
- Abdomen: abnormal masses, bruits, abnormal pulsations
- Extremities: decreased pulses, bruits, and edema

Initial lab tests for all hypertensive patients:

- Serum chemistries (Na^+ , K^+ , Cl^- , HCO_3^- , creatinine, fasting glucose)

Table 7-13: Causes of Secondary Hypertension

Cause	Clinical Clues
Renovascular HTN	Continuous abdominal bruit Asymmetric kidneys
Primary aldosteronism	Hypokalemia
Pheochromocytoma	Labile HTN, pallor; sometimes with medullary thyroid cancer, primary hyperparathyroidism (MEN2)
Cushing syndrome (hypercortisolism)	Moon facies, muscle weakness, striae, easy bruising
Coarctation of the aorta	Decreased BP in lower extremities or absent/delayed femoral pulses
Polycystic kidney disease	Abdominal or flank masses Family history
Chronic kidney disease	Elevated creatinine or abnormal U/A
Hyperparathyroidism Granulomatous disease	Hypercalcemia
Drugs	Use of NSAIDs, oral contraceptives, illicit drugs (cocaine, amphetamines), alcohol, VEGF inhibitors (for cancer treatment)
Obstructive sleep apnea	Snoring, daytime somnolence, obesity

- Fasting lipid panel (cholesterol, triglycerides, low-density lipoprotein, high-density lipoprotein), serum Ca^{2+}
- U/A
- 12-lead ECG

Use an online calculator to determine the patient's **10-year ASCVD (atherosclerotic cardiovascular disease) risk**. The 10-year ASCVD risk is determined by patient age, sex, race, cholesterol, BP, and history of diabetes mellitus or smoking. The 10-year ASCVD risk determines the BP threshold for HTN treatment (see [Treatment of HTN on page 7-63](#)). Assessment of 10-year ASCVD risk is recommended by both the 2017 ACC/AHA Hypertension Guidelines and by the 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease.

Most (95%) of all HTN is **primary** (i.e., essential, idiopathic). Both genetic and environmental risk factors contribute to primary HTN. Morbidity and mortality in primary HTN are higher for **men** than for women and are higher for **African Americans** than for Caucasians. Risk factors for primary HTN include black race and obesity.

Secondary HTN comprises only 5% of HTN cases and is discussed next.

SECONDARY HTN

Indications for evaluation for secondary causes of HTN:

- Sudden onset of HTN
- Onset at < 30 years of age
- Signs of end-organ damage
(See [Table 7-14 on page 7-66](#).)

- Severe or resistant HTN (BP above target despite at least 3 medications, with 1 being a diuretic)
- HTN with hypokalemia or metabolic alkalosis

Table 7-13 summarizes the causes of secondary HTN.

Renovascular HTN

Renovascular HTN is caused by stenosis of one or both renal arteries. Renal artery stenosis decreases perfusion of the kidney(s), leading to increased renin production. High renin leads to high aldosterone (secondary aldosteronism) and angiotensin II, which cause HTN via 1) systemic vasoconstriction and 2) increased renal sodium retention.

Renovascular HTN is relatively common. The 2 main causes of renovascular HTN are:

- 1) Atherosclerotic renal artery stenosis (unilateral or bilateral; mainly affects patients > 50 years of age, especially patients with DM and PVD)
- 2) Fibromuscular dysplasia (often bilateral; mainly affects patients < 40 years of age; female > male)

Less common causes of renovascular HTN include scleroderma and vasculitis (e.g., Takayasu arteritis, polyarteritis nodosa).

Consider renovascular HTN when you see moderate to severe HTN with onset in patients < 30 years of age (fibromuscular dysplasia), new onset of HTN in patients > 55 years of age (atherosclerotic), HTN + unexplained hypokalemia, or accelerated HTN.

A continuous epigastric or abdominal bruit in a hypertensive patient is a clue there may be renovascular HTN—especially if they have other risk factors. The finding of asymmetric kidneys (> 1-cm size difference) is often the result of renovascular HTN affecting the side with the smaller kidney.

Bilateral renal artery stenosis can cause recurrent flash pulmonary edema and/or rapid decline in kidney function after starting an ACEI/ARB.

Screen patients for renovascular HTN only if they are likely to benefit from intervention (see Treatment of HTN on page 7-63). Definitely do not screen elderly patients with mild HTN and a normal serum K⁺.

Noninvasive tests to assess for renal artery stenosis are CT angiography, MR angiography, and duplex Doppler U/S of the renal arteries, with the first 2 being the most sensitive.

Arteriography is the gold standard for diagnosis of renovascular HTN, but the procedure is invasive, with potential for serious complications. Use it to confirm positive noninvasive screening tests when there is an indication for intervention. Fibromuscular dysplasia shows up as a “string of beads” with multiple, small aneurysmal dilatations (Figure 7-21). An atherosclerotic lesion is usually a single, proximal stenosis with distal dilation.



Figure 7-21: Aneurysmal dilatations in fibromuscular dysplasia

Treat fibromuscular dysplasia with revascularization (percutaneous transluminal renal angioplasty [PTRA])—this can be curative and is almost always indicated. For atherosclerotic renovascular HTN, intervention with angioplasty or surgery is not usually beneficial. Large clinical trials, such as the Cardiovascular Outcomes in Renal Atherosclerotic Lesions (CORAL) and Angioplasty and Stenting for Renal Artery Lesions (ASTRAL), have shown no benefit of PTRA (with or without stenting) for patients with atherosclerotic renovascular HTN, when compared with medical therapy alone. Therefore, patients with renovascular HTN should be treated medically. BP in renovascular HTN often responds well to ACEI/ARB treatment, but you need to watch for a decline in renal function.

Intervention in patients with atherosclerotic renovascular HTN should be considered if 1 of these is present:

- 1) Uncontrolled BP despite ≥ 3 antihypertensive medications
- 2) Recurrent “flash” pulmonary edema
- 3) Progressive decline in renal function (as an attempt to prevent progression to ESRD, often unsuccessfully)

Primary Aldosteronism

Normally, aldosterone is secreted by the adrenal zona glomerulosa (outermost layer) in response to AT II and hyperkalemia. Aldosterone increases Na⁺ reabsorption and K⁺ secretion in the principal cells of the late distal tubule and collecting duct. Suspect a high aldosterone state (primary or secondary) in a person with hypokalemia and HTN because:

- aldo → ↑ K⁺ secretion → hypokalemia and
- aldo → ↑ Na⁺ reabsorption → ↑ intravascular volume → ↑ BP.

There are 2 main causes of primary aldosteronism: aldosterone producing adenoma (70%) and bilateral adrenal hyperplasia (~ 25%). Adrenal carcinoma rarely causes primary aldosteronism.

According to the 2016 Endocrine Society Guidelines, screen patients with the following BP and HTN values for primary aldosteronism:

- BP > 150/100 mmHg on 3 different occasions on different days
- BP > 140/90 mmHg despite treatment with 3 antihypertensive drugs (including a diuretic)
- Controlled BP (< 140/90 mmHg) on 4 antihypertensive drugs
- HTN and hypokalemia
- HTN and adrenal incidentaloma
- HTN and sleep apnea
- HTN and family history of early-onset HTN or cerebrovascular accident (CVA)
- HTN and 1st degree relative with primary aldosteronism

Note: The K⁺ is normal in > 50% of patients with primary aldosteronism, so normal K⁺ does not exclude the diagnosis.

The clinical approach to screening and diagnosis of primary aldosteronism is summarized in [Figure 7-22](#) and [Figure 7-23](#). Screen with a plasma aldosterone concentration (PAC, ng/dL) and plasma renin activity (PRA, ng/mL/hour) to calculate the aldosterone:renin ratio. A ratio > 20 with a PAC > 10 ng/dL is considered positive. This makes sense: In primary aldosteronism, the aldosterone level is high, but renin is suppressed. If the renin and aldosterone are both high and aldosterone:renin ratio is < 30, consider secondary aldosteronism, including renovascular HTN, diuretic use, or (rarely) a renin-secreting tumor.

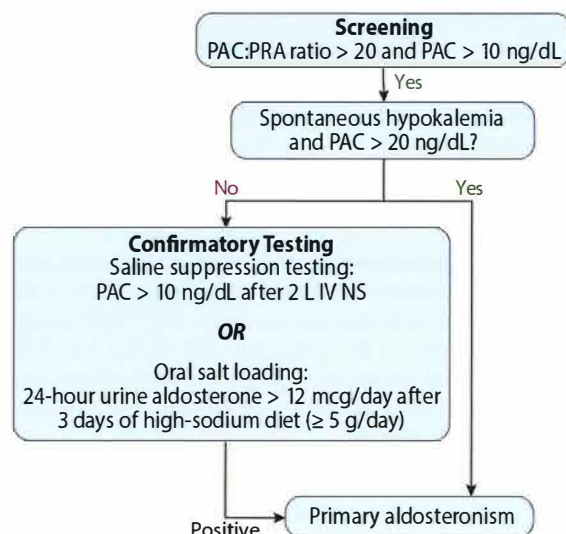


Figure 7-22: Diagnosis of primary aldosteronism

BP medications can interfere with the PAC:PRA ratio. Aldosterone antagonists and amiloride elevate the PRA; stop these at least 4 weeks before testing. ACEIs/ARBs will increase the renin and lower the aldosterone, so a high PAC:PRA ratio in a patient on an ACEI/ARB is highly suggestive of primary aldosteronism. If the PAC:PRA ratio is nondiagnostic, repeat it after stopping the ACEI/ARB (if possible).

If the PAC:PRA ratio is elevated, confirm the diagnosis of primary aldosteronism with a saline infusion test or oral Na⁺ loading. For the saline infusion test, give 2 L of normal saline IV over 4 hours while the patient is recumbent and then check the aldosterone level. Alternatively, give oral Na⁺ (5,000 mg/day, via high-Na⁺ diet or NaCl tablets) for 3 days and then check a 24-hour urine for aldosterone, Na⁺ (to assess compliance with the oral salt loading), and creatinine (to assess completeness of the collection). In either situation, if aldosterone is not suppressed, the patient has primary aldosteronism.

If the plasma aldosterone concentration is > 20 ng/dL and spontaneous hypokalemia is present, confirmatory testing with salt loading or saline suppression test is not necessary.

There are 2 main causes of primary aldosteronism: aldosterone-producing adenoma and bilateral adrenal hyperplasia. Aldosterone-producing adenoma can be treated either surgically (adrenalectomy) or medically (aldosterone antagonist, e.g., spironolactone). Bilateral adrenal hyperplasia can only be treated medically. Before pursuing further workup (e.g., imaging), determine if your patient would desire and be a candidate for surgery. If not, then you can stop here—just treat medically! If your patient is a good surgical candidate and would desire surgical management, then the next step is to determine if it is an aldosterone-producing adenoma or bilateral hyperplasia (see [Figure 7-23](#)).

Start with a CT scan of the adrenals. A solitary hypodense adrenal nodule in a young patient (< 35 years of age) with primary aldosteronism can go straight to surgical adrenalectomy. For older patients (> 35 years of age) and all patients with normal CT imaging, do adrenal vein sampling to determine if a functional adenoma is present. If an aldosterone-producing adenoma is confirmed, proceed with surgical adrenalectomy. If not, treat with spironolactone or eplerenone.

Pheochromocytoma

See the [Endocrinology](#) section for details on pheochromocytomas.

Other Secondary Causes of HTN

Endocrinologic causes of secondary HTN are pheochromocytoma, Cushing syndrome, hypothyroidism, primary hyperparathyroidism, and 11- β -hydroxylase deficiency. These are discussed in the [Endocrinology](#) section.

Other causes of secondary HTN are coarctation of the aorta, chronic kidney disease, sleep apnea, drugs (including oral contraceptive medications), excessive alcohol, and Liddle syndrome. Liddle syndrome is caused by an activating mutation in the Na⁺ channel of the collecting duct; patients present with HTN and hypokalemia from a young age. Sleep apnea is discussed in the [Pulmonary Medicine](#) section.

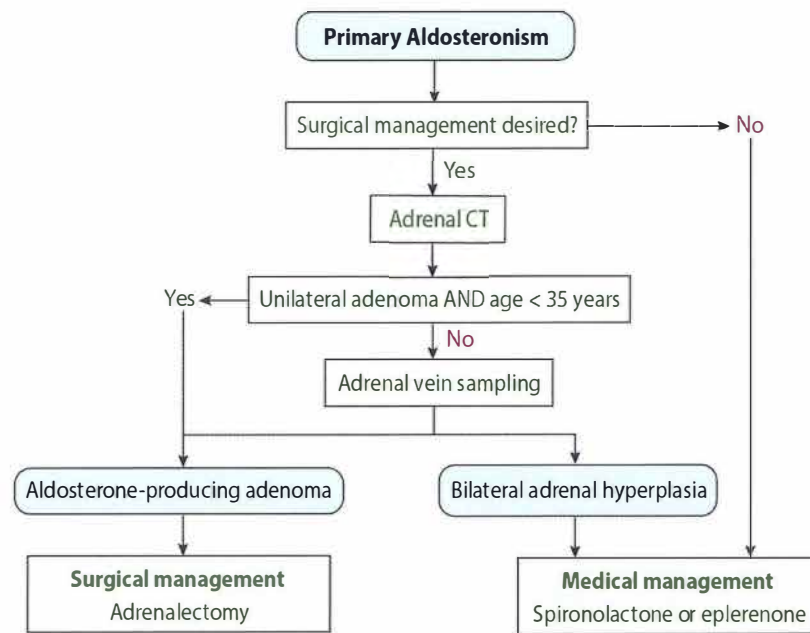


Figure 7-23: Primary aldosteronism subtype classification

TREATMENT OF HTN

Treatment of HTN with lifestyle interventions and BP-lowering medication is effective for both primary and secondary prevention of cardiovascular events. Lifestyle interventions are recommended in all hypertensive patients. 1st line pharmacologic agents for the treatment of HTN are thiazide diuretics, ACEIs or ARBs, and calcium channel blockers. We first discuss the lifestyle interventions and drugs used for HTN, and then we discuss BP targets. Treatment recommendations are according to the 2017 ACC/AHA Hypertension Guidelines.

Lifestyle Modification

Lifestyle modification is recommended in all adults with HTN:

- Counsel patients to **quit smoking** and to have no more than **moderate alcohol consumption** (≤ 2 drinks/day for men, ≤ 1 drink/day for women).
- For overweight and obese patients, **weight loss** will lower BP. Aim for at least 1-kg reduction in body weight in overweight adults. BP falls by about 1 mmHg for every 1 kg of weight loss!
- **Low-Na⁺ diet** ($< 1,500$ mg/day if possible) will lower BP by 5–6 mmHg.
- Recommend the **DASH diet**, a diet high in fruits, vegetables, whole grains, and low-fat dairy. Encourage fruits and vegetables—**K⁺-rich foods!**
- All forms of **exercise** are helpful: Aerobic exercise has the biggest impact, but dynamic resistance and isometric resistance are also beneficial.

Diuretics

Thiazide-Type Diuretics

Thiazide diuretics are 1st line agents for the treatment of HTN. The major thiazide-type diuretics are hydrochlorothiazide and chlorthalidone.

Hypokalemia is the most common side effect of thiazides. Diuretic-induced hypokalemia can be dangerous in patients with underlying cardiac problems and cirrhosis because of the potential for arrhythmias (especially if on digoxin) and hepatic encephalopathy/coma. Hypokalemia usually develops within the first 3 weeks of use. Use the lowest dose needed to achieve the desired effect and check the K⁺ level each time the dose is changed.

Thiazide diuretics can also cause hypomagnesemia. In HF and cirrhotic patients, it is best to keep the K⁺ > 4 mEq/L (4 mmol/L) with supplementation or K⁺-sparing diuretics. Thiazide diuretics can also cause severe hyponatremia in patients with poor solute intake, particularly the elderly.

Aldosterone Antagonists

The aldosterone antagonists are spironolactone and eplerenone. Aldosterone antagonists are not 1st line for HTN treatment but are useful in patients with resistant HTN. Hyperaldosteronism contributes to diuretic resistance, an effect that can be minimized by aldosterone antagonist therapy.

Remember: Aldosterone antagonists are K⁺ sparing, which means that they tend to cause **hyperkalemia**, not hypokalemia. They are helpful in patients with hypokalemia due to primary aldosteronism or thiazide/loop diuretics but can lead to hyperkalemia in patients on ACEIs or ARBs.

Other Diuretics

Loop diuretics are not usually used to treat chronic HTN unless there is severe volume overload and/or advanced chronic kidney disease. Other K^+ -sparing diuretics (e.g., amiloride) are sometimes used in combination with thiazide diuretics in patients with chronic HTN to prevent hypokalemia. Carbonic anhydrase inhibitors are not useful in the treatment of HTN.

ACEIs, ARBs, and Renin Inhibitors

Review

A brief review of the renin-angiotensin-aldosterone system (RAAS; [Figure 7-24](#)): Renin is released from the juxtaglomerular apparatus in the kidney in response to decreased effective arterial blood volume. Renin converts angiotensinogen to angiotensin I (AT I). AT I is converted to AT II by ACE. AT II increases BP by **direct vasoconstriction**, potentiation of the **sympathetic nervous system**, increased Na^+ reabsorption in the proximal tubule, and stimulation of **aldosterone production** by the adrenal gland.

ACEIs (e.g., lisinopril, enalapril, benazepril) inhibit conversion of AT I to AT II, decreasing AT II and aldosterone production. ARBs block the binding of AT II to its primary receptor (AT1). By blocking AT II production/effect, ACEIs/ARBs result in **dilatation** of the **efferent arteriole** (after the glomerulus), which decreases glomerular capillary pressure. This **decreased glomerular pressure** is beneficial in both **diabetic** and **hypertensive nephropathies**, as well as other types of chronic kidney disease. ACEIs/ARBs can also decrease GFR in patients with decreased effective circulating volume.

Indications for ACEIs / ARBs

ACEIs/ARBs are 1st line agents for antihypertensive drug therapy. Other indications for ACEIs/ARBs are systolic HF, history of ST-elevation myocardial infarction (STEMI) or anterior non-STEMI, chronic kidney disease (especially with proteinuria), and diabetic kidney disease (especially with increased albuminuria).

ARBs (i.e., candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan, valsartan) are recommended in patients with indications for ACEIs but who are unable to tolerate them, usually due to cough.

Complications of ACEIs / ARBs

ACEIs/ARBs can cause hyperkalemia and AKI. Stop or reduce the dose of the ACEI/ARB if the creatinine increases to > 30% over baseline and/or the serum K^+ is persistently high. Patients on NSAIDs or aldosterone antagonists are particularly susceptible to hyperkalemia with ACEIs/ARBs.

Up to 20% of patients have to stop an ACEI because of cough. Angioedema is a rare but potentially fatal side effect of ACEIs. ARBs do not cause angioedema or cough.

Know that the combination of an ACEI + ARB for the treatment of HTN can cause hypotension, syncope, and acute kidney injury. Prescribe an ACEI or an ARB but **do not combine** them.

ACEIs and ARBs are **teratogenic** and therefore contraindicated in pregnancy, particularly in the 2nd and 3rd trimesters (for more information, see the [Women's and Men's Health](#) section). Although ACEIs/ARBs can be very beneficial in patients with chronic kidney disease, renovascular HTN, HF, polycystic kidney disease, or

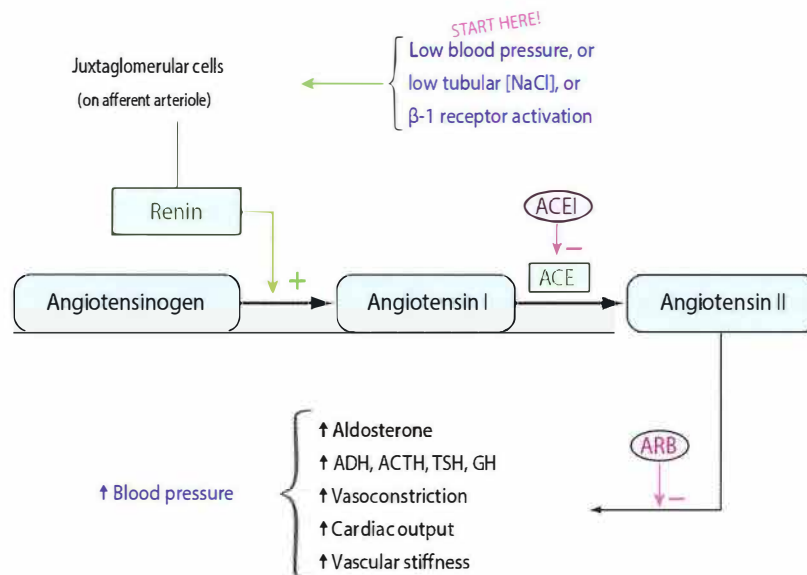


Figure 7-24: Renin-angiotensin-aldosterone system

hypertensive nephrosclerosis, they must be used with caution because there is risk of AKI and hyperkalemia. ACEIs/ARBs have minimal CNS and sexual side effects.

Direct Renin Inhibitor

The direct renin inhibitor, **aliskiren**, blocks renin production. Aliskiren may be used in patients who would benefit from blockade of the RAAS but cannot take ACEIs/ARBs. **Do not** combine aliskiren with an ACEI/ARB. Renin inhibitors are also teratogenic so are contraindicated in pregnant patients (for more information, see the [Women's and Men's Health](#) section).

Calcium Channel Blockers (CCBs)

CCBs include:

- Dihydropyridines (e.g., amlodipine, nifedipine)
- Nondihydropyridines (e.g., verapamil, diltiazem), which **also** reduce heart rate and cardiac contractility

Both drug types are used to treat HTN, as well as angina and arrhythmias.

Complications can include **constipation** (especially with verapamil) and **edema** (especially with dihydropyridines). Because of negative inotropic and chronotropic effects, do not give verapamil or diltiazem to patients who are also taking β -blockers or those who have heart block or severe HF.

Several studies have shown adverse events (e.g., increased risk of death after MI) with short-acting CCBs (but not with long-acting ones).

β -Blockers

β -blockers (e.g., atenolol, bisoprolol, carvedilol, labetalol, metoprolol) decrease cardiac output, sympathetic tone, and renin production. Each drug differs by its amount of lipid solubility, cardioselectivity, and sympathomimetic activity. The 2017 ACC/AHA guidelines **do not** recommend β -blockers for the initial treatment of HTN because they result in a higher rate of cardiovascular death, myocardial infarction, or stroke compared with the use of an ARB, especially in the elderly.

Use β -blockers for HTN in patients with:

- Previous MI
- Stable angina
- Stable HF with reduced ejection fraction
- Atrial fibrillation (rate control)

Avoid β -blockers in patients with:

- Reactive airway disease
- Frequent hypoglycemia
- Hyperlipidemia
- PVD

Recall that nonselective β -blockers (e.g., propranolol, labetalol) increase the serum K^+ level slightly (~ 0.5 mEq/L [0.5 mmol/L]). β -blockers can exacerbate symptoms in patients with decompensated HF. Other complications include fatigue, bradycardia, erectile dysfunction, depression, and weight gain.

Other Antihypertensive Agents

Patients with resistant HTN sometimes require additional medications to meet BP targets. 2nd line agents for BP treatment include:

- α -Blockers (e.g., terazosin, prazosin)
- Central α_2 -agonists (e.g., clonidine)
- Direct vasodilators (e.g., hydralazine, minoxidil)
- Aldosterone receptor antagonists (e.g., spironolactone, eplerenone)

BP Treatment Goals

BP treatment targets have changed over the years based on clinical trials and professional guidelines. Current BP guidelines are heavily influenced by the 2015 SPRINT trial, which showed a lower BP target (SBP < 120 mmHg, compared with SBP < 140 mmHg) decreased both all-cause mortality and the primary outcomes of MI, acute coronary syndrome, CVA, HF, and CVD death.

The 2017 ACC/AHA Guidelines for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults incorporate the SPRINT results, have been endorsed by most professional organizations, and are the basis for the HTN recommendations presented here.

ACC / AHA BP Targets

For most patients, the threshold for starting pharmacologic therapy is **$> 130/80$ mmHg**, and the treatment target BP is **$< 130/80$ mmHg**. The only exception is for the lowest-risk patients, with no clinical CVD and a 10-year ASCVD risk of $< 10\%$. For these patients, initiate pharmacologic therapy at a BP $\geq 140/90$ —but once treatment is initiated, your target is still $< 130/80$ (same as everyone else).

HTN is common in older patients (a 60–80% incidence!). **Isolated systolic** HTN is particularly common in the elderly. The degree of systolic HTN and the pulse pressure (SBP minus DBP) directly correlate with poor outcomes, so isolated systolic HTN should be treated.

The ACC/AHA guidelines recommend a **systolic BP target of < 130 mmHg in patients > 65 years of age**; this is the same as for younger patients.

Recommend lifestyle modification in all hypertensive patients (see [Lifestyle Modification on page 7-63](#)). 1st line agents for treatment of HTN include thiazide and thiazide-like diuretics, ACEIs/ARBs, and CCBs. For patients with Stage 2 HTN (SBP > 140 mmHg or DBP > 90 mmHg) whose BP is $> 20/10$ mmHg above target, the ACC/AHA recommends starting two 1st line agents from different classes.

Other ACC / AHA Recommendations

Additional ACC/AHA recommendations are:

- Simultaneous use of ACEI, ARB, and/or renin inhibitor is potentially harmful and is not recommended.
- Do not use nondihydropyridine CCBs (e.g., diltiazem) in patients with HF with reduced ejection fraction.
- In patients with stable ischemic heart disease, use a β -blocker, ACEI, or ARB. If angina is present and BP goal is not met, use dihydropyridine CCB (e.g., amlodipine).
- In patients with CKD and albuminuria, an ACEI/ARB is 1st line.
- In acute intracerebral hemorrhage, immediate lowering of SBP to < 140 mmHg is not beneficial and may be harmful.
- In acute ischemic stroke treated with IV thrombolytics, lower BP to < 180/100 mmHg.
- In acute ischemic stroke and BP > 220/110 mmHg not treated with IV thrombolytics, lower BP by 15% during the first 24 hours.
- In acute ischemic stroke and BP < 220/110 mmHg not treated with IV thrombolytics, treating HTN within the first 48–72 hours is not beneficial. Wait and initiate/restart antihypertensive therapy after the patient is neurologically stable.
- In pregnant patients, 1st line agents include methyldopa, nifedipine, and labetalol (see the [Women's and Men's Health](#) section). Do not use ACEIs/ARBs or direct renin inhibitors.

HYPERTENSIVE URGENCY AND EMERGENCY

Hypertensive crisis is defined as an acute and severe increase in systolic BP $\geq$ 180 mmHg or a diastolic BP $\geq$ 120 mmHg. There are 2 types, depending on whether there are signs of target organ damage.

Hypertensive emergency is defined as a severe elevation in BP (> 180/120 mmHg) associated with new or progressive end-organ damage. Signs of target organ damage include any of the signs and symptoms in [Table 7-14](#).

American College of Cardiology (ACC)/American Heart Association (AHA) guidelines recommend that patients with hypertensive emergency be admitted to an intensive care setting for continuous BP monitoring and control of BP with IV medications. Most patients with hypertensive crisis should have BP lowered by no more than 25% in the first hour, then to 160/100 within 2–6 hours, then cautiously to normal over the next 24–48 hours.

The following are important exceptions. Patients with aortic dissection should have systolic BP lowered to < 120 mmHg. Patients with severe preeclampsia/eclampsia or pheochromocytoma crisis should have systolic BP lowered to < 140 mmHg. Patients with acute CVA should be managed as noted in [Table 7-15](#).

IV medications used to treat hypertensive emergency include nicardipine, nitroprusside, labetalol, esmolol, hydralazine, enalaprilat, and fenoldopam (a peripheral dopamine-1 receptor agonist). IV drugs are preferred for initial management because oral drugs reduce the BP in a less rapid and less predictable way (see [Table 7-15](#)). Nitroprusside is metabolized to cyanide, so its use should be limited to < 24–48 hours, and it should not be used at all in patients with chronic kidney disease or pregnancy (for more on HTN during pregnancy, see the [Women's and Men's Health](#) section). Keep in mind that **too rapid** of a drop in BP can cause an ischemic stroke or myocardial infarction.

Hypertensive urgency is a severe increase in BP in an otherwise stable patient, with no acute signs of end-organ damage. These patients do not require hospitalization or emergency department evaluation but can be treated by restarting or intensifying antihypertensive medications, with close outpatient follow-up.

Table 7-14: End-Organ Damage in Hypertensive Emergency

End Organ	Signs or Symptoms	Type of Damage
Brain	Seizure (including eclampsia)	Posterior reversible leukoencephalopathy, hypertensive encephalopathy
	Focal neurologic symptoms	Transient ischemic attack, ischemic stroke, or intracerebral or subarachnoid bleed
	Headache, confusion, nausea/vomiting	Increased intracranial pressure Hypertensive encephalopathy
Heart	Dyspnea	Acute HF
	Chest pain, ECG changes	Acute coronary syndrome
Blood vessels	Severe/Acute back pain	Acute aortic dissection
	Anemia, low platelets	Microangiopathic hemolytic anemia
Kidney	AKI, proteinuria	Thrombotic microangiopathy
Retina	Papilledema, flame hemorrhages, exudates	Hypertensive retinopathy

Table 7-15: Treatment of Hypertensive Emergencies

Clinical Scenario	BP Reduction*	IV Drug Options	Additional Considerations
Hypertensive emergency without a compelling indication (below)	Reduce systolic BP by no more than 25% within the 1 st hour; to < 160/100 mmHg within the next 2–6 hours; then cautiously to normal in the next 24–48 hours.	Labetalol, esmolol, nicardipine	All patients with hypertensive emergency should be managed in an intensive care setting.
Acute ischemic stroke	tPA candidate: • Lower BP to < 185/110 mmHg before giving tPA; maintain BP < 180/105 after tPA. tPA not planned: • If BP ≥ 220/120 mmHg, lower by 15% over first 24 hours. • If BP < 220/120, lowering BP in the first 48–72 hours is not beneficial.	Labetalol, esmolol, nicardipine	Avoid nitroprusside (can lead to intracranial edema).
Acute hemorrhagic stroke	Reduce BP to < 180/105 mmHg. Do not lower BP to < 140/90 (potential harm).	Labetalol, esmolol, nicardipine	Avoid nitroprusside (can lead to intracranial edema).
Hypertensive encephalopathy	Reduce BP by 20–25% to reduce intracranial pressure.	Labetalol, esmolol, nicardipine	Avoid nitroprusside (can lead to intracranial edema).
Acute HF	Reduce BP to improve acute pulmonary edema.	Nitroglycerin, nitroprusside, furosemide	Avoid β-blocker and calcium channel blocker.
Acute coronary syndrome	Reduce BP to reduce cardiac workload and improve coronary perfusion.	Nitroglycerin, nitroprusside, labetalol, metoprolol, esmolol, nicardipine	Consider Type A dissection as the etiology of acute coronary syndrome. Avoid selective β-blockers if cocaine abuse is suspected.
Acute aortic dissection	Reduce BP to < 120/80 mmHg (lower if tolerable) and heart rate to < 60 bpm to reduce wall shear stress.	Labetalol, nitroprusside, nicardipine	Avoid β-blockers if severe aortic regurgitation is noted.
Acute renal failure	Reduce intraglomerular pressure.	Nitroprusside, nicardipine	Avoid ACEIs/ ARBs unless scleroderma renal crisis is suspected. Avoid nitroprusside (increased toxicity risk).
Severe preeclampsia and eclampsia	Reduce systolic BP to < 140 mmHg.	Labetalol, hydralazine, nicardipine	Definitive treatment is delivery of fetus. Avoid nitroprusside (can lead to fetal cyanide poisoning).
Sympathetic crisis	Reduce BP until symptom resolution.	Phentolamine, nitroglycerin, nicardipine, labetalol	Avoid β-blocker monotherapy (except for labetalol).
Pheochromocytoma crisis	Reduce SBP to < 140 mmHg.	Labetalol, phentolamine	Always give α-blocker (phentolamine) before β-blocker.

*General rule: BP should be lowered no more than 25% within the 1st hour and then to 160/100–110 mmHg within 2–6 hours.

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NORMAL RED BLOOD CELL (RBC) FUNCTION

HEMOGLOBIN (Hgb)

The Hgb protein within RBCs carries oxygen from the lung to the tissues. Oxygen is carried by the iron in the heme groups.

Adult hemoglobin (HbA) is a tetramer with 2 α - and 2 β -globular protein subunits (a.k.a. globin chains; Figure 8-1). Each of these globin chains is covalently linked to a single heme, which is a complex of ferrous iron and protoporphyrin. Adult hemoglobin is mostly HbA with a little HbA₂ and very little HbF.

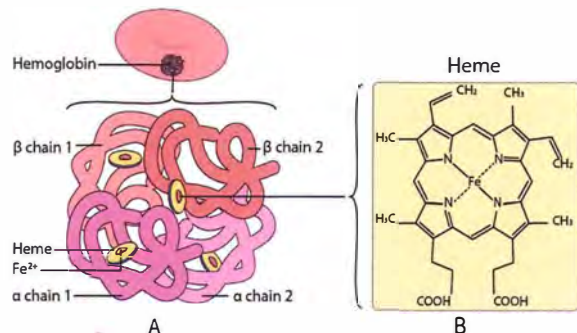


Figure 8-1: (A) Hemoglobin with 2 α - and 2 β -globin chains and 1 iron-containing heme group in each protein subunit. (B) The heme group with a porphyrin ring complexed with iron

Fetal hemoglobin (HbF) has 2 γ chains in the place of the 2 β chains. At birth, a child generally has 60–80% HbF, with the rest being HbA. By 1 year of age, most of the γ chains have converted to β chains.

The Hgb electrophoresis pattern in an adult is:

- HbA ($\alpha_2\beta_2$) > 97.5%
- HbA₂ ($\alpha_2\delta_2$) < 2.5%
- HbF < 0.6%

NORMAL ERYTHROPOIESIS

Erythropoietin (EPO) regulates RBC production. Normal erythropoiesis involves the maturation of pluripotent stem cells into proerythroblasts → erythroblasts → reticulocytes → mature RBCs (Figure 8-2). Reticulocytes are immature RBCs, each of which has lost its nucleus but retained its ribonucleic acid (RNA). The cytoplasmic RNA stains a gray-purple color (polychromasia) on Wright stain. Reticulocytes can be quantified by special stains or flow cytometry, yielding a reticulocyte count.

The mature RBCs contain no RNA and survive for approximately 120 days. Throughout their lifespan, RBCs pass repeatedly through the spleen, where old or damaged

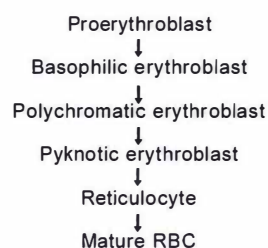


Figure 8-2: Erythropoiesis

cells are ingested by macrophages. The Hgb is catabolized into its heme (protoporphyrin ring + iron) and globin components.

The porphyrin ring is metabolized into unconjugated (i.e., indirect, water insoluble) bilirubin, which is then transported to the liver, where it is conjugated (i.e., direct bilirubin). Iron released from heme or absorbed in the intestine from the diet is transported by transferrin, the blood plasma protein, to the bone marrow and other tissues, where it is stored as ferritin and hemosiderin.

RBC INDICES

The amount of oxygen delivered to tissues depends on the supply and function of RBCs and Hgb. There are laboratory tests that demonstrate this.

The **mean corpuscular volume (MCV)** reflects the **size** of the RBCs, whereas the **mean corpuscular hemoglobin (MCH)** and the **mean corpuscular hemoglobin concentration (MCHC)** reflect the **amount** of Hgb in RBCs. MCH is the average mass of Hgb in each RBC. MCHC is a related value demonstrating the ratio of Hgb mass to the volume of RBCs.

Red blood cell distribution width (RDW) measures **variability** in RBC size (a.k.a. anisocytosis). An increased RDW means increased variation in RBC size.

A **reticulocyte count** (a.k.a. **retic count**) is often reported as the percentage of reticulocytes in the blood and indicates if the bone marrow is producing an adequate number of RBCs. When interpreting a reticulocyte count, it is important to adjust the percentage based on the degree of anemia (e.g., hematocrit) and the bone marrow maturation time of the reticulocytes, which constitute the **reticulocyte production index (RPI)**. An RPI > 3% is an adequate response to the level of anemia, and an RPI < 2% is an inadequate response.

IRON

Iron Absorption and Transport

Iron is absorbed from the gut by means of **ferroportin**, a transmembrane protein that transports iron through the cell walls of enterocytes and macrophages and subsequently releases the iron to **transferrin** in the hepatportal circulation. Transferrin, a plasma protein, binds the iron and transports it to transferrin receptors on cell surfaces, where it is then absorbed.

Ferroportin itself is controlled by **hepcidin**, the key regulator hormone for iron hemostasis. Hecpudin binds ferroportin, causing a decrease in the release of iron into the bloodstream, so high levels of hepcidin cause decreased iron absorption, while low levels allow for increased iron absorption. Hecpudin levels are decreased in low iron states and increased in iron overload states.

Hecpudin is also an acute-phase protein that increases in response to inflammatory cytokines (especially interleukin-6). A low C-reactive protein (CRP) helps rule out inflammation. A CRP > 10 mg/L means the hepcidin level is likely elevated due to inflammation and therefore is not a reliable indicator for iron overload.

Iron Studies

Free iron is produced from Hgb breakdown by RBC macrophages and by absorption from the duodenum. Free iron is toxic to the tissues.

Soluble transferrin receptor (sTfR) concentration is elevated in iron deficiency and normal in anemia of chronic disease (ACD). It is mainly used for differentiating ACD from iron-deficiency anemia (IDA).

Serum iron is a measurement of circulating iron bound to transferrin.

Total iron-binding capacity (TIBC) indirectly measures transferrin by determining the total amount of iron the blood can bind. Generally, it is **not** necessary to order both a transferrin level and TIBC.

The ratio of serum iron to TIBC, measured as a percentage, is called **transferrin saturation**.

Within the cell, iron is stored in protein complexes as **ferritin** or **hemosiderin**. Low values indicate iron deficiency, and high values can indicate iron overload (i.e., hemochromatosis, hemophagic lymphohistiocytosis, and adult-onset Still disease).

Like hepcidin, ferritin is also an **acute-phase reactant** and can be elevated with inflammation or chronic disease, although inflammation generally leads to only a 3-fold increase in ferritin levels. Also like hepcidin, a low ferritin helps rule out inflammation. Additionally, a high ferritin level is often a side effect of certain malignancies, especially hematologic cancer.

- Characterize the lab values in IDA vs. anemia of chronic disease. (See [Table 8-3 on page 8-11.](#))
- Which lab tests may be abnormal in hemolytic states?
- Which cells are seen in the peripheral blood of patients with glucose-6-phosphate dehydrogenase deficiency?
- Which virus is implicated in the development of aplastic crisis or worsening of anemia in patients with sickle cell disease?
- Which cells are seen on peripheral smear in patients with hereditary spherocytosis?
- What is the clinical presentation of paroxysmal nocturnal hemoglobinuria (PNH)?
- Which tests are used to diagnose PNH?
- Which leukemia/lymphoma is associated with autoimmune hemolytic anemia?

OVERVIEW

Anemia can be caused by an array of disorders, so a thorough history and physical examination followed by specific laboratory studies are needed to determine the etiology. Broadly, Hgb levels < 12 g/dL (120 g/L) in women and < 14 g/dL (140 g/L) in men define anemia, but there is variability with athleticism, ethnicity, and the elevation where the patient normally resides.

CLINICAL MANIFESTATIONS OF ANEMIA

Patients may be asymptomatic, even with significant anemia. Symptomatic clues include:

- Ice-eating (pagophagia), lethargy: iron deficiency
- Distal paresthesias: vitamin B₁₂ deficiency
- Left upper quadrant (LUQ) abdominal pain: hereditary spherocytosis with splenomegaly
- Right upper quadrant (RUQ) pain or intolerance to fatty foods: cholelithiasis from chronic hemolysis
- Constipation and cold intolerance: iron deficiency-related thyroid disease

MECHANISMS OF ANEMIA

Approach the anemic patient systematically. Excluding acute hemorrhage and rare sequestration, anemias can be broadly classified as production defects, maturation defects (hypoproliferative), or survival defects. The etiology of most anemias can be determined using the history, physical examination, reticulocyte assessment, and a thoughtful evaluation of the peripheral blood smear and RBC indices.

The 5 causes of anemia are discussed in [Table 8-1](#); refer to the table as you go through this material. Several images of normal blood smears and bone marrow aspirates are shown for your review in [Figure 8-3](#) through [Figure 8-8](#).

ANEMIA

PREVIEW | REVIEW

- List some extrinsic survival defects that cause anemia. (See [Table 8-1.](#))
- Is reticulocytosis increased or decreased for each of these: Production defect? Maturation defect? Survival defect? (See [Table 8-1.](#))
- When are Howell-Jolly bodies seen? (See [Table 8-2 on page 8-4](#) and [Figure 8-15 on page 8-5.](#))
- What are common causes of iron deficiency anemia (IDA)?
- What are the most common abnormal CBC findings in patients with α -thalassemia minor?
- What is the characteristic hemoglobin electrophoresis finding in patients with β -thalassemia minor?
- How many lobes must a neutrophil have to be considered hypersegmented?
- Which megaloblastic anemia is associated with neurologic disease?
- What are the methylmalonic acid and homocysteine levels in vitamin B₁₂ and folate deficiencies?

Table 8-1: Summary — Causes and Mechanisms of Anemia

Mechanism		Reticulocyte Count	Morphology	Etiology	Examples
1) Production defect		Decreased	Normal	Decreased EPO Bone marrow failure	Chronic renal disease* Aplastic anemia Pure red cell aplasia
2) Maturation defect	Cytoplasmic	Decreased	Hypochromic Microcytic	Impaired Hgb synthesis Globin synthesis deficiency	Iron deficiency Sideroblastic anemia Protoporphyrin deficiency Myelodysplastic syndrome Drugs, toxins Thalassemias
	Nuclear	Decreased	Megaloblastic	DNA synthesis defects	Vitamin B ₁₂ , folate deficiencies
3) Survival defect	Intrinsic (inherited)	Increased	Specific changes (e.g., spherocytes, sickle cells, bite cells)	Membrane cytoskeleton protein Metabolic enzymes Hemoglobinopathies	G6PD deficiency Pyruvate kinase deficiency SCD syndromes Hereditary spherocytosis and elliptocytosis Paroxysmal nocturnal hemoglobinuria
	Extrinsic (acquired)	Increased	Specific changes (e.g., spherocytes, schistocytes)	Antibody or complement mediated Microangiopathy Mechanical heart valves	Autoimmune hemolysis, malaria DIC, TTP/HUS HELLP
4) Sequestration		Increased	Normal	Hypersplenism	Portal hypertension or sickle cell (SC; not SS) disease
5) Blood loss		Increased if iron stores are adequate Not elevated if iron stores are depleted (e.g., as in chronic blood loss)	Normal or hypochromic	Acute or chronic bleeding	Peptic ulcer disease GI hemorrhage Menorrhagia Lacerations Severe blunt trauma

* Rarely can present as microcytic with burr cell/echinocytes.

DIC = disseminated intravascular coagulation
G6PD = glucose-6-phosphate dehydrogenase

HELLP = pregnancy complication featuring hemolysis, elevated liver enzymes, and low platelet count

HUS = hemolytic uremic syndrome
SCD = sickle cell disease
TTP = thrombotic thrombocytopenic purpura

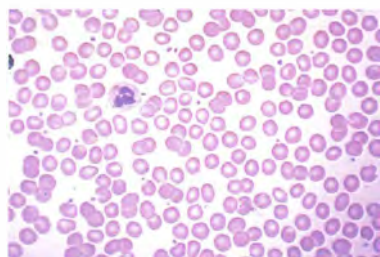


Figure 8-3: Normal peripheral smear (low power): RBCs, platelets, and segmented neutrophil



Figure 8-4: Normal peripheral smear (low-oil immersion): normocytic, normochromic RBCs, platelets, and normal segmented neutrophil

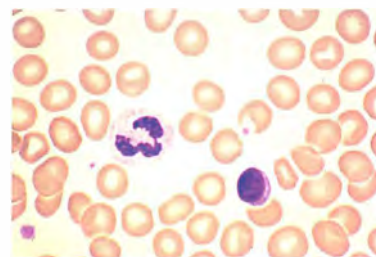


Figure 8-5: Normal peripheral smear (high power): RBCs, platelets, normal segmented neutrophil, and a normal lymphocyte

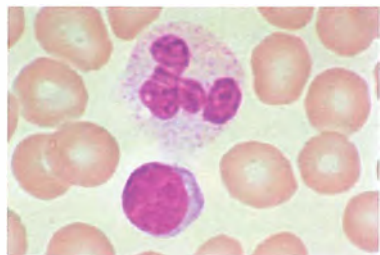


Figure 8-6: Normal peripheral smear (high-oil immersion): normal RBCs, segmented neutrophil, and lymphocyte; no platelets

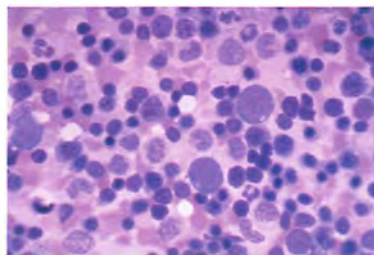


Figure 8-7: Normal BM aspirate (low power): Myeloid:erythroid ratio is usually 3:1. This field has more than the normal number of erythroid precursors, many of which have dark, condensed nuclei.

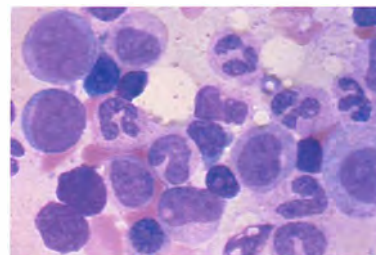


Figure 8-8: Normal BM aspirate (low-oil immersion): 5 erythroid precursors (dark condensed nuclei); remaining cells are myeloid precursors/cells (from myoblasts to segs).

Table 8-2: Significance of Specific Changes in the Peripheral Smear

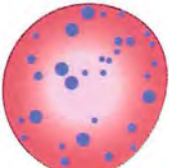
Change	Finding	Meaning
RBC fragments (schistocytes)		Microangiopathic hemolytic anemia (seen in TTP, HUS, HELLP syndrome, DIC, and occasionally vasculitis), severe burns, and valve hemolysis (Figure 8-20 on page 8-12)
Spherocytes		Autoimmune hemolytic anemia and hereditary spherocytosis (Figure 8-24 on page 8-15)
Target cells		Significant liver disease, thalassemia syndromes, sickle cell disease, homozygous hemoglobin C (HbC), and other hemoglobinopathies (Figure 8-9)
Teardrop cells (dacrocytes)		Classic for myelofibrosis and other infiltrating bone marrow processes; also seen with thalassemia (Figure 8-10)
Burr cells (echinocytes; top) vs. spur cells (acanthocytes; bottom)		Burr cells (Figure 8-11) are seen in uremic patients. These are distinct and different from spur cells (Figure 8-12), which are seen in liver diseases.
Hypersegmented polymorphonuclear leukocytes (neutrophils)		Megaloblastic anemia (e.g., pernicious anemia/B ₁₂ deficiency, folate deficiency; Figure 8-13)
Elliptocytes		Hereditary elliptocytosis, severe iron deficiency anemia; Figure 8-14
Sickle cells (crescent shaped)		Sickle cell disease (HbSS and HbS β -thalassemia; less common in HbSC; Figure 8-23 on page 8-14)
Howell-Jolly bodies (nuclear remnants)		Splenectomy or functional asplenia (as seen in sickle cell disease) Howell-Jolly bodies (Figure 8-15) are the result of nuclear remnants, causing the formation of small, round, black particles in erythrocytes. This is a normal occurrence, and the functioning spleen efficiently removes them.
Basophilic stippling (RNA)		Indicates ineffective erythropoiesis; lead poisoning, thalassemia, pyrimidine 5'-nucleotidase deficiency; Figure 8-16

Table 8-2 identifies the significance of some changes in the peripheral blood smear.

Causes and mechanisms of anemia:

1) **Production** defects result from chronic disease, acute inflammatory conditions, impaired renal function, bone marrow damage, and hypometabolic states (e.g., hypothyroidism, hypogonadism, adrenal insufficiency). Very little polychromasia and few reticulocytes are seen.

2) **Maturation** defects:

- Cytoplasmic—caused by:
 - Impaired hemoglobin synthesis—iron deficiency, sideroblastic anemia (the inability to incorporate iron into hemoglobin), protoporphyria deficiency, myelodysplastic syndrome, drugs, toxins
 - Globin synthesis deficiency (e.g., thalassemias)

- Nuclear: DNA synthesis defects (e.g., folate and vitamin B₁₂ deficiencies, myelodysplastic syndrome)

3) **Survival** defects result in premature destruction of RBCs:

- **Intrinsic (inherited):** membrane cytoskeletal protein (i.e., spherocytosis, elliptocytosis), metabolic enzymes (glucose-6-phosphate dehydrogenase [G6PD] deficiency), or hemoglobinopathies (e.g., sickle cell disease, thalassemias)
- **Extrinsic (acquired):** antibody- or complement-mediated, microangiopathy, mechanical heart valves (e.g., patients with autoimmune hemolysis, malaria, DIC, thrombotic thrombocytopenic purpura [TTP], hemolytic-uremic syndrome [HUS], or HELLP [pregnancy complication featuring hemolysis, elevated liver enzymes, and low platelet count])

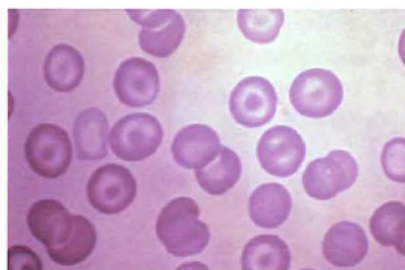


Figure 8-9: Target cells (low-oil immersion)

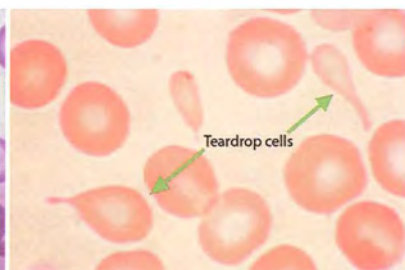


Figure 8-10: Teardrop cells. This patient has myeloid metaplasia. Also seen in thalassemias and other hemoglobinopathies

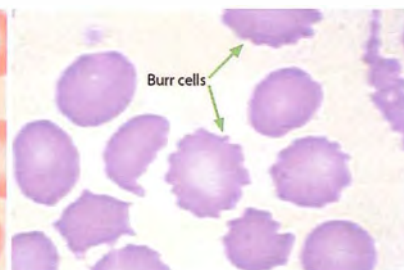


Figure 8-11: Burr cells (echinocytes) in uremia. These are RBCs with regularly spaced, short, spiny projections. These membrane changes disappear when uremia is corrected.

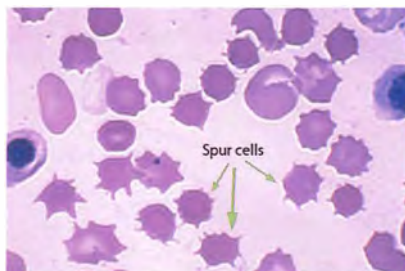


Figure 8-12: Spur cells (acanthocytes). Nucleated RBCs. Spur cells are RBCs with multiple irregular projections that vary in length, width, and regularity. The usual cause is hepatic failure.

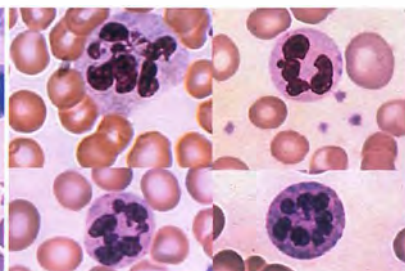


Figure 8-13: Various views of hypersegmented neutrophils

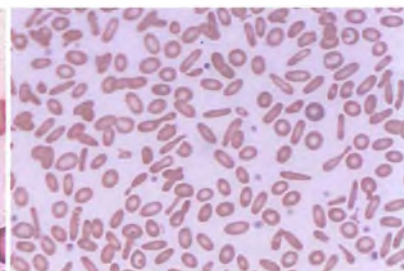


Figure 8-14: Elliptocytes



Figure 8-15: Postsplenectomy: Howell-Jolly bodies are the dense inclusion bodies in the RBCs. Also see target cells and a burr cell in this field.

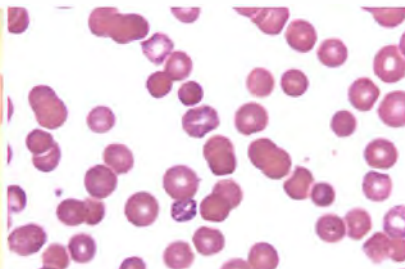


Figure 8-16: Basophilic stippling

- 4) **Sequestration:** hypersplenism (e.g., portal hypertension, early childhood sickle cell disease)
- 5) **Acute blood loss** with resultant iron deficiency (e.g., gastrointestinal [GI] hemorrhage, especially peptic ulcer disease) is the most common cause of anemia in the U.S.

WORKING UP ANEMIA

To evaluate the patient with anemia, use a combination of:

- 1) **Morphologic data:** peripheral smear to review for the presence of polychromasia and RBC indices (MCV, MCH, MCHC, and RDW)
- 2) **Kinetic data** as revealed by the presence of an appropriate reticulocyte response (with RPI, reticulocyte count [%], and/or absolute reticulocyte count): An appropriate reticulocyte response indicates that the bone marrow has the structural and functional ability to respond to an EPO-mediated stimulus of RBC production (a hyperproliferative anemia). With anemia, the count should always be elevated.

Reticulocyte response is an important fork in the road for both the etiology and treatment of the anemia. Look at the just-reviewed 5 causes of anemia (under [Mechanisms of Anemia on page 8-2](#)). Production and maturation defects lead to low RPI and reticulocyte count (< 2% of RBCs or < 100,000 cells/ μ L [10×10^{10} cells/L]), whereas shortened RBC survival, splenic sequestration, or blood loss stimulate a high reticulocyte count as new RBCs are produced. With a high reticulocyte count in the presence of anemia, assess the bone marrow response with the RPI; if it is low, there could be a combination of causes (i.e., additional production or maturation defects).

Initial lab work includes CBC, peripheral smear, retic count, and iron studies.

After taking a careful history and performing a full physical examination, check the MCV. Follow along in [Figure 8-17](#). The MCV quickly differentiates between microcytic, normocytic, and macrocytic anemias, each of which has generally nonoverlapping causes.

Microcytic RBCs (MCV < 80 fL/cell [8×10^{-15} L/cell]) are seen in IDA, thalassemia, and acquired sideroblastic anemias.

Normocytic anemia (MCV = 80–100 fL/cell) has many causes (i.e., acute blood loss, chronic disease states, and endocrine disorders). These anemias are either hypoproliferative (retic count < 2%) or hyperproliferative (retic count > 2%). Hemolytic anemias are a common cause. So, check the reticulocyte count and the peripheral smear to look for clues of hemolysis, including RBC fragments (microangiopathy) and spherocytes (hereditary spherocytosis); [Table 8-2 on page 8-4](#) has additional examples. ACD can result from kidney disease, cancer, or autoimmune or inflammatory disorders (e.g., rheumatoid arthritis). The MCV is an average of cell sizes, so it can have normal results even if the blood has populations of both small and large RBCs (dimorphic anisocytosis). Refer to [Table 8-3 on page 8-11](#) for lab value comparison of IDA and ACD.

Macrocytic RBCs (MCV > 100 fL/cell) are caused by either megaloblastic conditions (e.g., vitamin B₁₂ or folate deficiency, leukemia, myelodysplastic syndrome) or nonmegaloblastic conditions (e.g., chronic alcohol use, hypothyroidism, liver disease).

Notes of caution:

- 1) Note that both microcytic and macrocytic causes of anemia are maturation defects and, therefore, are hypoproliferative with a low reticulocyte count—so reticulocyte count is **not** considered for these conditions in [Figure 8-17](#). But if you have a mixed disorder

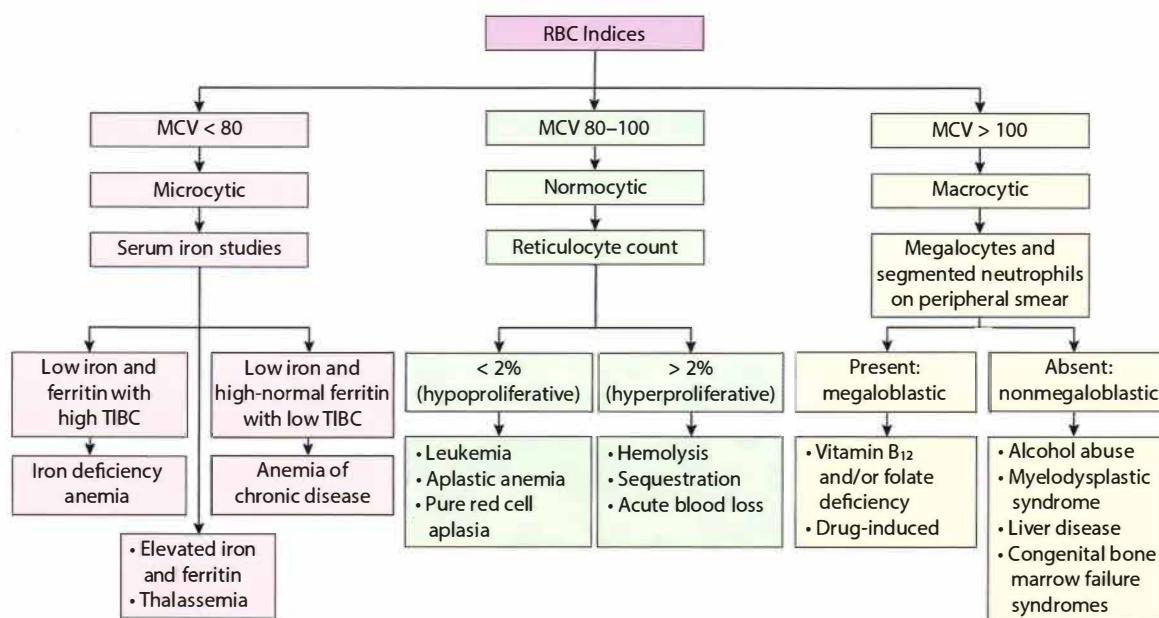


Figure 8-17: Anemia workup

with, for example, hemolysis or acute blood loss, you could have an abnormally high RPI. So, **always** check retic count in all cases of anemia.

- 2) Remember that MCV is an **average** of all RBC sizes and that you can get a normal MCV when there is a mixture of large and small RBCs (i.e., dimorphic population). In this case, a high RDW helps because it indicates a large variation in cell sizes.

Normal MCV with a high RDW occurs in the following contexts:

- Iron deficiency and/or thalassemia (i.e., microcytic RBCs) can be found with macrocytic RBCs of any cause.
- After blood transfusion for iron-deficiency or macrocytic anemias, there is a residual population of affected cells of small or large size and a new population of transfused normal-size cells.
- When reticulocytes are present, these larger cells coexist with small RBCs, such as those in iron deficiency or thalassemia.
- An unusual example is hereditary spherocytosis with microspherocytes and folate deficiency (from high compensatory RBC turnover).

Now let's learn a bit more about the different causes of anemia. The type of defect is noted in the heading of each main topic; this is to help you keep each one categorized into 1 of the 5 types of anemia.

ANEMIAS

Microcytic Anemias

Iron-Deficiency Anemia (IDA; Cytoplasmic Maturation Defect)

Iron is essential for the production of Hgb, and a deficiency leads to a cytoplasmic maturation defect of the RBC termed IDA. It features microcytosis, impaired erythropoiesis, and anemia.

Signs and symptoms include fatigue, pallor, weakness, irritability, koilonychia, and poor exercise tolerance. IDA is one of the major causes of restless leg syndrome. Pica for ice (a.k.a. pagophagia) is occasionally seen and is fairly specific for IDA.

Labs in IDA:

- RBCs are microcytic (MCV < 80 fL/cell [8×10^{-15} L/cell]) and hypochromic (decreased MCHC) with a low reticulocyte count.
- Serum iron is low. Low serum iron causes increased production of transferrin, which is measured as total iron-binding capacity (TIBC). So, with IDA, serum iron and ferritin are low and TIBC is elevated, and the ratio of serum iron to the TIBC is usually < 10% (normal is 25–40%).
- The serum ferritin level is considered the best test for assessing iron stores. In the patient with no known inflammatory or infectious disease, a ferritin level ≤ 40 ng/mL (89.88 pmol/L) is 98% sensitive and 98% specific for IDA.

Remember that ferritin is an acute-phase reactant and can increase during states of inflammation, so this test has poor sensitivity for IDA in patients who have ongoing inflammation. sTfR concentration is normally elevated in iron deficiency and normal in anemia of inflammation.

Once you diagnose IDA, you **must** pursue the etiology:

- Chronic blood loss is the most common cause:
 - In menstruating women, the source is usually menorrhagia.
 - In all others, it is GI bleed (e.g., NSAIDs, peptic ulcer disease, angiodysplasia, cancer) until proved otherwise!
 - If > 60 years of age, diagnosis is GI cancer until proved otherwise!
 - Also remember genitourinary (GU) blood loss and check U/A.
 - Worldwide, hookworm infection (*Necator americanus* or *Ancylostoma duodenale*) is the most common cause of chronic GI blood loss.
- Pregnancy can cause iron deficiency because of increased iron requirements.
- Insufficient dietary iron
- Malabsorption (e.g., celiac disease, gastric bypass surgery)
- Chronic low-grade intravascular hemolysis (as in paroxysmal nocturnal hemoglobinuria)

Celiac disease is a common cause of chronic, unresponsive IDA in a young person with a history of bulky, foul-smelling stools. However, presentation may be subtler in older patients. Screen with serologic testing—IgA anti-tissue transglutaminase (tTG) antibody is the preferred test.

Workup to define etiology almost always begins with GI evaluation with colonoscopy and possible esophagogastroduodenoscopy (EGD), depending on presentation.

Treatment of IDA begins with addressing the underlying cause, followed by iron replacement. Oral iron is the 1st choice because it is inexpensive and accessible. However, many patients are unable to tolerate oral iron or have difficulty with absorption (e.g., gastric surgery); they may be candidates for IV iron replacement. With adequate iron replacement, the Hgb should be close to normal level after 6 weeks.

Thalassemias (Cytoplasmic Maturation Defect)

Thalassemias are a group of inherited gene defects causing abnormal Hgb production. See [Normal Erythropoiesis on page 8-1](#) for normal Hgb production. Hgb is responsible for the oxygen-carrying capacity of the blood. These Hgb disorders are most prevalent in malaria-prone regions, such as southeast Asia, the Middle East, the Mediterranean, and sub-Saharan Africa. Like sickle cell trait, a small abnormality in the Hgb chain is thought to be protective against malaria (see [Sickle Cell Disease \(SCD\) on page 8-14](#)). Symptoms can vary from none to death in utero.

Thalassemias are characterized most commonly by absent or decreased production of either the α chain (α -thalassemia) or the β chain (β -thalassemia), leading to decreased production of Hgb tetramers and fewer healthy RBCs (review the structure of normal Hgb under Hemoglobin (Hgb) on page 8-1). In addition, there is unbalanced globin chain synthesis such that homotetramers are formed; these are insoluble and precipitate inside RBCs, leading to hemolysis and ineffective erythropoiesis. These processes result in anemia. Mutations can be deletional or nondeletional and affect many different aspects of transcription and translation.

Thalassemias (α - and β -thalassemia minor) are often misdiagnosed as IDA, and patients are incorrectly put on iron supplements. Iron therapy does not improve the microcytosis, and, even worse, it can cause secondary hemochromatosis (which can lead to cardiac failure, hepatomegaly, and diabetes). In both types, rule out IDA with normal iron studies (i.e., serum iron, ferritin, TIBC).

α -Thalassemia

α -Thalassemia is the most common hemoglobin genetic disease. Carrier state prevalence ranges from 2% to 98% depending on the population. In the U.S., it is very low in Caucasians but up to 15% in African Americans.

Chromosome 16 contains 2 copies of the α -gene at 2 different loci on each of the 2 genes. There are, therefore, 4 α -genes in normal individuals. The clinical manifestations correlate with the number of α -genes that are affected: The more loci affected, the worse are the symptoms (Figure 8-18).

There are 4 types of α -thalassemia:

- 1) **α -Thalassemia silent carrier:** 1 locus ($\alpha\alpha/\alpha-$), asymptomatic, no hematologic abnormalities
- 2) **α -Thalassemia minor** (a.k.a. α -thalassemia trait): 2 loci ($\alpha-/ \alpha-$) or ($\alpha\alpha/ - -$), asymptomatic, low MCV (often < 80 fL/cell [8×10^{-15} L/cell]), low Hgb, MCH < 27 pg/cell, little to no anemia
- 3) **HbH:** 3 loci ($\alpha-/-$); unpaired β chains form β_4 tetramers called HbH inclusions—these form faint blue precipitates near the RBC membrane in peripheral cells but not in the marrow. These precipitates are seen only with supravital stains and are not visible on the normal peripheral smear. Clinical features are intermediate and variable and can include moderately severe hemolytic anemia, requiring periodic transfusions. Extramedullary hematopoiesis is common with some level of iron overload.

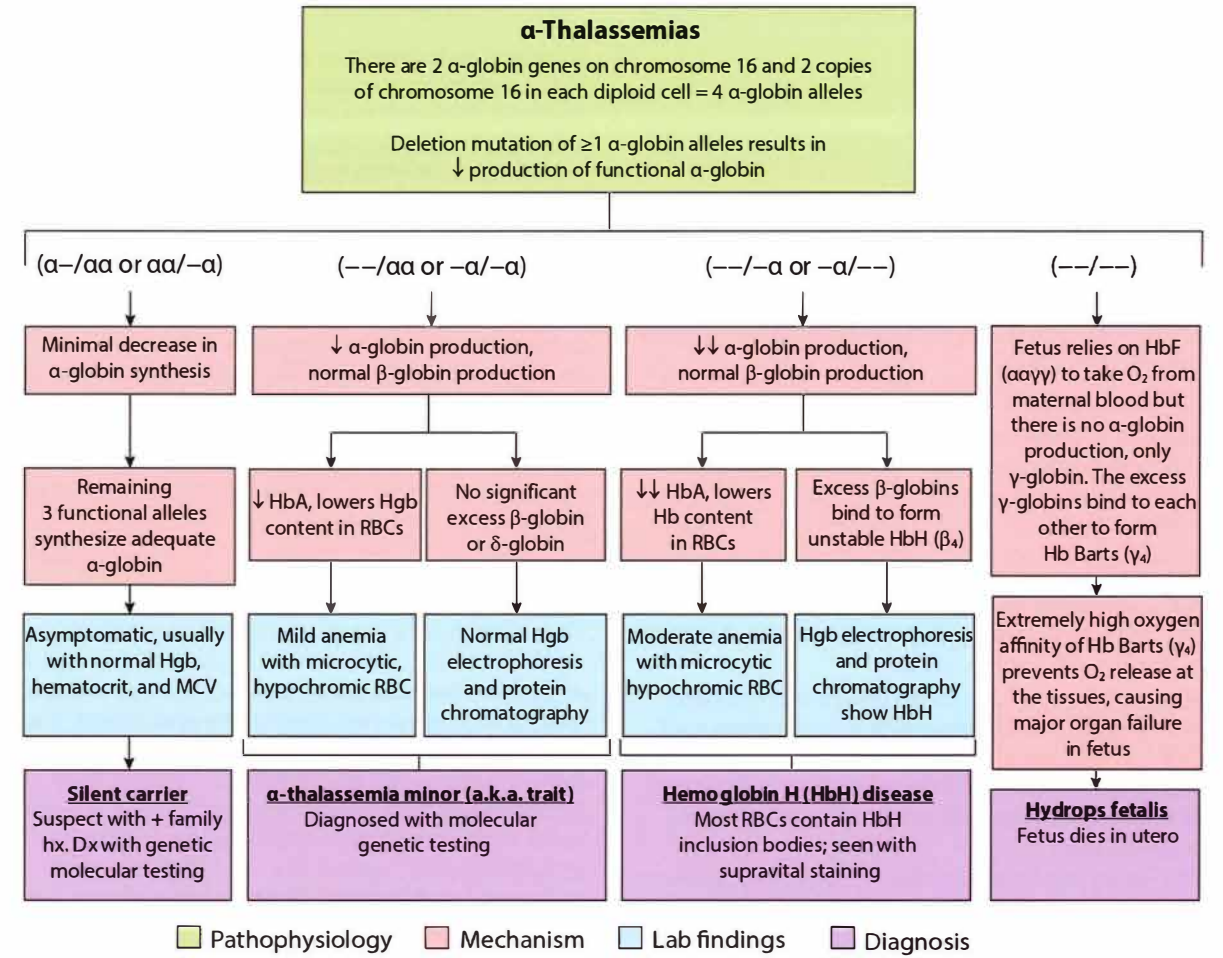


Figure 8-18: α -Thalassemia: pathogenesis and clinical findings

- 4) **α -Thalassemia major** (a.k.a. Hb Barts): 4 loci (---/---); no effective Hgb is produced beyond the embryonic stage. γ_4 tetramers form and have such high oxygen affinity that they do not deliver **any** oxygen to the tissues, causing death in utero (i.e., hydrops fetalis).

Diagnosis: Suspect α -thalassemia carrier from family history. Suspect α -thalassemia minor in patients with microcytic anemia, normal iron studies, and a normal Hgb electrophoresis. Because of the microcytic anemia, α -thalassemia minor is often misdiagnosed as IDA—which is why you should do iron studies for all patients with microcytic anemia. Molecular genetic testing is the only way to confirm the diagnosis.

In clinical practice, adult patients with a microcytosis and normal iron studies are assumed to have α -thalassemia minor, and even the electrophoresis is rarely ordered.

Treatment: No treatment is needed for an α -thalassemia carrier or a patient with α -thalassemia minor. HbH disease treatment is blood transfusions as needed.

β -Thalassemia

Patients with β -thalassemia have decreased β chain production and compensatory δ and γ chain production, leading to increases in HbA₂ ($\alpha_2\delta_2$) and HbF ($\alpha_2\gamma_2$). A range of mutations within the β -globin locus of chromosome 11 cause β -thalassemia.

There are 3 categories of β -thalassemia:

- 1) **β -Thalassemia minor** (heterozygotes; see Figure 8-19): mild or no anemia, with a disproportionately high number of microcytes. These patients are

asymptomatic and have no clinical sequelae. In most patients, this disorder has the specific finding of 2- to 3-fold elevations of HbA₂ ($\alpha_2\delta_2$) and the nonspecific finding of slight increases in HbF ($\alpha_2\gamma_2$) on Hgb electrophoresis.

- 2) **β -Thalassemia major** (homozygous): Patients with β -thalassemia major (a.k.a. Cooley anemia) have essentially no β -globin production. The remaining highly insoluble α -globin precipitates into homotetramers (a type of inclusion body), which are toxic to erythrocytes and cause them to die within the marrow. Surviving erythrocytes carry inclusion bodies that are detected by the spleen, leading to removal of the erythrocytes and chronic hemolytic anemia. The resulting severe anemia (developing over the 1st year of life) results in elevated EPO levels and, thus, erythroid hyperplasia. If the erythroid hyperplasia is severe, it can lead to **extramedullary hematopoiesis** in the liver and spleen, with an expanded bone marrow production in the cranial bones resulting in facial changes in children called chipmunk facies. Often, patients are transfusion dependent and develop iron overload. Hgb electrophoresis shows high HbF and HbA₂ and, in severe cases, no HbA production.

- 3) **β -Thalassemia intermedia** (homozygous): Not all patients with homozygous defects of β -globin production have the full clinical severity described previously. Modulating factors are minor qualitative defects of the β -globin; coinheritance of α -thalassemia trait, leading to decreased formation of the toxic RBC inclusion and, therefore, to less precipitation of insoluble homotetramers

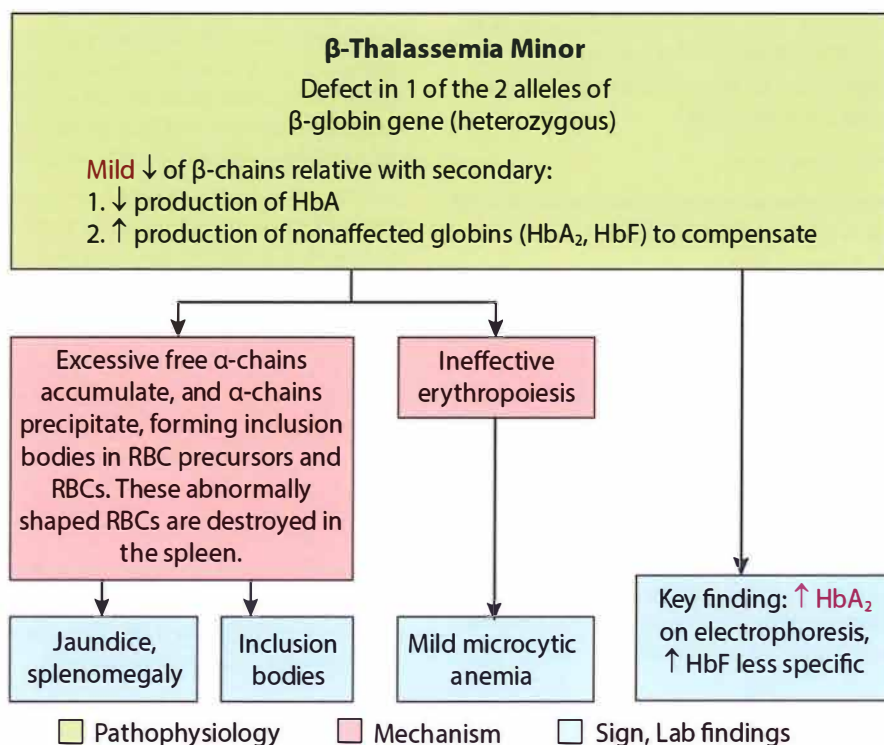


Figure 8-19: β -Thalassemia minor: pathogenesis and clinical findings

and less hemolysis; and increased production of HbF. The term “ β -thalassemia intermedia” is used to convey this heterogeneity and to describe those patients who range from asymptomatic to transfusion-dependent states.

Diagnosis: β -thalassemia minor has a mild microcytic anemia with normal iron studies. The key diagnostic finding is an increase in HbA₂. Patients usually have a smaller and less specific increase in HgF. As with α -thalassemia, molecular genetic testing confirms the diagnosis.

Treatment: No treatment for β -thalassemia minor. Transfusions as needed for intermedia and major types. Luspatercept is a recombinant fusion protein that inhibits the TGF- β superfamily, resulting in increased differentiation and proliferation of erythroid precursors, and improves hematology parameters associated with ineffective erythropoiesis. It is indicated for the treatment of anemia in adult patients with β -thalassemia who require regular RBC transfusions.

Macrocytic Anemias

Megaloblastic Anemia (Nuclear Maturation Defect)

Megaloblastic anemias result from impaired DNA synthesis. They are often the result of deficiencies of vitamin B₁₂ and/or folate but can also result from drugs that impair DNA metabolism.

Folate deficiency is caused by:

- Poor diet
- Increased demand (e.g., pregnancy, lactation)
- Alcohol use
- Medications:
 - Drugs that interfere with folate metabolism, such as methotrexate, phenytoin, and 5-fluorouracil
 - Drugs that interfere with folate absorption, such as metformin and cholestyramine

B₁₂ deficiency can result from:

- Pernicious anemia (due to autoimmune destruction of parietal cells that produce intrinsic factor)
- Strict vegetarian/vegan diet
- Alcohol use (rarely)
- Inability to release B₁₂ from food sources (common in the elderly, atrophic gastritis, and acid-suppressing medications; e.g., proton pump inhibitors [PPIs])
- Malabsorption of B₁₂ in the terminal ileum (e.g., inflammatory bowel disease, bacterial overgrowth, fish tapeworm, pancreatic insufficiency)
- Gastric surgery, including bariatric surgery

Know that the marrow is disturbed in these nutritional deficiencies and that multiple cell lines can be affected as the deficiencies progress. The megaloblastic RBCs are destroyed in the marrow (i.e., intramedullary hemolysis),

and erythropoiesis is ineffective. The characteristic megaloblastic findings are that surviving RBCs are macrocytic and neutrophils are hypersegmented (defined as ≥ 5 lobes in 5% of neutrophils or any neutrophil with 6 lobes). Platelets can be decreased as well.

Consider a megaloblastic process in patients who present with a macrocytic anemia, pancytopenia, and slight unconjugated (i.e., indirect) hyperbilirubinemia (from the continuous low-level intramedullary hemolysis).

In addition to anemia, deficiencies in B₁₂ can cause GI effects (e.g., glossitis, diarrhea) and neurologic deficits (ranging from paresthesias to frank psychosis). B₁₂ deficiency can be present without anemia but with serious neurologic problems. Atrophic glossitis is a classic symptom, but the less-well-defined neuropsychiatric symptoms (i.e., dementia, irritability, insomnia) may be the more common presentation. Know that folate deficiency is **not** associated with neurologic impairment.

Diagnose B₁₂ deficiency at a level < 200 pg/mL (147.56 pmol/L). If the level is borderline low (200–400 pg/mL [147.56–295.12 pmol/L]), check MMA and homocysteine (HC). Both are elevated in B₁₂ deficiency. Only HC is elevated in folate deficiency—and the serum folate level is decreased.

Once B₁₂ deficiency is diagnosed, pursue the etiology. **Pernicious anemia (PA)** is due to an autoimmune-mediated decrease in gastric IF. The absorption of vitamin B₁₂ is dependent on its forming a complex with IF. The presence of IF antibodies supports the diagnosis, but the sensitivity of the test is only ~ 70%.

If you highly suspect PA but IF antibodies are absent, check the serum gastrin and pepsinogen levels. In PA, the serum gastrin is increased and the pepsinogen I level is decreased. The ratio of pepsinogen I to pepsinogen II is also used; it is low in PA. The Schilling test, in which you follow the fate of radiolabeled B₁₂ ingested by the patient, was previously used to confirm the diagnosis but is rarely used and generally no longer available.

Treat B₁₂ deficiency initially with high-dose oral therapy. If not effective, then treatment requires daily injections for 1 week, followed by weekly injections for 1 month, and then monthly injections for life. Severely anemic patients can develop hypokalemia with treatment, so monitor K⁺ levels in these patients. Treat folate deficiency with daily oral replacement. **Do not ever** treat B₁₂ deficiency solely with folate—the anemia improves but the neurologic problems continue to worsen.

Nonmegaloblastic Macrocytic Anemias (Nuclear Maturation Defect)

Nonmegaloblastic macrocytic anemias occur much more frequently than megaloblastic anemias, so it is important to always consider the following causes when a patient presents with a macrocytic anemia.

Causes of nonmegaloblastic macrocytic anemia:

- Late pregnancy causes a mild elevation of MCV. This returns to normal after pregnancy.
- Chronic alcoholism, due to a direct toxic effect on the bone marrow
- Bone marrow disorders (e.g., myelodysplastic syndromes, lymphoma, myeloma, myelofibrosis, cancer)
- Cytotoxic drugs such as azathioprine, hydroxyurea, and 6-mercaptopurine
- Reverse transcriptase inhibitors, such as stavudine, lamivudine, and zidovudine, because these drugs interfere with DNA metabolism

Again, these anemias are macrocytic but do **not** have the megaloblastic findings (i.e., large RBCs and hypersegmented neutrophils).

Normocytic Anemias

Anemia of Chronic Disease (ACD; Production Defect)

ACD (a.k.a. anemia of chronic inflammation) results from decreased RBC production and impaired iron utilization, despite normal or increased iron stores.

In inflammatory states, macrophages produce interleukin 6 (IL-6), which induces the production of hepcidin by the liver. Hepcidin then inhibits iron absorption from the GI tract and decreases release of iron from macrophages. More on this process is described in [Iron Absorption and Transport on page 8-1](#).

The most common causes of ACD are chronic rheumatic, infectious, and neoplastic diseases. ACD and IDA can coexist, so it is best to work up both types of anemias in patients with chronic illness ([Table 8-3](#)).

Table 8-3: Some Laboratory Characteristics of Iron-Deficiency Anemia and Anemia of Chronic Disease

	IDA	ACD
Serum Iron	Low	Low
TIBC	High	Low
Transferrin Saturation	Low	Low to normal
Ferritin	Low	High/high-normal
sTfR	High	Normal

ACD = anemia of chronic disease

IDA = iron-deficiency anemia

sTfR = soluble transferrin receptor

TIBC = total iron-binding capacity

Labs in ACD:

- RBCs are typically normochromic and normocytic (occasionally hypochromic and/or microcytic) with a low reticulocyte count.
- Serum iron and TIBC are low.
- Transferrin saturation (iron/TIBC) is usually normal to low-normal.

- Ferritin is increased or high-normal.
- The sTfR test helps differentiate ACD from IDA: It is normal in ACD and increased in iron deficiency.

Anemia in chronic kidney disease is due to decreased EPO production and is commonly responsive to recombinant EPO. These patients can also have increased hepcidin, which binds ferroportin and decreases intestinal iron absorption. 20% of diabetics with Stage 3 chronic kidney disease (CKD) have anemia. This topic is discussed more fully in the [Nephrology](#) section.

Anemia of hypometabolic states can result from deficiencies in thyroid hormone, glucocorticoids, testosterone, or growth hormone and can be 1 of the presenting features of hypothyroidism, primary adrenal insufficiency, or pituitary disease (hypogonadism or panhypopituitarism).

Anemia from bone marrow damage includes the following:

- **Aplastic anemia:** pancytopenia secondary to a primary stem cell disorder, an autoimmune process, or a drug (Aplastic anemia is covered under [Disorders of the Bone Marrow on page 8-37](#).)
- **Pure red cell aplasia:** severe anemia due to decreased RBC precursors in the bone marrow. This can be congenital due to abnormal stem cells or acquired due to viral infection, thymoma (paraneoplastic), autoimmune disorders, lymphoproliferative disorders, or drugs. Suspect parvovirus B19 in these patients with severe anemia who also have HIV infection or sickle cell disease.
- **Marrow infiltrative disorders:** Fibrosis, granulomas, or malignancy can cause changes in the peripheral blood smear, including teardrop cells and immature red and white blood cells. These leukoerythroblastic changes reflect a weakened bone marrow (myelophthisis).

Sideroblastic Anemia (Cytoplasmic Maturation Defect)

Sideroblastic anemia can be congenital or acquired (e.g., alcohol, medications, copper deficiency). It is the result of disruption of heme synthesis and mitochondrial function, and its mechanism can be variable and complex. It is characterized by ring sideroblasts that are due to the accumulation of mitochondrial iron in erythroblasts on the bone marrow aspirate smear.

Sideroblastic anemia due to **copper deficiency** can be precipitated by zinc ingestion/intoxication. Copper deficiency has low serum copper and ceruloplasmin levels much like Wilson disease, but unlike those with Wilson disease, these patients have neutropenia and do not have Kayser-Fleischer rings. The urinary copper excretion is high in Wilson disease. See the [Gastroenterology](#) section for more details.

Lead poisoning often is cited as a cause of sideroblastic anemia, but sideroblasts often are not found on workup.

Medications linked to sideroblastic anemia most commonly include isoniazid, linezolid, and chloramphenicol.

Excessive alcohol use results in sideroblastic anemia in 25–30% of patients with alcoholism. Acquired forms of the anemia often respond to removal of the offending agent.

Hemolytic Anemia (Survival Defect)

Features

Hemolysis is the premature destruction of RBCs. Findings that indicate the possibility of hemolysis:

- Dark urine
- Jaundice
- Heart murmur
- Enlarged spleen
- Enlarged liver

Routine labs reveal anemia and elevated lactate dehydrogenase (LDH).

Causes of Hemolytic Anemia

Hemolytic anemias can be grouped by the underlying cause of premature RBC destruction:

- **Intrinsic** (or intracorpuscular):
 - Molecular defect inside the RBC (e.g., G6PD deficiency, hemoglobinopathies)
 - An abnormality in membrane structure or function (e.g., hereditary spherocytosis)
- **Extrinsic** (or extracorpuscular): an environmental factor outside the RBC (e.g., DIC; autoantibodies; thrombotic thrombocytopenic purpura/hemolytic uremic syndrome [TTP/HUS]; hemolysis with a microangiopathic blood smear, elevated liver enzymes, and low platelet count [i.e., HELLP syndrome]).

Additionally, hemolytic anemias can be grouped by location as intravascular or extravascular. Hemolysis is termed extravascular when RBCs are outside the vascular space, trapped in the reticuloendothelial system (mainly the spleen), and engulfed by macrophages. Intravascular hemolysis occurs when RBCs are lysed within the lumen of the blood vessels. This can result from nonimmunological mechanisms, including DIC, TTP/HUS, HELLP, and severe heart valve abnormalities that shear RBCs (Figure 8-20).

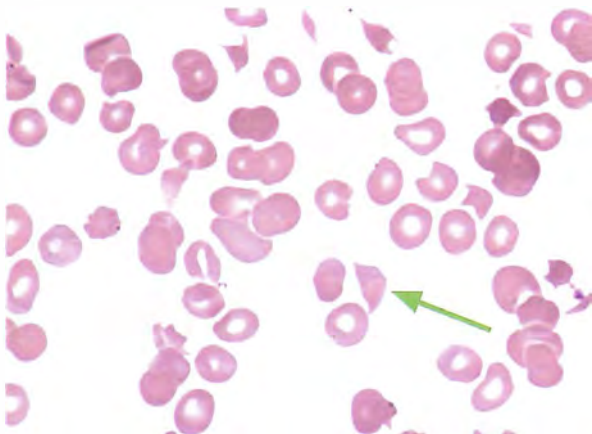


Figure 8-20: Hemolytic anemia with schistocytes

Lab Results with Hemolytic Anemia

Know all of the following.

CBC with low Hgb and hematocrit is the definition of all anemias. With hemolytic anemia, the WBC and platelet counts are usually normal.

Low haptoglobin occurs with both intravascular and extravascular hemolysis; released Hgb is quickly bound to haptoglobin and then engulfed by macrophages. The resultant low level of haptoglobin can be used to diagnose hemolysis—but does **not** help distinguish the type.

High unconjugated bilirubin = hemolysis. During normal breakdown, heme loses iron and the resultant porphyrin ring is converted to bilirubin and cleared in the urine or stool. With excessive hemolysis of either type, more of the bilirubin is **unconjugated** (indirect).

Elevated LDH levels can be caused by hemolysis. LDH is a sensitive test for hemolysis but is not very specific.

Elevated reticulocyte count is an indication of high RBC turnover. Like LDH level, high reticulocyte count is sensitive but not specific for hemolytic anemia.

RPI is elevated in hemolysis with an adequately functioning bone marrow.

Peripheral smear with **schistocytes** indicates **microangiopathic** hemolytic anemia (MAHA), in which damaged vascular endothelium causes traumatic breakage of RBCs.

High urine hemosiderin = intravascular hemolysis. More iron is lost in the urine with intravascular hemolysis, and this can be detected by the urine hemosiderin test.

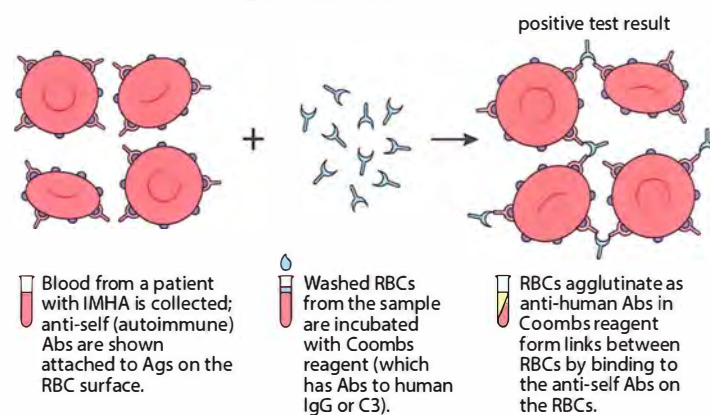
A positive direct antiglobulin test (DAT; a.k.a. direct Coombs test) = antibody- or complement-mediated hemolysis. The direct antiglobulin test identifies antibody or complement on the RBC surface, causing hemolysis. The indirect antiglobulin test method looks for specific anti-RBC antibodies in the serum. Let's review the "Coombs tests" a bit. Follow along using Figure 8-21.

The **direct antiglobulin test** (DAT; direct Coombs test) is done only if a patient's labs are **suggestive of hemolysis** (i.e., anemia with undetectable haptoglobin level and elevated bilirubin and LDH). DAT is used to determine if the hemolysis is **immune-related**. A positive test confirms that there is **IgG or C3** coating the surface of the patient's RBCs. This is usually caused by autoimmune hemolytic anemia (AIHA). In a newborn, the coating could be the result of hemolytic IgG from the mother due to Rh incompatibility.

Hemolysis due to intrinsic RBC membrane defects or enzyme deficiency such as HS and G6PD deficiency are **not** immune based and are DAT negative.

The **indirect antiglobulin test** (IAT; indirect Coombs test) is more of a **test method** used in screening tests that look for specific IgG in the patient's plasma that is known to cause hemolysis. Because there are many IgGs that can do this, you never simply order an IAT; rather, you order the test that reflects the antibody for which you are screening.

Direct Antiglobulin (Direct Coombs) Test



Indirect Antiglobulin (Indirect Coombs) Test

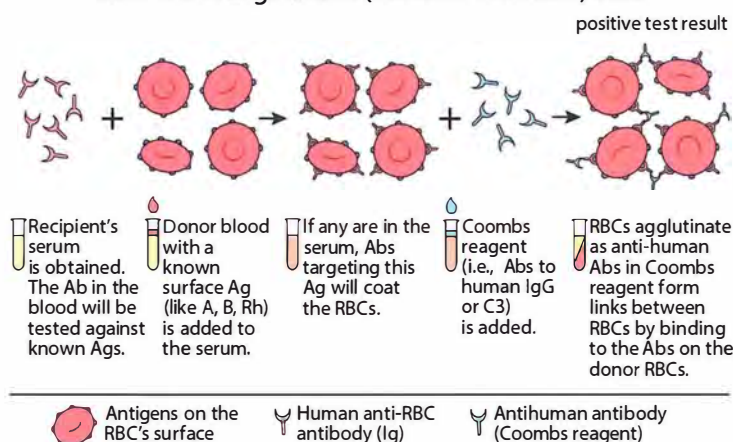


Figure 8-21: Antiglobulin (Coombs) testing

These tests are preventive; you are doing due diligence to prevent hemolysis. The most common screening tests that use the IAT method are those looking for:

- ABO antibodies in a patient prior to receiving a blood transfusion (RBCs with A antigens and ones with B antigens are tested against the patient's serum.)
- Rh antibodies in a Rh- mother's serum (due to having had an Rh+ baby [i.e., A+, AB+, B+, O+] indicating a danger of her next baby developing hemolytic disease of the fetus and newborn [HDFN])

Let's delve a little deeper. Common to both tests is the use of the same **antiglobulin agent**, which has the superpower of reacting with and cross-linking IgG (or C3) that is coating the surface of RBCs and thereby cause visible RBC agglutination—which is the same endpoint in each test.

The antiglobulin agent (a.k.a. antisera; anti-human IgG; Coombs reagent) is derived from the serum of animals that were injected with human IgG or C3 and have developed an immune response, now with immune globulins against human IgG (or C3). Originally, the animals used were rabbits, but now larger animals like sheep, goats, and horses are used. Monoclonal antibodies have been developed.

The DAT is quick and simple. The antiglobulin agent is mixed with a patient's washed RBCs (i.e., free of patient's plasma). Cross-linking with agglutination occurs if they are coated with IgG (or C3).

The IAT, instead of using the patient's RBCs (as in the DAT), uses nonpatient RBCs that express the antigen in question mixed with the patient's plasma (which may have the IgG in question). After incubation (to allow time for the patient's IgG to attach to the RBCs), the antiglobulin agent is added, and visible agglutination is a positive result.

Intrinsic Survival Defects

G6PD Deficiency

There are > 400 variants of the **X-linked G6PD** gene, affecting > 400 million people worldwide. Being X-linked means that if a male gets the *G6PD* gene, 100% of his RBCs are affected. If a woman gets 1 affected X chromosome, 50% of her RBCs are affected. Together, these result in widely variable deficiencies in the reduced state of glutathione, this reduced state being a protective mechanism against oxidative stress. Common strong oxidative stressors are infections, medications (including dapsone, sulfa drugs, and antimalarials), fava beans, and diabetic ketoacidosis.

Hemolysis in G6PD deficiency can be mild to massive. G6PD levels normally decline over the RBC lifespan, so measured levels of G6PD can be normal during an acute hemolytic episode if young cells enrich the test population;

i.e., a false-negative test is possible during acute hemolysis with brisk reticulocytosis. Measure G6PD levels 2–3 months after the hemolytic event if the original test is negative and suspicion remains. Other hematologic findings (and buzzwords) include **bite cells** on peripheral smear and **Heinz bodies** seen only with special stains (not seen on peripheral smear!). Heinz bodies are chunks of denatured Hgb (Figure 8-22). So, if a patient has hemolysis of unknown cause and bite cells, check a G6PD assay, order a special smear for Heinz bodies, and do the DAT (just to be sure the hemolysis is not autoimmune; it should be negative).



Figure 8-22: Heinz bodies in G6PD. Special stains are required.

Pyruvate Kinase Deficiency

Although G6PD deficiency is more common than pyruvate kinase deficiency, the latter is more likely to result in a symptomatic hemolytic anemia. Pyruvate kinase

deficiency and other enzyme deficiencies within the glycolytic pathway are subject to hemolytic crisis without exposure to oxidative stress. In fact, the mechanism of hemolysis in pyruvate kinase deficiency is not clearly understood. In contrast with other types of hemolysis, the peripheral blood smear does not reveal characteristic RBC abnormalities.

Sickle Cell Disease (SCD)

SCD is a group of disorders resulting from a point mutation in the β -globin gene ($\beta^{\text{Glu} \rightarrow \text{Val}}$), in which valine is substituted in place of glutamine on chromosome 11. When **both** β -globin chains are affected, the patient has **HbSS disease**. Typically, when we talk about SCD, we mean HbSS disease. The deoxygenated hemoglobin S (HbS) stiffens and distorts the RBC membrane, causing the characteristic sickle shape seen on peripheral blood smear; this shape prevents the cells from passing easily through small vessels. See [Figure 8-23](#).

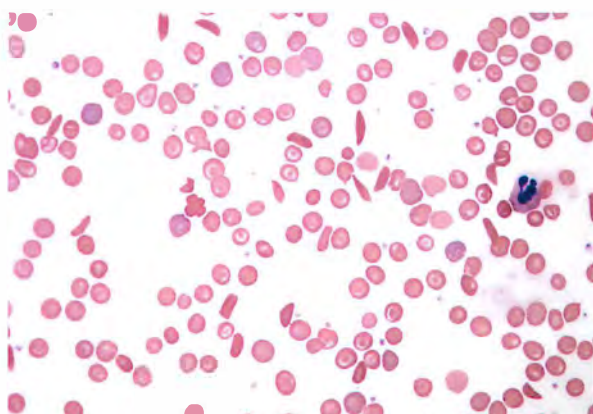


Figure 8-23: Sickle cell disease

Other SCDs result when only **1** β -globin gene is affected:

- **Sickle cell trait (HbS/A):** Half the Hgb in each RBC is HbS and half is HbA. Patients are typically asymptomatic but can have renal papillary necrosis with painless hematuria and isosthenuria.
- **HbSC disease ($\beta^{\text{Glu}} \rightarrow \text{Val}$ $\beta^{\text{Glu}} \rightarrow \text{Lys}$):** RBCs are rigid—but **not** sickled—and have a short lifespan. Symptoms are similar to those with SS disease but are less severe. Because the spleen does not always undergo early autoinfarction, as it does in HbSS disease, splenic sequestration is much more likely to be seen in adults with HbSC disease; consider this in adult SC patients presenting with a tender spleen and worsening anemia. Retinal problems are also common.
- Other Hgb disorders can be seen in combination with HbS in double-heterozygous individuals. They include HbS/ β -thalassemia and HbSD (D is an abnormal type of hemoglobin). Clinical features are varied.

SCD is confirmed with Hgb electrophoresis—usually when the patient is a child. You can screen prospective parents for the carrier state and provide genetic counseling.

Recurrent microinfarcts of the kidney lead to isosthenuria (inability to concentrate urine). Recurrent infarcts

of the spleen lead to functional asplenia with increased risk of infection from **encapsulated** organisms such as *Streptococcus pneumoniae*, *Neisseria meningitidis*, *Haemophilus influenzae*, and *Salmonella*. To protect against these organisms, penicillin prophylaxis is used in children until 5 years of age. Give all patients pneumococcal, meningococcal, *H. influenzae*, hepatitis B, and influenza vaccines.

Chronic hemolysis can cause bilirubin gallstones.

In SCD patients, a **parvovirus B19** infection can decrease erythropoiesis, causing a worsening of the anemia or even a pure red cell aplasia.

Recurrent vaso-occlusion pain episodes are the characteristic feature of SCD.

Vaso-occlusive pain in SCD can be mild to debilitating and last hours to days. Typically, it occurs in long bones, chest, back, and abdomen. Pain is typically deep and aching. Mild associated redness, warmth, and tenderness with a low-grade fever is common. Pain resolves with aggressive pain management.

With functionally asplenic patients, be sure to have a low threshold of concern for infection. Obtain blood cultures and start empiric IV antibiotics if any of the following is present:

- Temperature is $> 101.5^{\circ}\text{F}$ (38.6°C) (administer antibiotics within 1 hour of triage)
- Pain persists despite aggressive pain management (i.e., splenic sequestration, acute chest syndrome)
- There is localized swelling of a single painful site (e.g., osteomyelitis)

With increasing age, HbSS patients tend to also develop chronic neuropathic pain.

Acute chest syndrome (ACS) is vaso-occlusion causing chest pain and desaturation of oxygen. It often follows a vaso-occlusive pain episode in the abdomen or bones and is the main cause of death in patients with SCD. Patients can present with chest, rib, sternal, arm, and leg pain and shortness of breath. Differential includes pulmonary embolism and acute coronary syndrome. By definition, an ACS diagnosis requires an infiltrate on chest x-ray (CXR) or respiratory symptoms and fever, making it difficult to distinguish from pneumonia. ACS is categorized as:

- Mild— O_2 sat on room air $> 90\%$, 1 lobe infiltrate
- Moderate— O_2 sat on room air $> 85\%$, 1–2 lobes with infiltrate
- Severe—respiratory failure ($\text{P}_a\text{O}_2 < 60$ mmHg), $< 85\%$ O_2 sat on room air, ≥ 3 lobes with infiltrate
- Very severe—with acute respiratory distress syndrome (ARDS) or acute lung failure

Initial treatment of ACS includes IV fluids, antibiotics, analgesia, and oxygen supplementation. Transfusion requirements vary depending on degree of severity:

- Mild—often no blood transfusion needed
- Moderate—simple blood transfusion
- Severe—exchange transfusion until HbA level is $\geq 70\%$

Exchange transfusion is also sometimes required for treatment of priapism, cerebral sickling, and aplastic crisis. Occasionally, more conservative therapy with a simple transfusion and/or supportive care treats these presentations. A partial exchange transfusion program is reserved for those with a history of stroke. Folate supplementation is important. Medications such as hydroxyurea are used to increase HbF production, which offers some protection against sickle crisis.

Two new medications are available:

- Voxelotor (Oxbryta), approved in 2019 (mechanism: reduced HbS polymerization), is an option for individuals ≥ 12 years of age who continue to have vaso-occlusive pain episodes despite appropriately dosed hydroxyurea or who cannot tolerate hydroxyurea for any reason.
- Crizanlizumab (Adakveo), approved in 2019 (mechanism: anti-P-selectin), is an option for individuals ≥ 16 years of age with SCD who have acute vaso-occlusive pain episodes unresponsive to hydroxyurea, L-glutamine, or both. Crizanlizumab is a monoclonal antibody directed against P-selectin, an adhesion molecule expressed on activated platelets and endothelial cells. It is thought to reduce vaso-occlusive pain by reducing interactions between endothelial cells and circulating blood cells.

Long-term effects of SCD include avascular necrosis of the femoral head, sickle retinopathy, sickle nephropathy, and pulmonary hypertension.

Hereditary Spherocytosis (HS) and Elliptocytosis

HS and elliptocytosis are autosomal-dominant (AD) disorders of the RBC cytoskeleton that result in loss of membrane flexibility and are associated with chronic hemolysis. These disorders are seen in Northern European populations.

Complications of spherocytosis and elliptocytosis can include cholelithiasis, due to bilirubin stones, and splenomegaly. Think about these disorders in patients who demonstrate evidence of hemolysis and have spherocytes (Figure 8-24) or elliptocytes (Figure 8-14 on page 8-5) on their peripheral smear. Coombs test is negative.

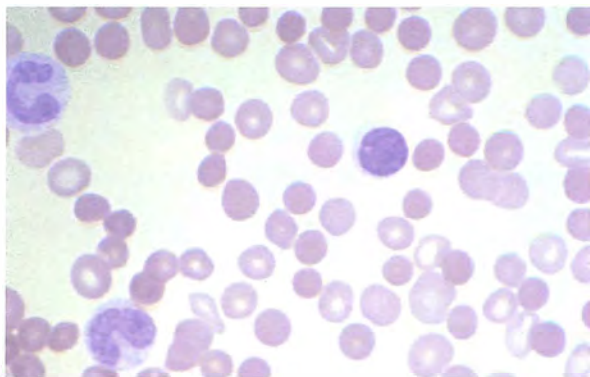


Figure 8-24: Hereditary spherocytosis. Note the lack of central pallor. The normal-size lymphocyte shows that these are microcytic spherocytes.

The osmotic fragility test was traditionally used in diagnosing HS. (The reduced surface:volume ratio makes spherocytes more susceptible to osmotic stress.) The eosin-5-maleimide (EMA) binding test is the favored diagnostic test due to its superior sensitivity and specificity and its rapid turnaround time. Sophisticated molecular membrane studies (usually available at research institutions) can be done to make a definitive diagnosis (e.g., sodium dodecyl sulfate–polyacrylamide gel electrophoresis [SDS-PAGE]), but it does not change management.

Treatment includes recombinant EPO with iron and folate supplementation and, if needed, supportive blood transfusions. Total or partial splenectomy may be required to prolong RBC survival.

Paroxysmal Nocturnal Hemoglobinuria (PNH)

PNH is a rare, acquired stem cell disorder resulting from a defective *PIGA* gene. The result is the loss of a membrane-bound protein, which, when present, anchors other proteins to the cell membrane. Some of these anchored proteins serve to protect the cell against complement-mediated lysis. Without the anchor protein, this protection is lost.

Clinical presentation includes a variable degree of complement-mediated intravascular hemolysis and free Hgb, which can lead to chronic hemoglobinuria and iron deficiency. The free Hgb causes a reduction in nitric oxide (NO), which then causes the classic symptoms of episodic abdominal and chest pain. NO effects on smooth muscle cause diffuse esophageal spasms that coincide with hemoglobinuria. The other major potential complication is arterial or venous thrombosis (especially of abdominal veins; think about PNH in cases of Budd-Chiari syndrome). Rarely, transformations to aplastic anemia, acute leukemia, and myelofibrosis occur.

Diagnosis is made using specific flow cytometry assays for CD55 (decay accelerating factor) and CD59 (homologous restriction factor)—complement proteins that are lost from the cell membrane when the anchor protein is absent.

Definitive treatment is allogeneic bone marrow transplant. Otherwise, treat hemolysis with corticosteroids. Use anticoagulants to treat thrombotic events. Eculizumab, an antibody to the C5 terminal component, decreases hemolysis and the need for transfusion and improves quality of life.

Extrinsic Survival Defects

Microangiopathic Hemolytic Anemia (MAHA)

MAHA is the nonimmune (i.e., Coombs-negative) destruction of erythrocytes, usually caused by physical shearing during passage through small vessels that have had endothelial damage with platelet aggregation or fibrin deposition. This platelet aggregation causes thrombocytopenia. See Table 8-4 on page 8-16.

Table 8-4: Classification of Thrombotic Microangiopathies

Microangiopathy	Causes
Thrombotic thrombocytopenic purpura (TTP)	Acquired (autoimmune)—antibodies against ADAMTS13 Congenital—ADAMTS13 mutations (Upshaw-Schulman syndrome)
Shiga toxin–producing <i>Escherichia coli</i> hemolytic uremic syndrome (STEC-HUS)	Shiga toxin–producing <i>E. coli</i> <i>Shigella dysenteriae</i>
Atypical hemolytic uremic syndrome (aHUS)	Complement alternate pathway regulatory defects Diacylglycerol kinase epsilon (DGKE) defects Cobalamin metabolic defects
Secondary thrombotic microangiopathy, associated with:	Malignant hypertension Mechanical hemolysis—malfunctioning aortic or mitral valve prostheses Pregnancy—preeclampsia/eclampsia, HELLP syndrome Infections—viral, bacterial, fungal Disseminated intravascular coagulation Cancer Hematopoietic stem cell or solid organ transplantation Antiphospholipid antibody syndrome Autoimmune disease Vasculitis Ionizing radiation Drugs (e.g., calcineurin inhibitors, mitomycin C, gemcitabine, vascular endothelial growth factor [VEGF] inhibitors, ticlopidine, quinine)

Adapted from Majerus, E.M. and Sadler, J.E., "Microangiopathic Hemolytic Anemia" in *Anemia: Pathophysiology, Diagnosis, and Management*. Benz, E., Berliner, N., and Schiffman, F.J. (eds). Cambridge University Press. 2018.

MAHA is seen in:

- TTP
- HUS
- Secondary thrombotic microangiopathy
- DIC
- Mechanical heart valve malfunction
- Intraaortic balloon pumps

Autoimmune Hemolytic Anemia (AIHA)

AIHA is usually caused by IgG or IgM antibodies. Antibodies that react with RBC membrane proteins are often IgG. These antibodies induce hemolysis either by stimulating macrophages and other cells in the spleen and reticuloendothelial system to gradually snip portions of membrane away (causing spherocytes) or by causing complement-mediated destruction. Review Table 8-5 during the following discussion.

IgG antibodies react best at body temperature (a.k.a. **warm antibodies**). They can be idiopathic or secondary to neoplasm or connective tissue disease. In AIHA, the direct Coombs test, which detects antibodies on the RBC surface, is positive using antibodies to IgG. Treat with corticosteroids. Splenectomy is reserved for refractory cases. The anti-CD20 monoclonal antibody rituximab is sometimes also used in difficult-to-treat patients.

IgM antibodies often bind to polysaccharides or complement. These antibodies react better at room temperature (a.k.a. **cold antibodies**). The direct Coombs test uses an antibody to C3 to detect complement (rather than the IgM antibody itself). IgG antibodies rarely induce complement fixation on RBC surfaces.

These IgM autoantibodies may be secondary to:

- Neoplasm (especially chronic lymphocytic leukemia [CLL] and, less frequently, non-Hodgkin lymphoma)
- Infection, **especially** *Mycoplasma pneumoniae* and infectious mononucleosis
- Systemic lupus erythematosus (SLE)

Treatment is best accomplished by maintaining a warm environment and identifying and treating the underlying cause. Steroids are **ineffective**.

Table 8-5: Autoimmune Hemolytic Anemia

	Warm Ab	Cold Ab
Temperature at which RBCs agglutinate	Body temperature	Below body temperature
Ab Type	IgG	IgM
Causes	Viral, autoimmune, transfusions, malignancy (e.g., CLL)	Infection (e.g., <i>Mycoplasma</i> , Epstein-Barr virus), lymphoma
Diagnosis	DAT-IgG or C3 fragment	DAT-C3 (negative for DAT-IgG)
Treatment	Corticosteroids/splenectomy/rituximab	Keep warm/treat the underlying cause/rituximab

Ab = antibody
CLL = chronic lymphocytic leukemia
DAT = direct antiglobulin test
RBC = red blood cell

Drug-Associated Hemolysis

Many drugs can cause hemolysis. Penicillin bound to RBCs may elicit an antibody response that can cause hemolysis. Quinine, methyldopa, and certain cephalosporin antibiotics are also known culprits. The pattern of abnormal Coombs testing varies with the type of drug. Treatment, of course, begins with discontinuing the offending agent.

Microbe-Induced Hemolytic Anemia

Several infections can cause hemolytic anemia through extrinsic mechanisms. Malaria, bartonellosis, and babesiosis cause anemia by direct parasitization of the RBCs. *Clostridium perfringens* and *Haemophilus influenzae* Type b cause hemolysis through bacterial byproducts. Treatment is aimed at the underlying infection and supportive care. This is also covered in the [Infectious Disease](#) section.

Sequestration Defect

Sequestration anemia occurs with overactive, often enlarged spleens in a variety of disorders—especially portal hypertension, where RBCs, WBCs, and platelets may be sequestered. Splenic sequestration may occur in early childhood with HbSC and HbS/β-thalassemia (before splenic infarction and fibrosis are seen). In fact, in adults with HbSC, splenic infarction and splenic sequestration crises (which is mainly seen in the young with HbSS) can occur.

Blood Loss

Anemia from acute blood loss is often obvious from injuries or GU and GI tract loss but can be less obvious in intrapulmonary, retroperitoneal, and rectus abdominis sites. And remember, again, any IDA is considered to be due to chronic blood loss until proved otherwise (see [Microcytic Anemias on page 8-7](#)).

Liver Disease

Anemia is common in liver disease:

- Cirrhosis causes spur cell anemia (see [Figure 8-12 on page 8-5](#)) due to abnormal cholesterol production. RBCs change shape and are hemolyzed.
- Portal hypertension causes splenic sequestration and cytopenias.
- Alcohol use is associated with nutritional (megaloblastic) anemias, especially from folate deficiency.
- Alcohol directly inhibits EPO production and erythropoiesis.
- Viral hepatitis can cause anemia through direct inhibition of the marrow and via autoimmune hemolysis.
- GI blood loss is common, especially if the patient has esophageal varices.

Chronic Kidney Disease (CKD)

Anemia in CKD is discussed extensively in the [Nephrology](#) section.

Cancer Patients

Cancer patients may have coexisting causes of anemia. Consider these possibilities:

- Bone marrow infiltration by cancer cells
- Chemotherapy-induced anemia
- Infection-causing bone marrow suppression
- Medications, including antibiotics/antivirals
- Autoimmune hemolytic anemia (e.g., lymphoproliferative disorders, such as CLL)
- Sequestration
- ACD
- Blood loss from bleeding tumors
- Iron deficiency (especially in GI cancers)
- Malnutrition

Treatment is often supportive, with transfusions provided as needed. EPO-stimulating agents are almost never indicated except in very specific scenarios, including some cases of myelodysplastic syndrome. These agents can be considered when chemotherapy for noncurative intent causes symptomatic anemia—but even in this context, they are still controversial.

MISCELLANEOUS DISORDERS THAT AFFECT RBCs

PREVIEW | REVIEW

- What is the most common neurologic manifestation of porphyria?
- What is the typical presentation of hereditary hemochromatosis (HH)?
- Which tests are used to diagnose HH?
- Which disorder(s) cause(s) a high ferritin? A high ferritin with multiple cytopenias and hemophagocytosis in the bone marrow?

METHEMOGLOBINEMIA

Oxidation of heme iron from the ferrous Fe^{2+} to the ferric Fe^{3+} state forms altered Hgb (methemoglobin), which has an impaired ability to reversibly bind oxygen. Methemoglobin gives the blood a dark color, so patients appear cyanotic despite a normal PaO_2 on arterial blood gas. Pulse oximetry is not reliable. The preferred diagnostic method is direct analysis for methemoglobin, rather than assessment of oxygen saturation or blood gas analysis. Symptoms include headache, dizziness, dyspnea, tachypnea, tachycardia, and obtundation. Severe tissue

hypoxia and death can result as levels rise. Causes are hereditary and/or acquired and can include industrial chemicals and drugs: nitrates/nitrites (e.g., nitroglycerin, amyl nitrite [a.k.a. Poppers], nitroprusside—but rarely NO), phenazopyridine (e.g., over-the-counter bladder analgesic), dapsone, sulfonamides, and anesthetics (e.g., oral benzocaine, lidocaine). Treat severe cases with methylene blue.

PORPHYRIAS

The porphyrias are inherited (most cases) or acquired metabolic disorders in which heme biosynthetic pathway enzymes are deficient, resulting in excess accumulation and excretion of porphyrins and their precursors. Porphyria cutanea tarda (PCT), the most common of the porphyrias, is an acquired mutation.

The porphyrias are classified as either acute or cutaneous. **Acute porphyrias** (especially acute intermittent porphyria) affect the **neurologic** system, causing neurovisceral abdominal pain (most common), psychiatric disorders, and other neurologic manifestations (e.g., neuropathic pain, encephalopathy). **Cutaneous porphyrias** cause either acute nonblistering or chronic blistering reactions (PCT) in sun-exposed areas.

Clinical manifestations can be extremely subtle and can mimic many other disorders.

Administer dextrose via intravenous infusion as the initial treatment in the absence of neurologic symptoms or organ failure. Treat severe cases with intravenous hematin. Both of these treatments decrease heme synthesis and slow the buildup of the toxic precursors.

Treat PCT with regular phlebotomy to decrease ferritin to less than ≤ 20 ng/mL.

HEREDITARY HEMOCHROMATOSIS (HH)

HH is an iron-overload disorder due to ≥ 1 mutations, with *HFE* gene mutations being the most common. These mutations cause the body's appetite for iron to be insensitive to the presence of adequate iron stores. The 2 most common *HFE* mutations are *C282Y* and *H63D*. Caucasians have the highest incidence of *C282Y* homozygosity, followed by Native Americans. Compound heterozygosity (*C282Y* with *H63D*) and heterozygosity for either *C282Y* or *H63D* are the next most common genotypes.

Other genotypic variations include mutations in genes that code for the transferrin receptor ferroportin and for hepcidin, a peptide that plays a central role in human iron metabolism. HH is ordinarily inherited in an autosomal-recessive (AR) fashion. HH should be distinguished from acquired secondary causes of hemochromatosis, including transfusional iron overload (think of a sickle cell patient requiring multiple blood transfusions). Iron can accumulate in the liver and other organs in a variety of both hereditary and acquired conditions when there is a genetic basis. In hereditary hemochromatosis, iron overload of the parenchyma of various organs—especially the

liver, pancreas, and heart—is progressive. Hemosiderosis is associated with systemic macrophage and reticuloendothelial iron accumulation from blood transfusions, hemolytic states, and ACD, and in some hepatitises, such as hepatitis C, alcoholic liver disease, PCT, and cirrhosis. Liver parenchyma and heart muscle can be secondarily affected in hemosiderosis.

Clinical disease does not develop in all patients who inherit the mutations, even with *C282Y* homozygosity. The phenotype of skin hyperpigmentation, arthropathy, cirrhosis, cardiomyopathy, and endocrinopathies that characterize fully penetrant HH may require ≥ 1 mutations in the *HFE* gene plus inheritance of ≥ 1 of the other genetic variations and/or exposure to environmental risk factors (e.g., excessive alcohol use).

The *HFE* protein is expressed in the deep crypt cells of the duodenum and normally acts as a sensor of the body's iron stores, modulating the uptake of transferrin-bound iron into these cells. *HFE* mutations decrease this transferrin receptor-mediated uptake of iron into crypt cells, sending a false signal of low iron stores to the intestinal cells and causing an up-regulation of the intestinal iron transporter DMT (divalent metal transporter) protein in the lumen. DMT also regulates lead, zinc, and copper. This unchecked absorption of intestinal iron leads to elevated levels of serum ferritin, with concomitant iron deposition into multiple organ systems, including the liver, heart, skin, gonads, joints, and pancreas.

Although classically described as a triad of cirrhosis, bronzed skin pigmentation, and diabetes mellitus, HH is more commonly diagnosed at an earlier stage in the disease. Patients most often present in middle age with early signs and symptoms of iron overload, including (from most to least common):

- Fatigue and weakness
- Abnormal liver transaminases
- Bronzing of the skin
- Diabetes mellitus
- Joint pain +/- calcium pyrophosphate crystalline disease (i.e., pseudogout, chondrocalcinosis)
- Erectile dysfunction/hypogonadism
- Restrictive cardiomyopathy

Women may present with symptoms after menopause (in their mid-to-late 50s) because the monthly menses served as adequate phlebotomy during their younger years.

The most sensitive test to diagnose HH is transferrin saturation (serum iron/TIBC $\times 100\%$). Once you suspect HH based on a transferrin saturation of $> 45\%$, include iron studies in the diagnostic workup to further quantify iron overload. A ferritin level $> 1,000$ ng/mL (2247 pmol/L) suggests iron overload. Genetic testing can be done for the most common underlying genetic mutations. Liver biopsy, the diagnostic gold standard, is largely used as a prognostic indicator or, in cases in which laboratory and genetic testing is equivocal, in the face of high clinical suspicion. Magnetic resonance imaging (MRI) at an

experienced facility can detect iron in the liver, heart, joints, and pituitary.

Also test 1st degree family members for the disease. (The role of population screening for HH remains uncertain.) Early diagnosis of HH is extremely important, however, because devastating consequences of the disease are easily preventable with timely treatment.

Phlebotomy remains the foundation of management of iron overload. Because it is not known who develops cirrhosis and hepatocellular carcinoma, treatment is recommended for those with elevated liver iron content. Initially remove one to two 500-mL units of blood (each containing about 250 mg of iron) weekly until the serum ferritin is 20–50 ng/mL (44.94–112.35 pmol/L) and the transferrin saturation is < 30%. The typical patient requires removal of 20–25 units of blood to complete this 1st stage. Even after treatment, transferrin saturation may remain high.

Lifelong maintenance phlebotomy, usually 2–4×/year, with regular monitoring of serum Hgb is then needed to keep serum ferritin levels < 50–100 ng/mL (112.35–224.7 pmol/L) and transferrin saturations < 50%. Although this regimen does not reverse previously established cirrhosis or other sequelae of iron deposition, progression can slow and new disease development prevented.

All patients are at increased risk for infection with *Listeria* (because the excess iron impairs macrophage function) and with bacteria that utilize iron as a substrate (e.g., *Vibrio* and *Yersinia*).

Patients need to avoid uncooked seafood because of the risk of disseminated *V. vulnificus*.

HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS (HLH)

HLH is a rare syndrome that mainly affects children but can affect adults. HLH is an **extreme** inflammatory state characterized by **uncontrolled** immune system activation.

There are genetic linkages (**familial** HLH), and there are several conditions that can trigger this disorder (**acquired** HLH), including rheumatologic, infectious, metabolic, and malignant conditions. Malignancies include leukemias and lymphoid cancers (especially T, NK, and anaplastic large cell lymphomas). Rarely, solid tumors trigger HLH.

HLH is not a malignancy, but it is often confused with or may accompany malignancies.

The **uncontrolled** immune activation can result in:

- Hepatosplenomegaly, lymphadenopathy, neurologic symptoms, and rash
- Cytopenia, usually involving ≥ 2 cell lines, is common.
- Very high serum ferritin levels (> 3,000 ng/mL [6741 pmol/L] is indicative of HLH, but it can exceed 50,000 [~112,000]; normal is < 300 [675].)

- Hemophagocytosis seen on bone marrow examination and in lymph node, spleen, and liver biopsies
- Fevers
- Hypertriglyceridemia
- Neurologic manifestations (i.e., seizures, mental status changes)

Other disorders with high serum ferritin levels include hemochromatosis and adult-onset Still disease.

Diagnosis of HLH can be difficult; not only are each of these findings fairly nonspecific, but patients usually do not have all of them on presentation! TTP, HUS, and drug-induced thrombotic microangiopathy (DITMA) can be confused with HLH. Given a transfusion history, transfusion-associated graft-versus-host disease is also in the differential diagnosis.

Urgently treat deteriorating clinical status with dexamethasone and etoposide. Methotrexate and alemtuzumab can also be used.

HEMOSTASIS

OVERVIEW

Clotting after a vascular injury consists of 2 stages: primary hemostasis and secondary hemostasis. Primary hemostasis is the function of the platelets, whereas secondary hemostasis is dependent upon the coagulation factors.

PRIMARY HEMOSTASIS

PREVIEW | REVIEW

- Explain how aspirin and nonsteroidal antiinflammatory drugs work to decrease platelet function.
- What is the lifespan of a platelet?

Primary hemostasis consists of platelet plug formation, vascular spasm, and capillary endothelial adhesion, with capillaries collapsing and sticking closed when empty. This “fix” is temporary and lasts for only 12–24 hours. (This is why hemophiliacs often do not have a deep bleed until 12–24 hours after trauma, as their platelet function is intact.)

Platelet plug formation = platelet attachment → platelet activation → platelet aggregation.

After endothelial injury, platelets rapidly attach to the newly exposed subendothelial collagen. The von Willebrand factor (vWF), released from the endothelium, reacts with the platelet surface glycoprotein 1b/9 to increase stickiness of platelets to each other and to exposed collagen. Platelets are then activated, releasing cytokines, including adenosine diphosphate (ADP) and arachidonic acid, which further stimulate platelet release and aggregation. Arachidonic acid is converted by cyclooxygenase into precursors of thromboxane A₂. Thromboxane A₂ recruits

more platelets and exposes platelet surface glycoprotein 2b/3a (GP 2b/3a). Thromboxane A₂ is also a potent vasoconstrictor. Fibrinogen then cross-connects the 2b/3a protein on platelets to form platelet plugs.

Therapeutic implications: There are several FDA-approved GP 2b/3a receptor inhibitors available (e.g., abciximab, eptifibatide, tirofiban). Approved indications include unstable angina and adjunctive therapy during coronary angioplasty. Aspirin (ASA) irreversibly acetylates cyclooxygenase and thus decreases platelet function. Chronic ASA use of as little as 40 mg/day causes suppression of 95% of thromboxane A₂. Nonsteroidal antiinflammatory drugs (NSAIDs) bind reversibly with cyclooxygenase; they may block the desired effect of ASA if they are administered at the same time. Clopidogrel irreversibly inhibits ADP binding to the platelet receptor, resulting in decreased platelet aggregation. The average lifespan of a platelet is about 1 week, which is why aspirin and NSAIDs are held for 7 days before surgery.

SECONDARY HEMOSTASIS — THE COAGULATION CASCADE

Follow along in Figure 8-25 as we go through the coagulation cascade. The green lines and arrows are the pathways that result in coagulation (i.e., clot formation).

The **extrinsic pathway** is where it all starts. Virtually all coagulation is initiated by **tissue factor** (released at the site of injury) interacting with Factor 7. Tissue factor is short lived and in short supply—so the extrinsic pathway can produce only a small amount of **thrombin**.

The **intrinsic pathway** (a.k.a. contact activation pathway, intrinsic amplification pathway) consists of Factors 8, 9, 11, and 12. It serves mainly to amplify the formation of **thrombin**, but it can do so only after a small amount of thrombin is first formed by the extrinsic pathway.

Thrombin is the key. As you can see in Figure 8-25, while it builds the **fibrin** clot, this little bit of thrombin also activates the intrinsic pathway to amplify the production of more thrombin.

Thrombin does the following:

- Converts **fibrinogen** to **fibrin**
- Activates Factor 13, which causes this fibrin to cross-link and form the thrombus
- Activates Factor 11, which, in turn, activates Factor 9
- Activates Factor 8; Factors 8a and 9a together activate Factor 10.

So, the first 2 processes help make the thrombus, while the second 2 are part of a powerful intrinsic amplification system that makes more thrombin.

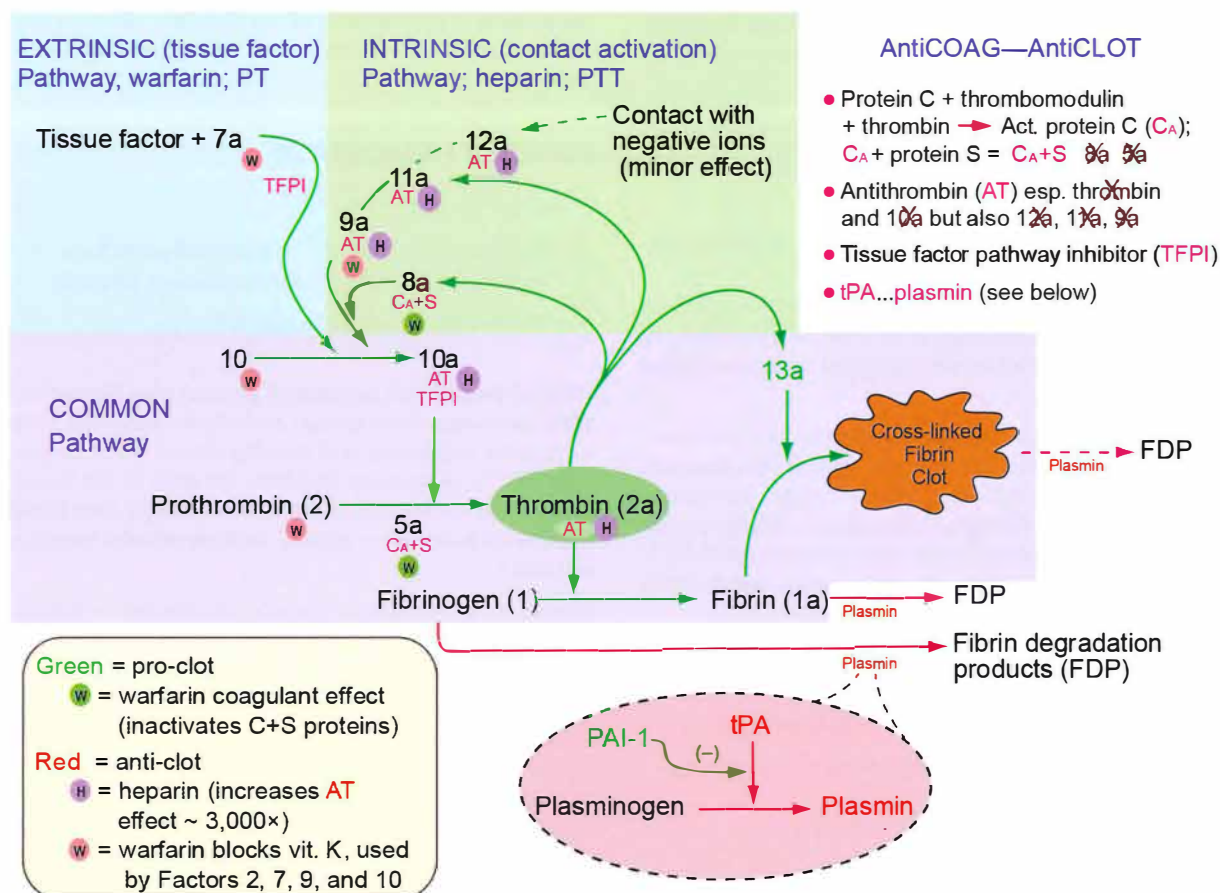


Figure 8-25: Coagulation cascade

Note that even though Factor 12 can be activated by negative ions on newly exposed tissue, this process and Factor 12 itself play a minor role in coagulation. Patients with Factor 12 deficiency have **no** bleeding problems.

Okay, so how does the body **stop** this process? Thrombus dissolution, or **fibrinolysis**, is initiated by tissue plasminogen activator (tPA) and released from the endothelial cells. tPA converts **plasminogen** to **plasmin**, which then breaks down fibrin and fibrinogen and limits the size of the thrombus. Proteins C and S are natural anticoagulants; they inactivate Factors 5a and 8a. Protein C also blocks the inhibitor of tPA, plasminogen activator inhibitor-1 (PAI-1). In healthy people, this results in fibrinolysis. In the absence of proteins C and S, thrombosis goes unchecked.

AN APPROACH TO THE PATIENT

PREVIEW | REVIEW

- At the bedside, how can you tell whether a hemostatic problem is primary or secondary?
- What are the 4 tests initially used to evaluate a bleeding disorder? What do they measure?

It is often possible to differentiate between a primary and a secondary hemostatic problem at the bedside:

- **Primary hemostatic problems** (90% involve either platelet dysfunction or low platelets) result in multiple, tiny, superficial hemorrhages, causing petechiae, purpura (large petechiae), ecchymoses, and **mucocutaneous bleeding** (e.g., gingival bleeding, menorrhagia, epistaxis).
- **Secondary hemostatic disorders** (e.g., hemophilia), on the other hand, develop **deep tissue bleeding**, including hematomas or hemarthroses.

Typically, 4 tests can quickly assess coagulation and platelet status:

- 1) Prothrombin time (PT) measures the function of extrinsic and common pathways.
- 2) Activated partial thromboplastin time (aPTT) measures the function of the intrinsic and common pathways.
- 3) Platelet count
- 4) Platelet function tests evaluate platelet aggregation when stimulated by epinephrine, ADP, and collagen.

DISORDERS OF PRIMARY HEMOSTASIS

PREVIEW | REVIEW

- What is the usual clinical presentation of immune thrombocytopenia (ITP) in an adult patient?
- What are the 1st and 2nd line treatments for ITP?
- Thrombotic thrombocytopenic purpura (TTP) is due to problems with which enzyme?

- Which 5 clinical manifestations occur with TTP? With atypical hemolytic uremic syndrome (aHUS)?
- What is the treatment of choice for TTP? For aHUS?
- Which bacterial infections are implicated with diarrhea-associated HUS?
- What do the letters in HELLP syndrome stand for? In which patients does it occur?
- Does heparin-induced thrombocytopenia Type II (HIT-II) cause bleeding or thrombosis?
- What is the treatment for HIT-II?
- When does posttransfusion purpura occur?
- What are Factor 8 activity levels in patients with von Willebrand disease (vWD)?
- What are the 2 most common types of vWD?
- What are the differences between Bernard-Soulier syndrome and Glanzmann thrombasthenia?

Disorders of primary hemostasis involve the vascular endothelium or platelets. This review focuses on platelet disorders of primary hemostasis, which include both quantitative and qualitative defects.

Thrombocytopenia has multiple etiologies, which can be categorized into defects of production, sequestration, and destruction.

Pseudothrombocytopenia (a.k.a. spurious thrombocytopenia) is due to platelet clumping after the blood draw, resulting in low platelets being detected by the automated counter. Such an artifact occurs fairly often, so the 1st test to do after observing a low platelet count result is a repeat platelet count. You can also get a peripheral blood smear to look for platelet clumping.

You can see **abnormal platelet function** after aspirin ingestion and in von Willebrand disease (vWD), Bernard-Soulier (giant platelet) syndrome, Glanzmann thrombasthenia, paraproteinemia (multiple myeloma), chronic kidney disease (CKD), and connective tissue disease.

Clotting factor deficiencies often present with deep bleeding, such as hemarthrosis and large hematomas, whereas disorders of platelet number or function typically involve mucocutaneous sites with petechiae or superficial bleeding.

Primary Hemostasis Disorders — Thrombocytopenias

Thrombocytopenia has 3 causes:

- 1) **Decreased production:** due to bone marrow failure from toxins (including alcohol), infiltration, aplasia, sepsis, and HIV infection. Often there is concomitant anemia and/or leukopenia.

- 2) **Sequestration:** pooling in an enlarged spleen (hypersplenism). Thrombocytopenia is typically modest and accompanied by a reduction in the other cell lines (leukopenia and anemia).
- 3) **Survival defects** (i.e., increased destruction):
 - Consumptive process, such as DIC, heparin-induced thrombocytopenia (HIT), TTP/HUS, and HELLP
 - Immune thrombocytopenia, either primary, secondary, or drug induced. Common drug offenders include quinidine, rifampin, sulfonamide combinations, and digoxin.

If the platelet count is $> 20,000/\mu\text{L}$ ($20 \times 10^9/\text{L}$), there is usually no serious spontaneous bleeding. When the count is $< 10,000/\mu\text{L}$ ($10 \times 10^9/\text{L}$), the risk of serious bleeding increases and platelet transfusions are often considered. Do not transfuse platelets if you suspect HIT or TTP unless the patient has active life-threatening bleeding.

Immune Thrombocytopenia (ITP)

ITP is an **autoimmune** syndrome that occurs in children and adults. In children, it often has an acute presentation, occurs after a viral illness, and is usually self-limited with a good prognosis. Chronic ITP generally occurs in adults and has a relapsing course. Both acute and chronic ITP are associated with IgG antibodies directed against the GP 2b/3a glycoproteins on platelets that lead to destruction of platelets. When associated with an underlying disease in which antiplatelet antibodies are formed, patients are said to have secondary ITP.

Underlying diseases that can be associated with secondary ITP include SLE, antiphospholipid syndrome, CLL, and viruses, including HIV and hepatitis C. Recall that many of these same diseases are also associated with autoimmune hemolytic anemias.

The adult patient with ITP typically presents with easy bruising, petechiae, and **nonpalpable** purpura (Figure 8-26; in contrast, IgA vasculitis is palpable.) Patients with ITP have **mucosal bleeding** (e.g., gingival bleeding, menorrhagia, epistaxis). When ITP occurs in an elderly patient, the patient can present with a GI or central nervous system bleed.

Platelets in patients with ITP are often hyperfunctional; and, even with severe thrombocytopenia, significant spontaneous bleeding is rare.

Primary ITP is a diagnosis of exclusion, so rule out other causes. Do **not** order an antiplatelet antibody test. The result is too nonspecific to be helpful!

Do the following:

- As with **all** cases of thrombocytopenia, repeat the platelet count.
- Examine the peripheral smear to make sure platelets are not clumping and that schistocytes

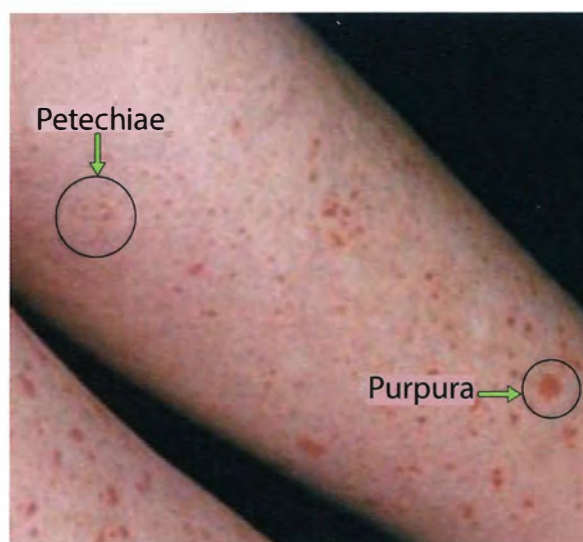


Figure 8-26: Petechiae and purpura

are absent. (Presence of schistocytes along with thrombocytopenia suggests TTP is the underlying diagnosis, not ITP.) Around 1/1,000 automated platelet counts are falsely low. Clumping is caused by platelet activation by ethylenediaminetetraacetic acid (EDTA). Collecting the sample in a citrate tube corrects this problem.

- The peripheral smear in ITP typically reveals few but **large** (young) **platelets** and normal RBCs and WBCs.
- Patients > 60 years of age may need a bone marrow biopsy to exclude myelodysplasia before being diagnosed with ITP. In ITP, marrow cellularity is normal with evidence of megakaryocyte hyperplasia.

Treat chronic ITP **only** if symptomatic or if the platelet count is very low ($< 30,000/\mu\text{L}$):

- Corticosteroids (prednisone 1 mg/kg or equivalent daily) are 1st line treatment.
- Give IV immunoglobulin (IVIG) as an adjunctive treatment when a rapid improvement in platelet count is desired, as in a preoperative or bleeding patient. IVIG satiates voracious macrophages, which then become less hungry for antibody-coated platelets, leading to an increase in platelet count. Response, however, is regularly transient—lasting only several weeks.
- Historically, many hematologists tried anti-D immunoglobulin if patients were Rh+ and had a functional spleen. This induces a mild hemolytic state, with resultant RBC stromal release and uptake by reticuloendothelial cells. The uptake of RBC stroma (as with IVIG) interferes with the ingestion of antibody-coated platelets and results in the elevation of platelet counts. Use of anti-D has now fallen out of favor with most hematologists due to an FDA black box warning of rare but potentially life-threatening acute hemolytic transfusion reactions.

- 2nd line therapy for ITP is indicated when you have:
 - No response to steroids
 - Frequent relapses
 - Inability to taper off steroids within 3-6 months
- 2nd line therapy options include splenectomy, thrombopoietin receptor agonists (TPO-RAs), or rituximab.
 - Splenectomy induces a complete response in 2/3 of patients, but there may be relapses. Remember: Give all patients vaccinations for *S. pneumoniae*, *H. influenzae*, and *N. meningitidis* at least 2 weeks prior to elective splenectomy, because splenectomized patients are at an increased risk of infections from these organisms.
 - Rituximab is an alternative to splenectomy and can achieve durable responses in steroid-refractory patients. Rituximab is a monoclonal antibody directed against CD20 present on B lymphocytes.
 - Romiplostim and eltrombopag are TPO-RAs approved by the FDA for refractory ITP. These may also be used to avoid splenectomy.
 - Fostatinib is a prodrug tyrosine kinase inhibitor approved by the FDA for refractory ITP after the TPO-RAs have failed.
 - Azathioprine, cyclosporine, and mycophenolate have also been used with some success.

Give platelet transfusions if there are signs of severe bleeding and prior to invasive procedures. While platelet counts may not rise, transfusions can be hemostatically effective. Even so, they are not effective for long-term management.

Thrombotic Microangiopathies

Thrombotic Thrombocytopenic Purpura (TTP)

Acquired TTP and atypical hemolytic uremic syndrome (aHUS) in adults were once considered variants on a spectrum of disease, although it is now understood they have different pathophysiologies. Both TTP and HUS are considered to be thrombotic microangiopathies. (See Table 8-4 on page 8-16.) In general, there are 2 types of TTP (inherited and acquired) and 2 types of HUS: atypical HUS and typical diarrhea-associated HUS (a.k.a. Shiga toxin-producing *E. coli* hemolytic uremic syndrome [STEC-HUS] and Shiga toxin-associated hemolytic uremic syndrome [ST-HUS]).

Inherited (congenital) TTP is extremely rare and is due to a defect in the *ADAMTS* gene that causes a deficiency in the ADAMTS13 enzyme.

Acquired (autoimmune) TTP affects adults and is due to an inhibitor that causes decreased activity of the ADAMTS13 enzyme. This enzyme is responsible for cleaving the ultra-large multimers of vWF. Such multimers otherwise build up, leading to platelet consumption and hemolysis.

TTP is a fulminant disorder of increased platelet consumption, with high mortality, that is marked by thrombocytopenia and microangiopathic hemolytic anemia. TTP generally affects younger adults, with a peak in the 3rd decade of life. Most commonly, TTP is idiopathic, but it is also associated with:

- Drug exposures (e.g., quinine, cancer chemotherapy, clopidogrel, ticlopidine)
- Post hematopoietic stem cell transplantation
- Pregnancy
- Oral contraceptives
- Disseminated occult mucin-producing adenocarcinomas
- HIV infection
- SLE
- Antiphospholipid syndrome (APS)

Clinical manifestations of TTP:

- 1) Hemolytic anemia (microangiopathic, with schistocytes on peripheral blood smear)
- 2) Thrombocytopenia
- 3) Neurologic changes (e.g., confusion, severe headache, seizure)
- 4) Fever
- 5) Chronic kidney disease (mild if it occurs; more common in HUS)

Patients infrequently present with all 5 findings. The dyad of thrombocytopenia and microangiopathic hemolytic anemia is sufficient to narrow the differential to TTP vs. aHUS (vs. HUS if patient is pregnant). TTP typically presents with neurologic involvement and minimal or no renal dysfunction.

Peripheral blood smear in TTP shows thrombocytopenia and anemia with schistocytes. Labs commonly indicate a Coombs-negative hemolysis with an elevated LDH and indirect bilirubin +/- increased creatinine. The reticulocyte count is elevated in the face of hemolytic anemia. TTP and DIC can have similar clinical presentation with microangiopathic hemolytic anemia and thrombocytopenia in an acutely ill patient.

Unlike in DIC, the PT, aPTT, fibrinogen, Factor 5, and Factor 8 are usually normal because the coagulation cascade is not activated in TTP.

Low functional ADAMTS13 enzyme levels can be used to support a TTP diagnosis, but results are generally not available in a timely manner.

Treat TTP with plasma exchange, using fresh frozen plasma (FFP) or cryosupernatant (plasma from which cryoprecipitate has been removed—because the cryoprecipitate contains vWF multimers that can contribute to increased clotting). Know that there are 2 situations where plasmapheresis has not been shown to have any effect:

- 1) In conjunction with cancer chemotherapy drugs
- 2) After hematopoietic stem cell transplantation

For acquired forms of TTP, glucocorticoids play a therapeutic role, and evidence for rituximab use is evolving.

LDH levels serve as a marker of hemolysis and platelet destruction; follow them to gauge the effect of therapy.

Unless life-threatening bleeding is present, do **not** give platelet transfusions because the extra platelets are simply consumed and cause more thrombosis. If the patient does not respond to plasmapheresis, then corticosteroids and/or rituximab are additional options.

Clinical question: When a previously healthy patient presents with petechiae, ecchymosis, normal mental status, thrombocytopenia, and anemia, what further evaluation is required?

Answer: Do a peripheral blood smear, PT, and LDH. If there are schistocytes, a normal PT, and elevated LDH, the patient likely has TTP. If there are no schistocytes, a normal PT, and normal LDH, the patient likely has ITP. This is a **very important** distinction, because TTP is a medical emergency even if the patient is feeling fine. The patient can have a precipitous stroke or deterioration in cognition or renal function. Check renal chemistries (BUN, creatinine) to evaluate for renal dysfunction, which is seen in TTP.

Atypical Hemolytic Uremic Syndrome (aHUS)

aHUS, a rare disorder, can be confused with TTP because aHUS has the same 5 manifestations and same labs as TTP except that **renal involvement** occurs in all cases and neurologic involvement either does not occur or is minimal.

aHUS has many causes, quite a few of which are related to disorders in complement regulation. ADAMTS13 enzyme levels are > 10% and generally stay within normal reference intervals.

Treatment is eculizumab, a monoclonal antibody that selectively inhibits the terminal complement cascade. Note that eculizumab predisposes the patient to fulminant meningococcal infections. For some types of aHUS, eculizumab is not effective and plasma exchange transfusion is done.

Diarrhea-Associated HUS

The most common form of the life-threatening HUS (same labs as TTP) is often precipitated by food- or waterborne infections with enterohemorrhagic Shiga toxin-producing *E. coli* O157:H7 or O104:H4 (STEC) or Shiga toxin-producing *Shigella sonnei* and is associated with a prodrome of bloody diarrhea. This presentation is termed diarrhea-associated or Shiga toxin-associated hemolytic uremic syndrome (**ST-HUS**) to differentiate the disease from aHUS. The Shiga toxin is absorbed into the circulation and binds to globotriaosylceramide receptors on the surface of vascular endothelial cells, with a predilection for the brain (e.g., seizures, cortical blindness) and kidney (e.g., renal failure). It directly activates the complement pathway, resulting in more inflammation.

Treatment is supportive, with IV hydration and possibly blood products. Eculizumab is sometimes tried in severe cases, as some individuals appear to respond rapidly, but in larger trials, no differences in outcomes were noted. There is no standard role for plasma exchange. Many patients require hemodialysis. Antibiotics are thought to worsen the HUS, so do not use. Those with neurologic sequelae have a higher morbidity. While the majority survive, some have permanent neurologic or renal impairment.

Also see [Hemolytic Anemia \(Survival Defect\)](#) on page 8-12.

HELLP Syndrome

HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets) occurs in 20% of patients with pre-eclampsia and in 10% of patients with eclampsia. The anemia is microangiopathic hemolytic, with schistocytes on the peripheral blood smear (as with TTP and aHUS). Hepatic rupture is an uncommon, but potentially devastating, complication. Treatment is delivery of the fetus, with no role for plasma exchange. Both HELLP syndrome and TTP/HUS can occur in the peripartum period, so it is important to consider each in the evaluation. TTP/HUS additionally has fever, renal involvement, and/or neurologic symptoms.

Heparin-Induced Thrombocytopenia (HIT)

HIT Type I is a clinically insignificant, nonimmune drop in platelets after starting heparin; platelets return to normal within 2 days.

HIT Type II occurs when an antibody is formed that recognizes heparin/platelet Factor 4 (heparin-PF4) complexes. The antibody activates platelets, causing clumping and thrombocytopenia within **5-10 days** of heparin initiation. Previous exposure to heparin and an anamnestic response may shorten the onset to < 12 hours. Venous and/or arterial **thrombosis**, not bleeding, is the major complication of HIT-II. Always suspect HIT-II in a patient presenting with clotting 1-2 weeks after a hospitalization, even if the platelet count is normal. (The highest risk of thrombosis occurs when the platelet count has returned to normal.)

Suspect HIT in any of the following scenarios involving patients with heparin exposure within the preceding 5-10 days:

- New-onset thrombocytopenia
- > 50% drop in platelet count within normal range
- Venous or arterial thrombosis
- Necrotic skin lesions at heparin injection sites
- Acute systemic reactions (i.e., fever, tachycardia, hypertension) occurring after heparin IV bolus administration

Making the diagnosis of HIT ([Figure 8-27](#)):

- Order heparin-PF4 antibody ELISA **first**. While awaiting the results of the ELISA test, use a clinical scoring system to assess the likelihood of HIT-II.

Two different clinical scoring systems, the 4 Ts and HIT Expert Probability (HEP) Score, are available. (See [The 4 Ts](#) and [HIT Expert Probability \(HEP\) Score](#).)

- **Stop all heparin products** if HIT is suspected.
- Depending on the ELISA optical density (OD), HIT antibody testing is limited to those with an intermediate- or high-probability 4 Ts score:
 - In patients with a low 4 Ts score: If the ELISA OD is < 0.40, HIT is excluded and no further testing is needed.
 - In patients with a high 4 Ts score: If the ELISA OD is > 2.00, HIT is confirmed and no further testing is needed.
 - In patients with an intermediate 4 Ts score: If the ELISA OD is 0.40–2.00, then a functional assay such as a serotonin release assay (SRA) or heparin-induced platelet aggregation (HIPA) assay is performed. (Note: Immunoassays that detect antibodies against platelet Factor 4 complexes are of limited value [i.e., are sensitive but not specific], whereas the SRA is specific and sensitive, though with a long turnaround time.)

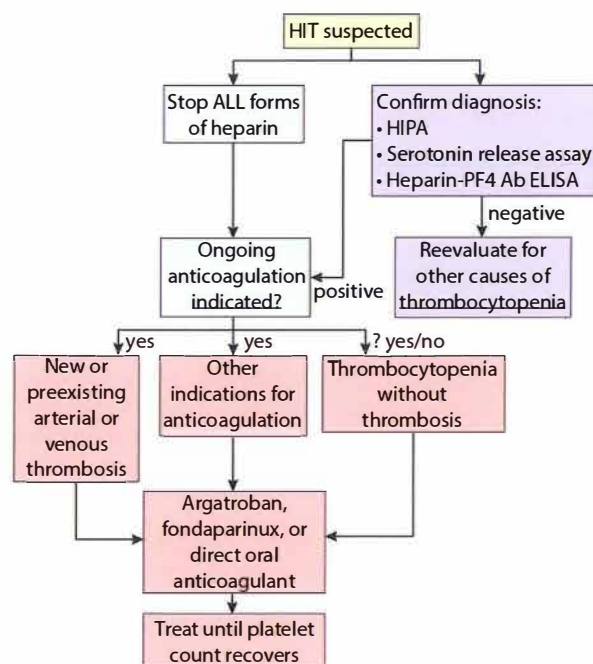


Figure 8-27: Approach to the patient with suspected heparin-induced thrombocytopenia

Continue nonheparin anticoagulants until the results of the functional assays are available.

The 4 Ts

To assess the likelihood of HIT-II, the 4 Ts scoring system evaluates the presence, timing, sequelae, and causes of the thrombocytopenia. See [Table 8-6 on page 8-26](#). Understand the key features; do not memorize the details!

HIT Expert Probability (HEP) Score

Another scoring system, based on the opinion of 26 HIT experts, yielded similar results to the 4 Ts.

The HEP Score is generated from the percentage of decrease in platelets, timing, nadir, thrombosis, skin necrosis, and acute systemic reaction to heparin, bleeding, and other causes.

Treatment of HIT-II

Stop all heparin exposure (including low molecular weight heparin [LMWH]), even though this does not fully resolve the problem. This is because once the antibodies to heparin-PF4 complex are formed, the antibodies continue to bind to PF4 alone and, thus, continue to activate platelets, causing clots. Do **not** substitute LMWH because of antibody cross-reactivity.

Treat this hypercoagulable state with nonheparin-like anticoagulants, such as IV direct thrombin inhibitors (e.g., argatroban, bivalirudin), fondaparinux, or a direct oral anticoagulant (DOAC; e.g., dabigatran, apixaban, edoxaban, rivaroxaban) at the time of diagnosis, even in the face of thrombocytopenia, whether or not a clot is present. Continue to administer the anticoagulant until the platelet count recovers. Remember that argatroban artificially elevates the INR (international normalized ratio); the goal INR during argatroban/warfarin overlap is > 4.

Do **not** start warfarin until the platelet count returns to normal. Since it transiently lowers levels of proteins C and S and can contribute to clot formation, do **not** start warfarin alone. Continue warfarin for at least 3 months. There is no role for platelet transfusions ([Figure 8-27](#)).

Once again: Remember that TTP and HIT are **thrombotic** thrombocytopenic disorders—so you **never** give these patients platelet transfusions for the thrombocytopenia unless there is life-threatening bleeding present.

Dilutional Thrombocytopenia

Dilutional thrombocytopenia occurs when massive transfusions of platelet-poor blood products are given, typically after major trauma. Treat with platelets.

Posttransfusion Purpura

Posttransfusion purpura is rare, occurring primarily in women sensitized by pregnancy. It occurs ~ 1 week after transfusion and can last days to weeks. The platelet count is extremely low, and the patient can present with petechiae or purpura. An anti-HPA-1a antibody (human platelet antigen-1a) is formed by alloimmunization from previous blood transfusions or pregnancies, and, inexplicably, it reacts against the patient's HPA-1a **negative** platelets, causing thrombocytopenia.

Table 8-6: 4 Ts Clinical Scoring for Probability of HIT-II

Variable	Score		
	2	1	0
Thrombocytopenia—is it present?	> 50% decrease in platelet count but remains $\geq 20,000/\mu\text{L}$	30–50% decrease in platelet count or nadir 10,000–19,000/ μL	< 30% decrease in platelet count or falls < 10,000/ μL
Timing of the thrombocytopenia	Days 5–10 of heparin exposure or $\leq$ Day 1 if anamnestic response + heparin exposure within past 30 days	> Day 10 of heparin exposure or Unclear heparin exposure (but probably days 5–10 of heparin exposure) or $\leq$ Day 1 if anamnestic response + heparin exposure within past 30–100 days	$\leq$ Day 4 without previous HIT-II
Thrombosis (or other sequelae)	New clot, necrotic skin lesion, or systemic reaction after heparin bolus	Recurrent clot or worsening of clot, skin lesion (necrotic), possible clot	None
Thrombocytopenia—other causes?	None	Possible	Definite
Probability of HIT-II*	6–8 = High	4–5 = Intermediate	0–3 = Low

HIT-II = heparin-induced thrombocytopenia Type II
Day 0 = the day heparin was started
Onset of HIT = the day platelet count begins to decrease
* Further evaluation is required for patients with an intermediate or high score or if scoring is difficult due to missing platelet count values or coexisting conditions causing thrombocytopenia.

Unlike patients with TTP, patients with posttransfusion purpura do not have evidence of microangiopathic hemolytic anemia on the peripheral smear (no schistocytes), and there is no CNS or renal failure.

Treat with IVIG. Steroids and plasma exchange have also been used, but the responses are slower than with IVIG. Platelet transfusions are not very effective because the transfused platelets are also destroyed by the underlying process.

Thrombocytopenia — Quinine and Other Medications

Quinine is an important cause of thrombocytopenia. It is available over the counter and used for nocturnal leg cramps. It was also once the “tonic” in gin and tonic, and in the 1970s this side effect was described as cock-tail purpura. Now, however, tonic water contains only a medically insignificant amount of quinine. Other drugs that can cause thrombocytopenia include sulfa combinations, rifampin, digoxin, and vancomycin.

Other Causes of Thrombocytopenia

If there is a dramatic drop in platelets from one day to the next (e.g., from 300,000/ μL to 5,000/ μL [$300 \times 10^9/\text{L}$ to $5 \times 10^9/\text{L}$]), suspect pseudothrombocytopenia. HIT platelet counts usually do not drop below 20,000. The EDTA anticoagulant in blood collection tubes can cause platelet clumping in some patients, resulting in a reading of low platelets and giant platelets by an automated counter.

Platelet Function Disorders

von Willebrand Disease (vWD)

The von Willebrand factor (vWF) binds platelets to exposed subendothelial collagen and to other platelets with the platelet receptors 1b/10 and 2b/3a, respectively. vWF is also the carrier protein for Factor 8, which is degraded in its absence.

vWF multimers in the bloodstream have little affinity for platelets. But this affinity increases dramatically when vWF attaches to an altered vascular surface, thereby causing an increased aggregation of platelets at that spot. vWF multimers in the bloodstream are various sizes, ranging from small to ultra-large. The larger the multimer, the more hemostatic potential.

vWD is the most common inherited bleeding disorder. Patients typically have mucocutaneous bleeding, including epistaxis, menorrhagia, postpartum and surgical bleeding, excessive bleeding after dental extractions, and excessive bruising.

The inheritance pattern of vWD is usually autosomal dominant (AD). Penetrance is variable, with some patients experiencing bleeding only after surgery or major trauma and others suffering from frequent spontaneous bleeds of the mucosal surfaces of the gastrointestinal and genitourinary tracts.

Individuals with Type O blood have lower baseline levels of vWF. Levels of vWF increase during pregnancy and with estrogen use.

The aPTT is often increased because of decreased levels of Factor 8. The bleeding time is prolonged.

Classification of vWD:

- **Type 1:** a **quantitative** defect with decrease in level and activity of vWF:Ag; most common type (~ 75%)
- **Type 2:** 4 subtypes (A, B, M, N)—all **qualitative** defects; disproportionate decrease in activity of vWF (ristocetin cofactor), compared with vWF:Ag
- **Type 3:** rare and severe; autosomal recessive (AR) inheritance. Minimal-to-undetectable levels of vWF lead to spontaneous bleeding. The presentation resembles that of classic hemophilia.

Diagnosis of Type 1 is confirmed with a combination of the following:

- Abnormal platelet function tests
- Decreased vWF antigen
- Proportional decrease in Factor 8 activity
- Proportional decrease in biologic activity as measured by the ristocetin cofactor (RCoF) assay

Note that the proportional decrease in vWF antigen and RCoF activity indicates that the decreased activity is due to a decrease in the **concentration** of vWF—not to dysfunctional vWF.

Patients with mild defects can have varying laboratory test results over time, often requiring repeated testing to confirm the diagnosis.

Treat most mild-to-moderate cases of vWD with desmopressin, which causes a release of vWF and Factor 8 from endothelial cells. Watch for hyponatremia when treating with desmopressin. Do not use desmopressin for the rare Type 2B variant, as it can worsen thrombocytopenia. For active bleeding, use Factor 8 concentrates, which typically have some vWF as well. Cryoprecipitate is almost never required.

Note: Desmopressin is a synthetic analog of antidiuretic hormone (i.e., ADH, vasopressin), which boosts plasma levels of Factor 8 and vWF. It does not have vasopressor activity, and it is **not** effective in severe vWD or severe Factor 8 deficiency. Recombinant vWF is increasingly being used, but more clinical experience is required.

Other Platelet Function Disorders

In **Bernard-Soulier syndrome**, patients have severely decreased platelet adhesion because they have no glycoprotein 1b-9-5 receptor (so platelets cannot bind vWF). The peripheral smear demonstrates giant platelets. These patients also have a modestly low platelet count due to accelerated platelet clearance. The inheritance pattern is AR.

Glanzmann thrombasthenia results from deficient glycoprotein 2b/3a complex (so fibrinogen does not cross-connect). Platelet count is normal. The inheritance pattern is AR.

ASA/NSAIDs: Platelet-release defects are often caused by ASA and NSAIDs, which block the synthesis of thromboxane A₂ by binding to cyclooxygenase. The effects of ASA

and clopidogrel last for the lifetime of the platelets, but those of non-ASA NSAIDs are transient.

Paraproteinemia, as in multiple myeloma (MM) or connective tissue disease, can cause platelet dysfunction. In these disorders, the paraprotein coats the platelets, inhibiting their function and interfering with fibrin formation.

Uremia causes platelet dysfunction with a reduction in platelet adhesion and aggregation from an increase in nitric oxide (NO) release from endothelial cells in uremic states. Treat with platelet transfusions (for active bleeding), conjugated estrogens (reduces NO), or desmopressin (improves platelet function). Conjugated estrogens have a longer effect than desmopressin in uremia and usually are reserved for chronic bleeding. Desmopressin is considered 1st line due to its rapid onset of action and its having the fewest side effects. If severe bleeding persists, then infuse cryoprecipitate.

DISORDERS OF SECONDARY HEMOSTASIS

PREVIEW | REVIEW

- Characterize the prothrombin time (PT) and activated partial thromboplastin time (aPTT) in patients with antiphospholipid syndrome.
- What are mixing studies, and when are they used?
- What is the usual cause when a mixing study shows the aPTT initially normalizing, but 2 hours later it is again prolonged?
- What determines the risk of bleeding in a patient with Factor 8 deficiency (hemophilia A)?
- When do you begin the treatment of a bleeding episode in a patient with Factor 8 deficiency?
- What is the clinical presentation of Factor 11 deficiency?
- How do patients present if they have Factor 12 deficiency?
- Which special diagnostic test is used to diagnose Factor 13 deficiency?
- How do the PT and aPTT differ in disseminated intravascular coagulation (DIC) vs. thrombotic thrombocytopenic purpura?
- Which disease states are associated with chronic DIC?
- How do broad-spectrum antibiotics cause vitamin K deficiency? How do certain cephalosporins cause vitamin K deficiency?
- With which deficiency are patients more likely to experience venous thrombosis during initial anticoagulation with warfarin?

People with coagulation factor disorders tend to experience discrete episodes of **deep tissue bleeding**, including

hemarthroses, muscle hematomas, and retroperitoneal hemorrhage. Refer to [Table 8-7](#), [Table 8-8](#), and [Table 8-9](#) as you review disorders of secondary hemostasis.

Prothrombin Time (PT) and Activated Partial Thromboplastin Time (aPTT) Variations

Review the following 3 variations of the PT and aPTT:

- 1) **PT is prolonged and the aPTT is normal:** There is a problem with the vitamin K-dependent Factors 2, 7, 9, or 10 or with fibrinogen. See [Figure 8-25 on page 8-20](#). The most common cause is the use of **warfarin** (a vitamin K inhibitor). See [Table 8-8](#). Vitamin K deficiency in the malnourished or postoperative patient also occurs. (See [Vitamin K Deficiency on page 8-31](#) and [Figure 8-25 on page 8-20](#).)
- 2) **PT is normal and aPTT is prolonged:** There is a problem with Factors 8, 9, 11, or 12. The most common cause is **heparin** in the blood sent to the laboratory. (See [Figure 8-25 on page 8-20](#) and [Table 8-8](#).) In the bleeding patient, think inhibitor to Factor 8 (see

below) or vWD. In the thrombotic patient, think **antiphospholipid syndrome** (discussed in the [Rheumatology](#) section).

- 3) **PT and aPTT are both high:** There is a defect in the common pathway or else a multiple factor deficiency involving both pathways (e.g., DIC). See [Table 8-9](#).

Regarding variation #2: If there is a greatly prolonged aPTT with a normal PT and normal platelet count, 1st check a heparin neutralization study. If there is no correction, then do a mixing study.

Mixing studies are done on plasma to differentiate factor deficiency from factor inhibitor. In a mixing study, the patient's plasma is mixed 50:50 with normal plasma. If the patient's prolonged aPTT is due to factor deficiency, the mixing with normal plasma provides the missing factor and corrects the problem (and the PTT). If the aPTT is still prolonged after the 1:1 mix with normal plasma, the problem is likely to be an inhibitor, usually a lupus anticoagulant (antiphospholipid syndrome) or Factor 8 inhibitor.

Table 8-7: Bleeding Disorder Evaluation — PT, aPTT, Bleeding Time, and Platelet Aggregation

Lab Results	Etiology
Elevated PT and aPTT	Factor deficiency from common pathway Multiple factor deficiency Warfarin affects Factors 2, 7, 9, and 10, so it can affect both PT and aPTT, but PT is more sensitive to warfarin. Liver disease DIC Combined heparin and warfarin administration Direct thrombin inhibitor (e.g., argatroban, dabigatran) Direct Factor 10a inhibitor (e.g., rivaroxaban, apixaban, edoxaban) Amyloidosis-associated Factor 10 deficiency
Elevated PT, nl aPTT	Factor 7 deficiency Vitamin K deficiency Warfarin Liver disease
Elevated aPTT, nl PT: immediate and sustained (2 hours) correction of aPTT by addition of normal plasma	Factor 8, 9, 11, or 12 deficiencies vWD
Elevated aPTT, nl PT: aPTT not corrected (or no sustained correction at 2 hours) by addition of normal plasma	Inhibitor syndrome (circulating anticoagulant): • If clotting: ◦ Antiphospholipid syndrome (esp. lupus anticoagulant) ◦ aPTT not normalized immediately • If bleeding: ◦ Factor 8 inhibitor ◦ aPTT initially normalized but not normalized at 2 hours
Elevated aPTT, nl PT—but no clinical bleeding disorder	Factor 12, prekallikrein, or HMW kininogen deficiency
Nl PT and aPTT, except elevated bleeding time: • Elevated bleeding time with nl platelet aggregation • Elevated bleeding time with nl platelet aggregation and decreased platelet count • Elevated bleeding time with abnormal platelet aggregation	Platelet problem vWD (has decreased platelet adhesion but normal aggregation) Bernard-Soulier (giant platelet) syndrome (absent GP1b) has similar presentation as vWD except lab also shows decreased platelet count. Glanzmann thrombasthenia (absent GP 2b/3a)
aPTT = activated partial thromboplastin time DIC = disseminated intravascular coagulation HMW = high molecular weight nl = normal PT = prothrombin time vWD = von Willebrand disease	

Some factor inhibitors take time to react with the factor. Factor 8 inhibitors are especially likely to be time dependent. For example, with acquired idiopathic or postpartum Factor 8 inhibitor antibodies, the aPTT may initially correct to normal with the mixing study, but after incubation with the normal serum for 2 hours, the inhibiting antibody begins to bind to the added Factor 8, and the aPTT is once again prolonged.

The **thrombin time** measures the time of conversion of fibrinogen to fibrin. A prolonged thrombin time reflects decreased or defective fibrinogen, elevated fibrin degradation products, or heparin or heparin-like anticoagulants.

Hereditary Coagulation Deficiencies

Factor 8 and 9 Deficiencies

Hemophilia is due to a Factor 8 (hemophilia A) or 9 (hemophilia B) deficiency; these are inherited deficiencies typically diagnosed in childhood. In the intrinsic pathway, activated Factor 8 accelerates by 1,000-fold the cleavage of Factor 10 by activated Factor 9. With both Factor 8 and 9 deficiencies, the aPTT is increased and the PT is normal.

Clinical presentation is similar in both Factor 8 and 9 deficiencies, with easy bruising, muscle and joint hemorrhages, and prolonged hemorrhage after surgery or trauma **but** no excessive bleeding after minor cuts.

Table 8-8: Effects of Anticoagulants on Coagulation Tests

Anticoagulant	Platelet Count	PT	aPTT	TT	Anti-Factor 10a Activity
Direct Factor 10a inhibitor	Normal	Variable to increased	N/A	N/A	Increased
Direct thrombin inhibitor	Normal	N/A	Variable to increased	Increased	N/A
Warfarin	Normal	Increased	Normal	N/A	N/A
Heparins	Normal (in absence of HIT)	Normal	Increased	Increased	Increased

aPTT = activated partial thromboplastin time
PT = prothrombin time
TT = thrombin time

Table 8-9: Test Results for Selected Bleeding Disorders

Bleeding Disorder	Platelet Count	PT	aPTT	TT	Fibrinogen
Disseminated intravascular coagulation	Low	Prolonged	Prolonged	Prolonged	Low
Factor 13	Normal	Normal	Normal	N/A	N/A
Hemophilia A (Factor 8 deficiency), Factor 9	Normal	Normal	Prolonged	Normal	Normal
Qualitative platelet abnormalities	Normal or low	Normal	Normal	Normal	Normal
Thrombocytopenia*	Low	Normal	Normal	Normal	Normal
Vasculopathies, connective tissue diseases, or collagen disorders affecting skin	Normal	Normal	Normal	Normal	Normal or increased [†]
vWD	Normal [‡]	Normal	Normal or Prolonged (if Factor 8 > 40%) [§]	Normal	Normal

* The platelet count in myeloproliferative disorders is usually high (e.g., essential thrombocythemia), and platelets may also be qualitatively abnormal, predisposing to hemorrhagic and thrombotic diatheses.

[†] Fibrinogen may be elevated as an acute-phase reactant in disorders of inflammation.

[‡] The platelet count may be low in some patients with Type 2B vWD.

[§] The aPTT may be normal in those with Factor 8 activity > 40%.

aPTT = activated partial thromboplastin time

PT = prothrombin time

TT = thrombin time

vWD = von Willebrand disease

Both Factor 8 and Factor 9 deficiencies are **X-linked recessive**. (Daughters, with only 1 chromosome affected, are carriers and exhibit no symptoms.)

In **Factor 8 deficiency**, the risk of bleeding correlates with Factor 8 serum levels. Patients with levels < 1% of normal have severe disease (bleeding even without trauma); patients with levels > 5% have mild disease.

Use desmopressin for mild Factor 8 deficiency. It works by causing a release of vWF and Factor 8 stores from endothelial cells. It is used as treatment for an acute hemorrhage and prophylactically for a tooth extraction in patients with Factor 8 levels > 5%.

For more severe Factor 8 deficiency, use Factor 8 (human concentrate or recombinant) to treat acute bleeds. Previously, human Factor 8 concentrate carried a risk of transmission of hepatitis viruses and HIV. Since 1985, all plasma used to produce Factor 8 concentrate is screened for HIV and hepatitis C virus, and steps that specifically inactivate these viruses are included in the production process.

Symptoms of a bleed often precede objective evidence by several days, and patients frequently inform their physician when a bleed is beginning. Early treatment delays or prevents hemophilia arthropathy, is cost effective, and can be lifesaving. Some centers advocate 2–3× weekly prophylactic Factor 8 infusions to keep levels above 1% and thus reduce bleeding risk. Prophylactic factor administration reduces the incidence of arthropathy in adult hemophiliacs, but the product is expensive and can cause an increased rate of development of Factor 8 inhibitors. Avoid use of ASA in patients with hemophilia.

Factor 9 deficiency (hemophilia B) is clinically indistinguishable from hemophilia A. Hemophilia B is only 1/10 as common as hemophilia A. Multiple recombinant Factor 9 concentrates are available for prophylaxis and treatment of bleeding. Gene therapy with a high-specific-activity Factor 9 variant is under development, with promising results thus far.

Manage acute bleeding episodes with either recombinant or highly purified human Factor 9 concentrate.

Factor 11 Deficiency

Factor 11 deficiency is an AR disorder that is less prevalent than hemophilia A or B. The risk of bleeding depends more on the gene mutation leading to the disorder than on the actual serum level of Factor 11. The disorder is more common in certain ethnic groups, with an especially high prevalence in Ashkenazi Jews.

Patients with Factor 11 deficiency tend to bleed at mucosal sites (epistaxis and menorrhagia), where fibrinolytic activity is high. Surgeries at sites with less fibrinolytic activity (e.g., orthopedic surgery, appendectomy) tend to have fewer bleeding complications. Antifibrinolytic agents alone can be used as prophylaxis for dental surgery.

Acute bleeds can be managed with FFP, recombinant Factor 11, or desmopressin.

Factor 12 Deficiency

Patients with a decreased Factor 12 (Hageman factor; AR inheritance) have a normal PT and a very prolonged aPTT (as with Factor 8, 9, and 11 deficiencies), but they do not have a clinical bleeding disorder and can even undergo surgery without worry of bleeding.

Factor 13 Deficiency

Factor 13 deficiency is an AR disorder. Severe bleeding results from the inability to cross-link fibrin strands. Coagulation tests, including PT, aPTT, and platelet function studies, are **normal**. Think about this in patients who have late postsurgical bleeding and poor wound healing.

Diagnose Factor 13 deficiency by performing a specialized **clot lysis assay**, in which dissolution of a clot is attempted, using urea. If the clot is solubilized with urea, then a Factor 13 deficiency exists. Treat with small amounts of FFP or specialized plasma derivative every 3–4 weeks.

Review of Basic Principles of Bleeding Disorders

As mentioned, while people with **platelet** dysfunction tend to experience **mucosal** bleeding (e.g., bruising, nosebleeds, menorrhagia), people with **coagulation factor** disorders tend to experience discrete episodes of **deep tissue** bleeding (e.g., hemarthroses, muscle hematomas, retroperitoneal hemorrhage). So, since platelets are required for thrombus formation, just as coagulation factors are required, why does a platelet deficiency cause only mucosal bleeding? The answer is that early thrombus formation only requires a few platelets to do the job.

What bleeding disorders can appear with a **normal** platelet count, PT, aPTT, and bleeding time? The major disorders to consider are:

- Mild vWD
- Mild hemophilia
- Factor 13 deficiency

Acquired Coagulation Deficiencies

Disseminated Intravascular Coagulation (DIC)

DIC is one of the most common acquired coagulopathies. It is always a **secondary** condition, so the underlying disease must be treated for the DIC to resolve.

DIC occurs in diseases that promote tissue factor release, including the following:

- Massive trauma
- Production of tumor necrosis factor, especially seen in solid tumors
- Sepsis, especially with endotoxin release
- Retained placental tissue in obstetric patients with placenta abruption, dead fetus, or amniotic fluid embolus
- Acute promyelocytic leukemia (APML)

Acute (Decompensated) DIC

Large amounts of released tissue factor activate Factor 7 and initiate the coagulation cascade. Excessive thrombin and plasmin are produced, resulting in both increased clot formation (via thrombin cleaving fibrinogen to fibrin) and clot breakdown (via plasmin degradation of fibrin clots). The plasmin breaks down fibrinogen and fibrin into fibrinogen/fibrin degradation products (FDPs, a.k.a. fibrin split products).

The massive depletion of coagulation factors and platelets and the increased FDPs (including D-dimer) can result in bleeding. Symptoms of DIC result from bleeding or microvascular thrombosis, as well as the underlying disorder. Patients with acute DIC become acutely ill with bleeding from IV sites/wounds and often multisystem organ dysfunction and shock.

Diagnosis of DIC:

- PT and aPTT prolonged (remember, normal in TTP, ITP, and HUS)
- Thrombocytopenia (from consumption)
- Fibrinogen level is decreased and trends downward during the disease process.
- Thrombin time is increased (due to both decreased fibrinogen and increased FDPs).
- Schistocytes (RBC fragments) are found in the peripheral smear in up to 50% of patients; they indicate microangiopathic hemolytic anemia. (The fibrin strands span the small blood vessels and shear the RBCs.)
- FDP/D-dimer increased. These are nearly always elevated in DIC but also occur in many other conditions. FDP and D-dimer are therefore a sensitive but not specific test.

Chronic (Compensated) DIC

Patients with chronic DIC can have either bleeding or thrombotic disorders. The thrombotic disorders range from migratory chronic thrombophlebitis (a.k.a. Trousseau syndrome) to pulmonary emboli.

Chronic DIC virtually always occurs in association with solid tumors.

With chronic DIC, a slower consumption of coagulation factors is compensated by increased synthesis of these same coagulation factors. Because of this, the lab results differ from acute DIC, and all may be normal except FDP/D-dimer (elevated).

In the setting of an underlying malignancy, diagnosis of chronic DIC can be made with the finding of microangiopathic hemolytic anemia on peripheral smear and increased FDP/D-dimer.

Treatment of DIC

Again, treat the underlying disorder, or the DIC does not stop. With severe bleeding, give fresh frozen plasma

(FFP) and platelets. Heparin is **not** usually effective except in specific, infrequent clinical situations (e.g., chronic DIC due to malignancy).

You can give cryoprecipitate if the fibrinogen level is < 100 mg/dL, and you can use FFP to replace other coagulation factors if PT and aPTT remain prolonged. Platelets are given only if platelet count is < 10,000–20,000/μL, there is an acute bleed, or to prepare a patient for surgery.

Vitamin K Deficiency

Vitamin K deficiency causes decreased production of the vitamin K-dependent factors (2, 7, 9, 10) and proteins C and S. Lab shows a prolonged PT.

Causes of vitamin K deficiency include decreased dietary intake, malabsorption, antibiotic use, and decreased storage resulting from liver disease.

Vitamin K deficiency results from:

- Decreased intake—patient is on total parenteral nutrition.
- Decreased production—broad-spectrum antibiotics can cause vitamin K deficiency by reducing the number of organisms in the intestine that synthesize vitamin K.
- Decreased storage—liver disease
- Decreased effectiveness—cefotetan or cefoperazone have *N*-methylthiotetrazole (NMTT) or similar side chains that block vitamin K epoxide reductase.

With vitamin K deficiency, the PT is prolonged and the aPTT is often normal. To further differentiate from DIC, check thrombin time and D-dimer, which are normal in patients with vitamin K deficiency.

Patients who are not bleeding can often be managed with vitamin K supplementation. If the patient has a normal GI tract, oral forms are more predictably absorbed than subcutaneous injections. IV vitamin K carries a very small risk for anaphylaxis. Do not administer IM vitamin K due to risk of hematoma formation. Vitamin K can take approximately 8 hours to work, so use FFP for immediate treatment if there is life-threatening hemorrhage.

Warfarin is a vitamin K antagonist, causing an effective vitamin K deficiency. Initiation of warfarin therapy carries a theoretical increased risk of thrombosis as the levels of proteins C and S (the proteins with the shortest half-lives) drop. This initial thrombotic effect can, for a short time, outweigh the antithrombotic effect on Factor 7; this is more likely with large loading doses of warfarin or if the patient is already protein C deficient. In patients with preexisting protein C deficiency, initial overlapping therapy with a parenteral anticoagulant (i.e., heparin) can prevent this transient hypercoagulable state. 1/3 of patients who develop warfarin-related skin necrosis have a protein C deficiency.

Encourage patients to report any new medications or dietary changes since these may inhibit or potentiate warfarin's effect.

Primary Fibrinolysis

Primary fibrinolysis is a rare disorder often associated with prostate cancer and/or surgery. This disorder occurs when plasmin is released into the circulation in response to endothelial agents like tissue plasminogen activator (tPA). The pathophysiology differs from that of secondary fibrinolytic states, such as DIC, which occur in response to thrombi formation in the microvasculature.

As in DIC, both primary and secondary fibrinolysis cause abnormalities of the PT, aPTT, fibrinogen level, FDPs, and D-dimer. Unlike in DIC, patients with primary fibrinolysis often have a normal platelet count.

Factor 8 Inhibitor

Factor 8 inhibitors are associated with:

- Hemophilia
- Malignancies (especially CLL, adenocarcinomas)
- Infections
- Pregnancy or the postpartum state
- Autoimmune disorders (e.g., SLE, rheumatoid arthritis)
- Aging
- Drugs

However, many cases are idiopathic. Most patients who develop a Factor 8 inhibitor have never had a blood transfusion. Patients with an inhibitor can present with severe bleeding, similar to hemophilia. In contrast to the lupus anticoagulant, mixing normal plasma and the patient's plasma may initially correct the aPTT, but after a 2-hour incubation, the inhibitor antibody inactivates Factor 8 and the aPTT again becomes prolonged. Therefore, a mixing study that does **not** maintain a **sustained** normalization of the aPTT suggests a Factor 8 inhibitor rather than factor deficiency.

THROMBOTIC DISORDERS

PREVIEW | REVIEW

- What are the most common genetic mutations that cause venous thrombosis?
- What battery of tests is done on patients with possible thrombophilia?
- What are the classes of oral anticoagulant drug therapies available for treatment of deep venous thrombosis (DVT)?
- What are established indications for an inferior vena cava filter in a patient with a DVT?

The **Virchow triad** (Figure 8-28) describes 3 factors that predispose patients to thrombosis:

- 1) Vascular damage
- 2) Stasis
- 3) Hypercoagulable state

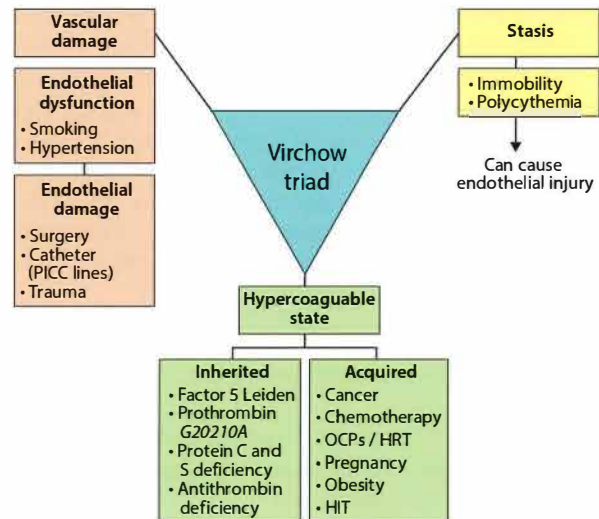


Figure 8-28: Virchow triad

Vascular damage can be caused by smoking and hypertension, as well as trauma from surgery or catheters, such as peripherally inserted central catheter (PICC) lines.

Stasis factors include immobility and polycythemia, which can also cause vascular damage.

Hypercoagulable states include both acquired and hereditary disorders. Note that patients may develop a thromboembolic event only after they have multiple prothrombotic conditions. For example, a woman with a moderately hypercoagulable state due to a Factor 5 Leiden mutation may not have her 1st deep vein thrombosis until she is pregnant or is immobilized after knee surgery.

Acquired Thrombotic Disorders

Acquired thrombotic disorders include:

- Malignancy
- Pregnancy (especially immediate postpartum period)
- Smoking
- Estrogen use (e.g., oral contraceptive pills [OCPs], hormone replacement therapy [HRT])
- Immobilization
- Major surgery
- Heparin-induced thrombocytopenia (HIT)
- Myeloproliferative disorders (especially polycythemia vera and essential thrombocythosis)
- Paroxysmal nocturnal hemoglobinuria (PNH)
- Multiple myeloma
- Antiphospholipid syndrome (APS)

Note: **Antiphospholipid syndrome** is a term used to describe the clinical relationship between a hypercoagulable state

and the presence of antiphospholipid antibodies. It is a systemic autoimmune disorder that can be primary or in the setting of autoimmune disorder, most commonly SLE. It is characterized by venous, arterial, or small vessel thrombosis. Often pregnancy complications, including repeated fetal loss, lead to its diagnosis. APS is discussed further in the [Rheumatology](#) section.

Inherited Thrombotic Disorders

The most common inherited causes of venous thromboembolism are the Factor 5 Leiden gene mutation and the prothrombin gene mutation (*G20210A*). These mutations typically cause thrombosis before 50 years of age and present more often when other acquired risks for clotting are superimposed (e.g., pregnancy, oral contraceptives, immobility).

Although Factor 5 Leiden and prothrombin gene mutations are more common, patients with protein C, protein S, or antithrombin deficiencies are **more likely** to thrombose and to have **recurrent** thromboses. In patients > 50 years of age, think about the acquired causes of thromboembolism.

Thrombophilia refers to an increased tendency to form thromboses.

Factor 5 Leiden Mutation

The Factor 5 Leiden (F5L) mutation is a very common AD disorder that expresses a modified Factor 5 with a resistance to the normally inhibitory (i.e., anticoagulant) effects of activated protein C (APC). 95% of APC resistance is the result of F5L mutation. Because APC can no longer cleave Factor 5 or Factor 5a effectively, there is both a decreased anticoagulant effect of Factor 5 and an increased coagulant effect of Factor 5a. 5% of Caucasians are heterozygous for the F5L mutation and have an ~ 20% lifetime risk of developing a venous thromboembolic problem. Homozygosity increases this risk to ~ 60%. The F5L mutation causes a mild increase in PT and aPTT.

Prothrombin Gene Mutation

Prothrombin gene mutation is a gain-of-function mutation that results in increased levels of prothrombin (Factor 2 in the coagulation cascade). Heterozygous carriers of the *G20210A* mutation have 2–3× increased risk of venous, and possibly arterial, thrombosis.

Antithrombin Deficiencies

Antithrombin (AT; formerly known as antithrombin III) inactivates thrombin both with and without the presence of heparin. In the presence of heparin, the antithrombin effects are accelerated roughly 4,000-fold. Antithrombin deficiencies include both quantitative (Type 1) and qualitative (Type 2) defects. Typically, 1st thrombotic events occur at a young age, and AT deficiencies are associated with a risk of venous thromboembolism of ~ 1% per year. Approximately 65% of patients heterozygous for AT have a thrombotic event by 50 years of age. Homozygous AT deficiency is fatal in utero.

Type 1 is diagnosed by immunoassay and Type 2 by functional studies (i.e., AT-heparin cofactor assay).

Protein C and S Deficiencies

Protein C and S deficiencies result in loss of the normal cleaving of Factors 5a and 8a. The deficiencies are normally AD inherited and increase the risk of developing venous thromboembolism. Both protein C and S are vitamin K-dependent proteins. Patients with protein C deficiency are at increased risk of developing skin necrosis while on warfarin. This is because protein C, with a very short half-life (6 hours) compared with the other vitamin K-dependent clotting factors, is rapidly depleted with warfarin initiation, resulting in a transient hypercoagulable state, which can lead to vascular occlusion and tissue infarction.

Testing for Thrombophilia

Who to Test?

Consider testing for thrombophilia when a patient has at least 1 of the following:

- 1st clot prior to 50 years of age
- Recurrent thrombosis
- 1st degree family members with clots prior to 50 years of age
- Thrombosis in multiple venous sites or unusual vascular beds (i.e., portal, mesenteric, hepatic, cerebral veins)

What to Test For?

Screen these patients for all of the following:

- F5L mutation
- Prothrombin *G20210A* mutation
- AT deficiency
- Protein C and S deficiencies
- APS
- JAK2 and PNH (if hepatic or portal vein thrombosis)

Again, the less common deficiencies (AT and proteins C and S) and APS are more severe, and these patients have recurrent clots more often than those with APC resistance and prothrombin *G20210A* mutations.

If the 1st clot occurs after 50 years of age, with negative family history, then an inherited thrombophilia is less likely. An acquired hypercoagulable state is most likely due to a malignancy. In most patients, a primary malignancy is already diagnosed at the time of clot. Screen for the following:

- APS, especially if the patient has any signs or symptoms of SLE
- Malignancy (e.g., solid tumors, lymphomas, myeloproliferative disorders)
- Use of certain drugs (especially hydralazine, procainamide, hydrochlorothiazide, propranolol, phenytoin, or phenothiazines)

When to Test?

Test for thrombophilia preferably at least 2 weeks after discontinuation of anticoagulation, when feasible.

Remember that acute thrombosis can transiently lower levels of antithrombin, protein C, and protein S. Heparin can cause decreased antithrombin levels. Warfarin can decrease functional (and to a lesser extent, quantitative) levels of proteins C and S and can (albeit rarely) raise antithrombin levels. In addition, warfarin yields a false-positive test for lupus anticoagulant. Direct oral anticoagulants (DOACs) may overestimate antithrombin levels. So, wait to test for C, S, and AT deficiencies until 2 weeks after completion of the initial 3–6 months of warfarin or at least 2 days (preferably longer) after stopping DOAC or LMWH.

Management of Thrombosis

An extensive discussion of deep venous thromboses and pulmonary emboli (DVT/PE) is included in the [Pulmonary Medicine](#) section.

Treatment of isolated calf vein thrombosis is guided by whether or not the patient is symptomatic. Options include anticoagulation or observation only, with serial ultrasounds over the first 2 weeks to determine whether the clot is extending proximally.

Acceptable drugs for initial treatment of an established DVT include low molecular weight heparin (LMWH), unfractionated (UF) heparin, fondaparinux, and oral Factor 10a inhibitors.

The oral Factor 10a inhibitors [rivaroxaban](#), [apixaban](#), and [edoxaban](#) are approved to treat symptomatic venous thromboembolism. Caution is advised with renal failure. The oral direct thrombin inhibitor [dabigatran](#), is approved for prevention and treatment of venous thromboembolism, as well as for stroke prevention in patients with atrial fibrillation.

UF heparin is more expensive due to the need for monitoring aPTT, but the infusion is easily titrated to meet the needs of an unstable patient. Thus, UF heparin is usually recommended in unstable patients.

LMWH is the preferred parenteral agent, except in unstable patients and in those with low creatinine clearance. LMWH and [fondaparinux](#) are **not** recommended in patients with low creatinine clearance (GFR < 30 mL/minute/1.73 m²).

Be sure to monitor the platelet count in any patient taking a heparin product because of the possibility of HIT-II.

Warfarin can be started simultaneously with the heparin product or fondaparinux. Continue both drugs for at least 5 days with subsequent discontinuation of heparin/fondaparinux after the INR is therapeutic for at least 48 hours. For venous thrombosis, target INR is 2.0–3.0.

Thrombolytic therapy is reserved for patients who are unstable due to a PE (i.e., hemodynamic compromise and/or right heart strain) or a massive iliofemoral thrombus.

Duration of anticoagulation is somewhat controversial for certain patient groups, but general guidelines include the following for DVTs:

- A **provoked** thrombosis with transient risk factor (e.g., OCP use, surgery, immobilization, HIT-II)—anticoagulate for at least 3 months.
- An **unprovoked** thrombosis—anticoagulate for at least 3 months. The 2016 American College of Chest Physicians (ACCP) guidelines recommend indefinite anticoagulation be considered and benefits weighed against the risks.
- **Recurrent** thromboses, 1 unprovoked life-threatening thrombosis, 1 spontaneous thrombosis with APS—indefinite anticoagulation.
- Thrombosis in pregnancy: LMWH is more effective for preventing future thrombosis and for treatment of an acute thrombosis. Remember that warfarin is contraindicated in pregnancy (especially 1st term and during labor) because it is teratogenic and because it causes fetal bleeding. Unfractionated heparin is an alternative, but it is considered less favorable than LMWH because of the need to use an increased dose during pregnancy and to monitor aPTT, in addition to the long-term risk of bone demineralization.

Consider an inferior vena cava (IVC) filter for DVT in these situations:

- When anticoagulation is contraindicated
- When there is a failure of anticoagulation
- In the presence of severe cardiopulmonary comorbidities, making a new PE life-threatening
- Preoperative prophylaxis in high-risk cases, where pharmacologic prophylaxis is contraindicated (e.g., major trauma, high-risk spine surgery)

Prior to surgery, consult the latest recommendations by the ACCP for discontinuation and resumption of anticoagulation therapy.

Additional uses of warfarin and heparin are described in detail in the following sections:

- Treatment of pulmonary embolism—the [Pulmonary Medicine](#) section
- Treatment of patients with valvular heart disease—the [Cardiology](#) section
- Pharmacologic interactions and as a factor in surgical procedures—the [General Internal Medicine](#) section

Direct oral anticoagulants (DOACs) have changed the landscape of anticoagulation and are being increasingly used in the prevention and management of thrombotic disorders. See [Table 8-10](#). These agents directly target the enzymatic activity of either thrombin (thrombin inhibitors) or Factor 10a (10a inhibitors). DOACs are

accepted as an equivalent, and in some cases preferred, alternative to warfarin in multiple indications, including prevention and treatment of venous thrombosis and in stroke prevention during atrial fibrillation.

Table 8-10: Direct Oral Anticoagulants (DOACs)

	Factor 10a Inhibitors	Thrombin Inhibitors
Drug Names	Rivaroxaban Apixaban Edoxaban	Dabigatran
Mechanism of Action	Direct Factor 10a inhibitor	Direct Factor 2a (thrombin) inhibitor
Relevant Indications	VTE treatment and prophylaxis Atrial fibrillation treatment	VTE treatment and prophylaxis Atrial fibrillation treatment
Reversal Agents	Andexanet alfa	Idarucizumab

DOACs offer several key advantages over warfarin. Use of DOACs does not require regular drug level monitoring or dietary restrictions, presents lower bleeding risk, and has significantly fewer drug interactions. Most patients achieve greater time in therapeutic range on DOACs vs. warfarin.

However, lack of a specific antidote for certain DOACs remains a concern in the event of major bleeding or emergent surgical procedures. Idarucizumab is an available, FDA-approved humanized anti-dabigatran monoclonal antibody fragment that can be used for emergency reversal of the thrombin inhibitor dabigatran. Andexanet alfa is an inactive form of Factor 10a and an emergency reversal agent for Factor 10a inhibitors. Due to the (small) risk of thrombosis with these reversal agents, they should be reserved only for serious, life-threatening bleeding.

DOACs are not preferred in selected patient subgroups where safety and efficacy have not yet been established, including children; the obese; individuals with cancer, pregnancy, or renal dysfunction; and those who may need thrombolytic therapy.

In patients with malignancy-associated venous thrombosis, LMWH remains the preferred standard. Recent pilot studies (National Comprehensive Cancer Network in 2020) suggest efficacy and safety of DOACs as an acceptable alternative in selected patients with malignancy-associated venous thrombosis.

Similar to warfarin, DOACs may affect interpretation of certain thrombophilia studies, including lupus anticoagulant.

FIBRINOLYTIC TREATMENT

Streptokinase and urokinase (the latter is no longer available in the U.S.) cause a **systemic** lytic state. tPA is more specific; it increases the conversion of plasminogen to plasmin in the presence of fibrin, so most of the plasmin made is localized to the fibrin clot.

However, tPA also results in systemic lysis and can be used to lyse a life-threatening pulmonary embolism (very specific situations) or an acute stroke or MI.

TRANSFUSION MEDICINE

PREVIEW | REVIEW

- Except in the case of life-threatening bleeding, which patients are not given platelet transfusions, regardless of the degree of thrombocytopenia?
- What is the most common reason for an acute hemolytic transfusion reaction? What is the clinical presentation?
- Which type of transfusion is most associated with transfusion-related bacterial infections? Why?

Red Blood Cell (RBC) Transfusions

Whole blood is rarely used. Exceptions include major hemorrhage from trauma or from pediatric cardiac surgery. A donated unit of whole blood is normally separated into platelets, plasma, and packed RBCs. In the absence of ongoing losses, 1 unit of packed RBCs increases the hemoglobin (Hgb) by 1 g/dL (10 g/L).

Alloimmunization can be a problem in multiple-transfused patients, and indications for RBC transfusion are varied. Many guidelines exist that try to balance risk vs. benefit of transfusion. The 2016 AABB (formerly the American Association of Blood Banks) guidelines recommend a strategy that considers not only Hgb levels, clinical setting, and patient preferences but also alternative therapies.

Platelet Transfusions

Wait to transfuse most patients with thrombocytopenia if they are not bleeding. A low platelet count that is $> 10,000/\mu\text{L}$ ($10 \times 10^9/\text{L}$) is acceptable for nonbleeding patients with acute leukemia. Platelet counts of $50,000/\mu\text{L}$ ($50 \times 10^9/\text{L}$) are adequate for most interventional procedures (a higher number is often used for neurosurgical procedures). Patients with ITP **almost never** require platelet transfusions, even with very low platelet counts. Their younger platelets seem to work better; transfusion does not result in an appreciable rise in the platelet count but can be hemostatically effective.

Because of increased risk of thrombosis, do **not** give platelet transfusions to patients with HIT or TTP/HUS unless there is life-threatening bleeding.

White Blood Cell (WBC) Transfusions

WBC transfusions are only rarely performed. Granulocyte colony-stimulating factor (G-CSF) or granulocyte-macrophage colony-stimulating factor (GM-CSF) is used instead to increase the neutrophil count, most commonly in patients receiving myelosuppressive chemotherapy.

Plasma and Cryoprecipitate Transfusions

Fresh frozen plasma (FFP) is transfused to replace coagulation factors. Use it to reverse anticoagulation in the context of dangerous bleeding when the PT and/or aPTT are supratherapeutic.

Cryoprecipitate is a plasma component enriched in fibrinogen. It is used in conditions like DIC to replace fibrinogen (indicated when fibrinogen is < 100 mg/dL [$< 1 \text{ g/L}$]).

Transfusion Complications

Acute hemolytic transfusion reaction is a medical emergency caused by rapid, intravascular hemolysis, commonly due to an ABO incompatibility—and most often a result of a clerical error.

The initial signs may be only fever and chills, which are very nonspecific. While other causes should be considered, in a patient receiving a blood transfusion, blame the blood! So, if a patient receiving a transfusion develops fever and chills, **stop** the transfusion immediately—the prognosis worsens as more blood is given. Provide supportive care, including normal saline infusion. Other signs and symptoms include back pain, hypotension, renal failure, and hemoglobinuria. Alert the blood bank immediately, because another patient may also be receiving the wrong blood. Diagnostic tests include Coombs testing, serum free Hgb, hemolysis labs (i.e., indirect bilirubin, haptoglobin, LDH), and urine for Hgb testing. Repeat type and cross-match in both the patient and on any blood left in the transfusion bag. The repeat blood sample can appear pink (as can urine), and peripheral smear may show schistocytes.

Delayed hemolytic transfusion reaction is caused by extravascular hemolysis associated with Rh incompatibility or minor antigen mismatches. Patients present approximately **7 days after transfusion** with anemia, mild fever, and mild unconjugated bilirubin elevation.

No treatment is necessary in the absence of brisk hemolysis. Match future transfusions appropriately.

Febrile transfusion reactions: Fever and chills **after** a transfusion are common and represent **nonhemolytic** reactions to leukocytes in the blood product. A normal peripheral smear differentiates this mild, benign reaction from the more dangerous acute hemolysis.

Stop the transfusion and assess for hemolysis by sending off the same labs listed above for acute hemolytic transfusion reaction. If the Coombs is negative, the symptoms are probably due to anti-HLA antibodies against the WBCs, which are transfused along with the component blood product.

Give antipyretics. Filters are used to remove WBCs in the transfused product (i.e., leukocyte depletion) to minimize this reaction. But filters do not remove cytokines, which can also cause the reaction.

Posttransfusion purpura is discussed under [Post-transfusion Purpura on page 8-25](#).

Transfusional hemosiderosis is iron overload from chronic repeat transfusions, usually in patients with sickle cell disease, thalassemia, or transfusion-dependent myeloproliferative or myelodysplastic disorders. Each 250 mL of packed RBCs contains approximately 250 mg of iron. Patients can become symptomatic after as few as 20 units. After 100 units (20–25 g of iron), patients almost always show some symptoms of iron overload, which include:

- Glucose intolerance
- Cirrhosis
- Cardiomyopathy
- Hypogonadism

Diagnosis of transfusional hemosiderosis is established by an elevated ferritin and an iron-laden liver biopsy. As with hemochromatosis, MRI can detect iron in the liver, heart, joints, and pituitary (use an experienced facility only). Start iron chelation treatment (deferoxamine or deferasirox) before symptoms appear, because symptoms are usually not reversible. Consider chelation after 20–25 units of packed RBCs (approximately 5 g of iron) if transfusions are ongoing.

Transfusion-related acute lung injury (TRALI) is a severe pulmonary reaction caused by antibodies present in transfused FFP. TRALI is one of the most common causes of transfusion-related fatalities. The timing of TRALI is typically during or shortly after transfusion (1–2 hours), but TRALI can be more delayed, occurring up to 6 hours after transfusion. Clinically, there is sudden onset of respiratory distress. This can include alveolitis, noncardiogenic pulmonary edema, and acute respiratory distress syndrome (ARDS). Treatment is supportive and can include mechanical ventilation. Stop the transfusion, and never use blood products from that donor again!

Pretransplant alloimmunization can occur if transfusions are given before transplant. To reduce risk:

- Do not use family members as donors.
- Use leukocyte-poor irradiated blood components.
- Use single-donor platelets if needed.

Allergic/Anaphylactic reactions to transfused blood: Simple urticaria and anaphylaxis can occur. Symptoms of anaphylaxis—including hypotension, shock, angioedema, and respiratory distress with wheezing—can begin immediately on starting transfusion. This requires immediate treatment, including discontinuing transfusion and giving epinephrine. Treatment of anaphylaxis is covered in the [Allergy & Immunology](#) section. Know that recipient IgA deficiency leads to anti-IgA antibody formation and donor blood with normal IgA levels can provoke anaphylaxis. Use IgA-deficient donors for such recipients.

Infectious complications are most likely to occur with platelet products, because they are stored at room temperature. Skin flora and gram-negative bacteria (e.g., *E. coli*, *Yersinia*, *Pseudomonas*) are the usual organisms.

Symptoms can be similar to other transfusion reactions and include fever, chills, and hypotension. Symptoms may develop during or up to 30 minutes after the transfusion. Management includes stopping the transfusion, supportive care, and blood cultures from the opposite arm, among others. Broad-spectrum antibiotics may be indicated if suspicion is high. Blood banks screen for the most common infectious agents as follows:

- HIV-1 and HIV-2
 - Risk of contracting HIV-1 or -2 from the U.S. blood supply is 1 in 2 million.
- Human T-lymphotropic virus 1 and 2 (HTLV-1 and HTLV-2)
 - Risk is < 1 in 2 million.
- Hepatitis C virus (HCV)
 - Risk is 1 in 1.3 million.
- Hepatitis B virus (HBV)
 - Risk is 1 in 200,000–500,000.
- West Nile virus
- *Treponema pallidum*
- *Trypanosoma cruzi*
 - Trypanosomiasis is of particular concern in South America.
 - Many U.S. blood banks are implementing universal screening using an enzyme immunoassay (EIA) test for *T. cruzi* antibody.
- Cytomegalovirus (CMV)
 - EIA for antibody
 - Only CMV-negative blood is transfused in CMV-negative transplant patients, and leukocyte-depleted blood is used to further reduce risk.

Hypotensive reactions can be seen in patients on ACE inhibitors whose blood is filtered through coils, such as those used to filter out WBCs. Kinin activation is the probable cause. Prestorage filtration eliminates this problem.

Graft-versus-host (GVH) reaction: Immunocompromised patients can develop GVH from lymphocytes in transfused blood, especially if receiving donations from a 1st degree relative (because they can be HLA-haploidentical), and the lymphocytes may engraft. Order irradiated blood for immunocompromised patients to ensure that the potentially harmful lymphocytes have been destroyed.

Transfusion-associated circulatory overload (TACO) is another common cause of transfusion-related fatalities. Symptoms and signs of respiratory distress and circulatory overload—including hypertension, tachycardia, and pulmonary edema—typically occur < 6 hours after transfusion. Prevent TACO by slowing the infusion and using diuretics.

Know how to differentiate between TRALI and TACO. Brain natriuretic peptide is often elevated in TACO but not in TRALI, because TRALI is not related to volume overload. Remember diuretics used to treat TACO can worsen TRALI!

DISORDERS OF THE BONE MARROW

PREVIEW | REVIEW

- What are the lab findings in a patient with aplastic anemia?
- How can you tell the difference between acute and chronic leukemias?
- What is the treatment for leukemic patients who have hyperviscosity symptoms due to a large number of circulating blasts (i.e., leukostasis)?
- What percentage of marrow blasts defines acute myeloid leukemia (AML)?
- What is a characteristic peripheral blood finding in a patient with AML?
- Characterize the acute promyelocytic leukemia (APML) genetic translocation and describe how it affects treatment. What is the prognosis for APML?
- Which category of AML is associated with disseminated intravascular coagulation?
- What physical findings do patients with acute lymphoblastic leukemia (ALL) often present with?
- Which ALL abnormalities are associated with a poor prognosis?
- What is 5q deletion syndrome?
- What is the main difference between the myeloproliferative disorders (MPDs) and acute leukemia?
- What are the 4 most common MPDs?
- JAK2 is found in what disease states?
- Chronic myeloid leukemia (CML) is associated with which cytogenetic abnormality in > 90% of cases?
- What is the current standard of care for treating chronic-phase CML?
- What side effects are associated with tyrosine kinase inhibitors?
- What symptoms necessitate treatment in patients with essential thrombocythemia?
- Which peripheral blood finding is seen in patients with myelofibrosis?

PANCYTOPENIA

Pancytopenia is associated with multiple causes discussed below and defined by reduction in peripheral circulating blood cells of all three cell lines. The differential causes of pancytopenia can be secondary to infection, autoimmune, medication-associated (e.g., chemotherapy), nutritional deficiency, malignancy-associated, or genetic inborn.

MAJOR CAUSES OF BONE MARROW FAILURE

Inherited bone marrow failure syndromes:

- Fanconi anemia
- Dyskeratosis congenita
- Shwachman-Diamond syndrome
- Amegakaryocytic thrombocytopenia
- Reticular dysgenesis

Acquired causes of bone marrow failure:

- Acquired aplastic anemia caused by drugs, chemicals, or radiation
- Acquired aplastic anemia associated with viral infection or immune disorder
- Myelodysplastic syndrome
- Paroxysmal nocturnal hemoglobinuria
- Large granular lymphocytic leukemia

APLASTIC ANEMIA

Aplastic anemia is an absence of hematopoietic stem cells that results in **pancytopenia** and a **hypocellular marrow**. It can be acquired or inherited. The etiology of acquired aplastic anemia is unknown in most cases.

Dose-related causes of aplastic anemia:

- Benzene
- Industrial chemicals
- Pesticides
- Radiation

Idiosyncratic causes of aplastic anemia:

- Sulfa
- Carbamazepine
- Valproate
- Phenytoin
- Gold
- Chloramphenicol
- Nifedipine
- Methimazole
- Propylthiouracil

Aplastic anemia is occasionally associated with viral infections with parvovirus B19, hepatitis viruses, and HIV. Other associated illnesses include thymoma, paroxysmal nocturnal hemoglobinuria, and SLE.

The presentation is determined by which cell lines are affected most: fatigue and weakness with anemia, infections with neutropenia, or bleeding with thrombocytopenia.

Aplastic anemia presents with pancytopenia, decreased reticulocyte count, and a hypocellular marrow (**< 20%**) with **normal maturation** of the cell lines. Differential diagnosis includes other causes of pancytopenia, such as

B₁₂ or folic acid deficiency, primary hematologic malignancies, myelodysplastic syndrome (MDS), infiltration of bone marrow with neoplastic cells, or fibrosis.

Aplastic anemia is classified as **severe** if:

- marrow cellularity is **< 25%** of normal or
- if the marrow is hypocellular, **< 30%** of the cells are hematopoietic, **and** at least 2 of the following 3 conditions are met:
 - 1) Absolute neutrophil count (ANC) **< 500/μL** ($0.5 \times 10^9/L$)
 - 2) Platelets **< 20,000/mm³** ($2 \times 10^9/L$)
 - 3) Reticulocytes **< 1%** (corrected for hematocrit)

Classification is **very severe** if severe criteria are met but the **ANC is < 200/μL** ($0.2 \times 10^9/L$). A low ANC indicates a poor prognosis. Younger age and higher cell counts are predictive of a better response rate to treatment.

For all patients, treatment includes withdrawal of any possible offending medications. In addition, if thymoma is found, surgical excision is indicated.

Definitive treatment of aplastic anemia is with hematopoietic stem cell transplantation (HSCT) for patients who are **young** and have an HLA-matched family member (10-year survival **> 80%**). See [Hematopoietic Stem Cell Transplantation \(HSCT\) on page 8-58](#) for more information.

If there is no suitable donor or the patient is **> 45** years of age, treat with immunosuppression using either antithymocyte globulin or antilymphocyte globulin in combination with corticosteroids and cyclosporine. The complete response rate is 65%, although relapses are common.

Hematopoietic growth factors are undergoing evaluation and are not yet recommended treatment.

Know that patients with aplastic anemia are at increased risk of developing acute leukemia.

THE ACUTE LEUKEMIAS

The acute leukemias are clonal disorders of **early** hematopoietic stem cells.

Normal hematopoiesis begins with pluripotent stem cells, which, in addition to reproducing themselves, are capable of differentiating into cells of either the myeloid lineage (i.e., granulocytes, monocytes, erythrocytes, and megakaryocytes) or the lymphocyte lineage (B or T cells). See [Figure 8-34 on page 8-44](#).

Acute leukemias occur when cells of either the early myeloid (acute myeloid leukemia [AML]) or early lymphoid (acute lymphoblastic leukemia [ALL]) lines lose their ability to differentiate while retaining their ability to replicate. These immature cells, called **blasts**, accumulate in the bone marrow and crowd out normal hematopoietic elements. In addition, the blast cells often spill out into the peripheral circulation.

Patients with acute leukemias present with symptoms related to cytopenias (e.g., infections, fatigue, mucosal bleeding).

Diagnosis and prognosis are made using morphologic analysis, cytogenetic studies (karyotype), cytochemical analysis (e.g., periodic acid-Schiff [PAS], peroxidase, esterase, Sudan black), molecular markers, and cell surface markers (flow cytometry and immunophenotyping for surface antigen cluster of differentiation [CD] markers).

Suspect acute leukemia when blasts (immature cells) are seen in the peripheral blood smear without mature cells. Note that **chronic** leukemias have overproduction of ≥ 1 developing cell lines but **not of blasts**.

Refer to Figure 8-29 for a summary of the workup for acute leukemia.

The general principles of management for acute leukemias include induction, consolidation, and (in select cases) maintenance therapies.

Induction therapy is intended to eradicate the leukemic clone in hopes that normal hematopoiesis returns without continual presence of leukemic disease. Induction with chemotherapy often involves a prolonged period of pancytopenia, during which the patient is highly susceptible to infection.

Myeloid growth factors can be used to shorten the time spent in a neutropenic state in patients with acute lymphoblastic leukemia, although their use in acute myeloid leukemia may also be considered. Although these agents may reduce the length of hospitalization and decrease the incidence of infection, they have **not** been proven to increase survival. Supportive care with blood and platelet transfusions is also given during cell count recovery after induction chemotherapy.

CNS-directed therapy may be incorporated throughout the treatment as needed given the potential for CNS involvement. This can include intrathecal chemotherapy, CNS irradiation, and/or high-dose systemic chemotherapy chosen for its CNS penetrance.

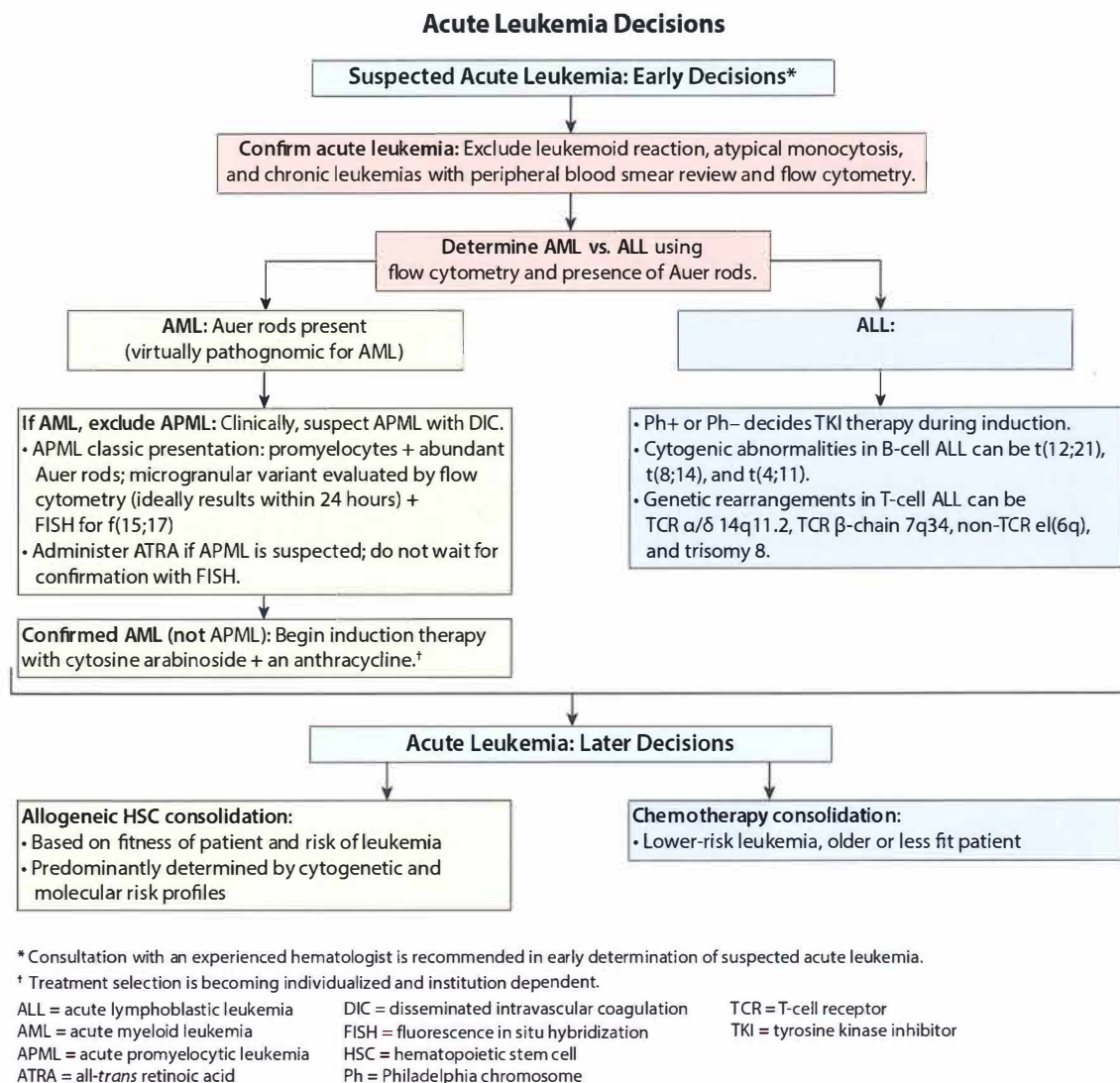


Figure 8-29: Acute leukemia decisions

Once remission is achieved and cell counts have recovered, **consolidation therapy** with further systemic therapy and potentially HSCT is used to prolong remission and survival. The purpose of this phase is to kill any remaining cancer cells after initial treatment.

Gene expression profiling using DNA microarrays is becoming an increasingly important tool to assist with prognosis, to assess depth of treatment response, and to guide therapy.

Note: Neutropenic colitis (a.k.a. typhlitis) can occur in patients after prolonged neutropenia of any cause. The neutropenia can be the result of induction therapy, immunosuppressive therapy, or the disease itself (especially with acute myeloid leukemia, multiple myeloma, and aplastic anemia). It is caused by gram-negative bacteria and presents with abdominal pain and (sometimes bloody) diarrhea. Appropriate therapy includes piperacillin-tazobactam, cefepime + metronidazole, or ceftazidime + metronidazole. Surgical intervention is reserved for perforation.

In select cases, a **maintenance phase** with chemotherapy and/or targeted agents may be incorporated after induction and consolidation with the intent to reduce the risk of disease recurrence.

Acute Myeloid Leukemia (AML)

Recall that during normal hematopoiesis, myeloid blast cells (Figure 8-30 and Figure 8-31) differentiate into granulocytes, monocytes, erythrocytes, or megakaryocytes. AML (a.k.a. acute myelogenous leukemia) is a clonal disorder of the early myeloid cells; there is overproduction of myeloblasts with reduced production of RBCs, platelets, and mature granulocytes. The blast forms accumulate in the peripheral circulation, marrow, and sometimes lymphoid tissues.

The disorder can develop from exposure to chemicals, such as benzene and certain chemotherapeutic agents. (Alkylators and topoisomerase inhibitors are the hallmark 2 classes that can cause therapy-related AML.) It can also arise after transformation from myeloproliferative disorders, myelodysplastic disorders, aplastic anemia, and paroxysmal nocturnal hemoglobinuria (PNH). Typically, these secondary leukemias have a worse prognosis than de novo AML.

Patients often seek medical care because of symptoms related to disordered hematopoiesis with pancytopenia. Patients often have fatigue and pallor related to anemia. The bone pain seen in ALL is uncommon with AML. When fever is present, it's usually from infection.

Know: Large numbers of blasts in the peripheral blood ($> 100,000/\mu\text{L}$ [$100 \times 10^9/\text{L}$]) can increase blood viscosity and cause end-organ disease, such as brain ischemia and hemorrhage (presents as altered sensorium), and sludging in the pulmonary vasculature (presents as respiratory distress). This combination of greatly increased blast cell count and decreased tissue perfusion is called **leukostasis**, a medical emergency. Urgent treatment often includes intravenous fluids, leukapheresis, hydroxyurea, and induction chemotherapy.

Thrombocytopenia predisposes to hemorrhage, especially in the presence of a high blast count. Qualitative and quantitative WBC problems predispose to serious infection of all kinds. Concurrent anemia may require RBC transfusions but should be avoided in the setting of profound leukostasis due to the potential of worsening hyperviscosity.

Diagnose AML by bone marrow biopsy if blasts are seen in the peripheral blood. Marrow and/or peripheral **blasts $\geq 20\%$** is the definition of acute myeloid leukemia. Because the blasts of AML and ALL look alike, cytochemical tests, immunophenotyping, and chromosomal analysis are performed on marrow cells in order to differentiate between the two. Note: The presence of certain cytogenetic changes ($t(15;17)$, $t(8;21)$, or $inv(16)$) is diagnostic of AML, regardless of the blast percentage. Know, however, that finding **Auer rods** inside peripheral blood blast cells (Figure 8-32) helps make the diagnosis of AML. Auer rods are azurophilic, reddish purple, needle-shaped crystals found in the cytoplasm of AML blast cells.

In 2016, a revision to the World Health Organization classification of myeloid neoplasms and acute leukemia was published. It attempts to incorporate clinical, prognostic, morphologic, immunophenotypic, and genetic data.

Currently, several factors are used to establish AML prognosis. Cytogenetic/Molecular findings represent one of the most powerful prognostic indicators. These genetic features can be used to classify patients into different risk

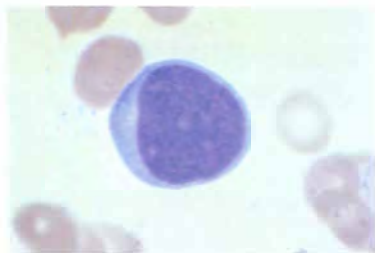


Figure 8-30: Normal myeloblast (high-oil immersion), few cytoplasmic granules, and several nucleoli

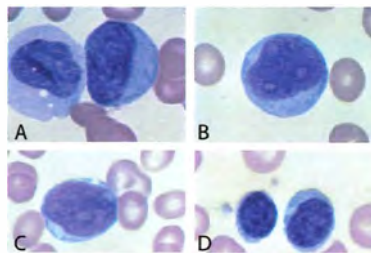


Figure 8-31: Myeloblast vs. lymphoblast: (A) young mono and a myeloblast; (B) myeloblast; and (C) lymphoblast. (D) Normal lymphocytes are smaller.

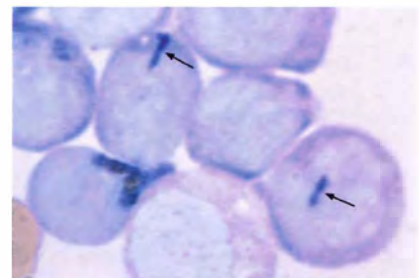


Figure 8-32: AML: bone marrow aspirate with peroxidase-positive blasts and 2 peroxidase-positive Auer rods

groups and allow for stratification of patients who would benefit from an earlier allogeneic HSCT in the 1st complete remission:

- **Favorable** → t(8;21), t(15;17), inv(16), or normal cytogenetics with *nucleophosmin 1* (*NPM1*) mutation
- **Intermediate** → normal karyotype, +8, or t(9;11)
- **Unfavorable** → monosomal karyotype, 11q23, t(6;9), t(9;22), inv(3), -5/5q-, -7/7q-, TP53 mutation, FLT3-ITD mutation, or more complex cytogenetics (≥ 3 aberrations)

Other **unfavorable** prognosticators for AML include:

- > 60 years of age
- Poor performance status
- WBC count > 100,000/μL ($100 \times 10^9/L$)
- Prior disease of the bone marrow (e.g., myelodysplasia, myeloproliferative disorder)

Standard induction therapy for AML is evolving, although it is historically based on the “7 + 3” combination of 7 days of cytosine arabinoside (ara-C) and 3 days of daunorubicin. Consolidation therapy can take the form of further chemotherapy with the same agents. For older patients, especially those with a poor performance status, the hypomethylating agents azacitidine or decitabine can be used. In the era of targeted therapies, agents targeting various mutations evident in AML (e.g., *FLT3*, *IDH*) are also being increasingly utilized in the various phases of treatment.

With standard therapy, remission is achieved in ~ 40–50% of patients > 60 years of age, but long-term, event-free survival is achieved in < 10%. For patients < 60 years of age, long-term survival, on average, is 20–30%.

Of particular importance is acute **promyelocytic leukemia** (**APML**), which is characterized by a translocation between chromosomes 15 and 17, involving the promyelocytic leukemia gene and retinoic acid receptor α gene. The expression of the PML-RAR α fusion protein renders physiologic levels of retinoic acid ineffective in their innate function to differentiate myeloid blasts, resulting in the development of APML.

Treatment of APML differs from treatment of other types of AML. It includes all-*trans* retinoic acid (ATRA), which is used to induce differentiation, along with either arsenic trioxide (ATO) or daunorubicin. In patients with low- to intermediate-risk APML, ATRA and ATO are as beneficial as ATRA + chemotherapy. Prognosis for APML is **very favorable**, and therapy provides a remission rate of > 80% and a cure rate of > 70%. These rates are much better than with other forms of AML.

Patients with APML are classically at an increased risk for developing disseminated intravascular coagulation (DIC) due to release of procoagulants from cytoplasmic granules. The diagnosis of APML needs to be made quickly, because DIC can change APML from a curable disease into a fatal one within hours.

Know that **differentiation syndrome** (formerly ATRA syndrome) is a potentially life-threatening adverse effect of

ATRA and ATO therapy. Clinical presentation includes fever, volume overload with pleural and pericardial effusions, respiratory distress, and hypotension. Treat with high-dose dexamethasone and withhold ATRA and ATO until resolution of symptoms.

An important distinction in AML with t(9;22) is whether the disease is de novo AML or chronic myeloid leukemia (CML) in degenerated blast crisis. CML in blast crisis arises because of the presence of the Philadelphia chromosome (Ph; *BCR-ABL* gene translocation or t(9;22)) and is vulnerable to treatment with a tyrosine kinase inhibitor (TKI), such as imatinib. See **Chronic Myeloid Leukemia (CML)** on page 8-43.

Allogeneic hematopoietic stem cell transplantation (HSCT) is an important treatment option in some patients with AML. It is typically reserved for physiologically fit patients with good organ function in whom the disease is prognostically intermediate or unfavorable or has relapsed after achieving a prior complete response. Morbidity and mortality are influenced by the level of disease before transplant, histocompatibility between donor and recipient, stem cell source (umbilical cord, bone marrow, or peripheral blood), conditioning regimen, and expertise of transplantation center.

Acute Lymphoblastic Leukemia (ALL)

ALL is a clonal disorder of early **lymphocytic** precursors. The blasts of ALL can be of B- or T-cell lineage. B-cell ALL characteristically stains positive for TdT, CD19, CD20, and does **not** stain for myeloperoxidase (a myeloid cell marker). While ALL is **primarily** a disorder of children, there is a bimodal age distribution with increased incidence **also** in patients > 45 years of age. ALL represents ~ 20% of adult leukemias. There are B- and T-cell types, and mediastinal masses may be present.

The 2016 WHO classification uses cytogenetic and molecular changes to classify subtypes of ALL.

Clinically, patients often present with cytopenias, constitutional symptoms, symptoms of CNS involvement (e.g., cranial nerve and/or retinal abnormalities; symptoms of meningeal irritation), and enlargement of the liver, spleen, lymph nodes, and testicles due to extramedullary deposits of blast cells.

The peripheral blood smear may show leukopenia or leukocytosis with blast counts > 100,000/μL ($100 \times 10^9/L$; **Figure 8-33**). Definitive diagnosis and important prognosticators are made by immunophenotyping and chromosomal analysis of the leukemic cells.

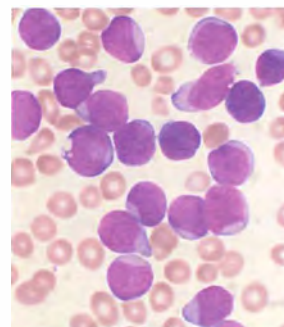


Figure 8-33: ALL: peripheral blood smear showing excessive lymphoblasts

Unfavorable prognostic factors in ALL:

- < 1 year or > 35 years of age
- WBC > 100,000/ μ L (100×10^9 /L) for T cell and > 30,000 for B cell
- Mature B-cell or early T-cell types
- Persistent minimal residual disease, as detected by flow cytometry after induction
- Complex cytogenetics (≥ 5 changes), hypodiploidy (< 46 chromosomes), t(4;11), Philadelphia chromosome t(9;22)
- CNS involvement

Treatment is with **multiple** chemotherapy agents, used in induction, consolidation, and maintenance phases. Prednisone, vincristine, and daunorubicin form the foundation, and cyclophosphamide + L-asparaginase are often added (may increase response). Complete response rates are in excess of 80%. Patients who have a Ph+ ALL are often considered for tyrosine kinase inhibitors (TKIs), such as imatinib, dasatinib, or ponatinib throughout the various phases of their treatment.

Postremission therapy in ALL includes CNS prophylaxis with intrathecal chemotherapy +/- cranial radiation, consolidative therapy, and 2–3 years of maintenance therapy.

For patients **without** unfavorable prognostic factors, chemotherapy alone results in a 60% long-term, disease-free survival. For patients with ≥ 1 unfavorable prognostic indicators, consider HSCT. (See [Hematopoietic Stem Cell Transplantation \(HSCT\)](#) on page 8-58.)

Other forms of therapy for those patients who relapse include monoclonal antibodies targeting CD19 receptors commonly found on B lymphocytes and, especially for younger patients at approved centers, the use of anti-CD19-directed, chimeric antigen receptor T cells (CAR-T therapy).

Supportive care is an important component of treatment. In addition to the effects of cytopenias, patients often have hyperuricemia, hyperphosphatemia, and hypocalcemia reflective of **tumor lysis syndrome**—all secondary to the high cell turnover. As mentioned under [Acute Myeloid Leukemia \(AML\)](#) on page 8-40, leukostasis is an oncologic emergency in this population and needs to be treated aggressively with IV hydration, cytoreduction with steroids, and leukapheresis. Red blood cell transfusions should be avoided in the setting of leukostasis given the risk for exacerbating hyperviscosity.

CHRONIC LEUKEMIAS

The chronic leukemias are:

- Chronic myeloid leukemia (CML)
- Chronic lymphocytic leukemia (CLL)

CML is a myeloproliferative disorder discussed under [Chronic Myeloid Leukemia \(CML\)](#).

CLL is an early form of small lymphocytic lymphoma (SLL); we discuss both under [Chronic Lymphocytic Leukemia \(CLL\)](#) / [Small Lymphocytic Lymphoma \(SLL\)](#) on page 8-49.

MYELOYDYSPLASTIC SYNDROME (MDS)

MDS includes clonal stem cell disorders that are characterized by ineffective blood cell production and variable progression to acute leukemia. MDS occurs de novo or secondary to previous chemotherapy (a.k.a. therapy-related MDS). While both MDS and the myeloproliferative disorders are clonal stem cell disorders, only patients with MDS exhibit cytopenias and inadequate (dysplastic) maturation of blood cells. (See [Myelodysplastic / Myeloproliferative Disorders](#) for additional information.)

MDS presents with symptoms secondary to cytopenias, including weakness, infection, and bleeding. Platelets can be dysfunctional and result in bleeding that is out of proportion to the degree of thrombocytopenia. Bone marrow biopsy reveals a **hypercellular** marrow (peripheral cytopenias due to ineffective hematopoiesis) and dysplasia. However, in the absence of dysplasia, an MDS diagnosis may also be considered on the basis of MDS-defining cytogenetics in patients in whom alternate causes of bone marrow disorders have been ruled out. Patients who have MDS with **> 20% blasts** are considered to have **AML**.

There are several prognostic point system scoring scales to risk stratify patients with MDS, including the International Prognostic Scoring System (IPSS), WHO classification-based Prognostic Scoring System (WPSS), and the revised international prognostic scoring system (Revised IPSS), which all help risk stratify patients, consider management strategies, and predict survival. Points are assigned based on percentage of blasts (the most important prognostic indicator), number/extent of cytopenias, and cytogenetic risks. The various scoring systems employ various iterations, and their use can be institutionally variable.

Unfavorable prognosticators for MDS:

- High percentage of bone marrow blasts
- Number/Severity of cytopenias
- Cytogenetic abnormalities, including complex cytogenetics (≥ 3 abnormalities), especially involving chromosome 7

The following factors confer a more **favorable** prognosis and are individually incorporated into the staging system:

- Bone marrow blasts < 2%
- Generally preserved cell counts with hemoglobin > 10 g/dL, platelets > 100,000/ μ L, absolute neutrophil count > 800/ μ L
- Normal cytogenetics, or -Y, del(20q), or del(12p)
- Deletion of chromosome 5q or 20q

Know 5q deletion syndrome: Patients with the favorable 5q deletion have refractory anemia and thrombocytosis. Know that these patients generally respond to lenalidomide therapy allowing transfusion independence lasting > 2 years and a more favorable biologic risk profile.

See [Table 8-11](#) for differential diagnoses of MDS.

Table 8-11: Differential Diagnoses of Myelodysplastic Syndrome

B ₁₂ deficiency
Folate deficiency
Copper deficiency
Excessive alcohol intake
Heavy metal exposure (e.g., lead, arsenic)
Autoimmune cytopenias
HIV infection
Anemia of chronic disorders (infection, inflammation, cancer)
Secondary MDS (cytotoxic therapy, irradiation)
Other hematopoietic stem cell disorders (AML, myeloproliferative disorders, aplastic anemia, paroxysmal nocturnal hemoglobinuria, large granular lymphocytic leukemia)

Treatment depends on patient performance status, comorbidities, and aggressiveness of disease necessitating transfusions. Treatments can include supportive measures, including transfusion, erythropoietin-stimulating agents, hypomethylating agents (e.g., azacitidine, decitabine), or intensive chemotherapy followed by an allogeneic HSCT for biologically adverse-risk disease. Mortality in MDS is usually a result of progressive cytopenias or progression to AML.

MYELOYDYSPLASTIC / MYELOPROLIFERATIVE DISORDERS

Chronic **myelomonocytic** leukemia (CMML) is classified as an overlap myelodysplastic/myeloproliferative disorder that includes features of both, including dysplasia with cytopenias (MDS-like) and hyperproliferative cell lines with splenomegaly (myeloproliferative disorders). CMML is a cousin of CML. It is a malignant hematopoietic stem cell disorder that requires persistent monocytosis ($\geq 1,000/\text{dL}$) over 3 months with the exclusion of alternate causes including CML and hypereosinophilic syndrome (especially among those with eosinophilia). Treatment is reserved for patients with profound leukocytosis and/or symptomatic splenomegaly. Optimal treatment for this condition is poorly defined but often utilizes cytoreductive agents, such as hydroxyurea. Check patients with CMML for the t(5;12)(q33;p13) oncogenic product. These patients may respond to imatinib therapy (tyrosine kinase inhibitor). General prognosis is poor, and the only curative approach with this disease is an allogeneic HSCT.

MYELOPROLIFERATIVE DISORDERS (MPDs)

MPDs are **clonal** malignancies of early hematopoietic stem cells, characterized by loss of the regulation of cell proliferation. The result is the overproduction of the entire pyramid of maturation of granulocytes, erythrocytes, and platelets. (Contrast this with acute leukemia, marked

by maturation arrest and proliferation of blasts.) MPDs variably progress to acute leukemias or myelodysplasia (Figure 8-34 on page 8-44).

The 4 most common MPDs:

- 1) Chronic myeloid leukemia (CML)
- 2) Essential thrombocythemia (ET)
- 3) Polycythemia vera (PV)
- 4) Primary myelofibrosis (MF; the rarest of these 4 MPDs)

JAK2 (Janus kinase, a tyrosine kinase) is an intracellular signaling molecule that is coupled to cell surface hematopoietic growth factor receptors (like the erythropoietin receptor). A **JAK2** mutation causes constitutive activation of the JAK2 kinase domain, inducing unregulated erythropoiesis. The mutation is found in almost all patients with PV and ~ 50% of those with ET or MF. The presence of this genetic lesion can be useful in the diagnosis and therapeutic targeting of the disease.

Thrombopoietin receptor gene (a.k.a. *myeloproliferative leukemia* gene [MPL]) and *calreticulin* (CALR) gene mutations are other markers, which may be mutually occurring in the MPDs, particularly ET.

Chronic Myeloid Leukemia (CML)

CML is a clonal stem cell disorder of myeloid cells. The clinical hallmark is one of uncontrolled production of **mature** neutrophils with relatively preserved function. Most patients present in the chronic phase with an elevated WBC count and a predominance of **granulocytes** (Figure 8-35 on page 8-45). There is often an elevated **basophil** count, eosinophilia, thrombocytosis, and a **low** leukocyte alkaline phosphatase (LAP) score. The expanded myeloid pool can lead to organ infiltration, causing hepatosplenomegaly.

The diagnosis of CML is dependent on detection of the **Philadelphia chromosome** (i.e., t(9;22)), or its products: BCR-ABL fusion mRNA or the BCR-ABL protein, a tyrosine kinase. > 90% of patients demonstrate this abnormality at the time of diagnosis.

Uncontrolled replication of the myeloid stem cells as the disease progresses inevitably leads to further genetic errors. The myeloid cells begin to lose their ability to differentiate from their blast stages, and the disease degenerates into acute leukemia (AML or ALL). This 2nd, or accelerated, phase of CML is characterized by increasing numbers of blasts (10–20%) and basophils and a declining platelet count.

The patient is considered to be in the **blast phase** once the percentage of blasts has progressed to > 20%. (See Figure 8-36 on page 8-45 and Figure 8-37 on page 8-45.) Survival is greatly diminished once this blast crisis has occurred.

Most patients (85–90%) present in the stable chronic phase, while 10–15% may present in the accelerated or blast phase. Fewer patients progress to the blast phase due to improvements in treatment during the chronic phase.

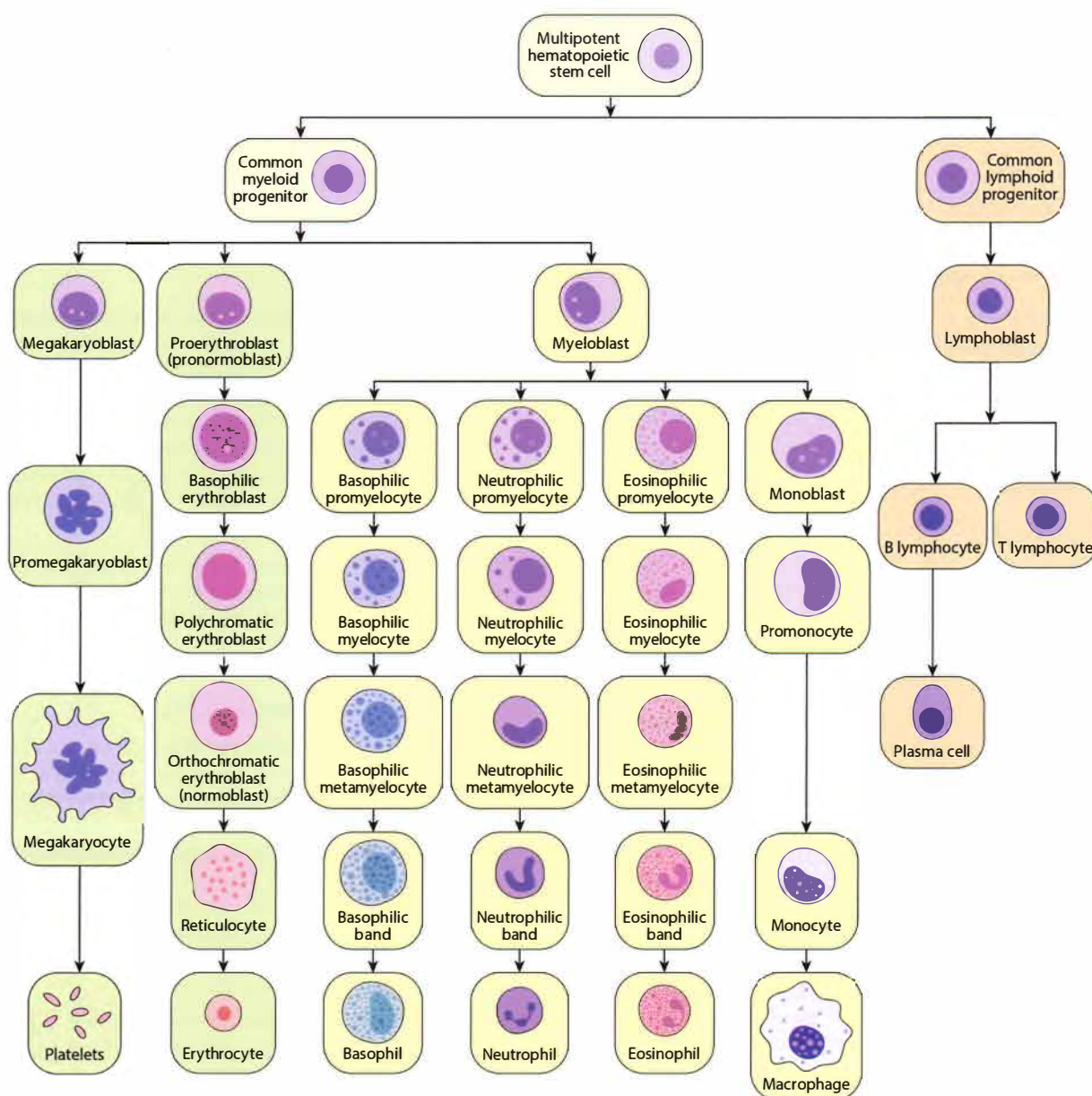


Figure 8-34: Hematopoiesis

A tyrosine kinase inhibitor (TKI)—either 1st generation (imatinib) or 2nd generation (dasatinib, bosutinib, or nilotinib)—is the 1st line treatment of CML in **chronic** phase. The 2nd generation TKIs provide faster hematologic and cytogenetic responses than imatinib, but so far no survival advantage has been shown. The 3rd generation of TKIs is reserved to ponatinib, which is only indicated for patients who have failed 2nd line therapies or have developed a point mutation to the T315I, rendering 1st and 2nd generation TKIs ineffective. Patients who initiate therapy with a baseline WBC > 100,000 at the time of diagnosis should be cytoreduced with hydroxyurea.

Side effects of TKIs vary depending on the agent and can include gastrointestinal intolerance, hepatotoxicity, cardiac toxicity, pulmonary toxicity, and thrombotic complications:

- Dasatinib should be avoided in patients with cardio-pulmonary effusion, pulmonary hypertension, and those on anticoagulation.
- Nilotinib may be associated with pancreatitis, arterial thrombus formation, and QT prolongation.
- Ponatinib has been demonstrated to increase the risk for thrombi and is reserved for earlier generation TKI failure as mentioned above.
- Also, TKIs are teratogens, so do not use them in women of childbearing age.

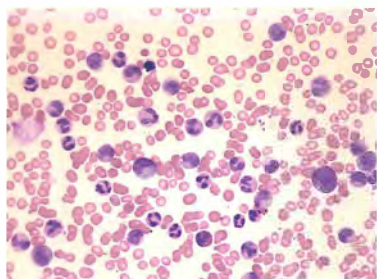


Figure 8-35: CML: peripheral blood smear showing excessive granulocytes

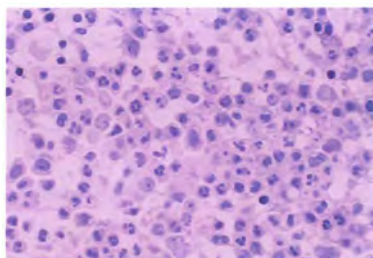


Figure 8-36: Myeloproliferative disorder (low power): CML. Hypercellular marrow. Myeloid elements are more abundant than the normal 3:1 myeloid:erythroid (M:E) ratio.

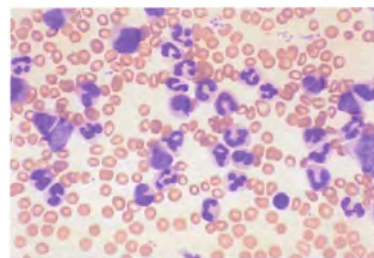


Figure 8-37: Myeloproliferative disorder: CML. Peripheral smear with the pyramid of maturation of granulocytes: promyelocytes, myelocytes, metamyelocytes, bands, and segmented neutrophils

Allogeneic HSCT remains the only proven curative therapy for CML but is reserved for select patients who develop TKI resistance.

Essential Thrombocythemia (ET)

ET (a.k.a. essential thrombocytosis) is the **least** aggressive of the myeloproliferative disorders. Suspect ET when an elevated platelet count is noted on a routine CBC. Although patients with ET have a normal life expectancy, they are at risk for thrombosis (venous and arterial) and hemorrhage.

Risk factors for clot with ET:

- > 60 years of age
- Previous history of thrombosis

Clinical presentation includes symptoms related to microthrombi (e.g., headaches, visual disturbances, erythromelalgia) as well as symptoms referable to larger clots (including miscarriages) and bleeding. **Erythromelalgia** is paroxysmal vasodilation of small arteries of the feet (mainly) and hands, causing burning pain, swelling, and erythema.

Diagnosis of ET based on the 2016 WHO criteria ultimately requires:

- the presence of > 450,000 platelets,
- megakaryocyte proliferation in the marrow,
- not meeting WHO criteria for other myeloproliferative disorders, and
- the presence of *JAK2*, *CALR*, or *MPL* mutations.

Alternatively, the diagnosis can be established by the exclusion of causes of reactive thrombocytosis (infection, inflammation, tissue injury, trauma, ischemia, splenectomy, surgery, and especially iron deficiency anemia) and the inclusion of the first 3 criteria above.

ET patients with *JAK2* mutation may have a higher risk of thrombosis than ET patients with *CALR* mutation.

Limit treatment for ET to:

- Patients with significant erythromelalgia
 - Prescribe aspirin to prevent thrombosis.
- Patients at high risk for thrombosis (i.e., > 60 years of age or any age with a history of thromboembolism or platelets > 1,000,000/ μ L)

- Give cytoreductive therapy with hydroxyurea. The goal is to reduce the platelet count < 400,000/ μ L (400×10^9 /L).
- Anagrelide, busulfan, and pegylated interferon are also used as alternative or 2nd line therapies.
- Patients with baseline platelets > 1,000,000/ μ L
 - These patients should receive a ristocetin cofactor assay to rule out acquired von Willebrand disease prior to being initiated on aspirin.
- For surgical patients with ET, there is a high perioperative risk of thrombosis and bleeding complications. Reduce very high platelet counts prior to surgery (with platelet pheresis if urgent surgery is required).

Like PV, ET can progress to MF and acute leukemia. Risk factors predicting decreased survival are age > 60, WBC > 11,000/ μ L, and history of thrombosis.

Polycythemia Vera (PV)

PV is characterized by increased RBC mass in the **absence** of erythropoietin and in association with the *JAK2* mutation. See Figure 8-38. Increased RBC mass most often results from erythropoietin stimulation, which can result from a primary or secondary disorder. Common secondary causes of increased RBC mass include hypoxemia (from obstructive sleep apnea, chronic obstructive pulmonary disease [COPD], smoking, right-to-left cardiac shunts, high altitude, carbon monoxide poisoning), tumor secretion of erythropoietin (from renal cell carcinoma, hepatocellular carcinoma), and androgens.

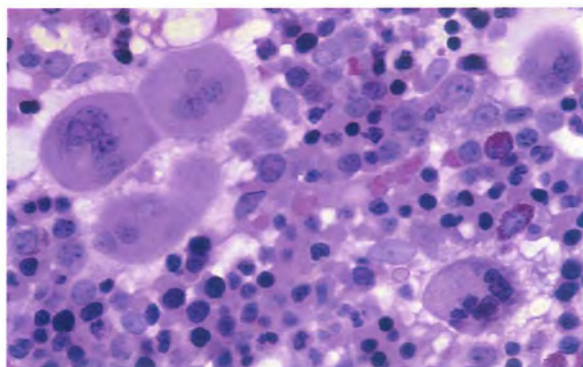


Figure 8-38: Myeloproliferative disorder: polycythemia vera. Bone marrow biopsy shows increased megakaryocytes and greatly increased erythroid precursors (with black condensed nuclei) and a decreased M:E ratio.

Patients with PV often present with an increased hematocrit with leukocytosis and thrombocytosis, the latter often causing erythromelalgia (more under [Essential Thrombocythemia \(ET\)](#) on page 8-45). Other common symptoms are headache, weakness, and dizziness, which are thought to be secondary to hyperviscosity from the elevated hematocrit. Patients with PV often complain of pruritus (perhaps secondary to increased histamine levels) after a hot bath or shower. Gout can result from rapid cellular turnover. Splenomegaly is common, and there is an increased risk for arterial and venous thrombosis (e.g., cerebrovascular accident, deep venous thrombosis) from disease.

Diagnose polycythemia with an elevated hemoglobin and hematocrit (Hgb/Hct) and/or RBC mass. Then evaluate for secondary causes of polycythemia via careful history and examination and pulse oximetry. Check serum erythropoietin (EPO) level, which is normal or increased in secondary causes and inappropriately low in PV. *JAK2* mutation testing is essential to confirm a diagnosis of PV, as virtually all patients will have a mutation in either exon 12 or 14 of this gene.

The 2016 WHO criteria for PV:

- Major criteria:
 - 1 of the following:
 - Hemoglobin > 16.5 g/dL (165 g/L) in men, > 16.0 g/dL (160 g/L) in women
 - Hematocrit > 49% in men, > 48% in women
 - Increased RBC mass (> 25% above mean normal predicted value)
 - Bone marrow biopsy showing hypercellularity for age with trilineage growth (panmyelosis), including prominent erythroid, granulocytic, and megakaryocytic proliferation with pleomorphic, mature megakaryocytes (differences in size)
 - Presence of *JAK2* V617F or *JAK2* exon 12 mutation
- Minor criterion:
 - Subnormal serum erythropoietin level

Diagnosis of PV requires meeting either all 3 major criteria or the first 2 major criteria and the minor criterion.

Note that bone marrow biopsy may not be required in cases with sustained absolute erythrocytosis (hemoglobin levels > 18.5 g/dL [185 g/L] in men, > 16.5 g/dL [165 g/L] in women; hematocrit 55.5% in men, 49.5% in women) if the 3rd major criterion (presence of gene mutation) and the minor criterion are present. However, initial myelofibrosis (MF; present in up to 20% of patients) can only be detected by performing bone marrow biopsy; this finding may predict a more rapid progression to overt MF (post-PV MF).

Treatment of PV is phlebotomy to a goal hematocrit of < 45% (to induce an iron-deficient state), which reduces mortality but may transiently increase the rate of thrombosis.

Low-dose ASA lowers the risk of thrombosis during this period. Cyto reduction therapy with hydroxyurea lowers

this thrombotic risk and is considered for older patients with leukocytosis. Pegylated interferon has also been used. Consider the *JAK2* inhibitor ruxolitinib for patients intolerant or refractory to hydroxyurea, particularly in the setting of symptomatic splenomegaly or severe constitutional symptoms. Allogeneic HSCT may be indicated in patients with evolving MF.

Increased mortality in patients with PV is related to thrombosis (venous or arterial)—an elevated hematocrit is prothrombotic. Mortality also results from conversion to AML and MF.

Primary Myelofibrosis (MF)

Primary MF is a clonal stem cell disorder of unknown cause that results in hyperplasia of atypical megakaryocytes. These megakaryocytes stimulate a nonclonal proliferation of fibroblasts, which then go on to cause fibrosis of the bone marrow ([Figure 8-39](#)). Secondary MF can result from transforming PV and ET, although it shares the same clinical manifestations as primary MF.

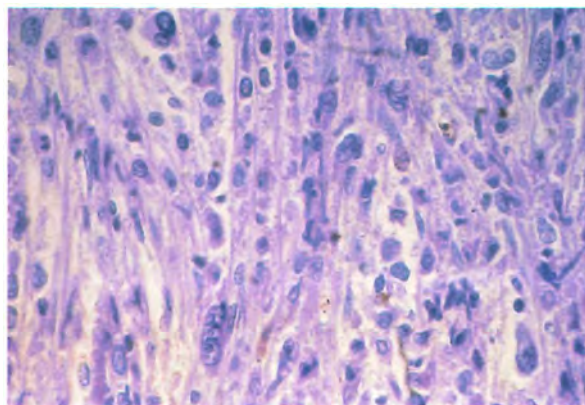


Figure 8-39: Myeloproliferative disorder: myelophthisis (replacement of bone marrow by a disease process)—in this case, myelofibrosis (replacement by reticulin)

The most common symptom of primary MF is fatigue. Early satiety and abdominal fullness are also common, attributable to hepatosplenomegaly. Screening labs show marked anemia and variable changes in WBCs and platelets, with eventual pancytopenia developing as disease progresses. Serum LDH can be increased.

The peripheral blood smear often shows teardrop cells—a finding that is common to diseases that infiltrate the marrow (e.g., metastatic cancer, tuberculosis, fungal infections). Marrow aspirate often results in a dry tap, and marrow biopsy is often strongly positive for the reticulin stain.

Allogeneic HSCT remains the only chance for cure, but this therapy is limited to younger patients. For the vast majority of patients, treatment is primarily supportive, including splenectomy for severe splenomegaly. The oral *JAK2* inhibitor ruxolitinib is approved to treat primary MF without the *JAK2* V617F mutation. The 2012 Comfort-II Phase 3 study showed significant improvement in weight loss, fatigue, splenic volume, and improved survival with the use of ruxolitinib.

LYMPHOPROLIFERATIVE DISORDERS

PREVIEW | REVIEW

- What are the common physical findings on initial presentation of non-Hodgkin lymphoma (NHL)?
- What is the term for an NHL that produces an IgM monoclonal gammopathy and is associated with hyperviscosity?
- What are the 2 general types of NHL?
- NHL prognosis depends on which 5 factors?
- Which monoclonal antibody targeting CD20 is incorporated into the treatment for most cases of NHL—whether indolent or aggressive?
- What is the treatment for asymptomatic follicular lymphoma?
- Marginal zone lymphoma is associated with which chronic infection?
- What is the difference between chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL)?
- What does rapid enlargement of previously stable lymph nodes in a patient with CLL/SLL suggest?
- What is the treatment for CLL/SLL without symptoms?
- What is the clinical presentation of hairy cell leukemia?
- What is the standard chemo regimen for diffuse large B-cell lymphoma?
- What cytogenetic abnormality is associated with Burkitt's? Characterize the clinical presentation.
- Which diseases are seen after radiation therapy to the chest during treatment of Hodgkin lymphoma?
- Primary central nervous system lymphoma in patients with HIV/AIDS is associated with which virus?
- Which virus is associated with posttransplant lymphoma?
- Which diseases are associated with an increased risk of lymphoma?
- What are the typical symptoms of multiple myeloma? The lab findings?
- Characterize the differences among monoclonal gammopathy of undetermined significance, smoldering myeloma, and multiple myeloma.

NOTE

Lymphoproliferative disorders range from slow-growing, asymptomatic tumors to the most aggressive malignancies. Some present mainly as **lymphomas** which are neoplastic cells growing as a **solid mass** in the lymph nodes, spleen, bone marrow, or solid organs. Others present more like **leukemias** which are neoplastic cells found

in the blood and bone marrow. It is not unusual to see overlap of these 2 entities. For example, patients with chronic lymphocytic leukemia (CLL) often have a solid component to their disease, termed small lymphocytic lymphoma (SLL). When present, the combined diagnosis of CLL/SLL is used. In other words, many lymphomas have small components of leukemia to them, and some leukemias have a component of lymphoma.

NON-HODGKIN LYMPHOMA (NHL)

The term non-Hodgkin lymphoma (NHL) encompasses a group of disorders characterized by clonal proliferation of lymphocytes (virtually all B or T cells). See Table 8-12 for prevalence of the cell-type neoplasms based on the 2016 revision of the World Health Organization (WHO) classification of lymphoid neoplasms.

Table 8-12: WHO Classification of the Most Common NHLs and Leukemias

Neoplasm	Type	Frequency (%)
B-cell	Diffuse large B-cell lymphoma	33
	Follicular lymphoma	22
	Extranodal marginal zone B-cell lymphoma	8
	CLL/SLL	7
	Mantle cell lymphoma	6
	Burkitt lymphoma	2
	Nodal marginal zone B-cell lymphoma	2
	Lymphoplasmacytic lymphoma	1
	Precursor B-cell neoplasms	< 1 each
	B-cell prolymphocytic leukemia	
	Splenic marginal zone B-cell lymphoma	
	Hairy cell leukemia	
	Plasma cell myeloma	
T-cell	Mature (peripheral) T-cell neoplasms	8
	Precursor T-lymphoblastic leukemia/lymphomas	2
	Primary systemic anaplastic large cell lymphoma	2

NHL may be associated with infectious etiologies, including tick-borne diseases, bacteria, and viruses, including human immunodeficiency virus (HIV), Epstein-Barr virus (EBV), human T-cell lymphotropic virus 1 (HTLV-1), and human herpesvirus 8 (HHV-8).

Patients with NHL often present with palpable adenopathy and constitutional symptoms (e.g., weight loss, fever, night sweats). Nodal growth can occur in nonpalpable areas as well, resulting in hepatosplenomegaly.

Airway obstruction or superior vena cava syndrome can result from nodal growth in the mediastinum; bowel or ureter obstruction may result from growth in the mesentery or retroperitoneum.

Some lymphomas, such as **Waldenström macroglobulinemia**, produce an IgM monoclonal gamma globulin that can lead to hyperviscosity (see **Waldenström Macroglobulinemia (WM)** on page 8-51) or autoimmune cytopenias (Coombs + anemia and/or thrombocytopenia), while others (CLL/SLL) cause agammaglobulinemia that leads to frequent infections. Cytopenias also can develop from hypersplenism and from bone marrow infiltration.

Diagnosis of lymphoma is made by an excisional biopsy or a core needle biopsy of a lymph node, which allows the pathologist to observe both the appearance of the cells and the architecture of the lymph node. Immunohistologic stains and flow cytometry also are performed. If there is a sizable leukemic component to the lymphoma, as in CLL/SLL, the diagnosis can be made by flow cytometry of the peripheral lymphocytes, looking for characteristic cell surface markers.

Once the diagnosis is made, staging is carried out using physical exam and CT scans of the neck, chest, abdomen, and pelvis. A bone marrow biopsy can be helpful to determine the nature of existing cytopenias.

Positron emission tomography (PET) scanning can be integrated into initial diagnostics and used in follow-up after treatment. PET uses radiolabeled glucose to image glycolysis in vivo. Areas that are relatively metabolically active (i.e., brain, heart, kidneys) take up the radiolabeled glucose and image brightly. Active malignancies also take up the tracer and become PET or 18-fluorodeoxyglucose (FDG) avid. Patients with NHL often have persistent masses seen on CT scan after treatment. These masses usually represent either residual lymphoma or fibrous scar tissue. A mass that does not fully resolve with treatment and is FDG avid represents persistent disease, while a lack of avidity likely represents remission or cure.

Indolent lymphomas have a long clinical course, measured over years. They are seldom cured with conventional chemotherapy, and early treatment has never been shown to improve survival over delayed treatment. Treatment is ordinarily held until symptoms develop, including bulky

adenopathy, constitutional complaints, or cytopenias from marrow infiltration—a close watch-and-wait strategy is employed. Treatment controls symptoms by placing the lymphoma in a temporary remission or decreasing the overall disease burden.

Aggressive NHLs grow more quickly—often becoming symptomatic early in the disease course. If left untreated, death follows within months. These rapidly growing lymphomas respond well to chemotherapy, and, while many ultimately relapse, an increasing number are being cured.

An individual patient's prognosis with NHL depends upon the subtype of lymphoma. The commonly utilized International Prognostic Index (IPI) uses 5 factors to help predict outcome:

- 1) Number of extranodal disease sites
- 2) Lugano stage (based on the Ann Arbor staging system with Cotswold modifications for both NHL and Hodgkin lymphomas; [Table 8-13](#))
- 3) Serum LDH (a marker for tumor burden)
- 4) Age
- 5) Performance status

Molecular and genetic markers can be incorporated for prognosis.

Know that there is growing use of monoclonal antibodies in the treatment of NHL.

Rituximab is a chimeric antibody directed against **CD20**, a surface marker found on many **B-cell** lymphomas. The binding of antibody to the neoplastic cell causes cell death by complement-mediated lysis, by cellular cytotoxicity, and directly by apoptosis. Rituximab is well tolerated even by elderly patients and can be used alone against indolent lymphomas or in combination with traditional chemotherapy against aggressive disease. Newer generation anti-CD20 antibodies, including **ofatumumab** and **obinutuzumab**, are being increasingly incorporated into the management of NHL.

Table 8-13: Lugano Staging System for NHL and HL

Stage		Involvement	Extranodal (E) Status*
Limited	I	1 node or a group of adjacent nodes	Single extranodal lesions without nodal involvement
	II	≥ 2 nodal groups on the same side of the diaphragm	Stage I or II by nodal extent with limited contiguous extranodal involvement
	II bulky†	Stage II as above, with bulky disease	N/A
Advanced	III	Nodes on both sides of the diaphragm; nodes above the diaphragm with spleen involvement	N/A
	IV	Additional noncontiguous extralymphatic involvement	N/A

* Tonsils, Waldeyer ring, and spleen are considered nodal tissue.

† Stage II bulky disease is treated as limited or advanced disease, depending on histology and prognostic factors.

Alemtuzumab is another monoclonal antibody directed against **CD52**, a cellular marker often found in CLL. This antibody can control otherwise refractory CLL, although its use has generally fallen out of favor due to its inherent risk for infectious complications.

Indolent B-Cell NHLs

Follicular Lymphoma

Follicular lymphoma is the most common of the indolent non-Hodgkin lymphomas (NHLs). Patients are often elderly and present at a late stage with diffuse, asymptomatic, peripheral lymphadenopathy. The hallmark is overexpression of the antiapoptotic protein **BCL-2**, caused by a **t(14;18)** translocation. As with other indolent lymphomas, follicular lymphoma is usually slow growing and generally incurable (except in very-early-stage disease in which it can sometimes be cured with local radiation therapy).

Treatment is **not** indicated in asymptomatic patients, and the decision to treat is based on disease grade, disease stage, symptoms, potential for organ compromise, cytopenias, and disease bulk. (Note: Grade 3B disease is treated as diffuse large B-cell lymphoma regardless of symptoms or stage.) For patients with asymptomatic advanced-stage disease, close observation is an appropriate option. For patients with low-grade/limited stage (Stage I and II) disease, acceptable considerations include close observation, single agent rituximab, or local curative radiation. For patients with asymptomatic low-grade/advanced-stage disease (Stage III or IV), the options may include close observation, single agent rituximab (R), R-chemotherapy, obinutuzumab chemotherapy, or clinical trials.

Symptomatic and bulky disease patients should be treated with chemoimmunotherapy over single agent rituximab given the importance for more rapid cytoreduction. The vast majority of patients with follicular lymphoma achieve excellent long-term survival, although those who relapse within 2 years of prior induction exhibit inferior long-term outcomes. Salvage options in the relapsed/refractory follicular lymphoma setting include a previously unused chemoimmunotherapy approach, targeted agents (including PI3K inhibitors), and Bruton tyrosine kinase inhibitors. Radioimmunotherapy, while studied extensively, is less utilized by most hematologists due to toxicity, logistical challenges in administration, and availability of better systemic options. Allogeneic HSCT is the only curative approach to follicular lymphoma and is reserved for clinically appropriate patients. CAR-T-based therapies are experimental and demonstrate promise in this cohort of patients.

Patients progress over time to develop cytopenias and die from infection or complications of anemia; ~ 10% of follicular lymphomas undergo a transformation to a more aggressive lymphoma—diffuse large B-cell lymphoma (DLBCL). Transformed DLBCL is more resistant to chemotherapy than its de novo counterpart, and such a transformation is often a sign of a rapidly fatal outcome.

Marginal Zone Lymphoma (MZL)

MZL is an indolent lymphoma that, in part, develops from chronic antigenic stimulation. It is separated into **mucosa-associated lymphoid tissue (MALT)** (extranodal), **nodal**, and **splenic** MZLs. Unlike many indolent lymphomas, MZLs are often found at an early stage. The most common location is the gastric or intestinal mucosa (MALT lymphoma), and the most common antigenic stimulant is chronic *H. pylori* infection. MZL can also occur in bronchial mucosa and salivary glands, and splenic MZL can arise from chronic **HCV** infection. Additional infectious agents associated with cutaneous lymphoma are *Borrelia burgdorferi*, *Chlamydomphila psittaci* (implicated in adnexal ocular lymphoma), *Campylobacter jejuni* (for the small intestine), and *Mycobacterium* species (for bronchial lymphoma).

When extranodal MZL is diagnosed, rule out infectious causes (i.e., *H. pylori* and HCV).

Early-stage gastric MALT lymphoma can be treated with antibiotics alone to eradicate *H. pylori* or with added radiation if the initial treatment fails. Early treatment of the other types of MZL with lung lobectomy (bronchial-associated lymphoid tissue [BALT] lymphoma) and splenectomy (symptomatic splenic MZL without hepatitis C) can result in a prolonged symptom-free remission. In patients with symptomatic splenic MZL, treat hepatitis C prior to considering splenectomy.

Advanced-stage MZL should be managed similarly to follicular lymphoma.

Chronic Lymphocytic Leukemia (CLL) / Small Lymphocytic Lymphoma (SLL)

CLL/SLL is an indolent disease characterized by the clonal proliferation of mature but poorly functioning B-cell lymphocytes (Figure 8-40) and smudge cells.

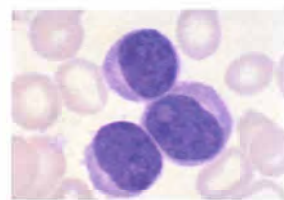


Figure 8-40: CLL/SLL (high-oil immersion): 3 leukemic lymphocytes

CLL and SLL are the same B-cell lymphocyte disease with different manifestations, depending on where the abnormal cells are found.

Typically, there is an initial leukemic phase (CLL; cells in the blood) that progresses to a lymphoma phase (SLL; cells in the lymph nodes).

Clinically, the majority of patients with CLL/SLL are diagnosed at an asymptomatic stage with a high lymphocyte count found on a routine CBC. Suspect CLL with the appearance of a **high lymphocyte count** and **smudge cells** (Figure 8-41 on page 8-50) on the peripheral blood smear. Smudge cells are cell remnants with no identifiable cytoplasmic membrane or nuclear structure. Of note, at least 5,000 B cells of a monoclonal origin (CD5+, CD20+, CD23+ cells; noted on flow cytometry) are required to diagnose CLL. Characteristic markers on the cell surface can differentiate CLL/SLL from other lymphomas with

leukemic components. The difference between CLL and SLL is largely semantic given the generally identical treatment implications. While CLL represents a more leukemic form of the disease, SLL represents the same clonal CLL population of cells encompassing lymph nodes.

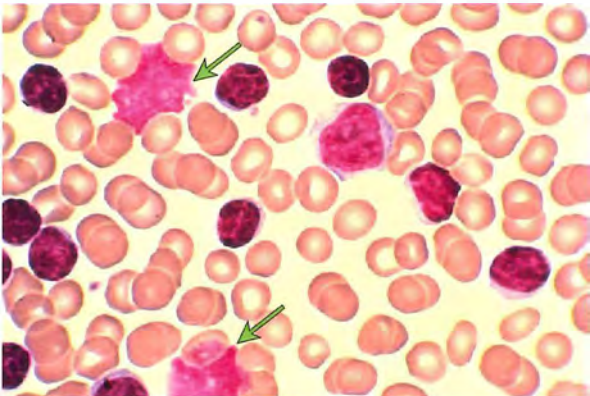


Figure 8-41: CLL/SLL: smudge cells

Prognosis has historically been based on the Rai staging system, a tool that is unique to CLL/SLL. It is shown in Table 8-14, along with the Binet system. The Rai system is used more often in the U.S., while the Binet system is used more in Europe. Molecular studies are increasingly being used and may offer better risk stratification.

Favorable prognostic findings:

- Mutated Ig heavy-chain variable region
- 13q deletion
- Low ZAP-70 and CD38 levels

Poor prognostic cytogenetics:

- 17p deletion
- 11q deletion

Asymptomatic patients with only high WBC are Rai system Stage 0 and have a near-normal life expectancy. (Although otherwise comparable in terms of staging and predicting patient outcomes, the additional subsets in the

Rai system have an advantage in predicting survival in the early stages of CLL; Binet Stage A includes Rai Stages 0, 1, and 2.)

With disease progression, the lymphoma element begins to dominate, and patients develop symptoms secondary to lymphadenopathy (Stage 1), hepatosplenomegaly (Stage 2), anemia (Stage 3), and thrombocytopenia (Stage 4). The cytopenias are due to bone marrow infiltration by leukemic cells, splenic sequestration, and antibody-mediated destruction (Coombs positive).

As with follicular lymphoma, ~ 10% of patients with CLL/SLL transform to diffuse large cell lymphoma (**Richter transformation**), a transformation often heralded by fever, rapid enlargement of previously stable nodal disease, and a rising LDH.

Treatment of asymptomatic CLL/SLL is mainly a watch-and-wait strategy, like other indolent lymphomas. However, indication for treatment includes advanced-stage disease (bulky disease or cytopenias), active symptoms, lymphocyte doubling in < 6 months, and steroid refractory autoimmune hemolysis. Treatment considerations include age, performance status, comorbidities, and genetic markers.

CLL/SLL is characterized by a disordered immune system. Frequent autoantibodies directed against RBCs and platelets develop, leading to immune-mediated hemolytic anemia and thrombocytopenia. The resultant cytopenias can be managed with prednisone. Paradoxically, CLL/SLL is also characterized by hypogammaglobulinemia. When patients with CLL/SLL and low immunoglobulin levels develop frequent infections (especially pneumococcus, *Staphylococcus*, *H. influenzae*, and herpes), they can be managed with monthly IVIG infusions.

Hairy Cell Leukemia (HCL)

HCL is a rare, indolent NHL with components of both lymphoma and leukemia characterized by immunohistochemical expression of CD11c, CD20, CD22, CD103, tartrate-resistant acid phosphatase (TRAP), and the

Table 8-14: Staging Systems for B-Cell Leukemias				
System	Stage	Clinical Findings	Risk Level	Median Survival (Years)
Rai	0	Lymphocytosis	Low	12
	1	Lymphocytosis + adenopathy	Mid	9
	2	Lymphocytosis + hepatosplenomegaly	Mid	7
	3	Anemia	High	1-2
	4	Thrombocytopenia	High	1-2
Binet	A	< 3 sites involved	Low	10
	B	≥ 3 sites involved	Mid	5
	C	Anemia and/or thrombocytopenia	High	3

*BRAF*V600E mutation. There is also a less common and aggressive variant HCL, which **lacks** the TRAP stain and *BRAF*V600E mutation. Patients with HCL often present with splenomegaly, pancytopenia, and a dry tap on bone marrow aspirate. Some patients may present with a leukocytoclastic vasculitis. The peripheral smear can show characteristic cytoplasmic “hairy” projections on the lymphocytes’ cell surface (Figure 8-42 and Figure 8-43). (Note: Patients with primary MF also may exhibit a dry tap, although they do not demonstrate the hairy cell projection cells as shown.)

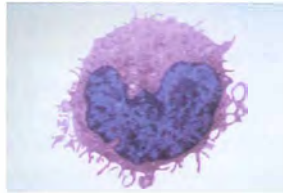


Figure 8-42: Hairy cell (electron microscope)

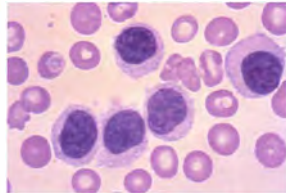


Figure 8-43: Hairy cell leukemia

Initial therapy is reserved for patients with symptomatic splenomegaly and/or cytopenias, while observation is appropriate for asymptomatic disease. Symptomatic disease is treated with purine analogs, such as cladribine (2-CDA) or pentostatin, with the capability of inducing long-term remissions. Anti-CD20 monoclonal antibody rituximab is often reserved in the salvage setting. Experimental use of *BRAF* inhibitors and alternate targeting agents, such as anti-CD22 antibodies, is a point of active investigation.

Waldenström Macroglobulinemia (WM)

WM (which is a subtype of lymphoplasmacytic lymphoma) is an indolent B-cell lymphoma characterized by the clonal expansion of lymphocytes with plasma cell properties that produce **monoclonal IgM**. Diagnosis is based on pathologic evaluation of lymph node/bone marrow, which often exhibit involvement by small lymphocytes, plasmacytoid lymphocytes, and plasma cells and production of IgM. The plasmacytic components of cells express CD138+ and CD38+ on IHC (immunohistochemistry), and the notable *MYD88* mutation is often present in these cases. Note: Patients with >10% of bone marrow involvement by disease generally have higher risk of developing symptomatic disease.

Clinical presentation includes:

- **Hyperviscosity syndrome** (e.g., headache, dizziness, vision disturbances) secondary to high levels of IgM. Look for “sausage-link veins” on funduscopy, which are tortuous veins caused by the hyperviscosity (Figure 8-44).
- **Constitutional** symptoms, oozing blood at mucosal surfaces, lymphadenopathy, and/or splenomegaly

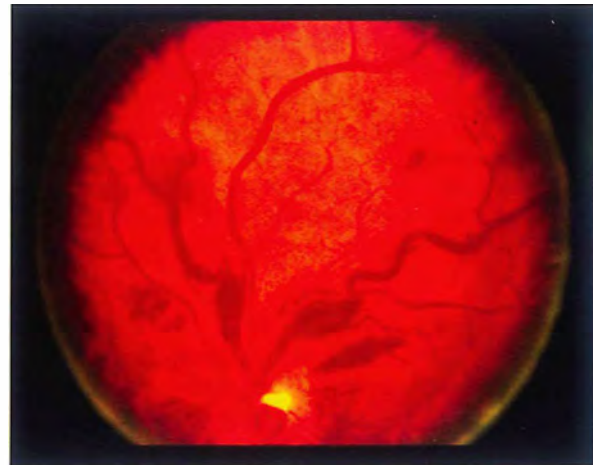


Figure 8-44: Retinopathy in Waldenström macroglobulinemia

Treat acute hyperviscosity syndrome with plasmapheresis. Prognosis depends upon age and the presence of anemia. As with other indolent lymphomas, initiate treatment only after symptoms develop. Therapy is typically rituximab-based and should only be started after plasmapheresis in the setting of hyperviscosity to prevent IgM flare.

Note: Hyperviscosity symptoms can occur with polycythemia vera (PV), leukocytosis > 100,000/ μ L (100×10^9 /L) in acute leukemias, WM, multiple myeloma (MM), and cryoglobulinemia. When the hyperviscosity and associated symptoms are due to **immunoglobulins** (i.e., WM, MM, cryoglobulins), it is called **hyperviscosity syndrome**. When hyperviscosity is due to **WBCs**, it is called **leukostasis**.

Aggressive B-Cell NHLs

Diffuse Large B-Cell Lymphoma (DLBCL)

DLBCL is the **most common** aggressive lymphoma. It can develop de novo or arise from a previously indolent lymphoma. While DLBCL is predominantly a disease of the lymph nodes, it can also develop in extranodal sites, such as the lung or liver. If left untreated, life expectancy is measured in months. The diagnostic work up for DLBCL includes a PET/CT, bone marrow biopsy, cytogenetics, and lymphoma FISH of diseased tissue to evaluate for *C-MYC*, *BCL-2*, and *BCL-6* translocations, which may influence the prognosis and treatment modality employed. Additionally, a baseline echocardiogram should be obtained to exclude cardiomyopathy in potential anticipation of cardiotoxic chemotherapy.

The most conventional regimen for DLBCL is **R-CHOP** (rituximab + cyclophosphamide, hydroxydaunorubicin [doxorubicin], Oncovin [vincristine], and prednisone), although iterations of this regimen may be modified based on molecular profiling of the disease. Localized DLBCL can be treated with 3 cycles of R-CHOP, followed by involved field radiotherapy. Advanced disease typically gets 6-8 cycles of R-CHOP.

Almost all patients respond to this treatment, and 50–60% get long-term disease control. 50% of these become refractory—or the lymphoma recurs soon after completing therapy. Patients with relapsed/refractory DLBCL should be referred for considerations of salvage treatment options, including chemoimmunotherapy and autologous HSCT, CAR-T therapy (presently FDA approved for relapsed/refractory disease after 2 lines of prior therapy), or clinical trial.

Burkitt Lymphoma

Burkitt's is the **most aggressive** of the NHLs and presents in the context of endemic EBV infection (Africa), sporadic occurrence (U.S. and Europe), and immunodeficiency (especially HIV/AIDS).

The genetic hallmark is translocation of the *C-MYC* (t(8;14)) oncogene, which results in aggressive cell turnover with rapid growth.

Know that for patients with HIV, the development of a Burkitt lymphoma is an **AIDS-defining illness** regardless of the CD4 count.

Presentation is typically an enlarging abdominal mass, and the rapid cell turnover may cause spontaneous tumor lysis syndrome. Dissemination to the CNS is common, and treatment with intrathecal chemotherapy is standard. Treatment consists of prolonged high-dose chemotherapy as well as treatment or prophylaxis for CNS involvement.

Mantle Cell Lymphoma (MCL)

MCL is a subtype of NHL that combines the least desirable characteristics of both classes of NHL. Like indolent NHL, it is incurable with standard chemotherapy, though modern therapies can lead to survival of 8–10 years. Like aggressive NHL, it can progress rapidly without treatment. There is usually bone marrow, peripheral blood, and spleen involvement, and patients often present with cytopenias and splenomegaly.

Extranodal involvement is common, especially in the GI tract, and there is often a leukemic component. The hallmark is overexpression of *MCL-1* gene product cyclin D1 due to the t(11;14) translocation. The decision to initiate treatment is often dependent on the aggressiveness of MCL and can range from close observation for indolent variants to multiagent chemoimmunotherapy for aggressive forms, followed by a consolidative autologous HSCT. Salvage options for relapsed/refractory patients includes lenalidomide, ibrutinib, or clinical trial.

T-Cell NHLs

T-cell NHLs are a heterogeneous group of lymphoproliferative disorders that include peripheral T-cell lymphoma not otherwise specified (PTCL-NOS), angioimmunoblastic lymphoma (AITL), and anaplastic large cell lymphoma (ALCL), among several other subtypes.

Risk factors include chronic immunosuppression, human T-cell leukemia virus Type 1 (HTLV-1) infection, celiac disease, Epstein-Barr virus (EBV) infection, and breast implants.

The most common PTCL-NOS includes **mycosis fungoides**, which is the most common subtype of T-cell lymphomas. Early disease is limited to the skin, but later disease develops in lymph nodes and peripheral blood. Patients with mycosis fungoides typically present with a generalized erythematous rash with plaque-like features, and biopsy often demonstrates small- to medium-sized atypical lymphoid cells that are positive for T-cell markers, including CD2+, CD4+, and CD20-. T-cell receptor gene rearrangement study often confirms mycosis fungoides. The disorder can be controlled in the early stages with photochemotherapy. Advanced disease involving systemic circulation (Sézary syndrome) is often treated with retinoids, interferon, pralatrexate, and brentuximab vedotin. As with other indolent lymphomas, the goal of treatment is control rather than cure.

The aggressive forms of T-cell NHL include a T-cell variety of diffuse large cell lymphoma, which is treated with multiagent chemotherapy, including CHOP (no rituximab, in contrast to R-CHOP used in DLBCL).

HODGKIN LYMPHOMA (HL)

HL (formerly called Hodgkin disease) is primarily a disease of the younger adult (unlike NHL), with an average age of 30 years at time of diagnosis. HL is also a **far more curable** illness than NHL, with cure rates of 95% in early stages and 65% in advanced stages. Patients with HL often present with an enlarged, painless lymph node, commonly in the neck and mediastinum.

Diagnosis is made by excisional biopsy—**not fine needle aspiration (FNA)**. Although the **Reed-Sternberg cell** (a B cell that resembles owls' eyes; [Figure 8-45](#)) is the classic and specific histological finding, the diagnosis is aided by immunohistochemical staining, which exhibits CD15, CD30, and CD45 positivity.

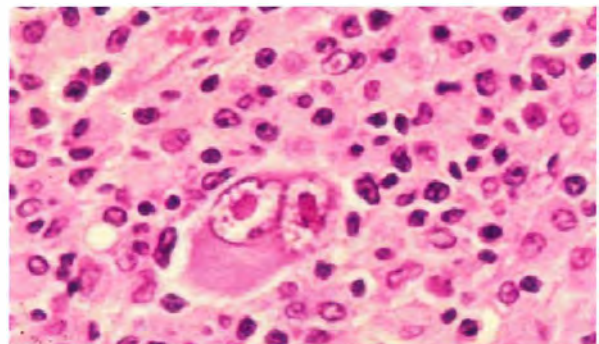


Figure 8-45: Reed-Sternberg cell as seen in Hodgkin lymphoma

The WHO classifies these lymphomas as follows:

- **Nodular lymphocyte-predominant Hodgkin lymphoma** (Treatment differs from classic Hodgkin lymphoma.)
- **Classic Hodgkin lymphoma** (most common):
 - Nodular sclerosis (most common)

- Lymphocyte-rich
- Mixed cellularity
- Lymphocyte-depleted

These 4 subtypes of classic lymphoma are similar and are typically treated in a similar fashion. Accurate staging using the Lugano classification ([Table 8-13 on page 8-48](#)) is critical in HL so as to avoid both undertreatment and overtreatment.

Workup/Staging: H&P; CXR; ESR, echocardiogram, pulmonary function test, CT of neck, chest, abdomen, and pelvis; and, in selected cases, bone marrow aspiration and biopsy. PET scan is used both for initial staging and to monitor response to treatment. Always restage after treatment.

Treat with **ABVD** (doxorubicin [Adriamycin], bleomycin, vinblastine, and dacarbazine):

- Early-stage disease (Lugano Stage 1 or 2 with or without bulky disease or B symptoms [i.e., fever, drenching night sweats, and weight loss]): 2–4 cycles of ABVD +/- radiation to disease sites
- Advanced disease (Stage 3 or 4): brentuximab vedotin + BVD for 6 cycles or 6–8 cycles of ABVD + radiation to any bulky sites
- Relapsed or refractory disease: high-dose chemotherapy + autologous HSCT
- Relapsed disease after transplant or multiple lines of chemotherapy: brentuximab vedotin, an anti-CD30 monoclonal antibody-drug conjugate that releases its antimitotic agent upon binding to CD30+ cells present in HL. Programmed cell death 1 (PD-1) and programmed cell death ligand 1 (PD-L1) inhibitors have shown good salvage activity.

ABVD is less likely than previous treatments to cause sterility (but still can), and it can cause cardiac, pulmonary, and neuropathic toxicities from the doxorubicin, bleomycin, and vinblastine, respectively.

Radiation to the chest is associated with increased risk of future solid tumors, including lung and breast cancer. Women who receive radiation to the chest should have an annual mammogram and breast MRI starting 8–10 years after treatment or at 40 years of age, whichever comes first. Also remember to watch for hypothyroidism and cardiovascular complications, including premature atherosclerosis.

LYMPHOMA AND IMMUNOSUPPRESSION

Patients with both congenital and acquired immunodeficient states are at increased risk for lymphoma. In adults, the 2 most common immunodeficient states are HIV/AIDS and iatrogenic immunosuppression after solid organ transplant.

Lymphoma and HIV

The majority of HIV-associated lymphomas are aggressive NHLs, with DLBCL and Burkitt's predominating. Whether or not antiretroviral therapy (ART) has

impacted the incidence of NHL in HIV/AIDS is unclear. ART seems to have reduced the incidence of lymphoma in patients with CD4 < 50 cells/μL (0.05×10^9 cells/L), but Burkitt's is increasing in incidence in patients with higher CD4 counts. Patients with HIV are also at increased risk for Hodgkin lymphoma, and control of the infection has not altered this risk.

Primary CNS lymphoma (DLBCL limited to the CNS) is universally associated with Epstein-Barr virus (EBV) in patients with HIV/AIDS. Primary effusion lymphoma (PEL) usually presents as ascites or pleural effusion and is associated with human herpesvirus 8 (HHV-8). HIV/AIDS-associated HL presents more often with extranodal disease and B symptoms.

Treatment is similar to that given to patients without HIV, except that rituximab may not show benefit in HIV+ patients with DLBCL and CD4 counts < 50 cells/μL due to the increased risk of death from infection.

More information is located in [Hematologic Manifestations of HIV and AIDS on page 8-55](#).

Lymphoma and Posttransplant

Posttransplant lymphoproliferative disorders occur in approximately 5% of patients with solid organ transplants. The risk of lymphoma is highest in the 1st year after transplant and is associated with exposure to chronic T-cell immunosuppression. The lymphoma is often composed of nonclonal B cells. > 90% of patients' early lymphomas are EBV+. When disease occurs, it is often at a late stage with extranodal manifestations.

Treatment consists of lowering the degree of immunosuppression—allowing anti-EBV immunity to attack the lymphoma cells. If this is not tolerated, attempt treatment with chemotherapy.

Quick Review

Remember these conditions associated with an increased risk of lymphoma:

- Chronic autoimmune thyroiditis (a.k.a. Hashimoto's)
- Sjögren syndrome
- Sarcoidosis
- Celiac disease
- Chronic *H. pylori*
- EBV
- HIV/AIDS
- Organ transplant

PLASMA CELL DISORDERS

Multiple Myeloma (MM)

MM is a neoplasm of B cells that results in a clonal expansion of plasma cells. These cells produce a monoclonal (M) component that can be intact immunoglobulin or fragments of heavy or light chains. Any immunoglobulin subclass (IgG, IgA, IgD, IgE, and IgM) can appear as the M component.

In MM, bone pain is the most common symptom—often localized in the back or ribs. Tumor cells invade bone and release osteoclast-activating factor, creating punched-out lytic lesions that are seen on radiographs but not on bone scans—because there is no associated new bone formation. Pathologic fractures are common.

Frequent infections result from a diffuse hypogammaglobulinemia. While total immunoglobulin levels are elevated, normal immunoglobulin production is suppressed and catabolism of immunoglobulin is accelerated.

Renal failure can result through a multitude of mechanisms, including hypercalcemia, amyloid deposition, tubular obstruction, and direct toxic effects of the paraproteins.

Additional clinical symptoms secondary to hypercalcemia, anemia, and neuropathy develop. Plasmacytomas (plasma cell tumors) can cause local symptoms, depending on their location, including spinal cord compression. Plasmacytomas are often treated with radiation with close follow-up.

Think about myeloma when you see:

- Presentation:
 - Back/Bone pain
 - Anemia
 - Renal failure
- **Plus ≥ 1 of the following labs:**
 - Rouleaux formation on peripheral blood smear (Figure 8-46)
 - Hypercalcemia
 - Increased creatinine +/- Type 2 (proximal) renal tubular acidosis
 - Normocytic/normochromic anemia
 - Elevated total protein but decreased albumin with **decreased** anion gap (due to increased positively charged paraprotein)

Think **CRAB** (calcemia [elevated], renal failure, anemia, bone involvement).

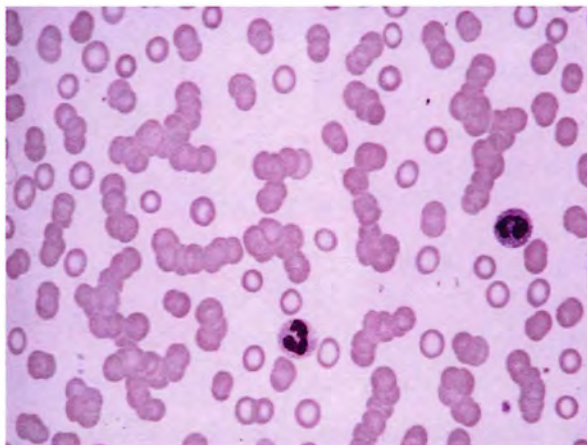


Figure 8-46: Rouleaux cell formation showing stacked long chains of RBCs

Diagnose with a serum (SPEP) and urine protein electrophoresis (UPEP) with immunofixation to detect the monoclonal protein, but know that the plasmacytoma variant may not have an M spike. Furthermore, myelomas that produce only light-chain immunoglobulins do not have an M spike. Serum/Urine immunofixation and serum free light chain assay are additional studies that can help confirm the monoclonal protein.

Measure serum viscosity if the M-protein concentration is > 5 g/dL (50 g/L) or if the patient has symptoms such as headache.

Whole-body low-dose CT or PET/CT is recommended as initial diagnostic workup for patients suspected to have multiple myeloma or plasmacytoma. However, skeletal survey (done by x-ray) is acceptable in certain circumstances, although it is less sensitive than CT or PET/CT to detect osteolytic lesions. Bone scan is **not** helpful here.

Bone marrow biopsy assists with determining the definitive diagnosis ($> 10\%$ plasma cells in bone marrow sample).

Patients with a 10–60% clonal plasma cell population in the bone marrow or those with symptomatic state with a negative skeletal survey should receive a whole body MRI or PET/CT to exclude bone involvement.

Measurement of serum β_2 microglobulin (β_2 MG) helps predict survival and is used in the International Staging System (ISS; Table 8-15). β_2 MG is a protein that is associated with MHC Class I heavy chains—found on the surface of nucleated cells. An increase in its amount tells you that extra lymphocytes are circulating.

Table 8-15: International Staging System for Multiple Myeloma

Stage	Definition	Median Survival (Months)
I	β_2 MG < 3.5 mg/L Albumin ≥ 3.5 g/dL (35 g/L)	62
II	Neither I nor III	44
III	β_2 MG ≥ 5.5 mg/L	29

Multiple myeloma must be distinguished from the vastly more common monoclonal gammopathy of undetermined significance (MGUS) and from smoldering myeloma, which is based on the number of plasma cells in the bone marrow and evidence of end-organ damage. See Table 8-16.

Staging for MM also includes the Durie-Salmon system (which utilizes level of anemia, hypercalcemia, presence of lytic lesions, and level of paraprotein) but may be supplanted by the much simpler ISS (Table 8-15).

Once the patient is diagnosed and stratified by cytogenetics into low-, medium-, or high-risk categories, decide if the patient is a candidate for autologous HSCT (based on age, functional status, and risk category). The chemotherapy regimen differs if a transplant is an option, and

Table 8-16: Monoclonal Gammopathies

Name	Diagnostic Criteria
Monoclonal gammopathy of undetermined significance	Serum monoclonal protein < 3 g/dL (30 g/L), bone marrow plasma cells < 10%, and absence of end-organ damage
Smoldering myeloma (asymptomatic myeloma)	Monoclonal protein $\geq$ 3 g/dL (30 g/L) or bone marrow plasma cells $\geq$ 10%, and absence of end-organ damage
Multiple myeloma	Presence of monoclonal protein (in urine or serum), and bone marrow plasma cells > 10% or biopsy-proven plasmacytoma, and evidence of end-organ damage (i.e., lytic bone lesions, anemia, hypercalcemia, chronic kidney disease attributable to the plasma cell disorder) or > 60% clonal population of plasma cells

melfalan chemotherapy is typically avoided with stem cells typically collected after 4–6 cycles of primary induction therapy. The disease-free interval can be improved by induction chemotherapy preceding the transplant. With the many effective remission-inducing therapies, including immunomodulatory derivatives (e.g., lenalidomide, pomalidomide, thalidomide), proteasome inhibitors (e.g., bortezomib, carfilzomib), and steroids (e.g., dexamethasone), some responses are similar to transplant, but the survival edge goes to the patients receiving early transplant after primary induction. Bisphosphonates are important to reduce the risk of skeletal-related events in patients with myelomatous skeletal involvement, osteopenia, or osteoporosis. Treat plasmacytomas (solitary plasma cell lesions without systemic end-organ damage) with local radiation.

Monoclonal Gammopathy of Uncertain Significance (MGUS)

Both MM and MGUS have an association with previous heavy exposure to pesticides. MGUS is seen in 1% of people > 50 years of age and 10% of people > 75 years of age. It is often found incidentally on protein electrophoresis on lab workup for other processes (e.g., neuropathy).

Patients with MGUS have:

- bone marrow plasma cells < 10%,
- no bony lesions,
- no end-organ damage, and
- M components < 3 g/dL (30 g/L).

Any immunoglobulin subtype may be seen (i.e., G, A, M, D, E). Urinary light chains are absent. There is no increased risk of infection, renal failure, or anemia.

A risk stratification model including M spike > 1.5 g/dL (15 g/L), non-IgG subtype, and an abnormal serum free light chain ratio is useful for predicting progression. Depending upon these 3 variables, 5% (with no risk factors) to 58% (with all 3 risk factors) progress to multiple myeloma within 20 years.

There is no role for preemptive therapy with MGUS.

Follow-up for patients with MGUS includes serial monitoring of SPEP, UPEP, CBC, and chemistry panel.

Patients with smoldering myeloma (asymptomatic myeloma) do not require treatment either but are at higher risk of progression to symptomatic myeloma and should have more involved follow-up, including a CBC, creatinine, calcium, and SPEP/UPEP every 3–6 months, along with an annual skeletal survey.

HEMATOLOGIC MANIFESTATIONS OF HIV AND AIDS

PREVIEW | REVIEW

- What is the cause of thrombocytopenia in HIV-infected patients?
- What is the pathophysiologic rationale of venous thromboembolism in HIV patients?

OVERVIEW

CD4+ lymphopenia is the hallmark of HIV infection. However, RBC, WBC, and platelet numbers and functions are affected by HIV/AIDS. Approximately 75% of patients develop anemia, 50% develop neutropenia, and 40% develop thrombocytopenia.

Myeloid and erythroid colony-forming precursor activity is inhibited by HIV infection. In vivo HIV infection of stem cells occurs rarely, but infection by HIV leads to the depletion of granulocytic, monocytic, erythroid, and megakaryocytic colony-forming units. Suppression of hematopoiesis by HIV will occur through induction of TNF- α . With highly active antiretroviral therapy (HAART), counts rise for WBCs (especially polymorphonuclear neutrophils, platelets) and CD4+ T cells.

Review of the peripheral blood smear is a key element of the evaluation of cytopenias in patients with HIV. Lymphocytosis and the presence of atypical or activated lymphocytes is seen early in the disease, with lymphopenia present when the disease becomes more advanced. Anemia is usually normochromic and normocytic, but macrocytic anemia can occur because of antiretroviral drug effects (e.g., zidovudine, stavudine). Macrocytosis can also be seen with advanced disease, as well as anisocytosis, poikilocytosis, and rouleaux formation. In advanced infection, hypogranular neutrophils and Pelger-Huët forms (WBCs with bilobed nuclei instead of trilobed) also may be seen. When thrombocytopenia occurs, the mean platelet volume can be normal; however, if there is immune-mediated destruction of platelets, large platelets may be seen on peripheral smear. Bone marrow examination may show hyper-, normo-, or hypocellularity. Marrow stromal effects may be seen, and when megakaryoblastic changes occur, they are usually associated with zidovudine and stavudine.

In general, cytopenias encountered in HIV can be due to multiple causes, and infection may directly or indirectly affect the bone marrow. Medications and malignancies can be factors in anemia, neutropenia, and thrombocytopenia.

ANEMIA

In the anemia associated with HIV, anemia of chronic disease, there is blunted production/response to erythropoietin, suppression of CFU-GEMM (HIV inflammatory cytokines), infiltration of the marrow by plasma cells, and the possibility of infections, such as parvovirus, typical and atypical mycobacterium, histoplasmosis, and CMV. Medications, such as reverse transcriptase inhibitors, ganciclovir, trimethoprim/sulfamethoxazole, and amphotericin B, can cause decreased production of RBCs. Hemolysis may be induced by indinavir, trimethoprim/sulfamethoxazole, and dapsone in G6PD deficiency. B₁₂, folic acid, and iron deficiencies also are causes of anemia in patients with HIV. Hematologic toxicities of antiretroviral agents and of anti-infectious agents can cause anemia.

Anemia is an independent risk factor for clinical progression of HIV disease and impacts survival as well. Treatment involves discovering the precise etiology of the anemia and beginning HAART. Improvement can be seen in 2–3 months, with maximum improvement at 12 months after HAART. Erythropoietin may help accelerate recovery from anemia.

LEUKOPENIA AND NEUTROPENIA

Patients with HIV often become neutropenic and especially leukoneutropenic. Inflammatory cytokines, including TGF- β and TNF- α , will suppress myelopoiesis, as will the HIV proteins tat and p24. G-CSF levels also are reduced. Medications may suppress WBC production in patients who have opportunistic infections, such as *Pneumocystis jiroveci*, toxoplasmosis, or CMV. Myelosuppression is associated with high dosages of zidovudine but usually improves with HAART. Bone marrow involvement may be a cause of neutropenia, as with other cell lines, when mycobacterium, CMV, or HIV malignancies compromise the marrow. Patients with advanced HIV may have functional defects in platelets. As with anemia, the use of HAART and the stimulation of WBC production with GM-CSF or G-CSF may accelerate recovery.

THROMBOCYTOPENIA

Thrombocytopenia can be seen in 40% of HIV-infected patients. Megakaryocytes may be infected and production decreased, but as in non-HIV patients, immune thrombocytopenia can also be seen. Besides the usual mechanisms of platelet coating by antibodies, antiplatelet glycoprotein antibodies cross-react with HIV envelope proteins and anti-HIV antibodies bind to platelets.

Start with HAART for HIV to raise the platelet count. Further treatment usually involves corticosteroids, IVIG, anti-RhD, and even splenectomy or splenic irradiation.

For refractory cases, dapsone, danazol, vincristine, and interferon- α are options. The role of romiplostim and eltrombopag has not been reviewed in major controlled studies.

THROMBOTIC MICROANGIOPATHY

TTP incidence does not seem to be increased in HIV patients over the general population, but atypical hemolytic uremic syndrome (aHUS) appears more frequently in patients with advanced HIV infection. Treatment, as in patients who are not HIV infected, involves plasma exchange and corticosteroids. In severe aHUS, eculizumab (a complement C5a inhibitor) may be useful.

THROMBOEMBOLIC DISEASE

In advanced HIV disease there can be a decrease in protein S and an increase in Factor 8 along with inflammatory cytokines such as TNF- α , IL-1, and IL-6, which may activate the coagulation and downregulate activity of protein C, leading to thromboembolic disease. The roles of anticardiolipin antibodies and protease inhibitors are yet to be fully implicated as mechanisms for thromboembolic disease in HIV patients.

There is a higher incidence of venous thromboembolism (VTE)—compared to uninfected matched controls—in HIV-infected patients with clinical AIDS who are > 45 years of age and taking indinavir or megestrol acetate. It seems that HIV-infected patients < 50 years of age have a higher incidence of VTE, and patients with HIV/AIDS who develop thromboembolic disease have increased mortality. Management of VTE in HIV patients is the same as in those who are not infected with the virus, but the use of warfarin anticoagulants can be complicated by its interactions with drugs used in HAART.

HEMATOLOGIC CHEMOTHERAPY DRUG HIGHLIGHTS

PREVIEW | REVIEW

- What is the hallmark toxicity associated with cyclophosphamide?
- What is the signature toxicity associated with anthracyclines?

NOTE

There is quite a bit of overlap between hematologic and oncologic therapies. The agents used in both areas are duplicated, with the relevant hematologic malignancies shown in **green font** in this topic.

CYTOTOXIC CHEMOTHERAPY

Alkylating Agents

Melphalan (Alkeran) is an alkylating agent used to treat **multiple myeloma** and other plasma cell tumors. Myelosuppression is common.

Cyclophosphamide is used to treat **B-cell lymphoma** (as part of R-CHOP, a drug regimen that also includes rituximab, doxorubicin, vincristine, and prednisone), breast cancer, **multiple myeloma**, and some **leukemias**. Like temozolomide (which is used to treat brain cancer), it can cause nausea, vomiting, and myelosuppression. Cyclophosphamide can cause hemorrhagic cystitis when used in high doses.

Anthracyclines

Doxorubicin (Adriamycin), **daunorubicin**, and **idarubicin** are antitumor anthracycline antibiotics used to treat many malignancies, including breast cancer, **lymphomas**, acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), soft tissue sarcoma, and ovarian cancer. Doxorubicin in its liposome form is used to treat Kaposi sarcoma, ovarian cancer, and **multiple myeloma**. Anthracyclines can cause irreversible cardiomyopathy, and risk is dose dependent. A baseline echocardiogram is required prior to administering this agent. Also note that therapy-related MDS/AML can occur approximately 1–3 years after anthracycline exposure.

Antimetabolites

Hydroxyurea (Hydrea, Droxia) inhibits ribonucleotides reductase. It is used in **myeloproliferative disorders** (especially CML and **polycythemia vera**), **sickle cell disease**, and in **blast crisis of AML**. Myelosuppression is potentially dose limiting. Leg ulcers can occur.

Methotrexate is a folate antimetabolite used in several malignancies, including breast cancer, head and neck cancer, **leukemias**, and **CNS lymphomas**. To minimize toxicity, follow high-dose methotrexate with leucovorin “rescue” and monitor drug levels. Methotrexate toxicities include myelosuppression, mucositis, diarrhea, renal dysfunction, hepatotoxicity, and acute cerebral toxicity.

Azacitidine (Vidaza) is a demethylating agent used to treat **myelodysplastic syndrome**.

Purine and Pyrimidine Analogs

Cladribine (2-CDA [chlorodeoxyadenosine]; Leustatin) is an extremely interesting drug used in **hairy cell leukemia**, **CLL**, and **low-grade lymphomas**. It is a purine analog that induces apoptosis, the normal programmed death of cells, by blocking DNA synthesis. Cladribine can induce durable remission in hairy cell leukemia. Side effects include fever and infection.

Fludarabine and **pentostatin** (Nipent) are other drugs that appear to work similarly to cladribine. They are

used to treat **low-grade lymphomas** and **CLL**. Both of these purine analogs are associated with increased risk of opportunistic infections, so long-term prophylaxis for *Pneumocystis jiroveci* pneumonia and herpes simplex virus is recommended.

Cytarabine (a.k.a. cytosine arabinoside) is a pyrimidine analog used to treat several **leukemias** and **non-Hodgkin lymphomas**. Side effects are nausea/vomiting, myelosuppression, and conjunctivitis (treated with steroid eye drops).

Decitabine (5-aza-2'-deoxycytidine; Dacogen) is a pyrimidine analog used to treat **myelodysplastic syndrome**. Myelosuppression is common. **Azacitidine** is also in this class.

Vinca Alkaloids

Vinblastine and **vincristine** are vinca alkaloids, which are antimicrotubule agents used to treat **lymphomas** and testicular cancer. **Peripheral neuropathy** and **constipation** can occur.

Topoisomerase Inhibitors

Etoposide inhibits topoisomerase II, a DNA replication enzyme. It is used to treat testicular germ cell tumors, small cell lung cancer, gastric cancer, and **lymphomas**. Myelosuppression is common. Therapy-related MDS and secondary AML can occur.

TYROSINE KINASE INHIBITORS (TKIs)

The TKIs prevent cell proliferation by blocking a variety of cell-signaling pathways. These agents have antiangiogenic and/or antiproliferative properties.

Imatinib (Gleevec) was the first TKI. It blocks the initiation of the BCR-ABL1 pathway and is used in chronic myelocytic leukemia (CML) and gastrointestinal stromal tumors (GIST).

Dasatinib (Sprycel) and **nilotinib** (Tasigna) are other TKIs used to treat CML. All can cause edema and nausea.

Ibrutinib (Imbruvica) is a Bruton TKI, which inhibits malignant B-cell proliferation. It is used in **CLL/SLL**, **Waldenström macroglobulinemia**, and **mantle cell lymphoma**. Potential toxicities include bleeding and arrhythmias.

BIOLOGICS — IMMUNOTHERAPY AGENTS

Pembrolizumab, **atezolizumab**, **avelumab**, **durvalumab**, and **nivolumab** are humanized IgG4 anti-PD-1 or anti-PD monoclonal antibodies. They act as immunomodulators by blocking activation of the programmed cell death 1 (PD-1) receptors on T cells. This class of immune therapy drug has had a high impact in the treatment of cancer patients, as long-term responses are possible even in metastatic disease. They are used to treat lung, renal, head/neck, urothelial, and hepatocellular cancers; melanoma; and **Hodgkin lymphoma**. Pembrolizumab has been approved for any cancer that exhibits **microsatellite instability** or a **mismatch repair defect**. These agents can have immune-related adverse events (IRAE) with nearly every organ system at risk. Examples include hypothyroidism, pneumonitis, nephritis, hypophysitis, skin toxicity, adrenal insufficiency, and neuritis.

Lenalidomide (Revlimid) and **pomalidomide** are derivatives of **thalidomide**. All 3 of these drugs have immunomodulatory, antiangiogenic, and antitumor effects. They are used to treat **multiple myeloma** and **myelodysplastic syndrome**. They are extremely teratogenic and contraindicated in pregnancy. Other side effects include venous thrombosis and Stevens-Johnson syndrome.

MISCELLANEOUS

Arsenic trioxide (Trisenox) is a differentiation agent used to treat acute promyelocytic leukemia (**APML**), usually in conjunction with **all-trans retinoic acid (ATRA)**. 30% of APML patients can subsequently develop differentiation syndrome (formerly retinoic acid syndrome) with fevers, weight gain, and hypoxia. This can be fatal, and prompt treatment with steroids is required while withholding therapy. Monitor for QT prolongation.

Denileukin diftitox (Ontak) is a unique compound that binds to the IL-2 receptor (CD25) on T cells. After binding, the diphtheria toxin is introduced into the cell, which then inhibits protein synthesis. It is used in patients with **cutaneous T-cell lymphomas**. It can cause hypersensitivity reactions.

Bortezomib (Velcade) and **carfilzomib** (Kyprolis) are proteasome inhibitors, a class of agents that prevent targeted proteolysis, affecting intracellular signaling cascades. These agents are used for **multiple myeloma** and **mantle cell non-Hodgkin lymphoma**.

Idelalisib (Zydelig) is a signal transduction inhibitor that is approved to treat **CLL** and other **indolent lymphomas**. Monitoring for hepatotoxicity is required.

HEMATOPOIETIC STEM CELL TRANSPLANTATION (HSCT)

Allogeneic HSCT is the procedure utilizing the transfer of a donor's hematopoietic stem cells to the recipient. Potential stem cell donor sources include umbilical cord, sibling, haploidentical (parent or offspring), or an unrelated donor. If the donor and recipient are identical twins, it is more specifically called a **syngeneic** transplantation. Allogeneic HSCT is often used in the management of acute leukemias and in certain lymphomas. The pretransplant chemotherapy, donor type, and stem cell collection source (i.e., peripheral blood or bone marrow) influences cellular engraftment (acceptance of donor stem cells by the recipient's marrow) as well as toxicity.

Autologous HSCT is a procedure using a patient's own hematopoietic stem cells after they receive high-intensity chemotherapy. This procedure is typically used in multiple myeloma, relapsed/refractory Hodgkin's, relapsed/refractory non-Hodgkin lymphoma, and in solid tumors (e.g., testicular cancer).

HSCT survivors are at risk for several long-term complications:

- **Secondary cancers** can include both **solid tumors** and **hematologic malignancies** (e.g., leukemia, myelodysplastic syndrome). Women who undergo chest radiotherapy are at particularly high risk for **breast cancer**; screen with annual mammography or breast MRI.
- Risks of **atherosclerotic cardiovascular disease** and **heart failure** are both increased. Use of calcineurin inhibitors (e.g., cyclosporine), steroids, anthracycline chemotherapy, and chest irradiation are all risk factors for heart disease after HSCT. Screen all patients with a history of HSCT for modifiable cardiovascular risk factors.
- **Lung disease** after HSCT can be due to infections, toxicity from bleomycin, or chronic graft-versus-host disease. Use periodic pulmonary function testing to screen patients who have undergone allogeneic HSCT.
- Patients can develop **liver disease** after HSCT from chronic graft-versus-host disease, iron overload (from recurrent blood transfusions), or HBV/HCV infection or reactivation.
- HSCT patients are chronically immunosuppressed and at risk for **infections**. For more on solid organ transplantation, see the **Allergy & Immunology** section.
- **Graft-versus-host disease (GVHD)** is unique to allogeneic HSCT recipients: The donor immune cells react to recipient cells as foreign. GVHD can be acute or chronic. **Acute** GVHD presents with a maculopapular rash, GI symptoms (e.g., nausea, vomiting, diarrhea), and high bilirubin and occurs within the first 100 days. **Chronic** GVHD presents with a skin rash (thickening/tightening of the skin), dry mouth, oral and gastrointestinal ulcers and erosions, and high bilirubin. Steroids without calcineurin inhibitors are the main treatment for both acute and chronic GVHD.

Table 8-17 reviews the indications for HSCT.

Table 8-17: Uses of Hematopoietic Stem Cell Transplantation (HSCT)

	Disease	Effectiveness / Notes
Malignant Diseases	AML	40–70% cure if done during 1 st complete remission
	ALL	Typically indicated for transplant-eligible, high-risk patients in 1 st remission of ALL Also done in 2 nd remission if 1 st remission is short
	CML	Consider for CML in accelerated phase, blast phase, or tyrosine kinase inhibitor (e.g., imatinib, dasatinib) failure.
	Myelodysplastic syndrome	Allogeneic HSCT is appropriate in high-risk disease.
	CLL*	Allogeneic HSCT is the only curative approach. Short-term follow-up reveals 50% are disease free.
	NHL*	Autologous HSCT is used in relapsed aggressive NHL, and allogeneic is reserved for higher-risk disease.
	Hodgkin lymphoma*	Indicated in relapsed disease Up to 90% disease-free survival at 3 years
	Multiple myeloma*	Autologous HSCT is indicated as a consolidative approach in patients who achieve an acceptable response to primary induction chemotherapy. It can improve remission after patient achieves primary response to chemotherapy.
	Breast cancer*	Multiple studies have not confirmed an established role for transplant in this disease.
Nonmalignant Diseases	Testicular cancer*	Consider in relapsed disease after chemotherapy Disease-free survival in 10–20% with severe disease suggests there are much better results if HSCT is done earlier.
	Thalassemia	75% 1-year disease-free survival
	Sickle cell disease	Potentially curable with HSCT
	Aplastic anemia	> 50% disease-free survival after HSCT for severe aplastic anemia
	Genetic disorders	Most genetically based immunologic or hematopoietic disorders are potentially curable.

Note: All HSCTs require an HLA-identical donor.

* Autologous HSCTs; all others are allogeneic.

ALL = acute lymphoblastic leukemia

AML = acute myeloid leukemia

CLL = chronic lymphocytic leukemia

CML = chronic myeloid leukemia

NHL = non-Hodgkin lymphoma

Ph+ = Philadelphia chromosome positive

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OVERVIEW

Several key concepts are essential for basic understanding of oncology for the internist:

- Recall clinical features and management of common cancers, including risk factors, screening recommendations, diagnostic workup, and basic approach to therapy.
- Recognize and manage cancer complications—both paraneoplastic syndromes and direct invasion/dissemination (e.g., superior vena cava [SVC] syndrome, pericardial effusions).
- Understand major therapeutic drug classes, including chemotherapy, targeted therapy, and immunotherapy. Recognize common toxicities associated with each of the major drug classes.
- Recognize complications of cancer therapy, including tumor lysis syndrome and febrile neutropenia.

The most common types of cancer are prostate (in men) and breast (in women). In both genders, the 2nd and 3rd most frequent cancers are lung and colorectal, respectively.

The most common causes of cancer deaths in the U.S. in men are lung, followed by prostate, and then colorectal. For women in the U.S., they are lung, followed by breast, and then colorectal.

It's good to be familiar with chemo, hormonal, and biologic agents and their side effects; however, as a general internist, you will not be ordering chemotherapy and it is not necessary that you know specific chemotherapeutic regimens. Leave this to the medical oncologists!

As you go through the following, keep in mind that there is more information on chemotherapeutic agents at the end of this section (see more under [Cancer Therapies on page 9-35](#)).

- What are the indications for breast-conserving therapy in women with ductal/intraductal carcinoma in situ?
- What is the most important prognostic indicator for localized invasive breast cancer?
- How important is the size of the tumor?
- How does *HER2/neu* oncogene overexpression affect breast cancer treatment?
- How does estrogen and progesterone receptor status affect breast cancer treatment?
- List the known factors that influence the type of adjuvant therapy selected for a breast cancer patient.
- What factors can cause decreased efficacy of tamoxifen?
- What are the significant risks of tamoxifen therapy?
- What is the role of aromatase inhibitors in the treatment of breast cancer?
- What is the role of tamoxifen in the prevention of breast cancer? For which women is it considered?

OVERVIEW

Breast cancer is the most common malignancy in women and the second leading cause of cancer death in U.S. women (after lung cancer). 12% of women born today develop breast cancer at some point in their lives. As of 2019 in the U.S., there were ~ 260,000 new cases diagnosed annually, and ~ 41,000 women die from breast cancer each year. The incidence of breast cancer decreased by 1.8% per year between 1999 and 2007, likely due to the reduced use of hormone replacement therapy. Breast cancer mortality has been decreasing since the 1980s—likely due to earlier detection, greater awareness, and better treatment.

BREAST CANCER

PREVIEW | REVIEW

- List the factors associated with an increased risk for breast cancer.
- Which cancers are associated with *BRCA* mutations?
- For which age group of women should you recommend mammography every 1–2 years?
- When should you consider magnetic resonance imaging screening for breast cancer?
- Clinical mastitis in a woman who is not breastfeeding should make you consider what diagnosis?
- What is the appropriate workup of a suspicious breast mass?

RISK OF BREAST CANCER

General Risk Factors

Risk factors for breast cancer include:

- Personal history of previous breast cancer
- Female sex (100-fold higher than men)
- Caucasian
- Obesity
- Postmenopausal hormone replacement therapy
- Early menarche, nulliparity, late 1st pregnancy
- Increasing age (highest risk in patients > 70 years)
- Breast cancer in one or more 1st degree relative, especially premenopausal and/or bilateral breast cancer
- Alcohol use
- Chest radiation exposure
- Inherited genetic mutations, such as *BRCA1* and *BRCA2*

Breast Cancer in Women

Although only about 10% of breast cancer cases are attributable to a specific genetic abnormality, mutations of *BRCA1* or *BRCA2* genes account for 30–50% of all inherited breast cancer. In women with a *BRCA* mutation, **bilateral mastectomies** decrease the incidence of breast cancer by up to 90%. Bilateral oophorectomies decrease the risk of ovarian cancer by up to 90% and can also decrease the risk of breast cancer in premenopausal women.

BRCA1 was the first breast cancer gene to be identified (in 1994). It carries a 50–85% lifetime risk of developing breast cancer, with a 50% chance of breast cancer occurring before 50 years of age (compared to a 12% lifetime risk in the general population). The presence of *BRCA1* is also associated with a 40% lifetime risk of developing ovarian cancer (compared to a 1.5% lifetime risk in the general population) and accounts for most cases of familial ovarian cancer. *BRCA1* is also associated with colorectal and prostate cancer.

BRCA2 is associated with a similarly high risk of breast cancer and a 10–20% risk of ovarian cancer. *BRCA2* is also associated with melanoma, pancreatic cancer, and prostate cancer.

Certain pathologic features are associated with an increased risk of subsequent breast cancer:

- With **atypical ductal hyperplasia** in breast biopsy samples, risk is ~ 4× normal.
- With **DCIS** or **LCIS** (ductal/lobular carcinoma in situ), risk is ~ 10× normal. LCIS is associated with increased risk of cancer in either breast. LCIS is a marker for invasive carcinoma; DCIS evolves into invasive carcinoma.

In postmenopausal women, treatment with estrogen replacement therapy (ERT) increases the risk of breast cancer after 5 years of use. The 2002 Women’s Health Initiative trial of combined estrogen plus progestin was stopped early because overall risks, including invasive breast cancer, exceeded benefits. Estrogen therapy without progesterone also increased the risk of endometrial cancer in women who have not undergone a hysterectomy.

The oncologic risks of postmenopausal ERT were thought to be offset by the benefits (i.e., decreased incidence of hip fractures, sexual dysfunction, and cardiovascular disease); however, the 1998 Heart and Estrogen/Progestin Replacement Study (HERS) trial showed that ERT is associated with an increased risk of secondary cardiac events in the 1st year of treatment and that there was no cardiovascular benefit at the 7-year follow-up. Long-term ERT therapy also increased the risk of thromboembolism and biliary tract surgery. Due to the results of this trial, routine use of ERT has fallen out of favor.

Breast Cancer in Men

Breast cancer is rare in men, accounting for < 1% of all breast cancer diagnoses. As in women, men with *BRCA* mutations have an increased risk for breast cancer—particularly with *BRCA2*, where male carriers have a 6% lifetime risk of breast cancer (compared with < 0.1% in the general male population).

SCREENING FOR BREAST CANCER

The following text summarizes the current breast cancer screening guidelines published by the American Cancer Society (ACS), the U.S. Preventive Services Task Force (USPSTF), and the American College of Physicians (ACP). There are some inconsistencies among these guidelines and on how various other medical societies, government groups, and coalitions propose screening; however, the guidelines agree on these:

- Screening mammography is most useful for women 50–74 years of age, and it should be done every 1–2 years in this age group.
- Screening has less utility for women < 50 and > 74 years of age.
- Most groups no longer recommend breast self-exam and clinical breast exam for early detection of breast cancer.

For a comparison of the ACS, USPSTF, and ACA guidelines, see Table 9-1.

Table 9-1: Breast Cancer Screening Guidelines Comparison				
Group (Date)	Screening Frequency (Years)	Screening for Women at Average Risk		
		40 to 49 Years of Age	50 to 69 Years of Age	≥ 70 Years of Age
American Cancer Society (2015)	Yearly, age 45 to 54 1 to 2 years, age ≥ 55 years	Individualize* through age 44. Yes, start at age 45.	Yes	Yes†
U.S. Preventive Services Task Force (2016)	2	Individualize*	Yes	Yes, to age 74
American College of Physicians (2019)	2	Individualize*	Yes	Yes, to age 74
* Women should be counseled about the harms and benefits of mammography; individualized decisions should include shared decision-making based on risks, benefits, patient values and preferences.				
† If in good health and life expectancy is > 10 years.				

Mammography is **less sensitive** in women with **dense breasts** (especially premenopausal women) and in those who have used **ERT** or **oral contraceptives** (which delay the transition of breast tissue from dense to fatty). Breast MRI and screening breast ultrasound are companion imaging modalities that are considered for patients who are higher risk and/or have dense breast tissue.

American Cancer Society (ACS) Screening Guidelines

The ACS 2015 guidelines for women at **average risk** for breast cancer recommend the following:

- Give women 40–44 years of age the choice to start annual breast cancer screening with mammograms after being informed of the risks vs. benefits.
- Mammograms are recommended every year for women 45–54 years of age.
- Mammograms are recommended every 2 years for women ≥ 55 years of age. They can opt to continue yearly screening. Continue screening as long as a woman is in good health and expected to live ≥ 10 years longer.
- Clinical breast exam and breast self-exams are not routinely recommended.

ACS has different recommendations for women who have the following risk factors:

- Personal history of breast cancer
- Family history of breast cancer
- A genetic mutation known to increase risk of breast cancer (e.g., *BRCA1* or *BRCA2*)
- History of radiation therapy (RT) to the chest before 30 years of age

Dense breasts also pose special problems, and different screening techniques may be suggested.

U.S. Preventive Services Task Force (USPSTF) Screening Guidelines

USPSTF 2016 guidelines for women at **average risk** for breast cancer:

- Women 40–49 years of age who place a higher value on a potential benefit than the potential harms may **choose** to begin mammograms every 2 years.
- Mammograms every 2 years are recommended for women 50–74 years of age.
- Of all the age groups, women 60–69 years of age are the most likely to avoid death due to breast cancer by using mammographic screening.
- For women ≥ 75 years of age, the current evidence is insufficient to assess the balance of benefits and harms of screening mammography, although it may be considered for treatment of eligible patients based on life expectancy and comorbidities.

Like the ACS, the USPSTF states that women with a parent, sibling, or child with breast cancer are at a higher risk for breast cancer, and they benefit more than average-risk women from beginning screening in their 40s.

American College of Physicians (ACP) Screening Guidelines

The ACP 2019 guidelines state:

- For women 40–49 years of age and in good health, discuss the benefits and harms and order screening by mammography every 2 years if a woman **requests** it.
- Women 50–74 years of age and in good health should be encouraged to undergo mammography every 2 years.
- Screening for breast cancer is not recommended for women < 40 or > 75 years of age or for women of any age not in good health or with a life expectancy of < 10 years.

Putting It Together

The vagueness of the USPSTF and ACP guidelines arises because their recommendations are data driven or evidence based—not expert driven like the ACS guidelines. Thus, if only limited data exists for or against an intervention, the USPSTF and ACP will not make a definitive recommendation for or against it.

Magnetic Resonance Imaging

Breast MRI is not routinely recommended for average-risk patients but reserved for high-risk patients in combination with mammography. Notably, patients with a history of Hodgkin disease treated with chest or axillary radiation are recommended to have annual breast cancer screening 8–10 years after completing therapy (or at 40 years of age, whichever comes first) with mammograms in addition to breast MRI. Breast MRI has a **high sensitivity** but **limited specificity**. The procedure requires injection of gadolinium contrast and is significantly more expensive than mammography. The ACS supports breast MRI screening **in addition** to mammogram for the following high-risk women only:

- *BRCA1*- or *BRCA2*-positive status
- 1st degree relatives with *BRCA1* or *BRCA2* and patient is untested
- Lifetime risk of breast cancer ≥ 20–25%
- Radiation to the chest between 10 and 30 years of age
- Carrier of, or 1st degree relative with, the *TP53* gene (e.g., Li-Fraumeni syndrome), *PTEN* mutation (e.g., *PTEN* hamartoma syndrome, Bannayan-Riley-Ruvalcaba syndrome, Cowden syndrome), or hereditary diffuse gastric cancer syndrome

PRESENTATION

Breast cancer is usually either detected by the patient (either incidentally or during a self-exam) or by mammography. A breast cancer mass can be any shape or size. Typically, it forms a hard, fixed, well-defined **dominant mass** with irregular borders, in contrast to diffuse fibrocystic changes. On physical examination, assess for

evidence of locally advanced disease, including fixation to surrounding tissue, palpable axillary or supraclavicular lymphadenopathy, or skin findings such as erythema, thickening, or dimpling.

Workup **asymmetric eczema** of the nipple in a non-breastfeeding woman for **Paget disease** of the breast (Figure 9-1). This is done by a nipple scraping for cytology or a nipple punch biopsy. Note that **allergic eczema** is a symmetric disease. Paget disease is accompanied by underlying carcinoma in most cases with or without a palpable mass. Mammogram is indicated in suspected Paget disease of the breast. For more on Paget disease of the nipple, see the **Dermatology** section.



Figure 9-1: Paget disease of the breast

Inflammatory breast cancer is very aggressive and can present as a mastitis with **warmth**, **redness**, and **swelling**. There can be a **peau d'orange** ("skin of the orange") appearance and nipple retraction (Figure 9-2). Mastitis in a nonlactating woman is rare, so initiate a workup for inflammatory breast cancer in nonlactating women with this presentation. Inflammatory breast cancer has a poor prognosis.



Figure 9-2: Inflammatory breast cancer with peau d'orange skin and nipple retraction

Nipple discharge that is not milky and bilateral is always considered abnormal. **Greenish** discharge is an indication of a draining cyst. **Bloody** discharge is commonly due to a papilloma but can be a sign of breast cancer. **Clear** discharge can also be caused by breast cancer. Cancer is less likely when the discharge occurs from both breasts.

BREAST CANCER — DIAGNOSIS AND STAGING

At the time of diagnosis, determine the stage of breast cancer, as this determines prognosis and treatment. The 4 broad categories are:

- Carcinoma in situ (i.e., noninvasive breast cancer)
- Early-stage, invasive breast cancer (primarily Stages I and II)

- Locally advanced, invasive breast cancer (primarily Stage III)
- Metastatic breast cancer

For a suspicious breast finding, start with the following workup:

- 1) Diagnostic mammogram, +/- U/S, +/- MRI
- 2) Fine needle aspiration (FNA)/biopsy
- 3) Determine hormone receptor and *HER2/neu* status.

Step 1: Mammography is required for all suspicious breast lesions (e.g., a breast lump or mastitis not associated with lactation; for eczematous nipple—see **Presentation on page 9-3**). Send any breast discharge for cytology.

Mammography findings concerning for malignancy include:

- Clusters of **irregular** microcalcifications (25–40% are malignant)
- Densities with irregular borders (stellate or spiculated lesions)
- Distorted architecture

Ultrasound the mass to determine whether it is **cystic** or **solid**. If the mass is a simple cyst, consider fluid aspiration and analysis. U/S cannot differentiate solid malignant tumors from solid benign tumors—so, if the mass is solid by U/S, refer for biopsy.

Breast **MRI** is not usually necessary in the evaluation of a palpable breast mass, but, occasionally, suspicious lesions will be detected by screening MRI. Nearly all invasive breast cancers enhance with gadolinium. MRI is also helpful in evaluating both the ipsilateral and contralateral breasts for occult lesions once malignancy establishes itself. Finally, MRI is the best modality to assess the breasts for an occult primary tumor in a woman with adenocarcinoma involving the axillary lymph nodes but with an unknown primary site.

Step 2: Biopsy with FNA or core needle biopsy to confirm the diagnosis of breast cancer. At this time, the ultrasonographer also looks in the axilla for enlarged lymph nodes.

Likewise, biopsy any palpable noncystic masses—even if the mammogram is negative—because the sensitivity of mammography for identifying malignancy is only 75–80%.

Step 3: If the biopsy shows invasive cancer, evaluate estrogen and progesterone **receptor status**, *HER2/neu* status, and grading of the cancer. This has important implications for **treatment** as discussed in the next topics.

CARCINOMA IN SITU (LOBULAR AND DUCTAL) — PROGNOSIS AND TREATMENT

The 2 types of carcinoma in situ are **lobular** carcinoma in situ (LCIS) and **ductal/intraductal** carcinoma in situ (DCIS). Both are benign and curable with resection; however, both also carry a 10-fold increased risk of invasive breast cancer and an increased risk of multifocal

and/or bilateral breast involvement. LCIS is frequently bilateral (30%).

LCIS appears to be a marker indicating that either breast is at risk of developing an invasive carcinoma but, by itself, does not evolve into an invasive carcinoma. Rather, it is an “innocent bystander,” seen in ~ 2–3% of biopsies.

DCIS is more common than LCIS, comprising 20% of all newly diagnosed breast cancers. It frequently presents with distinct microcalcifications on mammogram. The calcifications are often clustered and are rod-shaped or angulated. DCIS is divided into low-, intermediate-, and high-grade types. High-grade DCIS, also called comedo-carcinoma, has a high risk of becoming invasive. DCIS evolves into an invasive carcinoma at the rate of 1% per year.

Treatment of Lobular Carcinoma in Situ (Stage 0)

LCIS is a **benign** lesion and best managed with observation. However, because of the increased risk of breast cancer and because the disease is frequently multifocal and bilateral, some patients opt for a bilateral mastectomy—especially those with other risk factors, such as *BRCA1* or *BRCA2* mutation. This is an extreme approach but might be considered in the woman whose mammograms show very dense breast tissue that is difficult to evaluate.

The selective estrogen receptor modulators (SERMs), tamoxifen and raloxifene, reduce the risk of invasive breast cancer in patients with LCIS by ~ 30%. However, there are risks with these therapies (e.g., venous thromboembolism, endometrial cancer). Carefully discuss these risks with the patient before beginning such treatment.

Treatment of Ductal / Intraductal Carcinoma in Situ (Stage 0)

Treat DCIS with surgical excision. Breast-conserving therapy (BCT), which consists of lumpectomy (local excision with adequate margins) followed by RT, is preferred if the following criteria are met:

- Negative margins are achieved, with the optimal margin being ≥ 2 mm.
- The resection lends itself to a cosmetically acceptable result. This depends on the size and number of lesions in relation to breast size.
- Multifocal disease often requires a simple mastectomy.

Important **prognostic** factors include **resection margin width** and **grade** of lesion. High-grade lesions (e.g., comedo subtype) are more likely to recur than are low-grade lesions (e.g., cribriform subtype).

For patients who elect BCT, local **RT** reduces the risk of in-breast recurrence by **50%**. However, the addition of RT has no demonstrated survival benefit.

Treatment with tamoxifen or anastrozole (an aromatase inhibitor) is recommended to prevent invasive breast cancer in women with estrogen-receptor positive DCIS. Like RT, these agents prevent invasive cancer, but they have not been shown to have a survival benefit. Endocrine therapy is not recommended in women with **ER–** DCIS or in women who have undergone bilateral mastectomy.

INVASIVE BREAST CANCER

Prognosis

The most common invasive breast cancer is the invasive ductal type (accounting for > 80% of cases), then invasive lobular (10%), and then medullary (5%).

Know: The most important prognostic factor is the presence or absence of **lymph node metastases**. The more nodes involved, the worse the prognosis. Note that > 50% of breast cancer patients have negative axillary nodes at the time of diagnosis.

A technique using **sentinel nodes** can determine the need for axillary dissection. Sentinel nodes are the first nodes that the tumor drains into, and they are identified during surgery by the injection of a radioactive substance around the tumor or into the biopsy cavity. These sentinel nodes then are removed by probe-guided resection and examined pathologically for the presence of malignant cells. (The majority of breast cancers drain to nodes in the axilla.)

The positive or negative status of the sentinel nodes is **97% accurate** in reflecting the positive or negative status of all the axillary nodes. If the sentinel node is negative, no further sampling is required. If the sentinel node is positive, a full axillary dissection is usually performed.

The next most important prognostic factor is the size of the **primary tumor**:

- If the tumor is < 1 cm and axillary nodes are negative, the 5-year relapse rate is ~ 10%.
- If the tumor is > 2 cm, the 5-year relapse rate is 20%.
- If **any** axillary nodes are positive, 5-year relapse rate rises to 50–80%.

Overexpression of the **HER2/neu oncogene** occurs in ~ 15–20% of breast cancers and is associated with an increased likelihood of **distant metastases**, as well as with a **more aggressive** cancer. Overexpression of **HER2/neu** is predictive of a benefit from adjuvant chemotherapy and of a lesser benefit from adjuvant endocrine therapy.

Hormone receptor (HR) status should be determined for both **ER+ or ER–** and progesterone receptors (**PR+ or PR–**). Positive ER and/or PR are **favorable** prognostic indicators because they predict a benefit from adjuvant endocrine therapy (i.e., tamoxifen or aromatase inhibitor).

Genomic technologies are increasingly being applied to breast cancer specimens to refine prognosis. In patients with HR+, **HER2–**, node-negative tumors, gene profiling using Oncotype DX is used for risk stratification

(see more on **recurrence score** under **Initial Treatment of Invasive Breast Cancer**) and the likelihood of benefit from adjuvant chemotherapy. This information is part of staging and can be used to guide treatment decisions.

An aggressive histologic grade and the presence of nodal metastases are poor prognostic factors.

Overall, the most powerful prognostic factor is **stage of disease**—indicated by lymph node status and size of tumor. The presence of **distant metastasis (Stage IV)** usually indicates **incurable disease**.

Initial Treatment of Invasive Breast Cancer

Management of invasive breast cancer is based on staging. The 8th edition of the TNM (tumor, node, metastasis) staging system from the American Joint Committee on Cancer (AJCC) includes anatomic, clinical, and pathologic staging groups. Staging includes the following elements:

- Characteristics of the **primary tumor (T0-T3)**: T0 is no evidence of a primary tumor, T1 is a tumor < 20 mm, T2 is a tumor 20–50 mm, T3 is a tumor > 50 mm, and T4 is any size tumor with direct extension to the chest wall or skin.
- Regional **lymph node involvement (N0-N3)**: N0 is no evidence of regional lymph nodes, and N3 indicates ipsilateral infraclavicular, internal mammary, or supraclavicular nodes are involved.
- Presence or absence of **metastatic disease (M)**
- **Histologic grade** (Grade 1 = most favorable; Grade 3 = least favorable)
- **HER2/neu status** (positive or negative)
- **Hormone receptor status** (ER+ vs. ER–; PR+ vs. PR–)
- **Recurrence score**: result of a multigene assay (e.g., Oncotype DX) used in patients with HR+, **HER2–**, node-negative tumors < 5 cm
- Whether the patient is pre- or postmenopausal (not a determining factor but enters into the conversation)
- Patient preferences

Note that, except for the last 2, these are the same factors used to determine prognosis. Review [Table 9-2](#) and [Table 9-3 on page 9-8](#) (you do not need to memorize the information).

The primary treatment for invasive breast cancer is broken down into 2 parts:

- 1) **Local control**: This entails **removal** of the tumor, whether by modified radical mastectomy or BCT (i.e., lumpectomy followed by RT). When lumpectomy is performed, it is **always** followed by **RT** to the breast.
- 2) **Systemic control**: While lumpectomy and radiation decrease the risk of the cancer returning to the affected breast, they do **not** prevent the cancer from recurring at distant sites. For this, adjuvant therapy is given. There are 3 types of **adjuvant** therapy: hormonal, chemotherapy, and biologic therapy (see [Adjuvant Therapy for Invasive Breast Cancer](#)).

Note on local and systemic control: Local control with a modified radical **mastectomy** is often the surgery of choice when the tumor is > 4 cm or the breast is comparatively small, because good cosmetic results are difficult to achieve with BCT.

An alternative and increasingly popular option for primary treatment is to give systemic chemotherapy in the preoperative setting. This neoadjuvant approach addresses the systemic risk of relapse and provides some shrinkage to the primary tumor, thus increasing the chance that local control can be achieved with lumpectomy and RT. A preoperative evaluation by a medical oncologist helps facilitate this option. To date, this technique has not shown a survival benefit.

Adjuvant Therapy for Invasive Breast Cancer

As noted previously, be familiar with the agents and side effects, but leave the specific therapy regimens to the oncologists!

The types of adjuvant therapy used for systemic control depend on the following factors:

- **Size of tumor and nodal status**: Chemotherapy is generally reserved for patients with a high risk of relapse. This includes patients with tumors > 1 cm in size or those with positive lymph nodes. Oncotype DX analysis can help identify which HR+ and node-negative tumors benefit from adjuvant chemotherapy.
- **Hormonal status** of the tumor: Using tissue from the initial core biopsy, the pathologist determines if the tumor expresses receptors for estrogen or progesterone. If the tumor is HR+, the patient benefits from adjuvant hormone therapy (e.g., tamoxifen, aromatase inhibitor).
- **Gene expression**: Most women whose tumors over-express **HER2/neu** (except very small tumors < 6 mm) benefit from trastuzumab in combination with chemotherapy.

Chemotherapy

Chemotherapy decreases the risk of recurrence in many patients. It is generally given as **drug combinations** that follow these general rules:

- Each agent is effective.
- Each agent has a different mechanism of action.

Combination chemotherapy regimens frequently include ≥ 1 of the following: cyclophosphamide, methotrexate, fluorouracil, docetaxel, and doxorubicin.

Endocrine Therapy

Tamoxifen is a **SERM**. It is effective **only in HR+** patients (both pre- and postmenopausal), in whom the overall effect is comparable to chemotherapy in selected patients.

Know that tamoxifen is converted to its active metabolite (endoxifen) by CYP2D6. Enzyme inhibitors (mainly

selective serotonin reuptake inhibitors (SSRIs)) and genetic variation can lead to decreased efficacy of tamoxifen. If a patient needs an SSRI (for depression or hot flashes) while on tamoxifen, venlafaxine is considered the best choice because it is a weaker inhibitor of CYP2D6. More recent data regarding CYP2D6 did not show an association between poor/extensive metabolizers and outcome with tamoxifen.

Tamoxifen's principal adverse effects include hot flashes, weight gain, increased risk of thromboembolic events, and a slight increased risk of endometrial cancer (but only in postmenopausal women). Premenopausal women should be offered tamoxifen treatment for 10 years, according to the 2016 Guidelines by the American Society of Clinical Oncology. Women with a contraindication to tamoxifen (history of DVT/PE or endometrial cancer) can be treated with an aromatase inhibitor alone for 5 years.

Letrozole, anastrozole, and exemestane are aromatase inhibitors. These agents markedly suppress estrogen levels in postmenopausal women by inhibiting the enzyme responsible for synthesizing estrogens from androgenic substrates. Meta-analysis data supports a lower rate of recurrence with 5 years of an aromatase inhibitor over tamoxifen in postmenopausal women. Aromatase inhibitors cannot be used as monotherapy in premenopausal women because they do not block ovarian estrogen production.

Aromatase inhibitors do not increase the risk of thromboembolic events or endometrial carcinoma. However, arthralgias, myalgias, and osteoporosis are more common with these agents. Use dual-energy x-ray absorptiometry (DEXA) scans to screen breast cancer survivors who were treated with aromatase inhibitors every 1–2 years to assess for evolving osteopenia.

Fulvestrant is an ER antagonist without any agonist features. It is approved for use in patients with advanced, HR+ breast cancer. It is given as a monthly intramuscular injection.

Biologic Agents

Biologic agents are drugs made from living organisms or that contain components of living organisms.

Trastuzumab and pertuzumab are monoclonal antibodies that target a growth factor receptor on the surface membrane of breast cancer cells. Around 25–30% of breast cancers have an overexpression of the *HER2/neu* oncogene, which leads to an increase in the amount of growth receptor protein. This, in turn, leads to an increase in cell proliferation. Trastuzumab (with or without pertuzumab) is approved for early-stage and advanced cancer with evidence of overexpression of *HER2/neu*. Trastuzumab decreases recurrence by 50% when used as an adjuvant in combination with chemotherapy for high-risk (> 1 cm or node-positive) tumors.

Know that trastuzumab, along with other chemotherapeutic agents used in the treatment of breast cancer (including anthracyclines, such as doxorubicin and daunorubicin), can induce cardiomyopathy and heart failure.

Additionally, approved agents in breast cancer include palbociclib (cyclin-dependent kinase inhibitor), lapatinib (dual tyrosine kinase inhibitor), and ado-trastuzumab emtansine (antibody-drug conjugate).

Let's review treatment again from a slightly different perspective.

Adjuvant Therapy for the Node-Negative Patient

See Table 9-2. If the tumor is < 1 cm, adjuvant chemotherapy may be unnecessary because breast cancer specific survival is > 90%. Exceptions include *HER2*+ tumors, triple-negative tumors > 0.5 cm, and HR+ tumors with high-risk Oncotype DX scores. Women are routinely placed on endocrine therapy if the tumor is HR+.

If the tumor is ≥ 1 cm, adjuvant chemotherapy is recommended for all HR– tumors. Oncotype DX gene expression analysis can be done to better risk-stratify HR+ patients and to determine whether they need chemotherapy. Give adjuvant endocrine therapy to women with HR+ tumors. Tamoxifen is used for premenopausal women; an aromatase inhibitor can be used alone or sequentially after tamoxifen for postmenopausal women. Add trastuzumab to chemotherapy for *HER2/neu*+ tumors ≥ 1 cm. Most oncologists add trastuzumab even for small tumors > 5 mm.

Table 9-2: Treatment of Node-Negative Invasive Breast Cancer

Treatment	Size of Tumor	
	< 1 cm	≥ 1 cm
Local regional	BCT (lumpectomy plus radiotherapy) or Modified radical mastectomy	BCT or Modified radical mastectomy
Adjuvant systemic	HR+: Endocrine therapy Consider Oncotype DX testing in tumors 0.5–1 cm if high-risk features are present. Triple neg: chemotherapy for tumors > 0.5 cm (or node-positive) <i>HER2/neu</i> +: trastuzumab Chemotherapy for tumors > 0.5 cm can be considered.	HR+: Endocrine therapy Consider chemotherapy, depending on the Oncotype DX risk score. Triple neg: chemotherapy <i>HER2/neu</i> +: chemotherapy + trastuzumab

BCT = breast-conserving therapy

HR = hormone receptor

Adjuvant Therapy for the Node-Positive Patient

See Table 9-3. Chemotherapy is recommended for chemotherapy-eligible node-positive patients. If the tumor overexpresses the *HER2/neu* oncogene, add trastuzumab. For premenopausal women with HR+ tumors, give adjuvant endocrine therapy—use tamoxifen alone or ovarian suppression plus an aromatase inhibitor in selected patients. An aromatase inhibitor can be used alone or sequentially after tamoxifen for postmenopausal women.

Give most patients RT after lumpectomy. Contraindications to RT include pregnancy and previous RT to the same breast for breast cancer. Relative contraindications include connective tissue disorders affecting the skin, tumors > 5 cm, and women ≥ 35 years of age with a *BRCA* mutation. Consider omission of RT in women ≥ 70 years of age with small node-negative tumors with good features and HR+. Give radiation after chemotherapy is completed and before endocrine therapy is started.

Recurrent Breast Cancer

If there is local recurrence of breast cancer, the patient undergoes the diagnostic protocol again and is re-treated based on the same criteria **except** for the chemotherapeutic drugs that are used. Many oncologists consider an anthracycline or paclitaxel for recurrences.

METASTATIC BREAST CANCER

Although there is **no cure** for metastatic disease (Stage IV), effective palliation and survival extension is possible with treatment. There are many chemotherapy agents that are effective in metastatic breast cancer.

Patients can present with de novo metastasis at diagnosis or, more commonly, with a recurrence following prior therapy for early-stage breast cancer.

Recognize the following clinical scenarios in a patient with prior history of early-stage breast cancer:

- New-onset headaches, focal neurologic findings, or seizures—suggestive of CNS metastasis; check MRI brain; if brain mets are present, treat with steroids.

- New-onset back pain or bowel/bladder incontinence—suggestive of spinal cord compression; check MRI spine; if cord compression is present, treat with steroids.
- New-onset focal bone pain—suggestive of bone metastasis +/- pathologic fracture; check x-rays, bone scan, and/or PET/CT.
- Altered mental status—suggestive of hypercalcemia of malignancy; check Ca²⁺.

In patients with HR+ disease, initiating or changing endocrine therapy is often effective. **Aromatase inhibitors** are more effective than tamoxifen for the **initial** treatment of **metastatic** disease in **postmenopausal** women.

Bisphosphonates can effectively reduce **bone pain** and fractures due to skeletal metastasis.

Denosumab is a receptor activator of nuclear factor-κB ligand (RANKL) inhibitor that also decreases the risk of skeletal-related events.

RT is useful in providing palliation and local control to symptomatic regional disease, **brain metastasis**, skeletal metastasis, and soft tissue metastasis.

PROPHYLAXIS / PREVENTION OF BREAST CANCER

Tamoxifen is FDA approved for the prevention of breast cancer in both pre- and postmenopausal women. Tamoxifen reduces the risk of invasive breast cancer in high-risk women by ~ 30%. Tamoxifen prophylaxis for a duration of 5 years is recommended for women at high risk for invasive breast cancer (defined as a 1.67% 5-year risk of developing breast cancer, calculated using the Gail model available on the National Cancer Institute website [cancer.gov/bcrisktool], or the risk present in an average 60-year-old woman). There is an increased risk of endometrial cancer with the use of tamoxifen; it is the same risk as in postmenopausal women taking single-agent estrogen replacement therapy. The risks of DVT (~ 1.5× normal) and pulmonary embolism (~ 3× normal) are also increased.

Table 9-3: Treatment of Node-Positive Invasive Breast Cancer		
Treatment	1-3 Lymph Nodes	> 3 Lymph Nodes
Local regional	BCT plus radiotherapy (nodal basin RT considered vs. axillary dissection) or Modified radical mastectomy (nodal basin RT considered vs. axillary dissection)	BCT plus radiotherapy + axillary dissection or Modified radical mastectomy + axillary dissection
Adjuvant systemic	HR+ premenopausal: Adjuvant chemotherapy + endocrine therapy HR+ postmenopausal: Consider Oncotype DX testing* to determine benefit of chemotherapy; add endocrine therapy. Triple neg: Adjuvant chemotherapy for all patients HER2/neu+ : Adjuvant chemotherapy + trastuzumab	HR+ pre- and postmenopausal: Adjuvant chemotherapy + endocrine therapy Triple neg: Adjuvant chemotherapy for all patients HER2/neu+ : Adjuvant chemotherapy + trastuzumab
* Gene expression profiling (i.e., Oncotype DX) helps determine the benefit of chemotherapy in lymph node-positive disease (1-3 positive lymph nodes). BCT = breast-conserving therapy		

Raloxifene is FDA approved for breast cancer prevention in **postmenopausal** women and has a lower risk of endometrial cancer and DVT compared to tamoxifen.

Aromatase inhibitors (e.g., anastrozole, exemestane) have similar efficacy to tamoxifen and raloxifene for prevention of invasive breast cancer in postmenopausal women (per the 2014 IBIS-II trial) and are reasonable alternatives to these agents (although they are not yet FDA approved for this indication).

CERVICAL CANCER

PREVIEW | REVIEW

- What are the established risk factors for cervical cancer?
- Which patient populations should receive the human papillomavirus vaccine?
- At what age and with which test results is it appropriate to stop screening for cervical cancer?
- What is the appropriate procedure to follow up a low-grade squamous intraepithelial lesion?

RISK OF CERVICAL CANCER

Since the introduction of the Papanicolaou (Pap) smear in 1947, mortality due to cervical cancer in the U.S. has dropped by 70%. Still, over 12,000 new cases of cervical cancer are diagnosed in the U.S. each year, with over 4,000 cervical cancer deaths each year. Cervical cancer diagnosis and mortality rates in developing countries are significantly higher.

The major **risk factor** for cervical carcinoma is **HPV** (human papillomavirus) infection. Other risk factors reflect the risk of exposure to HPV: early onset of coitus, number of sexual partners, smoking, and history of other sexually transmitted diseases. In addition, patients who are chronically immunosuppressed are at an increased risk of developing HPV infection (e.g., HIV/AIDS is a risk factor). Invasive cervical cancer is an AIDS-defining illness.

HPV isolates are found in 85–90% of cervical carcinomas, especially Types **16** and **18**. HPV is the cause of the **cervical intraepithelial neoplasia** (CIN). Without treatment, 65% of CIN evolves into carcinoma in situ, and 30–70% of CIN evolves into invasive carcinoma over 10–12 years.

PREVENTION AND SCREENING

Because most cervical cancer is caused by chronic HPV infection, the development of the HPV vaccine was a significant advancement for the prevention of cervical cancer. Universal vaccination has had a huge public health impact, with large decreases in the incidence of HPV infection and transmission of the virus. Several international trials have shown the vaccine is 97–100%

effective in preventing HPV, HPV-associated CIN, and more advanced cervical cancer. The HPV vaccine is approved for individuals 9–45 years of age to prevent cervical, vulvar, vaginal, and anal cancer in **females** and to prevent anal cancer and genital warts in **males**.

In addition to vaccination, the American Cancer Society (2016) recommends routine screening using Pap tests. For immunocompetent women, start screening at **21** years of age, regardless of whether they are sexually active. Repeat the Pap test every **3** years in women < 30 years of age. For women > 30, screen either with a Pap test every 3 years or cotest with both a Pap and HPV every 5 years. HPV screening is of unclear value in women < 30 years of age, primarily because HPV infection in this age group is often transient. For women with consistently negative Pap results over the past 10 years, screening can be discontinued after **65** years of age.

Women with low-grade squamous intraepithelial lesion (LSIL) Pap with negative HPV should repeat Pap test and HPV in 1 year. Women with an abnormal Pap smear may require **colposcopy** (with biopsy of any suspicious lesions). Indications for colposcopy include:

- High-risk (Types 16 or 18) HPV genotyping in patients with normal cytology
- LSIL with high-risk HPV+ (or no HPV test)
- High-grade squamous intraepithelial lesions (HSIL)
- Atypical squamous cells for which a high-grade epithelial lesion cannot be excluded (ASC-H)
- Atypical squamous cells of unknown significance (ASC-US) and high-risk HPV+
- Persistent ASC-US on repeat Pap smear (usually repeated 1 year after 1st positive test)

CLINICAL PRESENTATION OF CERVICAL CANCER

Cervical cancer most commonly presents with vaginal bleeding—either between menses or after menopause (sometimes triggered by intercourse). More advanced disease may present with pelvic or low back pain. Physical examination may demonstrate abnormal appearance of the cervix. Diagnosis is confirmed by biopsy (often guided by colposcopy).

DIAGNOSIS AND STAGING OF CERVICAL CANCER

Cervical cancer is staged clinically, using the International Federation of Gynecology and Obstetrics (FIGO) system. Tumor stage is defined at the time of initial diagnosis based on physical exam and a staging protocol that includes cervical biopsy, endoscopy (i.e., hysteroscopy, cystoscopy, proctoscopy), IV pyelogram (to assess for urinary obstruction), and skeletal radiograph (to assess for metastatic disease). In many locations, CT, MRI, PET, or integrated PET/CT (which allow for assessment of lymph nodes) are used in place of IV pyelogram.

FIGO staging of cervical cancer is almost exclusively based on tumor characteristics. Node positivity is not included in FIGO stages (the spread may or may not include lymph nodes), except Stage IVB, which requires involvement of paraaortic nodes. However, assessment of lymph node status and the presence of distant metastases is still important, as they affect both treatment and prognosis. The FIGO stages are:

- Stage I: The cancer is confined to the uterus.
- Stage II: The cancer invades beyond the uterus but does not involve the pelvic wall or lower 1/3 of the vagina.
- Stage III: The tumor extends to the pelvic wall and/or the lower 1/3 of the vagina, and/or it causes kidney dysfunction.
- Stage IV: The tumor invades the mucosa of the bladder or rectum and/or extends beyond the true pelvis (including peritoneal spread; supraclavicular, mediastinal, or paraaortic nodes; and visceral or bone metastases).

TREATMENT OF CERVICAL CANCER

The treatment of cervical cancer depends on the FIGO stage (i.e., extent of the tumor), lymph node status, and presence or absence of metastatic disease.

Early-stage cervical cancer is defined as Stage I disease, provided a visible cervical cancer is < 4 cm in size. Surgery is the preferred treatment for these patients. For patients who wish to preserve fertility, selected patients may be candidates for removal of the cervix without removal of the uterine body (i.e., radical trachelectomy).

Advanced-stage cervical cancer is defined as bulky Stage I disease (≥ 4 cm) or Stage II–III disease. For these patients, treatment typically consists of chemoradiation, using weekly cisplatin during RT. A hysterectomy is not required at the completion of definitive chemotherapy.

For patients with Stage IV cervical cancer and for those with metastatic disease, systemic treatment consists of cisplatin, paclitaxel, and the angiogenesis inhibitor, bevacizumab. For patients who progressed following chemoradiation, carboplatin is a reasonable substitute for cisplatin. Immune checkpoint inhibitors such as pembrolizumab have also shown benefit in patients with disease recurrence after chemotherapy.

ENDOMETRIAL CANCER

OVERVIEW

Endometrial cancer is the most common gynecologic cancer in the U.S., with > 60,000 cases diagnosed annually. The majority of women present with dysfunctional uterine bleeding and often have early-stage cancer at the time of surgery, with a high probability of cure. However, endometrial cancer represents a heterogeneous group of diseases with varying risks of recurrence. Among the subtypes, serous and clear cell cancers are far more aggressive than the more common variant, endometrioid carcinoma.

RISK OF ENDOMETRIAL CANCER

The main risk factor for endometrioid adenocarcinoma (the most common form of endometrial cancer) is excess exposure to estrogen, which occurs with obesity, or exogenous estrogen use without progestin. Estrogen exposure is not a risk factor for the less common serous or clear cell endometrial cancers.

STAGING OF ENDOMETRIAL CANCER

The staging of endometrial cancer is clinical and performed at the time of operative assessment. Staging is performed using the FIGO system, rather than AJCC's TNM classification:

- Stage I: The tumor is confined to the uterus. If the tumor extends to < 1/2 of the myometrium, it is considered Stage IA. If it is more than that, it is Stage IB.
- Stage II: The tumor extends to the cervical stroma.
- Stage III: The tumor invades by direct extension to the vagina (IIIA), the ovaries (IIIB), or the pelvic or paraaortic nodes (IIIC).
- Stage IV: The tumor invades the bladder or bowel (IVA) or is metastatic beyond the true pelvis (IVB).

TREATMENT OF ENDOMETRIAL CANCER

The treatment of endometrial cancer is surgical. Adjuvant therapy is appropriate for women at high risk of relapse.

High-risk criteria in endometrial adenocarcinoma:

- Grade 2–3 endometrioid histology
- Invasion of the outer 1/2 of the myometrium
- Invasion of the lymphatic space or vasculature

The determination of whether a woman is high risk depends on age:

- ≥ 70 years of age—only 1 risk factor is required.
- 51–69 years of age—2 risk factors are required.
- For women ≤ 50 years of age—all 3 risk factors are required.

For women with high-risk, early-stage endometrial cancer, the treatment of choice is typically surgery with adjuvant chemotherapy. Early-stage patients without high-risk features can either be observed or managed with adjuvant radiation in the postoperative setting.

OVARIAN CANCER

PREVIEW | REVIEW

- Which type of ovarian tumor is usually benign? In what age group do you typically find these tumors?
- What is the lifetime risk of ovarian cancer in a woman with BRCA1? With BRCA2?

OVERVIEW

Ovarian cancer is the 4th leading cause of cancer deaths in women. It is the 7th most common malignancy in women; 1 out of 70 women develop this type of cancer. The incidence increases with age, and 50% of affected patients are > 65 years of age. Ovarian cancer is the most common cause of an ovarian mass in postmenopausal women.

Most (85%) ovarian cancers are epithelial cell cancers, and most of these are serous and mucinous; however, they also can be endometrioid, clear cell, Brenner, or undifferentiated. The next most frequent type is germ cell cancer (5%), but most ovarian germ cell tumors are benign. (Note that germ cell cancers account for 95% of testicular cancers but only ~ 5% of ovarian cancers.)

Know the following:

- The 2 most common ovarian cancer types are epithelial cell (85%) and germ cell (5%).
- Epithelial cell tumors are more common among postmenopausal women.
- Germ cell tumors typically occur in young women (10–30 years of age).

RISK OF OVARIAN CANCER

Increased risk:

- Positive family history of ovarian cancer
- Nulliparity
- Positive *BRCA1* or *BRCA2*
- Lynch syndrome

Decreased risk:

- Oral contraceptive use
- Tubal ligation
- Breastfeeding
- Early age of 1st pregnancy
- Multiparity (10% decrease in risk with each pregnancy)

BRCA1 accounts for most cases of familial ovarian cancer. *BRCA1* is associated with a 40% lifetime risk of ovarian cancer. This compares to a 1.5% lifetime risk in the general population. *BRCA2* is associated with a 10–20% risk of ovarian cancer. All women with invasive ovarian cancer should be offered *BRCA* testing. Remember: *BRCA1* and *BRCA2* are also associated with increased risk of breast cancer. For more on *BRCA* risks, see [Breast Cancer in Women on page 9-2](#).

Lynch syndrome (a.k.a. hereditary nonpolyposis colorectal cancer [HNPCC]) is caused by a germline mutation in a mismatch-repair gene and is associated with a 12% lifetime risk of ovarian cancer.

PRESENTATION, DIAGNOSIS, AND STAGING OF OVARIAN CANCER

Presentation

Ovarian cancer can present with abdominal bloating, early satiety, pelvic pain, and/or abdominal pain. Due to the nonspecific nature of symptoms, cancer may not be detected until later stages. Evaluate with pelvic exam and CT of abdomen and pelvis.

Biologic Markers

CA 125 (cancer antigen 125) levels are often increased in ovarian cancer. When CA 125 is elevated at the time of diagnosis, it can be used to monitor for treatment effect and for recurrence during follow-up. However, CA 125 should **not** be used to diagnose ovarian cancer in lieu of pathology.

Data shows that treatment of a CA 125 relapse **does not** impact survival. Routine screening for ovarian cancer with either CA 125 or transvaginal U/S (or both) is of no benefit and is not recommended for the general population.

Human epididymis protein 4 (**HE4**) is a product of the *WFDC2* gene, which is overexpressed in serous and endometrioid ovarian cancers. Serum measurements of HE4 were approved by the FDA in 2008 as a tumor marker for women with ovarian cancer. HE4 is used in combination with CA 125 to evaluate the risk of malignancy in women who present with an adnexal mass, as part of the risk of ovarian malignancy algorithm (ROMA). Human chorionic gonadotropin (**hCG**) and α -fetoprotein (**AFP**) are **not** elevated in epithelial cancers; however, **both** may be elevated in the less common ovarian germ cell tumors.

Staging

Ovarian cancer staging is based on the FIGO system:

- Stage I: confined to the ovary
- Stage II: extends to adjacent pelvic structures
- Stage III: spreads to peritoneal surfaces, including liver and diaphragmatic surfaces, or to lymph nodes
- Stage IV: distant metastases

Staging is performed by a gynecologic oncologist, typically at the time of exploratory surgery. The disease stage is often found to be higher at the time of initial surgery than originally estimated.

TREATMENT OF OVARIAN CANCER

Treatment for Stages I, II, and III consists of surgically removing all visible tumor from the peritoneal surfaces. This debulking (i.e., cytoreduction) surgery includes a total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH-BSO), omentectomy, and node sampling, as well as sampling of pelvic washings. The goal is to leave < 1 cm of residual disease, known as an

optimal cytoreduction. Survival is inversely correlated to residual disease volume ($\downarrow$ residual disease $\rightarrow$ $\uparrow$ survival rate). Following the American Society of Clinical Oncology and the Society of Gynecologic Oncology (ASCO/SGO) 2016 clinical practice guidelines, if a gynecologic oncologist believes an optimal cytoreduction is not possible (due to volume of disease or the patient's performance status), neoadjuvant IV chemotherapy is often given.

For women with newly diagnosed ovarian cancer, treatment consists of a platinum (e.g., carboplatin) and a taxane (e.g., paclitaxel). Patients with Stage II–III optimally cytoreduced ovarian cancer are candidates for intraperitoneal (IP) therapy. Alternatively, standard IV carboplatin and paclitaxel are usually recommended in all women with disease $>$ Stage IA Grade 1–2 disease. Patients with Stage III suboptimally cytoreduced or Stage IV ovarian cancer may benefit from bevacizumab, in addition to standard chemotherapy. Optimally, start chemotherapy 4–6 weeks after surgery to allow for adequate postsurgical healing.

Overall, the 5-year survival rate is 42%. If diagnosed and treated while the cancer is still localized, the 5-year survival rate is 90%, but only 23% of patients are diagnosed at this stage. The 5-year survival rate is 65% for Stage II disease and 40% for Stage III disease. In Stage III disease, optimal cytoreduction is a favorable prognostic factor.

PROSTATE CANCER

PREVIEW | REVIEW

- What are the risk factors for prostate cancer?
- What are the current recommendations for prostate cancer screening?
- Where are the most common sites of metastases in patients with prostate cancer?
- Name the side effects of androgen deprivation therapy.
- What are the treatment options for metastatic castration-resistant prostate cancer?

OVERVIEW

Prostate cancer is the most common cancer and the 2nd leading cause of cancer death (after lung cancer) in men in the U.S. The availability of the prostate-specific antigen (PSA) has increased detection of prostate cancer. The vast majority (95%) of prostate cancers are adenocarcinomas.

PRESENTATION

The majority of patients are asymptomatic at the time of diagnosis, although obstructive urinary symptoms and hematuria may occur in early-stage disease. Advanced prostate cancer can result in weight loss, cytopenias from bone marrow involvement, fractures, spinal cord compression, and disseminated intravascular coagulation.

RISK

Major risk factors for prostate cancer are increased age, race (African Americans $>$ Caucasians $>$ Asians), and diet (increased risk with animal fats). Family history is an important risk factor. Prostate cancer has been associated with *BRCA* mutations. Men with metastatic prostate cancer as the initial presentation should be referred for genetic counseling.

Benign prostatic hyperplasia (BPH) is not a risk factor for prostate cancer.

PREVENTION AND SCREENING

Prevention of Prostate Cancer

Finasteride has been studied for the prevention of prostate cancer. Although finasteride decreases over-all prostate cancer incidence by $\sim$ 25%, it appears to increase the risk of high-grade prostate cancer, and there is no effect on overall survival. As a result, finasteride has not been approved by the FDA for prostate cancer prevention.

Screening

The 2 major screening tests for prostate cancer are PSA measurement and digital rectal examination (DRE). The routine use of both PSA and DRE remains controversial, as strong evidence of a survival benefit from screening is lacking.

PSA levels normally increase with age, reflecting the influence of BPH. PSA levels also vary by race, with higher levels in African Americans without prostate cancer than in Caucasians without prostate cancer. These variations should be kept in mind when interpreting PSA results.

PSA screening effectively detects early-stage prostate cancer, but most of these remain clinically silent if left undiagnosed. Data on a mortality benefit of screening is conflicting. In 2014, the European Randomized Study of Screening for Prostate Cancer (ERSPC) showed a 21% relative risk reduction in prostate cancer mortality in the PSA screening group among men 55–69 years of age. However, 781 men needed to be screened and 27 additional cases of prostate cancer diagnosed to prevent 1 prostate cancer death over 13 years. In contrast, the Prostate, Lung, Colorectal and Ovarian [PLCO] Cancer Screening Trial, which published 15-year follow-up results in 2017, showed **no** decrease in mortality with PSA screening during a 15-year follow-up. However, that study has been criticized because $>$ 50% of the patients in the control group had at least 1 PSA test during the study. Although there is a potential mortality benefit from PSA screening, there are also potential harms, primarily related to the diagnosis and treatment of subclinical early-stage prostate cancer:

- Prostate biopsy can cause anxiety and physical discomfort.
- Prostate biopsy carries a risk of bleeding, urinary obstruction, infection, and even mortality (as high as 0.2%).

- There is a risk of overdiagnosis (detection and treatment of cancer that never will become clinically significant).
- Risk of treatment: Radical prostatectomy and radiation can cause urinary incontinence, sexual dysfunction, bowel problems, and perioperative mortality.

Society Guidelines for Prostate Cancer Screening

The 2016 **American Cancer Society (ACS)** guidelines recommend that men discuss the risks and benefits of screening with their physicians, beginning at 50 years of age (age 45 for men at high risk, and age 40 for men at very high risk). In men who choose to be screened, order a PSA with or without a DRE. PSA may be repeated every 2 years in men with a PSA < 2.5 ng/mL (2 µg/L), and annually in men with a PSA ≥ 2.5 ng/mL.

The **USPSTF** 2018 guidelines and the **American Urological Association** 2015 guidelines agree on the following:

- PSA screening is not recommended in men < 50 years of age who are at average risk.
- The decision to perform PSA screening should be individualized in men 55–69 years of age. Providers should discuss potential benefits and harms with patients.
- PSA screening is not recommended in men > 70 years of age, or those with a life expectancy of < 10 years.

If PSA is > 4 ng/mL (4 µg/L) or > age-specific normal values, the next step is a transrectal U/S-guided needle biopsy (12 cores).

For DRE screening, no high-quality trials have shown a survival benefit, either alone or in combination with PSA. The **USPSTF** (2018) states the DRE is not recommended. The **ACS** and the **American Urological Association** take no strong position on DRE screening, with the ACS stating that in men who choose screening, PSA is the primary screening test, but DRE may also be done as part of screening. Promptly refer any patient who exhibits a palpable abnormality to a urologist for formal biopsy.

STAGING OF PROSTATE CANCER

The **TNM staging system** (Table 9-4) is the most widely utilized staging method for prostate cancer. The TNM system distinguishes disease confined to the prostate (T1–T2) from disease that extends outside the gland (T3–T4).

A combination of pretreatment tumor stage, PSA level, and histologic tumor grade (better known as the Gleason score) can predict the risk of prostate cancer recurrence after radical prostatectomy. The Gleason score is a histologic scoring system ranging between 2 (least aggressive) and 5 (most aggressive). The composite Gleason score is the sum of the 2 most prevalent histologic patterns on biopsy. Biopsies with composite Gleason score < 6 are not usually diagnosed as prostate cancer; thus, prostate cancers generally have composite Gleason scores between 6 and 10, where 10 is the most aggressive.

Table 9-4: TNM Staging of Prostate Cancer

Tumor Stage	Description
T1	Clinically inapparent tumor (neither palpable nor visible by imaging)
T2	Tumor is palpable and confined within the prostate
T3	Tumor extends through the prostate capsule but is not fixed or does not invade adjacent structures
T4	Tumor is fixed or invades adjacent structures other than seminal vesicles: external sphincter, rectum, levator muscles, and/or pelvic wall
N	Regional lymph nodes assessed
M	Distant metastases

Adapted from: The American Joint Committee on Cancer, *Cancer Staging Manual*, Eighth Edition (2017).

In 2016, the International Society of Urologic Pathology (ISUP) introduced a Grade Group classification, which incorporates the Gleason score.

At the time of diagnosis, prostate cancer is classified into risk categories. The system that is most commonly utilized is provided by the National Comprehensive Cancer Network (NCCN), with the recent modifications based on ISUP grade groups.

Pretreatment staging of prostate cancer includes a bone scan plus either CT or MRI of the pelvis because the **bone and lymph nodes** are, by far, the most likely sites of metastasis. In patients who elect surgery, lymph nodes are often sampled at the time of surgery.

TREATMENT OF PROSTATE CANCER

All treatments for prostate cancer can have serious side effects (e.g., impotence, urinary incontinence). For this reason, active surveillance (PSA every 6 months; digital rectal exam every 12 months; repeat prostate biopsy every 12 months) is often appropriate for patients with early-stage, low-risk (Grade Group 1) disease. Any patient with localized prostate cancer and a predicted actuarial survival of < 10 years should be considered for watchful waiting. Patients with asymptomatic metastatic disease or PSA elevation after primary therapy can also be observed, with therapy (i.e., androgen deprivation) delayed until there is rapid PSA doubling time or symptoms develop.

Localized Prostate Cancer

Definitive management of **localized prostate cancer** can include:

- Radical prostatectomy
- RT (+/– androgen suppression)
- Active surveillance

Radical prostatectomy is reserved for patients with clinical T1–T2cN0M0 disease with a life expectancy of > 10 years. **RT** can be offered to patients with clinical

T1–T3bN0M0 with a n acceptable life expectancy. Data supports the use of androgen deprivation therapy along with radiation in patients with Gleason score 7–10 disease.

Also remember that pretreatment **PSA**, **tumor stage**, and **Gleason score** are helpful in predicting extracapsular spread. For example, patients with T1–T2 lesions with a high pretreatment PSA (> 10–20 ng/mL) or high Gleason score (8–10) are less likely to have organ-confined disease and are more suitable for RT.

Endocrine therapy consists of androgen deprivation. This is achieved by a luteinizing hormone–releasing hormone (LHRH) agonist (i.e., leuprolide, goserelin) combined with an **androgen receptor antagonist** (e.g., flutamide, bicalutamide) or by **orchiectomy**. Endocrine therapy was once thought of as benign treatment, but there are significant adverse effects: weight gain, osteoporosis, gynecomastia, loss of muscle mass, anemia, sexual dysfunction, hot flashes, and an increased risk of diabetes mellitus. In retrospective analysis, endocrine therapy has been associated with a 5–8% increased risk of cardiac mortality.

Endocrine therapy can be appropriately offered to patients:

- With metastatic disease (best reserved for symptomatic patients or patients with a rapidly rising PSA)
- With a PSA-only recurrence after primary therapy with a short PSA doubling time (< 6–10 months)
- With node-positive disease discovered after RP: adjuvant therapy for 36 months
- As adjuvant therapy in patients undergoing RT (in those with Gleason 7–10 disease)

Two recent studies, the Chemohormonal Therapy Versus Androgen Ablation Randomized Trial for Extensive Disease in Prostate Cancer (CHAARTED, 2015) and the Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy (STAMPEDE, 2017), revealed that **docetaxel** chemotherapy given to men with high-volume, castration-naïve prostate cancer improves median survival. Subsequently, similar evidence has been noted with the addition of abiraterone, apalutamide, or enzalutamide to androgen deprivation therapy in men with newly diagnosed metastatic, castration-naïve prostate cancer, which may limit the exposure to toxic chemotherapy.

Eventually, most patients with metastatic disease become **refractory to endocrine therapy**. This is referred to as castration-resistant prostate cancer (**CRPC**).

Treatment options for CRPC include:

- Alternative endocrine therapy: abiraterone plus prednisone, or enzalutamide. Enzalutamide and abiraterone work by inhibiting the enzyme CYP17, which is required for the formation of the testosterone precursors, DHEA and androstenedione.
- Older endocrine therapies (now considered 2nd line) include glucocorticoids, ketoconazole, and estrogens.
- Immunotherapy with sipuleucel-T prolongs overall survival for patients with few to no symptoms from

metastasis. In this therapy, autologous antigen-presenting cells from the patient are collected, activated with granulocyte-macrophage colony-stimulating factor (GM-CSF; a.k.a. CSF2) and prostate acid phosphatase, and then reinfused.

- Chemotherapy: taxanes (specifically docetaxel and the semisynthetic taxane cabazitaxel because each has shown survival benefit), mitoxantrone, estramustine
- Palliative RT for painful bone disease
- Radiopharmaceuticals therapy with radium-223 for patients with primarily osseous metastases

Bisphosphonates are useful in decreasing bone pain from metastases and decreasing osteoporosis caused by endocrine therapy. Denosumab is available as an alternative to bisphosphonates to prevent skeletal-related events.

TESTICULAR CANCER

PREVIEW | REVIEW

- What are the risk factors for testicular cancer?
- Describe the diagnostic approach to a painless testicular mass.
- Which biologic markers are used for testicular cancer, and how are they used?
- What is the significance of finding α -fetoprotein elevation in a patient with a testicular mass?

OVERVIEW

Testicular cancer is the most common solid malignancy affecting men between 15 and 35 years of age. It is one of the most curable cancers. Stage I cancer is localized to the testis with 99% disease-specific survival (DSS). Stage II cancer indicates metastasis to retroperitoneal lymph nodes with 96% DSS. Stage III disease indicates visceral metastasis with 71% DSS.

95% of testicular carcinomas are germ cell tumors (GCTs; i.e., seminomas, nonseminomas). The remaining 5% consist of sex cord stromal tumors, adenocarcinomas of the rete testis, mesotheliomas, carcinoids, lymphomas, and gonadoblastomas. Testicular cancer can also occur in extragonadal primary sites (e.g., retroperitoneum, mediastinum).

RISK

Risk factors for testicular cancer include **cryptorchidism** (undescended testes), a personal or **family history** of testicular cancer, **infertility**, and **HIV infection** (especially seminoma). Cryptorchidism increases the risk of testicular cancer in both the undescended and normal testes. The risk increases with delayed orchiopexy (surgical repositioning of undescended testis). Isochromosome 12p is present in 70–80% of testicular GCTs; however, its role in familial GCTs is unknown. Klinefelter syndrome is a risk factor for primary mediastinal germ cell tumors.

PRESENTATION, DIAGNOSIS, AND STAGING

Presentation

Patients usually present with a **painless scrotal mass**. If a testicular mass is palpated, obtain a **scrotal U/S** to determine if it is solid. If the mass is **solid**, **inguinal orchiectomy** is the next step. Do not perform needle biopsy because of the risk of seeding the biopsy track.

Biologic Markers

Biologic markers for testicular cancer include **LDH**, **AFP**, and **hCG**. Although tumor markers alone are not diagnostic, they have several important functions:

- Staging and prognosis
- Monitoring for disease relapse
- Monitoring for efficacy of therapy

Check these markers prior to surgery, after surgery, and during follow-up. See [Figure 9-3](#).

AFP is **never** produced by **seminomas**. If morphology from a specimen suggests a pure seminoma but the AFP is elevated, the testicular cancer is classified as a **nonseminoma**. AFP is secreted by all yolk sac tumors and, less frequently, by embryonal cell carcinomas. The half-life of AFP is 5 days. AFP is also produced by hepatocellular carcinomas and other GI tract tumors, and it is elevated in chronic liver disease.

hCG is secreted by all choriocarcinomas, many embryonal cell carcinomas, and 15–20% of seminomas. Syncytiotrophoblast cells produce hCG in pure seminomas; thus, it is possible to have a pure seminoma with an elevated hCG. Clinically, laboratories measure the β subunit (β -hCG). False-positive hCG values can occur in hypogonadal states, other cancers, and marijuana use. The half-life of hCG is 18–36 hours.

LDH (lactic acid dehydrogenase) is a cytoplasmic enzyme found throughout the human body. Elevations indicate tumor cell turnover and can occur with higher tumor burdens. There are many sources of LDH; it is the least specific testicular cancer tumor marker, but it is used in staging.

Staging

Testicular cancer follows a predictable progression. Stage I disease is limited to the testicle. Stage II disease involves the retroperitoneal nodes, and Stage III disease includes distant metastatic disease—often to the lung. Note that there is no Stage IV classification for testicular cancer.

The staging process includes CT of the abdomen and pelvis, CXR, and tumor markers. See [Table 9-5](#) for the TNM classification of germ cell tumors.

Table 9-5: TNM Classification of Germ Cell Tumors in Males

Stage	Definition
I	Confined to testes with normal or abnormal serum tumor markers
II	Node-positive disease, no distant metastases, with node size/markers as follows: • Biologic markers in lymph node ◦ LDH < 1.5 × normal, ◦ β-hCG < 5,000 mU/mL, and ◦ AFP < 1,000 ng/mL • Lymph node or lymph node mass size ◦ Stage IIA: < 2 cm ◦ Stage IIB: 2–5 cm ◦ Stage IIC: > 5 cm
III	Distant metastases or lymph node metastasis with tumor markers above the levels listed for Stage II

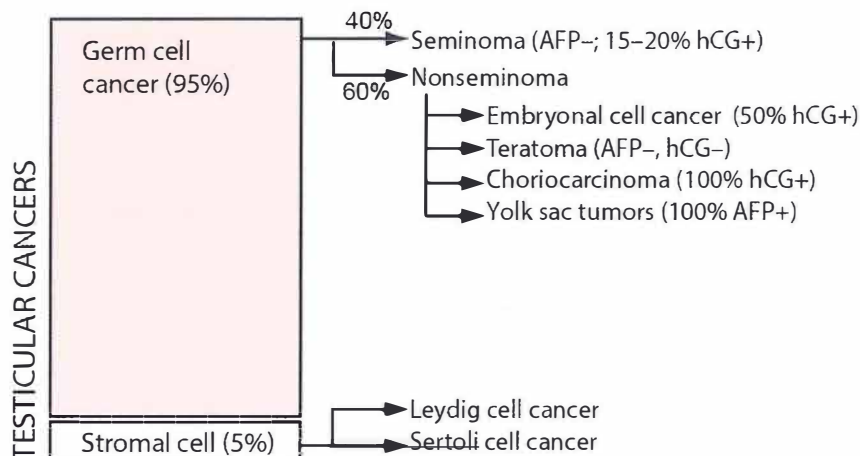


Figure 9-3: Testicular cancers and their associated biologic markers

TREATMENT OF TESTICULAR CANCER

Management of testicular cancer is determined by the type of germ cell tumor. Nonseminoma is the more aggressive type; therefore, when there are elements of both types, the tumor is considered a nonseminoma (even if the nonseminoma portion comprises only 1% of the tumor). The nonseminoma subtypes include teratoma, yolk sac tumor, embryonal carcinoma, and choriocarcinoma.

Seminomas are highly radiosensitive. Standard therapy includes inguinal orchiectomy followed by radiation to the retroperitoneal lymph nodes, chemotherapy, or surveillance. Most patients with Stage I seminoma should have surveillance only after orchiectomy. Positive nodes ≤ 2 cm in size are treated with RT. Positive nodes > 2 cm and ≤ 5 cm are usually treated with chemotherapy, though RT is sometimes used. If nodes are > 5 cm, or if there is metastatic disease elsewhere, chemotherapy is used. Note that there is no poor-risk seminoma: Even metastatic disease is curable!

Treatment of **nonseminomas** is complicated, and only a general approach is reviewed here. The initial management always includes **inguinal orchiectomy**. Patients with disease limited to testes (negative abdominal/pelvic CT for adenopathy, negative CXR, and negative tumor markers postorchiectomy) can be managed with observation (there is a 20% relapse rate, but salvage chemotherapy is 90% successful) or with nerve-sparing **retroperitoneal lymph node dissection (RPLND)**. A short course of adjuvant chemotherapy is also an option, especially when lymphovascular invasion is present (indicative of a poor prognosis, with a 50% relapse rate). Patients with persistently elevated tumor markers after orchiectomy should always be treated with a full-dose schedule of chemotherapy.

Stage II disease can be treated with either chemotherapy or RPLND. Adjuvant chemotherapy is used after RPLND in high-risk situations. Stage III disease is treated with chemotherapy. Patients sometimes have residual masses in the chest or the abdomen with normal tumor markers after chemotherapy. These masses are often mature teratomas; surgically excise them because local growth and malignant transformation is possible.

Conventional chemotherapy used in testicular cancer often includes bleomycin, etoposide, cisplatin (**BEP regimen**) or VP-16 (a.k.a. etoposide), ifosfamide, and cisplatin (**VIP regimen**). Potential therapy complications associated with chemotherapy include secondary malignancies—most notably, therapy-related acute myeloid leukemia (tAML) secondary to etoposide exposure.

Before chemotherapy, semen cryopreservation should be offered to preserve fertility.

Table 9-6 summarizes some key clinical features and the treatment of seminomas and nonseminomas.

Table 9-6: Clinical Features and Treatment of Seminoma and Nonseminoma Testicular Cancer

	Description	Seminoma	Nonseminoma
Clinical Features	Incidence	Most common	Less common
	Elevated AFP	No	Common
	Elevated β -hCG	Rare	Common
Treatment	Radical inguinal orchiectomy	Yes	Yes
	RT	Depends on stage	No
	Chemotherapy	Depends on stage	Depends on stage and risk factors
	RPLND	No	Depends on stage and risk factors

AFP = α -fetoprotein

β -hCG = β subunit of human chorionic gonadotropin

RPLND = retroperitoneal lymph node dissection

RT = radiation therapy

BLADDER CANCER

PREVIEW | REVIEW

- Which is the most common type of bladder cancer in the U.S.?
- Which is the most common type of bladder cancer worldwide?
- Which carcinogen exposures confer increased risk of bladder cancer?
- What is the classic presentation of bladder cancer?

OVERVIEW

Bladder cancer is the 6th most common cancer in the U.S. It occurs more often in men than women, and the majority of tumors arise in patients > 55 years of age. In North America and Western Europe, **transitional cell carcinomas** account for 90% of all bladder cancers. In other parts of the world, the majority (75%) of bladder cancers are **squamous cell carcinomas**. Adenocarcinomas cause 2% of bladder cancer, and other nonurothelial types (i.e., carcinosarcoma, primary lymphoma, sarcoma, small cell lung cancer [SCLC]) rarely occur. Nearly all tumors arise in the urothelium of the bladder (the inner lining).

Figure 9-4 illustrates the stages of bladder cancer; they are described in more detail in Table 9-8 on page 9-18.

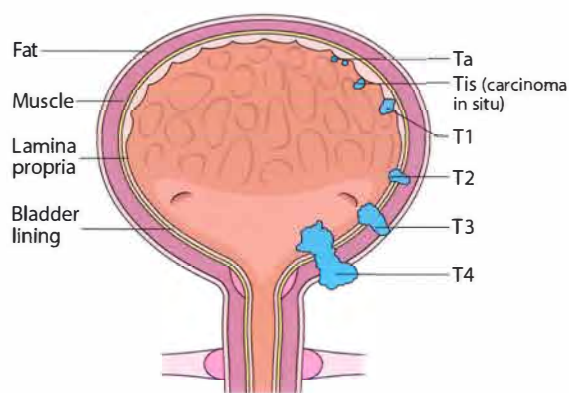


Figure 9-4: Stages of bladder cancer

RISK

Important risk factors for bladder cancer include:

- Smoking (3-fold increased risk)
- Dietary supplements containing aristolochic acid
- Medication exposure: pioglitazone, cyclophosphamide
- Arsenic (e.g., exposure through polluted drinking water)
- Low fluid intake
- Caucasian
- Male gender
- Age (> 55 years)
- Chronic bladder infection or irritation (e.g., chronic indwelling bladder catheter, bladder stones)
- Schistosomiasis (associated with squamous cell cancer; rare in U.S.)
- Personal history of bladder, urethral, or ureteral cancer
- Certain genetic syndromes: retinoblastoma, multiple hamartoma syndrome (a.k.a. Cowden disease), hereditary nonpolyposis colorectal cancer (a.k.a. Lynch syndrome)
- History of pelvic radiation

SCREENING

Routine bladder cancer screening is not recommended among normal-risk individuals. Screening may be considered in patients at very high risk; however, even in these groups there is no clear evidence for a survival benefit of screening. Screening tests include urinalysis to detect hematuria, urine cytology testing for cancer cells, and urine testing for tumor markers.

PRESENTATION

The classic presentation of bladder carcinoma is painless hematuria. Hematuria can be gross or microscopic. Evaluation of gross hematuria leads to a diagnosis of bladder cancer in up to 20% of patients, and evaluation

of microscopic hematuria leads to a diagnosis of bladder cancer in up to 5% of patients.

Patients can present with urinary voiding symptoms, which can be irritative (e.g., urinary frequency, dysuria, urge incontinence, urgency) or obstructive (e.g., straining, decreased force of stream, sensation of incomplete emptying). Bladder carcinoma in situ can present with the triad of dysuria, frequency, and urgency.

Symptoms can be intermittent, and, given the similarity of symptoms to benign disorders, there can be delays in diagnosis that can lead to poor prognosis.

Metastatic disease (most often to the lymphatic system, bones, lungs, liver, and peritoneum) can lead to presenting symptoms. Pain can occur as a result of metastases or from locally advanced disease (Table 9-7).

Table 9-7: Causes of Pain in Advanced Bladder Cancer

Location of Pain	Source of Pain
Suprapubic	Local invasion or bladder outlet obstruction
Flank	Ureteral obstruction
Bone	Bone metastases
Headaches	Intracranial metastases
Abdominal	Liver metastases
Hypogastric	Obturator fossa or presacral nerve involvement

Constitutional symptoms such as failure to thrive, weight loss, and anorexia occur with metastatic disease.

DIAGNOSIS

The finding of hematuria in patients > 35 years of age warrants workup of the entire urinary tract, including cystoscopy to examine the bladder and imaging of the upper urinary tract. Biopsy of the bladder during cystoscopy provides the definitive diagnosis of bladder cancer. Urine cytology and urine culture comprise additional workup.

A diagnosis of bladder carcinoma is followed by staging, including complete blood counts, liver and renal function tests, CXR, and MRI or CT (see Table 9-8 on page 9-18). Understaging can occur in 35% of patients, in part due to limited resolution by imaging.

STAGING AND TREATMENT

Bladder cancer is staged using the TNM staging system. After basic imaging (see Diagnosis), a transurethral resection of bladder tumor (TURBT) and pelvic examination is performed, which allows for appropriate staging to guide treatment.

The depth of primary tumor invasion is the most important factor that determines prognosis, and it is defined by tumor stage (T; Table 9-8 on page 9-18). No lymph

Table 9-8: Bladder Cancer — Staging and Basic Management Principles

Stage	Description	Treatment
Ta	Papillary lesions (generally noninvasive), limited to the inner lining of the bladder	Low-grade Ta–TURBT and: • observation or • intravesical therapy (single dose) High-grade Ta–TURBT and: • intravesical BCG, • mitomycin, or • close observation
Tis	Carcinoma in situ (CIS); limited to the inner lining of the bladder but high-grade	TURBT and recurrent intravesical BCG
T1	Invasion of the submucosa or lamina propria but not into the muscle	TURBT for staging and initial treatment; repeat to determine need for further treatment (intravesical BCG, cystectomy, and/or radiation).
T2	Invasion of the muscle layer	TURBT for staging, then partial or radical cystectomy and lymph node dissection; neoadjuvant chemotherapy is often used.
T3	Invasion through the bladder muscle into the fatty layer around the bladder	TURBT for staging, then usually radical cystectomy with chemotherapy
T4 and metastatic disease	Spread to adjacent organs (e.g., vagina, uterus, bowel, prostate)	Chemotherapy; might need diversion surgery and/or checkpoint inhibitor therapy (e.g., atezolizumab, pembrolizumab)
BCG = bacille Calmette-Guérin TURBT = transurethral resection of bladder tumor		

node involvement is N0 disease; a single node in the pelvis indicates N1 disease; multiple pelvic nodes is N2 disease; involvement of common iliac nodes is N3 disease. M1 indicates metastatic disease.

Treatment depends on the stage of the tumor and presence of nodal and metastatic disease. Low-risk, early-stage cancer is often treated with **TURBT** followed by single-dose intravesical chemotherapy. Intermediate and high-risk localized (Ta or Tis) tumors are treated with prolonged intravesical chemotherapy.

Intravesical therapy usually consists of bacille Calmette-Guérin (BCG), which is an attenuated form of *Mycobacterium bovis* that works by activating the local immune system. Intravesical mitomycin and other agents are also sometimes used. Close surveillance is important, as recurrence is common.

For invasive and advanced disease (T2 and higher), **cystectomy** is usually indicated, along with systemic **chemotherapy** (usually cisplatin). **Immune checkpoint inhibitors** are used in recurrent disease, as well as in chemotherapy-ineligible disease.

- Name the classic presentation of renal cell carcinoma.
- What are the most common sites to which renal cell cancer metastasizes?

OVERVIEW

Renal cell carcinomas are primary malignant tumors of the kidney, making up ~ 80% of primary kidney malignant tumors. They begin in the proximal convoluted tubules of the renal cortex. Other, less common, primary malignancies of the kidney are transitional cell carcinomas in the renal pelvis, oncocytomas, and renal sarcomas; in children, Wilms tumors also occur. This topic focuses on the clinical presentation, diagnosis, staging, and treatment of renal cell carcinomas.

The majority of renal cell carcinomas (70%) are clear cell carcinomas. The types of kidney tumors are listed in Table 9-9.

SCREENING

Patients with higher risk of developing renal cell carcinoma include those with tuberous sclerosis (a genetic disorder caused by mutations of the *TSC* genes) and von Hippel-Lindau syndrome (a genetic disorder caused by mutations in the *VHL* gene, which predisposes to a range of tumors). Also at increased risk are patients with end-stage renal disease who are on dialysis, patients with a strong family history of renal cell carcinomas, and those with prior kidney irradiation. Consider screening these patients, possibly with CT scanning or U/S, to find early disease.

RENAL CELL CANCER

PREVIEW | REVIEW

- What is the most common type of primary kidney tumor?
- Which cell type comprises most renal cell carcinomas?
- What patients have an increased risk of developing renal cell carcinoma?

Table: 9-9: Types of Kidney Tumors

Type of Tumor		Frequency (%)	Origin
Renal cell carcinoma	Clear cell	55–70	Proximal tubule
	Papillary tumor	5–15	Proximal tubule
	Chromophobic (eosinophilic cytoplasm)	5–10	Cortical collecting duct
Oncocytic (generally benign)		5–10	Cortical collecting duct
Collecting duct tumors		< 1	Medullary collecting duct
Angiomyolipoma (benign)		1	Epithelioid, derived from blood vessels

PRESENTATION

The classic presentation of renal cell carcinoma is hematuria, flank pain, and a palpable renal mass; however, a minority of patients present with this classic triad. Renal cell carcinoma more commonly presents with isolated microscopic hematuria, abdominal pain, weight loss, or a renal mass found incidentally on abdominal imaging. Up to 25% of patients present at a later stage of disease because they are asymptomatic in the earlier stages; the outcome for these patients is less favorable than for those with earlier diagnoses.

Other signs and symptoms of renal cell carcinoma include abdominal pain, weight loss, fever, and cachexia. Hypercalcemia can be caused by bone metastases, production of PTHrP, or production of prostaglandins that lead to bone resorption. Scrotal varicoceles may occur if the tumor obstructs the gonadal vein. Tumors involving the inferior vena cava may cause edema, ascites, and liver dysfunction with Budd-Chiari syndrome or pulmonary emboli.

Anemia is present in up to 88% of patients; paraneoplastic syndromes can occur as well. Stauffer syndrome (hepatic dysfunction without liver metastases) is an unusual paraneoplastic occurrence.

Other findings related to renal cell carcinoma are erythrocytosis (due to excess production of erythropoietin), AA (secondary) amyloidosis, thrombocytosis (possibly IL-6 production), and polymyalgia rheumatica (for more on polymyalgia rheumatica, see the [Rheumatology](#) section).

Metastasis most commonly occurs to the lungs, lymph nodes, bone, liver, and brain.

DIAGNOSIS

Abdominal CT is the imaging modality of choice. Perform abdominal U/S to determine whether a cyst is simple or complex and to differentiate between cystic

lesions and solid tumors. Consider MRI to determine involvement of the inferior vena cava. **Recall** the risk of nephrogenic systemic fibrosis (NSF) when ordering MRI studies in patients with impaired renal function.

Angiography (preferably CT or magnetic resonance angiogram [MRA]) localizes the vasculature prior to surgery.

Tissue diagnosis is usually made by nephrectomy or partial nephrectomy, rather than percutaneous biopsy. Percutaneous biopsy is used only in patients who are not surgical candidates, when cryotherapy or radiofrequency ablation is planned.

STAGING

The renal cell carcinoma TNM staging system is as follows:

- T1 tumors are confined to within the kidney and limited to < 7 cm.
- T2 tumors are confined to within the kidney but are > 7 cm.
- T3 tumors extend outside the kidney (e.g., to the perinephric tissues or the renal vein) but not past the Gerota (i.e., renal) fascia or into the ipsilateral adrenal gland.
- T4 tumors invade past the Gerota fascia or into the ipsilateral adrenal gland.
- Metastases to lymph nodes and other organs are noted as absent or present.

TREATMENT

Treatment of renal cell carcinoma depends on the size and stage of disease and whether the disease is localized or advanced.

Surgery

Localized disease is treated with surgical resection—either partial or radical nephrectomy. Patients with advanced disease (Stage T4 tumors or metastatic disease) are generally considered unresectable.

Tumors < 4 cm in diameter are usually treated with a **partial nephrectomy**. Patients in this category who are poor surgical candidates due to advanced age or comorbidities may be observed with active surveillance or treated with **cryotherapy** or **radiofrequency ablation** (RFA).

Tumors between 4 and 7 cm in diameter are treated by partial nephrectomy, if feasible, or by **radical nephrectomy**.

Tumors between 7 and 10 cm are treated with radical nephrectomy.

Larger tumors with no metastases or those that involve the renal vein, the adrenal gland, and/or the perinephric fat **within** the Gerota fascia are treated by radical nephrectomy with resection of adjacent organs and tumor removal from the renal vein or inferior vena cava. Cure may occur in up to 60% of these patients.

Tumors that either extend beyond the Gerota fascia or those that have metastasized to a distant lymph node are treated with cytoreductive nephrectomy prior to systemic therapy for tumors that are resectable. Resection of metastasis may be effective in patients who have solitary metastases or in those with a long interval between primary diagnosis and development of metastasis.

Patients with low burden of metastatic disease may be observed initially; however, patients with metastatic disease are considered candidates for systemic treatments. These treatments are not considered curative and the decision to treat with systemic treatments is predicated on disease risk and the patient's functional status.

Systemic Therapy

Immunotherapy with checkpoint inhibitors (e.g., pembrolizumab, avelumab, nivolumab + ipilimumab) is the 1st line treatment for patients with advanced clear cell carcinoma.

Tyrosine kinase inhibitors (e.g., axitinib, cabozitinib, sunitinib, pazopanib) may be used in combination with checkpoint inhibitors as the initial treatment or as a secondary treatment in patients who progress or fail to respond to checkpoint inhibitors.

Interleukin-2 is an older, more toxic treatment for renal cell cancer that is still used in some patients with excellent performance status, given its potential to induce long-standing remissions.

- Which types of calcifications indicate a benign solitary pulmonary nodule?
- Which lung cancers are associated with hypercalcemia? With syndrome of inappropriate antidiuretic hormone? With gynecomastia? With hypertrophic pulmonary osteoarthropathy?

OVERVIEW

Lung cancer is the #2 cancer among men (after prostate); the #2 cancer among Caucasian, Native American, and Alaska Native women (after breast); and #3 among African American and Hispanic women (after breast and colorectal).

Lung cancer is the leading cause of cancer-related death in men and women (except Hispanic women, in whom breast cancer is the leading cause of death).

85% of lung cancers are linked to smoking! The risk decreases after smoking is stopped and continues to decrease for as long as the patient remains smoke free, but the risk never returns to the baseline risk of a person who has never smoked. (Similarly, lung function also improves after smoking cessation—but not to normal.)

Remember the cancers that most often metastasize to the lung include breast, colon, kidney, and prostate.

Lung cancer can be asymptomatic, be discovered incidentally, or manifest with pulmonary or systemic signs and symptoms. Pulmonary symptoms include cough, dyspnea, sputum production, hemoptysis, hoarseness (related to tumor involvement of the recurrent laryngeal nerve), and/or chest pain, and in some cases, patients may develop symptoms related to postobstructive pneumonia. Systemic or extrapulmonary manifestations include weight loss, fatigue, paraneoplastic syndromes, venous thrombosis, thromboemboli, and symptoms related to metastases in specific areas, including pathologic fractures or bone pain.

Chest x-ray and computed tomography (CT) scan are necessary tests that often will lead to CT/positron emission tomography (PET) to further evaluate metabolic activity of a specific lesion, lymph nodes, and other sites that may be metastatic. CT/PET is not specific for diagnosing malignancy, as infections and inflammatory conditions can also cause fluorodeoxyglucose (FDG) avidity.

Tissue diagnosis, preferably with staging, can be done with CT-guided percutaneous needle biopsy and/or bronchoscopy (+/- navigational bronchoscopy for small peripheral lesions). Endobronchial ultrasound with lymph node aspiration is used to stage the mediastinum preoperatively.

Thoracentesis of pleural effusions and interventional radiology-guided needle biopsy of extrapulmonary lesions can be performed.

Enlarging pulmonary nodules thought to be malignant can be resected without biopsy if there is no disease elsewhere. Treat more extensive lesions with surgery if resectable, or with chemotherapy in patients with non-resectable disease.

LUNG CANCER

PREVIEW | REVIEW

- List some risk factors for the development of lung cancer, besides smoking cigarettes.
- Which lung cancers are usually central in the chest?
- Which lung cancers are usually peripheral?
- Which lung cancer is most likely to cavitate?
- For patients with a lung mass and palpable cervical lymphadenopathy, which procedure is useful for diagnosis?
- How sensitive are pleural fluid analyses for diagnosing lung cancer?
- Which stages of non-small cell lung cancer are treated with surgery?
- Characterize the course of small cell lung cancer.
- What do you do with the solitary pulmonary nodule in the patient with risk factors for cancer?

Some patients may be restaged after chemotherapy and reconsidered for surgery. Radiation therapy may also be used for those whose disease is not resectable or who need palliation of symptoms or signs of the tumor (e.g., hemoptysis, bone pain).

RISK FACTORS FOR LUNG CANCER

Again, smoking is the most important risk factor for the development of lung cancer. With significant asbestos exposure alone, the risk of lung cancer is 6× that of normal; with smoking alone, it is 10× that of normal. With asbestos and smoking, the risk is 60× that of normal (synergistic). Asbestos increases the risk of the 2 most common lung cancers: adenocarcinoma and squamous cell carcinoma. There is also an increased incidence of lung cancer with uranium and nickel mining and exposure to diesel exhaust, hexavalent chromium, beryllium, cadmium, coal, steel industrial processes, aluminum processing, silica, and arsenic. Silica, when it causes silicosis, is considered a carcinogen. Heavy doses of radon in underground miners are linked with lung cancer, but home/office exposure as a cause is controversial.

Atmospheric pollution is a risk factor for lung cancer. Second-hand smoke in childhood (> 25 pack years) increases the chance of lung cancer in adulthood. Nonfilter cigarettes are worse than those with filters. And there is a definite genetic factor in susceptibility.

Malignant mesothelioma is caused by asbestos but is **not** caused by **smoking**. Malignant mesothelioma generally presents with pleuritic chest pain and a unilateral hemorrhagic pleural effusion.

SCREENING

Based on findings of the National Lung Screening Trial, the NCCN, the American College of Chest Physicians, and other professional societies, low-dose CT (LDCT) scanning for lung cancer screening is now recommended in high-risk individuals. The demonstrated benefit of LDCT is a relative reduction in mortality from lung cancer of 20% and a 6.7% reduction in all-cause mortality. The risk reduction is achieved by finding lung cancer at an early stage and surgically resecting it. USPSTF 2020 draft guidelines recommend annual screening with LDCT for patients who are between 55 and 80 years of age, have smoked ≥ 20 pack years, and are either current smokers or have quit within the past 15 years. Additional caveats to those who should be screened include:

- The patient should be counseled about very frequent false-positive results on the LDCT. Most pulmonary nodules are, in fact, benign. The patient needs to be counseled expectantly regarding false positives and the risk of harm and excess cost, as well as benefits. The greatest potential harm is the identification of nodules that end up being benign but may result in invasive procedures, such as bronchoscopy, needle biopsy, thoracoscopy, mediastinoscopy, and

thoracotomy. Many patients who were diagnosed with a nodule as a result of screening also have reported significant psychological distress or anxiety regarding such findings.

- Because the demonstrated benefit is for patients whose lung function is adequate to undergo surgical resection, this is primarily the patient group that should undergo screening. It is controversial whether to screen patients who are not surgical candidates, but there are advocates who argue that stereotactic body radiation therapy can provide reasonable results. This requires further study, though retrospective studies support this approach.
- Patients should be screened only if the screening can occur at a multidisciplinary facility with staff experienced in the interpretation of pertinent imaging and the management and treatment of pulmonary nodules.

TYPES OF LUNG CANCER

There are 4 major categories of lung cancer (shown with the proportion of incidence):

- 1) Adenocarcinoma (~ 40%)
- 2) Squamous cell (~ 30%)
- 3) Small cell (15%)
- 4) Large cell (~ 15%)

Adenocarcinoma beats out squamous cell as the most common form of lung cancer.

Squamous and small cell cancers are usually central lesions (**S-S-Sentral**).

Adeno and large cell are peripheral.

Nowadays, lung cancer is frequently classified as small cell vs. non-small cell, based on differences in tumor biology, management, and prognosis. Non-small cell lung cancer collectively represents adenocarcinoma, squamous cell, and large cell.

Non-Small Cell Lung Cancer (NSCLC)

Types of NSCLC

Adenocarcinoma is typically peripheral and is usually found incidentally. Adenocarcinoma metastasizes **early**, especially to the CNS, adrenals, and bones. It generally presents as a **solitary** nodule. A bronchoalveolar carcinoma is a subclass of adenocarcinoma and is now referred to as adenocarcinoma in situ or adenocarcinoma with lepidic growth. This type of neoplasm can be mucinous, nonmucinous, or of mixed type. This tumor may produce a large amount of frothy sputum. It has the **weakest** association with smoking and a strong association with pulmonary scars (as in idiopathic pulmonary fibrosis). In some cases, it is mistaken for pneumonia or a slow-growing, vague-appearing nodule, and in cases of very extensive disease, chest imaging may resemble acute respiratory distress syndrome.

Squamous cell cancer, unlike adenocarcinoma, generally does **not** metastasize early. It is usually a central/**hilar** lesion with local extension, and it often presents with obstructive findings (e.g., atelectasis, pneumonitis) and occasionally (7%) as thick-walled (> 4 mm) cavitation. Squamous cell lung cancer is by far the most likely to **cavitate**.

Large cell lung cancer is typically a peripheral lung lesion and tends to metastasize to the CNS and **mediastinum** (and can cause hoarseness or SVC syndrome).

If there is a history of asbestos exposure, think of squamous cell cancer, adenocarcinoma, and mesothelioma.

See [Figure 9-5](#) and [Figure 9-6](#).

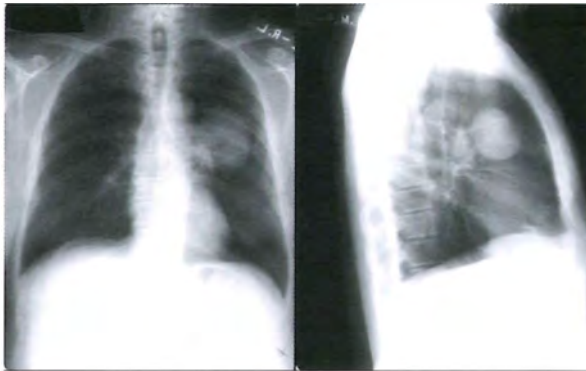


Figure 9-5: Chest posteroanterior/lateral—upper lobe lung mass

Source: Vinay Maheshwari, MD

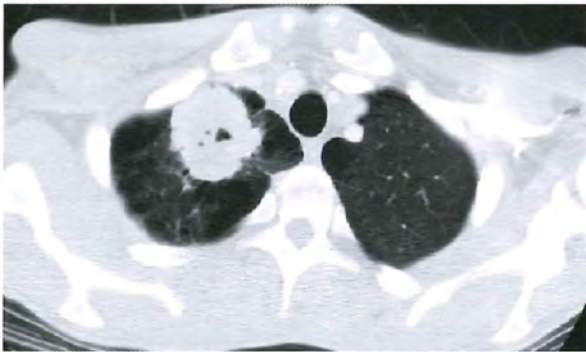


Figure 9-6: CT chest—upper lobe lung mass

Source: Vinay Maheshwari, MD

Diagnosis and Staging of NSCLC

First, do a careful history and exam with lab tests (CBC, Ca^{2+} , bilirubin, AST, ALT, and alkaline phosphatase).

Then order a contrasted CT scan of the chest, which includes cuts through the liver and the adrenal glands. Further CT imaging may be indicated by clinical presentation and/or suspicion for pathology elsewhere. In general, CT/PET is obtained subsequently to identify sites other than the primary lesion or the extent of disease. This can be helpful in selecting sites for diagnosis and staging. Further imaging, such as CT/MRI of the brain and bone scan, depends on the results of a full review of systems, physical exam, labs, and prior imaging.

Then, get tissue for diagnosis. Many different procedures exist to get lung tissue—e.g., different types of bronchoscopy (conventional light, endobronchial ultrasound [EBUS], or navigational), image-guided percutaneous needle biopsy, mediastinoscopy, or surgical resection. The procedure of choice is based on the location of the lesion, the need to assess other areas (e.g., local lymph nodes), and patient comorbidities and tolerance for procedures. The combination of imaging studies (including PET scans) and transbronchial procedures, in particular EBUS (for lymph nodes) and navigational bronchoscopy (for biopsy of peripheral lesions as well as placement of fiducial markers), is making more invasive diagnostics unnecessary. Fiducial markers help the radiation oncologist in stereotactic ablative radiotherapy.

Know: If a patient has palpable supraclavicular or cervical lymphadenopathy, fine-needle aspiration or excisional biopsy helps with both diagnosis and staging and is less invasive.

Pleural effusion cytology is helpful in staging if an effusion is present. If the 1st sample does not show malignant cells, submit a 2nd sample. (The diagnostic yield is > 90% in 3 samples if malignancy is the cause of effusion.) Closed pleural biopsies are no longer done to diagnose cancer.

The approach differs based on patient-specific parameters. **Know** that after imaging, you want tissue of the primary tumor for diagnosis (unless you can get the diagnosis and staging done in a single procedure using lymph nodes or other metastatic site). Aim to biopsy the safest site that gives you both a diagnosis and the most advanced stage, so that only 1 procedure is needed. Due to breakthroughs in the development of chemotherapy, additional tissue is often required to ascertain if there are specific gene mutations or other molecular changes present that indicate sensitivity to specific, targeted or immunotherapy agents, discussed under [Treatment of NSCLC](#).

The 8th edition **TNM** staging system describes tumor, node, and metastasis (updated in 2018). Updates include new subsets because there is worsening survival with each increase in tumor size. Refer to the classification in [Table 9-10](#) when going over the treatment of NSCLC (do not memorize it!).

Stages of NSCLC are defined as follows:

- Stage 1: T1aN0 or T2aN0
- Stage 2A: T2bN0
- Stage 2B: T1N1, T2N1, or T3N0
- Stage 3A: T1N2, T2N2, T3N1, T4N0, or T4N1
- Stage 3B: T1N3, T2N3, T3N2, or T4N2
- Stage 3C: T3N3 or T4N3
- Stage 4A: any T, any N, with M1a or M1b
- Stage 4B: any T, any N, with M1c
- Note: There are no metastases (i.e., M0) until Stage 4.

Treatment of NSCLC

Stage 1 and 2 disease: Treat with surgical resection whenever possible, giving the best chance for long-term survival and cure. Add adjuvant chemotherapy (cisplatin based)

Table 9-10: TNM Staging System

TNM Category	Stage	Description	Subsets	Description
T (tumor): primary tumor size and local invasiveness	T1	≤ 3 cm in greatest diameter, surrounded by lung or sternal pleura but not in a main bronchus	T1a(mi)	Minimally invasive
			T1a	≤ 1 cm
			T1b	> 1 cm but ≤ 2 cm
			T1c	> 2 cm but ≤ 3 cm
	T2	> 3 cm but ≤ 5 cm, or the tumor has any of the following: involves the main bronchus (without involving the carina); invades visceral pleura; or is seen in conjunction with atelectasis or obstructive pneumonitis that extends to the hilar region	T2a	> 3 cm but ≤ 5 cm, or the tumor directly invades any of the following: the parietal pericardium, chest wall, phrenic nerve, or associated separate tumor nodules in the same lobe as the primary tumor
			T2b	> 7 cm, a tumor of any size invades any of the following: mediastinum, heart, great vessels, trachea, esophagus, vertebrae, diaphragm, recurrent laryngeal nerve, vertebral body, carina, or the tumor exists as separate nodules in a different ipsilateral lung than the primary
N (node): lymph node involvement	T3	> 5 cm but ≤ 7 cm, or separate tumor nodules in same lobe as primary tumor, or invasion of any of following: chest wall, phrenic nerve, parietal pericardium		
	T4	> 7 cm, or separate tumor nodules in different ipsilateral lobe than primary tumor, or invasion of diaphragm, mediastinum, heart, great vessels, esophagus, vertebral body, carina, trachea		
	N0	No lymph node involvement		
	N1	Ipsilateral peribronchial and/or ipsilateral hilar nodes and intrapulmonary nodes		
M (metastasis)	N2	Ipsilateral mediastinal and/or subcarinal nodes		
	N3	Contralateral nodes or ipsilateral scalene or supraclavicular nodes		
	M0	Metastasis absent		
	M1	Metastasis present	M1a	Includes malignant pleural or pericardial effusions and tumor nodules in the contralateral lung
			M1b	Includes single tumor spread to the liver, bone, brain, or distant lymph nodes
			M1c	Includes > 1 tumor spread to the liver, bone, brain, or distant lymph nodes

for Stage 2 and high-risk Stage 1B disease, to improve survival. If the patient is not a candidate for surgery, treat with radiation, including stereotactic radiosurgery.

Stage 3 disease: Treat with combined modality nonsurgical approach using concurrent chemoradiation, followed by immunotherapy.

According to NCCN 2020 recommendations, after completion of treatment for Stage 1/2/3 disease, monitor the patient with posttreatment surveillance, including chest CT every 6 months for 2 years and then annually thereafter.

Stage 4 disease: Treat with systemic therapy, with palliative intent. Choice of treatment is guided by molecular characterization of the tumor (personalized medicine).

Options include chemotherapy vs. targeted vs. immunotherapy. Checkpoint inhibitor immunotherapy has become an integral component of lung cancer therapy. Programmed cell death-1 inhibitors such as pembrolizumab are now 1st line therapy, either in combination with or in place of cytotoxic chemotherapy.

Test tissue specimens for selected molecular mutations, including *EGFR* (epidermal growth factor receptor), *ALK*, *ROS-1*, and *BRAF*, because targeted therapies can be used, such as osimertinib for EGFR-positive lung cancer. Test tumor for programmed cell death ligand-1 to assess the role of checkpoint inhibitor immunotherapy. Angiogenesis inhibitors such as bevacizumab may also be incorporated in the treatment of advanced lung cancer.

Small Cell Lung Cancer (SCLC)

Notes

SCLC is extremely aggressive, so its treatment is usually discussed separately from the others. It rarely occurs in nonsmokers. Cavitation never occurs (unlike other lung cancers). SCLC can cause syndrome of inappropriate antidiuretic hormone secretion (SIADH), ectopic adrenocorticotrophic hormone (ACTH) production, Lambert-Eaton syndrome, and various paraneoplastic syndromes (more under [Paraneoplastic Syndromes](#)).

Diagnosis and Staging of SCLC

Compared to NSCLC, SCLC is a very bad disease. The tumor grows fast and metastasizes early.

Most patients with SCLC present with advanced disease. Although most patients respond to initial treatment, there is a high rate of subsequent relapse and limited long-term survival. The historical staging system that is still widely used today is the Veterans Affairs Lung Study Group (VALSG): The patient has limited disease if the tumor is confined to the ipsilateral hemithorax and extensive disease if the tumor has metastasized outside of the ipsilateral hemithorax. Up to 70% of patients present with extensive disease. The conventional TNM staging system is most useful for identifying the minority of patients with very-early-stage disease who can undergo surgical resection.

Diagnosis requires a good physical exam and review of systems, chest x-ray, and chest CT. Once tissue is obtained for diagnosis, additional imaging studies are performed; e.g., contrast CT of the head, abdomen, and pelvis; PET/CT; bone scan; and marrow biopsy (if indicated).

Know that SCLC is rapid growing—usually all symptoms evolve within 8 weeks prior to diagnosis. You must absolutely **not** delay staging a patient > 1 week after diagnosis. The patient can get very sick very quickly.

Treatment of SCLC

Survival periods for the majority of SCLC patients (and 5-year survival rates):

- Limited disease = 15–20 months (10–13%); initial treatment is chemotherapy and radiation and then, if the patient shows improvement, prophylactic whole brain radiation.
- Extensive disease = 8–13 months (1–2%); initial treatment is chemotherapy +/- immunotherapy, and prophylactic whole brain radiation.
- Surgery is reserved for the fortunate patient with a solitary nodule without distant spread.
- The 5-year survival rate for Stage 1A1 is 92%, for Stage 1B is 68%, for Stage 3A is 36%, for Stage 3C is 13%, for Stage 4A is 10%, and for Stage 4B is 0%.

SOLITARY PULMONARY NODULE

The solitary pulmonary nodule is a nodule usually located in the middle-to-lateral 1/3 of the lung, surrounded by normal parenchyma. The odds that a solitary pulmonary nodule is malignant depend on the patient's risk factors and the size of the nodule. The odds of being malignant also vary by country. Recent studies suggest that between 1% and 35% in the U.S. are malignant.

Most solitary pulmonary nodules are found on chest CT and require rescanning with CT at intervals. The size and characteristics of the nodule and the patient's risk for lung cancer determine whether to follow the nodule with several scans at intervals or to take it out. Additionally, always check for prior chest imaging (if available) to establish the chronicity and growth rate of the nodule in question.

When a nodule is > 0.8 cm in diameter, a PET scan can be done to assess the probability of malignancy and guide further management.

Calcification of a solitary pulmonary nodule suggests it is benign. It is virtually always benign if the calcification is popcorn-like (hamartoma), is laminated (bull's-eye = granuloma), or has multiple punctate foci or a dense central calcification ([Figure 9-7](#)). Asymmetric or ground glass-type calcification suggests malignancy.

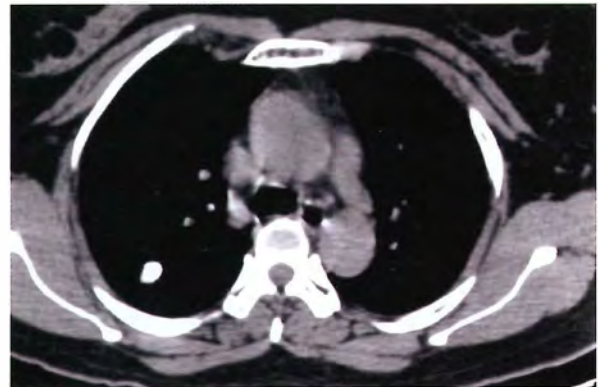


Figure 9-7: CT chest—diffusely calcified pulmonary nodule with well-defined borders

Source: Vinay Maheshwari, MD

Follow-up imaging is guided by Fleischner Society tables for incidentally discovered nodules. The follow-up interval is determined by the patient's risk for lung cancer, the size of the nodule, and whether it is a solid or sub-solid nodule. Most solid nodules are followed for up to 18–24 months in high-risk individuals, but some sub-solid nodules are followed for up to 5 years. For a small solid nodule (< 6 mm), with low malignancy risk, no further follow-up is indicated. Radiologists generally provide interpretations with follow-up imaging recommendations based on the 2017 Fleischner Society guidelines. Growing or highly suspicious nodules require shorter-interval follow-up imaging, CT/PET, biopsy, and/or resection. Close consultation with an experienced pulmonary nodule management team is needed for larger, growing, or suspicious nodules.

A tissue-based diagnosis is accomplished using any of the following:

- If nodules are ≥ 0.8 cm in diameter, FDG PET/CT scan can be used to sort out scars from malignant lesions. However, PET is not sensitive for bronchoalveolar (adenocarcinoma in situ) or carcinoid tumors or metastasis from renal cell, and it can demonstrate FDG uptake in infectious or inflammatory lesions. Thus, be aware of limitations in the specificity and sensitivity of PET/CT.
- CT-guided fine-needle aspiration—sample the center of the nodule unless it appears necrotic; then a more peripheral approach is best; there is a 10–15% average risk of pneumothorax.
- Traditional bronchoscopy does not reach peripheral lesions. Navigational bronchoscopy helps the bronchoscopist reach those difficult peripheral lesions, and endobronchial ultrasound (EBUS) can biopsy most mediastinal lymph nodes, and sometimes even the primary tumor, and is increasingly the procedure of choice for nodal staging.
- Surgical lobectomy or wedge resection can remove the nodule at the same time.

PARANEOPLASTIC SYNDROMES

Paraneoplastic syndromes (favorite topics for exam questions) occur in ~ 2–20% of lung cancer patients:

- **Hypercalcemia** (from a parathyroid hormone [PTH]-secreting cancer) is caused by **squamous** cell lung cancer (think sCa^{++} mouse). The Ca^{2+} level is proportional to the tumor bulk. Hypercalcemia is seen less often in large cell lung cancer (12%).
- **SIADH, ectopic ACTH production, and Lambert-Eaton syndrome** are linked with **SCLC**. (Wow, small cells do all that?) Note: Diabetes insipidus is not a paraneoplastic syndrome. If a patient presents with this and a lung cancer, consider brain metastases.
- **Gynecomastia** is linked with large cell lung cancer (think “large” breasts).
- **Hypertrophic pulmonary osteoarthropathy (HPOA)** is especially seen in conjunction with **adenocarcinoma**, but it occurs in all 3 NSCLC types. With HPOA, patients get clubbing and new bone formation on the long bones, which appear dense on x-rays. These patients often present with only painful ankles and clubbing.
- **Horner syndrome**—cancers located in the apex of the lung can invade the sympathetic nerve and cause ipsilateral miosis, ptosis, and anhidrosis.

HEAD AND NECK CANCER

A majority of head and neck cancers are associated with tobacco and/or alcohol abuse—thus, most cases are preventable. There is increased head and neck cancer with:

- Tobacco use (both smoking and chewing)
- Heavy alcohol use
- HPV-16/-18 infections
- Epstein-Barr virus (EBV; nasopharyngeal carcinoma only)
- Leukoplakia

95% of head and neck cancers are **squamous/epidermoid**.

Patients present with various symptoms, depending on the location of the primary tumor (e.g., otalgia, nonhealing oral ulcers). There can be an enlarged cervical lymph node or neck mass on presentation. If a suspicious cervical node is present, diagnose with FNA, and, if positive for squamous cell carcinoma with unknown primary, obtain a CT and/or MRI of the head/neck. This is commonly followed by panendoscopy.

In early-stage disease, there is a real potential for cure with surgery and/or radiation therapy (RT). Make every effort to preserve function. Clinical trials have demonstrated that the addition of chemotherapy or biologic therapy (e.g., cetuximab, an EGFR inhibitor) to a primary therapy of RT improves outcomes in head and neck cancer. If the disease is metastatic, treatment is palliative and typically involves cisplatin, 5-fluorouracil (5-FU), taxanes, cetuximab, and, more recently, immune checkpoint inhibitors (e.g., nivolumab). HPV-positive tumors respond better to treatment.

PRIMARY BRAIN CANCER

Malignant brain tumors can have an array of presenting symptoms, depending on their size, location, and growth rate. Most primary tumors involve the cerebral hemispheres and present with headaches or seizure. Other symptoms can include nausea, vomiting, weakness, aphasia, and changes in personality and cognition. There are no clear environmental risk factors for brain cancer. Long-term cellphone use was not shown to be a risk factor in a large study in Denmark in 2012.

The most common type of primary brain tumor is **astrocytoma**, which includes anaplastic astrocytoma and glioblastoma (a.k.a. glioblastoma multiforme). Both are aggressive, but glioblastoma is the most aggressive of all brain tumors. Typical age of onset for anaplastic astrocytoma is 35–55 years of age, while it is 45–65 years of age for glioblastoma.

Diagnosis is made by MRI. Treatment includes initial debulking surgery, followed by adjuvant radiation plus alkylating agent temozolomide. Many patients achieve initial response, though recurrence risk is high.

Consider bevacizumab, a vascular endothelial growth factor (VEGF) inhibitor, for treatment of recurrent gliomas. Median survival rates for anaplastic astrocytoma and glioblastoma are 2–3 years and 12–15 months, respectively. Molecular characterization of brain cancers can further refine prognosis and guide therapy. For glioblastomas, *O*-methylguanine-DNA methyltransferase (MGMT) methylation and/or isocitrate dehydrogenase (IDH) mutation predicts favorable response to chemotherapy and improved survival outcomes.

See the [Neurology](#) section for additional information on CNS tumors.

GASTRIC CANCER

PREVIEW | REVIEW

- What are the clinical and environmental risk factors for gastric cancer?
- What is the relationship between alcohol and gastric cancer?
- How do you rule out gastric cancer in a patient with a nonhealing gastric ulcer?

There are 4 significant malignancies of the stomach:

- 1) Adenocarcinoma ([Figure 9-8](#); **most common**—95%!)
- 2) Lymphoma
- 3) Neuroendocrine tumors (See discussion under [Neuroendocrine Tumors \(NETs\)](#) on page 9-31.)
- 4) Gastrointestinal (GI) stromal tumors (e.g., leiomyosarcoma)

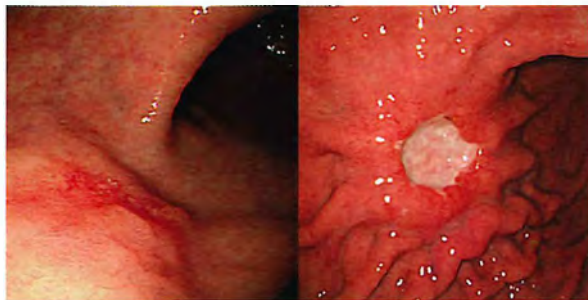


Figure 9-8: Gastric adenocarcinoma, early and late

There are 2 distinct forms of gastric adenocarcinoma: a **proximal diffuse type** and a **distal intestinal type**. Up until 20 years ago, the incidence of distal gastric cancer had been decreasing; since then, its incidence has been holding steady. The proximal type has been steadily increasing.

Gastric cancer risk factors and associations include:

- Chronic *H. pylori* infection
- Metaplastic (chronic) atrophic gastritis
- Ménétrier disease (large stomach folds from epithelial cell hyperplasia)
- Adenomatous gastric polyps (rare)

Distal gastric cancer has strong environmental associations and risk factors, especially:

- A diet low in fruits and vegetables and high in dried, smoked, and salted foods
- Processed meats (e.g., sausage, ham, bacon)
- Foods rich in nitrates and nitrites (animal studies)

Acanthosis nigricans

([Figure 9-9](#)) is a reactive skin condition with velvety dark plaques in the intertriginous areas (where opposing skin surfaces touch and rub). It is usually due to Type 2 diabetes and obesity, but it is also associated with various GI and lung malignancies. Of these malignancies, acanthosis nigricans is most often associated with gastric cancer.



Figure 9-9: Acanthosis nigricans

Note that some *H. pylori*-infected patients can develop extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT). Diagnose this by esophagogastroduodenoscopy (EGD; upper endoscopy) with biopsy. Most cases of MALT resolve with eradication of *H. pylori*. Close endoscopic follow-up is necessary and confirmation of eradication of *H. pylori* is mandatory.

Neither alcohol consumption nor gastric ulcers have been proved to cause gastric cancer—as previously thought—even though gastric cancer can present as an ulcer.

Diagnosis of gastric cancer: Often an ulcer is picked up on EGD or barium contrast study (double contrast is better). If it appears benign, it can be treated. Biopsy gastric ulcers to rule out cancer if the etiology is not clear (i.e., *H. pylori* and NSAIDs have been ruled out).

Perform endoscopy with multiple biopsies to rule out cancer in nonhealing ulcers. Tumor markers, such as carcinoembryonic antigen (CEA) and α -fetoprotein (AFP), are **not** useful as early markers for gastric cancer.

Prognosis is based on cancer stage (TNM classification), which is evaluated using CT scan and endoscopic ultrasound. Because gastric cancers are largely asymptomatic until advanced, < 10% are found in the early gastric cancer (EGC) stage—confined to the mucosa and submucosa, T1N0M0.

The 5-year survival rate is 85–90% for treated EGC and only 3% for treated invasive, metastatic gastric cancer.

Treatment consists of surgical removal of the cancer and adjacent lymph nodes. Adjuvant combination chemoradiation prolongs survival.

COLORECTAL CANCER

PREVIEW | REVIEW

- Endocarditis due to _____ or _____ (organisms) warrants a colonoscopy to search for colorectal cancer.
- What size and histologic features of colon adenomas are considered advanced features with increased malignant potential?
- What is the relationship between hyperplastic polyps and colorectal cancer?
- How frequently should you do surveillance colonoscopy in patients with adenomatous polyps?
- Which 2 familial polyposis syndromes have the highest risk of carcinoma?
- What is the risk of cancer in Peutz-Jeghers syndrome?
- At what age should colorectal cancer screening begin for patients with Lynch syndrome?
- Under what circumstances should periodic colonoscopy be started at 40 years of age?
- Which common colon problem in increased-risk patients is an indication for colonoscopy?
- Are carcinoembryonic antigen levels useful for primary diagnosis, recurrence, or both in colon carcinoma? Why?
- Surgery for cure is the rule in colorectal cancer. When is adjuvant chemotherapy used? When is radiation used?

OVERVIEW

The lifetime risk of colorectal cancer is 6% in average-risk persons. Risk factors for colorectal carcinoma, or colorectal cancer, include:

- Age > 50 years of age
- Adenomatous polyps (current or past)
- Ulcerative colitis
- Crohn colitis
- Acromegaly
- Obesity
- Smoking
- Diets high in calories and animal fat

Hereditary risk factors:

- 1st degree relatives with colorectal cancer or adenomatous polyps
- Familial polyposis syndromes (See [Familial Polyposis Syndromes on page 9-28.](#))
- Lynch syndrome (See [Lynch Syndrome \(LS\) on page 9-28.](#))
- *BRCA1* mutation

Diagnostic flags for colorectal cancer:

- Anorexia
- Unexplained weight loss
- Iron deficiency anemia
- Bloody or heme+ stools
- Change in bowel habits, especially with nocturnal stools
- Onset of symptoms > 45 years of age

Remember: Endocarditis caused by either *Streptococcus bovis* or *Clostridium septicum* is associated with colorectal cancer, so perform a colonoscopy in these patients.

Most GI cancers arise from adenomas ([Figure 9-10](#) and [Figure 9-11](#)). 25% of colorectal cancers are located distal to the splenic flexure.

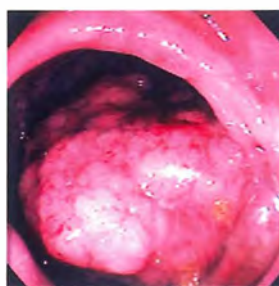


Figure 9-10: Colorectal cancer
Source: Jim Smith, MD



Figure 9-11: Polyps in the colon

Adenomas with advanced features are defined as any of the following:

- Presence of high-grade dysplasia
- Presence of villous histology
- Size > 10 mm
- Sessile serrated adenomas

Advanced means that they are likely to develop into cancer. Progression to cancer from an early adenoma takes 5–10 years. Diet plays a role in GI cancer—possible dietary factors include high animal protein and fats, low fiber, and low calcium.

Again, large or villous adenomatous polyps are likely to harbor or progress to cancer ([Table 9-11](#)).

Table 9-11: Malignant Potential vs. Polyp Type & Size

Polyp Type	Polyp Size		
	< 10 mm	10–20 mm	> 20 mm
Tubular	1%	10%	34%
Mixed (TV)	4%	9%	45%
Villous	10%	10%	54%

Perspective: ~ 30% of people > 40 years of age have adenomatous polyps, but only 1% of adenomatous polyps ever become malignant.

Hyperplastic polyps have **no** malignant potential and contain **no** features of dysplasia. This makes sense because hyperplasia, by definition, is increased growth of **normal** tissue.

After polyps are found, follow-up depends on the type, size, and number of polyps and on family history. Only **adenomatous** polyps require specific follow-up. Hyperplastic polyps, if < 10 mm (except for those with a hyperplastic polyposis syndrome), have the same follow-up as no polyps (i.e., colonoscopy every 10 years).

The 2020 Guidelines for Colonoscopy Surveillance Consensus Update by the U.S. Multi-Society Task Force on Colorectal Cancer recommend the following:

- Patients with 1 or 2 small (< 10 mm) tubular adenomas with low-grade dysplasia should have repeat colonoscopy 7–10 years after initial polypectomy.
- Patients with 3–10 small adenomas, or 1 adenoma > 10 mm, or any adenoma with villous features or high-grade dysplasia should have repeat colonoscopy in 3 years.
- Patients with > 10 adenomas should have repeat colonoscopy in 1 year. (Consider the possibility of an underlying familial syndrome—see **Inherited Colorectal Cancer**.)
- Sessile serrated polyps < 10 mm should have repeat colonoscopy in 5 years. If > 10 mm, the patient should have a repeat colonoscopy in 3 years.
- Patients with a large adenomas (≥ 20 mm) removed in a piecemeal fashion should have repeat colonoscopy in 6 months to ensure complete removal.

INHERITED COLORECTAL CANCER

Inherited colorectal cancer can be categorized into either polyposis or nonpolyposis syndromes.

Familial Polyposis Syndromes

All the familial (or hereditary) polyposis syndromes are **autosomal dominant** (AD).

The 4 types are listed here in order of **decreasing** cancer potential. The first 2 are adenomatous, and the second 2 are hamartomatous:

- 1) **Familial adenomatous polyposis** (FAP)—hundreds of adenomas in the colon, with 100% risk of cancer if not treated. These patients often require a prophylactic proctocolectomy by **age 20**! In addition, they can get duodenal adenomas, which also have a high risk of cancer. After colectomy, patients with FAP tend to get duodenal cancer. They are also at increased risk of developing secondary tumors (e.g., ampullary adenomas and carcinomas). Giant stomach tumors are common in patients with FAP, but they are benign. Follow these patients closely. Do front-viewing and side-viewing EGDs every 1–3 years depending on the number, size, histology, and degree of dysplasia of

the duodenal adenomas. The front-view EGD allows for the detection of gastric and duodenal polyps. The side-view duodenoscope allows for the examination of the ampulla of Vater. Additionally, sigmoidoscopy is usually done yearly.

- 2) **Gardner syndrome**—a variant of FAP with more extraintestinal benign growths. The adenomas have the same risk of cancer as FAP (100%). These patients often have bone lesions (osteomas) and soft tissue or desmoid tumors. Treatment is the same as FAP. Question: Your patient has multiple osteomas found incidentally on an x-ray. What do you do? Colonoscopy!
- 3) **Peutz-Jeghers syndrome**—multiple hamartomatous polyps throughout the small bowel and occasionally in the colon, rectum, and stomach, plus melanotic pigmentation (freckles) on the lips and buccal mucosa. The most common presentations are abdominal pain due to intussusception or bowel obstruction by a large polyp. Even though these polyps are hamartomas, which have no risk of cancer, these patients still have a higher than baseline risk of cancer because they occasionally develop adenomas that can become carcinomas. Risk of cancer is 50% by 60 years of age.
- 4) **Juvenile polyposis** also consists of hamartomas (> 10 juvenile polyps [juvenile polyposis syndrome]). Colonoscopy should be performed every 1–3 years beginning at age 12, or sooner if patients present with symptoms.

Lynch Syndrome (LS)

LS (a.k.a. hereditary nonpolyposis colorectal cancer [HNPCC]) is the most common type of hereditary colorectal cancer syndrome, accounting for 2–4% of all colorectal cancer cases. LS is caused by a germline mutation in any of 4 DNA repair genes (mismatch repair [MMR] genes), which leads to DNA microsatellite instability that increases cancer risk. In addition to increased risk of colorectal cancer, LS is associated with a significantly increased risk of endometrial and ovarian cancer and a slightly increased risk of multiple other cancers (e.g., gastric, small bowel, urinary tract, brain, pancreatic).

Clinical criteria to identify potential LS patients have been developed and refined, including the Amsterdam II criteria—defined as the occurrence of an HNPCC-associated cancer (as noted above) in at least three 1st degree relatives (1 is a 1st degree relative of the other 2) over at least 2 generations and with at least 1 person diagnosed at < 50 years of age. Additionally, tumor-based testing is now used to increase the sensitivity of LS patient identification, with many guidelines recommending “universal” testing of all new colorectal cancers for MMR deficiency that could indicate LS.

Start screening with colonoscopy at 25 years of age.

COLORECTAL CANCER SCREENING

Review

The 2017 U.S. Multi-Society Task Force on Colorectal Cancer screening recommendations divide screening tests into 3 tiers, based on their effectiveness:

- Tier 1:
 - Colonoscopy every 10 years
 - Fecal immunochemical test (FIT) every year
- Tier 2:
 - CT colonography every 5 years
 - FIT-fecal DNA every 3 years
 - Flexible sigmoidoscopy every 5–10 years
- Tier 3:
 - Capsule colonoscopy every 5 years

Timing of initial screening and subsequent testing is based on patient risk, as follows.

Average-risk patients (adults with no family history of colorectal cancer or adenomatous polyps): Screen with a Tier 1 test beginning at 45 years of age for African Americans and 50 years of age for all others.

If polyps are found, repeat colonoscopy timing is based on polyp pathology. (See the 2020 Guidelines for Colonoscopy Surveillance at the end of [Overview on page 9-27](#).)

Strong family history (one 1st degree relative with colorectal cancer or advanced adenoma diagnosed < 60 years of age, or two 1st degree relatives at any age): Surveillance colonoscopy should begin at 40 years of age or 10 years younger than the age at which the index case is diagnosed—whichever is earlier. Repeat colonoscopy every 5 years.

For example: Start at 40 years of age if a 1st degree relative was diagnosed with an adenoma or colorectal cancer at 52 years of age; start at 20 years of age if a 1st degree relative was diagnosed with colorectal cancer at 30 years of age.

Moderate family history (one 1st degree relative with colorectal cancer or advanced adenoma diagnosed at ≥ 60 years of age): Screen with a Tier 1 test beginning at 40 years of age and repeat at the same time interval as average-risk patients.

FIT is less expensive and obviously less invasive than colonoscopy, but it can miss ~ 1/5 of advanced cancers. Colonoscopy has a higher yield of finding polyps and cancers but is more expensive and invasive. Follow up all positive screening tests with a full colonoscopy with biopsy of any identified abnormalities/polyps per guideline recommendations.

Virtual colonoscopy or CT colonography is a CT scan with special software. It has high yield for detecting larger polyps and cancers. Areas of adherent stool can be mistaken for small polyps. However, it is an excellent test to visualize the entirety of the colon for a patient who cannot complete a standard colonoscopy. If abnormalities are

found on CT colonography, proceed directly to colonoscopy if possible (since the patient has already been prepped).

Sigmoid colorectal cancer can perforate the bowel wall and simulate diverticulitis. Screen for colorectal cancer after an episode of diverticulitis in increased-risk patients. To avoid risk of perforation, wait for resolution of acute inflammation (6 weeks after episode of diverticulitis) before proceeding with colonoscopy.

Indications for colonoscopy:

- Occult bleeding
- Iron deficiency anemia, unless other explanation
- Gross lower GI bleeding, except bright red blood in a younger person
- Abnormal barium enema
- Adenomatous polyp, initially and for all follow-ups
- History of colorectal cancer
- 1st degree relative with colorectal cancer
- Familial polyposis syndromes, LS
- Inflammatory bowel disease (IBD): suspicion, follow-up, surveillance
- *S. bovis*, *C. septicum* bacteremia
- Ischemic colitis
- Persistent diarrhea with negative blood/stool tests and not meeting criteria for diagnosis of irritable bowel syndrome (IBS)
- 4–8 weeks after new-onset, presumed diverticulitis to rule out colorectal cancer

Fecal Occult Blood Test (FOBT)

FOBT is positive 2% of the time. This varies with age, with > 5% of patients testing positive after 60 years of age. Of patients with positive FOBTs, 2% have GI cancer. The FIT for hemoglobin has replaced guaiac-based testing in most centers.

Remember: The FOBT is negative in up to 66% of patients with colorectal cancer, and it is negative in ~ 33% of cases of advanced colorectal cancer. Use of 6 Hemoccult cards (the full FOBT series) detects advanced colonic cancer in only ~ 25% of patients. The USPSTF recommends screening adults for colorectal cancer using FOBT, sigmoidoscopy, or colonoscopy, beginning at 50 years of age and continuing until 75 years of age.

Even if 1 FOBT is positive, do a colonoscopy.

Flexible sigmoidoscopy plus air-contrast barium enema is also acceptable but less desirable.

Carcinoembryonic Antigen (CEA)

Note: CEA levels are useful only for surveillance for recurrence of colorectal cancer—and only if levels were elevated before surgery and reduced after surgery. CEA levels lack sufficient sensitivity or specificity to be used in primary diagnosis and can be mildly elevated in patients who smoke or who have benign biliary disease, sclerosing cholangitis, or IBD.

STAGING OF COLON CANCER

Colorectal cancer is staged via the TNM (tumor/node/metastasis) classification, which was updated in 2018.

In general, the cancer stage becomes more advanced as the tumor enlarges and invades the colonic wall:

- TNM Stage I: invades submucosa (T1) or muscularis (T2); no nodal involvement; no metastases
- TNM Stage II: invades through the muscularis into the pericorectal tissues (T3) or into visceral peritoneum (T4a), or invades or is adherent to other organs or structures (T4b); no nodal involvement; no metastases
- TNM Stage III: any combination of T1–T4b with nodal involvement and no metastases
- TNM Stage IV: any combination of T1–T4b, any N, with distant metastases

Colorectal cancer most commonly metastasizes to the liver first (via portal circulation). However, if it involves only the rectum, the blood supply bypasses the portal circulation, so the patient may have lung, bone, and brain metastases without liver metastases.

TREATMENT OF COLORECTAL CANCER

Surgical resection is the 1st treatment option for Stages I–III disease and is potentially curative. Recurrences after surgery are probably due to micrometastases.

Adjuvant 5-FU-based chemotherapy should be considered for Stage III and high-risk Stage II disease, with the goal of reducing relapse risk and improving long-term survival. The optimal regimen consists of 5-FU/leucovorin or capecitabine, plus oxaliplatin (FOLFOX or CAPOX).

Adjuvant chemotherapy is effective only for Stage III or high-risk Stage II.

Radiation therapy prior to surgery is helpful for rectal lesions only.

If you remove a cancerous polyp, you must do a bowel resection if the cancer extends to either a blood vessel or the cautery line.

According to 2020 NCCN guidelines, surveillance for recurrence after treatment for early-stage colorectal cancer is:

- Check CEA every 3–6 months for the first 3 years, then every 6 months in years 4 and 5.
- Repeat colonoscopy at 1 year, then every 3–5 years.
- CT scan of chest and abdomen 1×/year for 3 years.

For metastatic disease, give 5-FU-based combination chemotherapy, often with palliative intent. However, if there is limited metastatic disease (solitary liver or lung metastasis), then aggressive local therapy (resection vs. ablation) may increase long-term survival. Other active systemic agents for metastatic colorectal cancer include oxaliplatin, irinotecan, VEGF antibodies (i.e., bevacizumab), and EGFR antibodies (i.e., cetuximab).

CANCER OF UNKNOWN PRIMARY SITE

Cancers of unknown primary site account for 4–5% of all invasive cancers. In each case, perform immuno-histochemistry and imaging with CT and/or PET scan to attempt to ascertain the diagnosis. Classification by histologic group determines further workup and treatment:

- Adenocarcinoma accounts for 70% of cases. In a woman with isolated axillary node involvement, consider breast MRI and treatment for Stage II breast cancer. Often, occult primary tumors can be found at mastectomy. In a woman with peritoneal carcinomatosis or ascites, treat as a Stage III ovarian cancer. Men with blastic bone metastases or an elevated PSA may respond to treatment for prostate cancer.
- An isolated supraclavicular node has a high risk of malignancy, and the primary site of malignancy depends on which side it arises. If it is on the left, look for an abdominal tumor (e.g., GI, genitourinary); if it is on the right, suspect mediastinum, lungs, or esophagus.
- Squamous cell carcinomas in cervical lymph nodes should be evaluated for a head and neck primary tumor.
- Poorly differentiated carcinoma accounts for 20% of cases. Consider germ cell tumors. Elevated LDH, AFP, and/or β -hCG suggests an extragonadal germ cell tumor (especially if in a retroperitoneal or mediastinal location), so treat as a Stage III germ cell tumor.
- High-grade neuroendocrine tumors are aggressive and typically respond to chemotherapy, although the response is usually short lived. Determining the primary site is not of great importance because all forms of aggressive neuroendocrine cancer are treated with the same chemotherapy regimens (i.e., are treated like SCLC with a platinum agent and etoposide; see [Small Cell Lung Cancer \(SCLC\)](#) on page 9-24).

MISCELLANEOUS

NOTES

Several cancers are discussed in organ-specific topics and sections:

- Esophageal, pancreatic, and liver cancer—see the [Gastroenterology](#) section.
- Kidney—see the [Nephrology](#) section.
- Thyroid and pheochromocytoma—see the [Endocrinology](#) section.
- CNS—see the [Neurology](#) section.

- Lymphomas, leukemias, and multiple myeloma—see the [Hematology](#) section.
- Skin cancer, including melanoma—see the [Dermatology](#) section.

Retinoblastoma, the most common intraocular malignancy of childhood, confers a high risk of 2nd malignancy in adulthood. The risk of 2nd malignancy is up to 35–40% at 50 years after the original treatment, especially if the original treatment included radiation. These 2nd malignancies often include osteosarcoma and soft tissue sarcoma.

HIV AND MALIGNANCY

HIV-infected individuals have an increased incidence of a wide range of malignancies. These include AIDS-defining malignancies (i.e., Kaposi sarcoma, cervical cancer, non-Hodgkin lymphoma [NHL] with both systemic and CNS involvement) and several non-AIDS-defining cancers (i.e., Castleman disease, lung cancer, anal cancer, liver cancer, Hodgkin lymphoma). Pathogenesis of these cancers may be related to the direct effects of HIV, prolonged immunosuppression, antiretroviral therapy, and coinfection with other oncogenic viruses. Fortunately, the widespread use of highly active antiretroviral therapy has decreased the incidence of HIV-associated cancers and improved prognosis/response to treatment.

Treatment of malignancies in HIV-infected patients is generally the same as in those without HIV. When cytotoxic chemotherapy is used with antiretroviral medications, the cumulative toxicities of all drugs and drug interactions (especially immunosuppressive agents) should be considered.

NEUROENDOCRINE TUMORS (NETs)

Well-differentiated NETs, previously described as carcinoids, most commonly originate in the GI tract, including the appendix, small bowel, or rectum. These tumors are usually asymptomatic—especially the rectal carcinoids—until they have metastasized to the liver or lungs. NETs are seen in patients with multiple endocrine neoplasia Type 1 (MEN1). Hormone-secreting NETs can produce serotonin, bradykinins, growth hormone (GH), ACTH, calcitonin, and/or prostaglandins. Overproduction of these hormones leads to **carcinoid syndrome**.

Signs and symptoms of carcinoid syndrome include:

- Flushing
- Valvular heart disease
- Diarrhea
- Venous telangiectasias (usually on the face)
- Wheezing

Include a urinary 5-hydroxyindoleacetic acid (5-HIAA) level and a serum chromogranin A level in the initial evaluation. Localize disease with newer somatostatin

receptor imaging, including the use of gallium-68 PET/CT scanning (NetSpot), which uses a novel tracer (gallium-68 DOTATATE) to increase the sensitivity for detection of small or occult NETs.

Treatment: Surgically resect localized disease (tumors < 1 cm rarely have metastases). There is an 80% cure rate for localized NETs. If the NET has metastasized, the treatment is typically symptomatic. Even a metastatic NET is slowly progressive and indolent and often can be managed with symptomatic therapy for many years (e.g., using an antidiarrheal medication, avoiding food and alcohol triggers). Treat with a somatostatin analog, octreotide (Sandostatin) or lanreotide, to help control symptoms and prolong time to tumor progression. Everolimus is also used.

CARCINOGENS

PREVIEW | REVIEW

- Which cancers are associated with a history of radiation therapy?

Some known agents and processes that can cause cancer are listed below, along with the types of cancer they are linked with:

- **Tobacco:** lung, bladder, head and neck, kidney, and esophagus. Tobacco is related to 30% of U.S. cancer-related deaths.
- **Alcohol:** liver, head and neck, and esophagus
- **Tobacco + alcohol:** synergistic effect on the development of head, neck, and esophageal cancers
- **Asbestos:** lung, mesothelioma of the pleura, and abdominal peritoneum (greatly increases risk if combined with tobacco use)
- **Immunosuppressive agents:** NHL, squamous and basal cell skin cancers
- **Estrogens:** uterine, vaginal, and breast cancers. Both birth control pills and postmenopausal estrogens appear to increase risk after 5 years of use.
- **Nitrites:** stomach
- **Animal fat:** colon, breast, and prostate
- **Ionizing radiation:** many cancers, especially leukemia, sarcoma, and thyroid cancer. There is a slightly increased risk of breast cancer in Hodgkin patients who received RT. There is also a slightly increased risk of bladder and rectal cancer in patients who received prostate radiation. Generalized, high-dose exposure to radiation (e.g., nuclear bomb) is associated with an increased risk of all malignancies.
- **Ultraviolet radiation:** skin (skin cancers—basal cell, squamous cell, and melanoma)
- **Radon gas:** lung
- ***H. pylori*:** gastric

- **Viruses:**

- Human herpesvirus 8 (HHV-8): Kaposi sarcoma, primary effusion lymphoma
- Hepatitis B and C viruses: hepatocellular carcinoma
- Human papillomavirus (HPV): cervical, anal, and oropharyngeal cancers
- EBV: Burkitt lymphoma, nasopharyngeal carcinoma, and 30–50% of AIDS-related lymphomas (and 100% of AIDS-related primary CNS lymphomas)
- HIV: Kaposi sarcoma, NHL
- HTLV-1: adult T-cell leukemia

HYPERCALCEMIA OF MALIGNANCY

PREVIEW | REVIEW

- Hypercalcemia occurs most commonly in which type of lung cancer?
- What is the 1st step in the management of acute hypercalcemia?

Hypercalcemia due to cancer occurs most frequently in patients with the following malignancies:

- Squamous cell carcinomas arising in the lung or the head and neck
- Multiple myeloma
- Breast carcinoma
- T-cell lymphoma/leukemia
- Renal cell carcinoma
- Hepatocellular carcinoma

Symptoms include fatigue, constipation, anorexia, nausea, polyuria, polydipsia, and alteration in mental status. Patients often present with profound hypovolemia. Obtundation and dysrhythmias can occur in severe cases. Symptom severity is associated with the rate of rise in serum Ca^{2+} and the severity of hypercalcemia.

Mechanisms of hypercalcemia of malignancy include:

- Increased osteoclastic activity induced by local bone metastasis where tumor cells produce locally acting cytokines (receptor activator of nuclear factor κB ligand [RANKL])
- Ectopic production of a PTH-related protein (PTHrP)
- Overproduction of $1,25\text{-(OH)}_2\text{-D}$ (i.e., calcitriol, the active form of vitamin D)

PTHrP is the usual cause of malignancy-associated hypercalcemia in patients with squamous cell carcinomas. The receptor-binding area for PTHrP is similar to PTH, which results in increased Ca^{2+} resorption from the bones and increased Ca^{2+} resorption in the distal tubules. Given the high incidence of concomitant hyperparathyroidism in patients with malignancy, evaluation should include PTH, PTHrP, and $1,25\text{-(OH)}_2\text{-D}$.

Albumin binds Ca^{2+} . With hyperalbuminemia, the patient can have a high total Ca^{2+} level but a normal free

or ionized Ca^{2+} (iCa^{2+}) level. With hypoalbuminemia, the patient can have a normal total Ca^{2+} level but a high iCa^{2+} level. When interpreting any serum Ca^{2+} level, check the albumin level. If the albumin is abnormally high or low, calculate the corrected Ca^{2+} as follows:

$$\text{Ca}^{2+}_{\text{corrected}} = \text{Ca}^{2+}_{\text{measured}} + 0.8 \times (4.0 - \text{alb}_{\text{measured}})$$

(Ca^{2+} is in units of mg/dL, and albumin is in units of g/dL.) Note that in hyperalbuminemia, the corrected Ca^{2+} will be lower than the measured Ca^{2+} ; for hypoalbuminemia (more common), the corrected Ca^{2+} will be higher than the measured Ca^{2+} .

On ECG, hypercalcemia can cause a short QT interval. With Ca^{2+} levels > 16 mg/dL (4 mmol/L), the T wave widens.

Know management: The 1st and most important step in the management of severe hypercalcemia of malignancy is vigorous hydration with IV normal saline. If edema develops, furosemide can be given, which will allow continued IV fluid administration and enhance calciuresis. Do not give furosemide unless volume overload develops—it can exacerbate the hypercalcemia and hypovolemia. Volume expansion helps treat hypercalcemia but does not maintain Ca^{2+} levels within the normal reference interval. Calcitonin, given IM or SQ, is useful in the first 48 hours in cases of severe hypercalcemia. It quickly reduces Ca^{2+} levels by increasing Ca^{2+} excretion and decreasing bone reabsorption. It is important to administer a bisphosphonate. Zoledronic acid 4 mg IV over 15 minutes is preferred because of its increased potency and decreased infusion time; it can be used even with mild to moderate renal insufficiency. Pamidronate is an alternative bisphosphonate option, when zoledronic acid is not available. In patients refractory to bisphosphonates or with severe renal insufficiency, use the RANKL inhibitor denosumab.

Osteonecrosis of the jaw is an uncommon adverse effect seen with IV doses and prolonged use of bisphosphonates and denosumab. This osteonecrosis presents as pain, infection, and sometimes fracture of the mandible. There can be exposed bone along the gumline. Patients receiving long-term bisphosphonates should have necessary dental work performed prior to taking the drugs, or, if possible, defer the work until the drugs are discontinued. Counsel such patients that any emergent dental work should be as conservative as possible (e.g., preserve the dental root in lieu of extraction). X-rays, CT, and MRI can diagnose severe disease but can be nonspecific in early disease. Treat by stopping the bisphosphonate and follow a conservative approach with minimal debridement, antibiotic therapy, and oral rinses.

The definitive treatment of hypercalcemia of malignancy is to treat the underlying tumor. Patients with hypercalcemia of malignancy have a poor prognosis. See the [Endocrinology](#) section and the [Nephrology](#) section for more on hypercalcemia.

See [Table 9-12](#) for a review of hormone-related paraneoplastic syndromes.

Table 9-12: Hormone-Related Paraneoplastic Syndromes

Clinical Syndrome	Major Forms of Underlying Cancer	Causal Mechanism
Hypercalcemia	Squamous cell carcinomas arising in the lung or the head and neck Multiple myeloma Breast carcinoma T-cell lymphoma/leukemia Renal cell carcinoma Hepatocellular carcinoma	Bone metastasis with increased osteoclast activity PTHrP Overproduction of 1,25-(OH) ₂ -D
Cushing syndrome (See the Endocrinology section.)	SCLC Pancreatic carcinoma Neural tumors	ACTH or ACTH-like substance
Polycythemia (See the Hematology section.)	Gastric carcinoma Renal carcinoma Hepatocellular carcinoma	Erythropoietin
Carcinoid syndrome (See Neuroendocrine Tumors (NETs) on page 9-31.)	Neuroendocrine tumors of the appendix, small bowel, colon, or rectum	Serotonin Bradykinin
Syndrome of inappropriate antidiuretic hormone (SIADH; see the Endocrinology section.)	SCLC Intracranial neoplasm	Antidiuretic hormone (vasopressin)
Hypoglycemia (See the Nephrology section.)	Fibrosarcoma Islet-cell tumor Hepatocellular carcinoma	Insulin or insulin-like substance

1,25-(OH)₂-D = active form of vitamin D ACTH = adrenocorticotropic hormone PTHrP = parathyroid-related protein SCLC = small cell lung cancer

DIRECT TUMOR EFFECTS

PREVIEW | REVIEW

- What are the symptoms of superior vena cava syndrome? What is the treatment?
- Name the cancers that commonly metastasize to bone.
- What is the urgent treatment when you suspect spinal cord compression due to bone metastasis?
- Which treatment option is available to patients with ≤ 3 small brain metastases?
- Which malignancies are associated with pericardial metastases?

SUPERIOR VENA CAVA (SVC) SYNDROME

The most common causes of SVC syndrome are lung cancer (especially SCLC), lymphoma (i.e., Hodgkin's, NHL), and mediastinal germ cell tumors.

The classic symptoms are:

- Swelling of the face, neck, and arms (typically worse when the patient is supine)
- Cough
- Dyspnea
- Hoarseness (due to laryngeal edema)
- Headaches (due to increasing intracranial pressure)

Physical examination findings include:

- Periorbital and upper extremity edema
- Facial plethora
- Elevated jugular venous pressure
- An increased number of collateral veins covering the anterior chest wall
- Stridor due to airway compression
- Altered mental status secondary to cerebral edema

Diagnose by CT venogram of the chest, which typically shows a large mediastinal and/or right hilar mass with SVC occlusion.

Although SVC syndrome was previously thought to require emergent treatment, there is often time to establish a diagnosis prior to treatment. A tissue diagnosis prior to therapy is recommended in those without a known malignancy. Immediate treatment to shrink the tumor is required for signs of airway compromise or increased intracranial pressure. Chemotherapy is used as the initial therapy for most SCLCs, germ cell tumors, and lymphomas. Endovascular stents can be used for emergent relief. RT, once the mainstay of treatment, is now limited to those tumors that do not respond rapidly to chemotherapy. Use of corticosteroids is controversial, except in cases of a steroid-responsive malignancy (e.g., lymphoma).

BONE MALIGNANCY AND METASTASES

Bone Metastases

Bone metastases can occur in **any** malignancy. They are most commonly caused by cancer of the lung, breast, prostate, and kidney, and they may occur with multiple myeloma and NHL.

Pain with or without pathologic fracture is the usual presenting symptom. The large bones with bone marrow (e.g., pelvis, vertebral body, sternum, ribs, femur) are the ones typically affected.

Confirm the diagnosis by CT or bone scan (abnormal technetium uptake). Note: Lytic-only lesions, as commonly seen in multiple myeloma and less commonly in breast and renal cancer, are **not** evident on the bone scan but can be diagnosed by plain radiographs, CT, or MRI.

RT can provide pain relief and prevent fractures. Opiate analgesics and NSAIDs are used to treat pain. Bisphosphonates can reduce skeletal-related events (i.e., pathologic fractures, hypercalcemia of malignancy, spinal cord compression, need for radiation or surgery to bone), as can the RANKL inhibitor denosumab in solid tumors.

Bone-targeted radioisotopes localize to areas of osteoblastic metastasis; radium-223 has been shown to palliate pain and improve overall survival in metastatic prostate cancer.

Other developing therapies include radiofrequency ablation (RFA), especially in previously irradiated regions, and vertebroplasty for vertebral metastasis leading to painful compression fractures. When a lytic lesion occurs in a weight-bearing long bone, orthopedic surgery can prevent or stabilize a pathologic fracture.

Osteosarcoma (OS)

Metastatic disease to bone needs to be distinguished from primary bone malignancy. OS is the most common primary bone malignancy, often presenting in adolescence or young adulthood. A plain radiograph of an OS tumor will typically demonstrate sclerotic changes without clear margins. New periosteal formation along the margin of the tumor can cause the classic Codman triangle to be visualized on the radiograph. The diagnosis is usually made by radiography; however, further evaluation includes CT or MRI of the primary tumor site, a bone scan, and CT of the chest for staging.

OS becomes metastatic early in the disease, with the most common site being the lungs. Other sites of metastasis include distant bony sites, local and regional lymph nodes, and soft tissues.

A prompt referral to an orthopedic surgeon who has expertise in bone malignancy for tissue sampling is more appropriate than interventional radiology in this case. Care must be taken when approaching the biopsy to avoid possibly seeding the biopsy tract with tumor cells.

SPINAL CORD COMPRESSION

Spinal cord compression is a serious oncologic emergency that can lead to paralysis if not recognized and promptly managed. Back pain and localized tenderness are ordinarily the 1st symptoms and can precede

neurologic deficits by days to weeks. The pain is often worse with activity but typically continues with rest. Radiation of pain in a radicular manner is common. Escalating narcotic needs for a patient's baseline pain can be a warning sign of impending cord compression.

Promptly evaluate all cancer patients with new-onset or worsening back pain with a careful history and neurologic exam, looking for paresthesias, paralysis, incontinence, and pain. Although plain film of the back will likely be the first test performed, it is not diagnostic. MRI is the procedure of choice for definitive diagnosis. You must conduct a spinal screen of all levels (cervical, thoracic, lumbar, and sacral) since screening often reveals occult, incipient structural problems.

As soon as you suspect spinal cord compression due to bone metastases, give dexamethasone at 4–8 mg and continue q 6 hours—do not wait for radiologic confirmation! RT is the treatment of choice for spinal cord compression due to radiosensitive cancers, including multiple myeloma, lymphoma, and SCLC. Surgical intervention is recommended for radioresistant cancers (e.g., melanoma, kidney cancer, NSCLC, GI cancers), any patient with progressive neurologic decline, those with no tissue diagnosis, and those who have had previous RT in the involved region.

METASTATIC DISEASE TO THE BRAIN, LUNG, AND LIVER

Brain metastases can cause significant morbidity. Symptoms include headache, focal neurologic dysfunction, cognitive dysfunction, and new-onset seizure. Malignancies that commonly cause brain metastasis include malignant melanoma and cancers of the lung, breast, renal cells, and stomach. On the other hand, malignancies such as prostate cancer and colorectal cancer rarely cause brain metastasis. Treat immediately with IV dexamethasone if neurologic abnormalities, seizures, or significant tumor-associated edema are seen on MRI. If the metastatic lesion is solitary and the systemic disease is well controlled, consider neurosurgical resection. Prophylactic antiepileptics are not recommended for patients with no previous seizure history.

Stereotactic radiosurgery is an option for patients with ≤ 3 brain metastases that are all < 3 cm in size. In all other patients, the best option is to proceed with whole-brain radiotherapy for palliation.

The **lungs** and **liver** are common sites for metastasis in most malignancies. Surgical resection of liver and lung metastases is reserved for patients who are carefully selected based on primary site of disease, single organ involvement, and low tumor burden. RFA can be useful to palliate painful liver metastasis. Systemic therapy can also be used, usually with palliative intent, depending on the primary tumor.

MALIGNANT EFFUSIONS

Pleural Effusions

Symptoms of pleural effusion include cough, shortness of breath, and pleuritic chest pain. Malignant pleural effusions have 3 major causes:

- 1) Exudative reactions due to metastases or local extension to major lymphatic structures or the pleural surface
- 2) Chylous effusions due to lymphatic/thoracic duct obstruction
- 3) Primary pleural malignancy (i.e., mesothelioma)

Lung cancer, by far, is the most common cause of exudative malignant effusions. However, many malignancies can metastasize to the pleura. Chylous effusions are more commonly seen in patients with NHL.

Evaluation includes a thoracentesis with cytologic analysis and measurement of pleural fluid protein and LDH to apply Light's criteria (exudative vs. transudative effusions; more detail is in the [Pulmonary Medicine](#) section). Repeat thoracentesis with cytology if malignancy is suspected, but initial cytology is nondiagnostic. Consider thoracoscopic pleural biopsy when the diagnosis is uncertain.

In patients with symptomatic malignant effusions (e.g., dyspnea, chest pain), drainage is indicated. Most effusions quickly recur if effective treatment of the underlying malignancy with systemic therapy is not achieved. For recurrent effusions, consider chest tube placement with talc pleurodesis or placement of a pleural catheter with repetitive drainage.

Pericardial Effusions

Malignant pericardial effusions are caused by either local disease extension into the pericardium or hematogenous spread to the pericardium. The most commonly associated malignancies are lung cancer, breast cancer, and NHL.

Closely monitor patients with suspected malignant pericardial effusions for signs and symptoms of tamponade (e.g., hypotension with muffled heart sounds, pulsus paradoxus, jugular venous distention [JVD]; see the [Cardiology](#) section for additional details). Echocardiography confirms the presence of the effusion and gives an immediate determination of presence and severity of hemodynamic compromise. If the effusion presents a risk for tamponade, perform a pericardial window procedure and send fluid for cytology.

Ascites

Malignant ascites is due to peritoneal seeding of the malignancy. Ovarian cancer is the most common primary malignancy. All GI cancers, breast cancers, urothelial cancers, and NHLs can cause malignant ascites. Paracentesis can be both diagnostic and therapeutic. In refractory cases, peritoneal catheters are placed for palliative therapy.

CANCER THERAPIES

PREVIEW | REVIEW

- Know the following associations: rituximab and hypersensitivity reactions, including bronchospasm; cyclophosphamide and hemorrhagic cystitis; doxorubicin and cardiomyopathy; 5-fluorouracil and sun sensitivity; platinum compounds and ototoxicity.
- What type of cancer is tamoxifen used to treat? What type of cancer can tamoxifen cause?
- Which agent causes Mg^{2+} wasting?
- What are the late side effects of radiation therapy for breast cancer?

NOTE

As noted previously, be familiar with the agents and side effects, but leave the specific therapy regimens to the oncologists!

There is quite a bit of overlap between oncologic and hematologic therapies. The agents used in both areas are duplicated, with the relevant malignancies in [burgundy](#) font; i.e., this topic will show oncologic malignancies in [burgundy](#).

[Table 9-13](#) summarizes the major toxicities of each drug or drug class.

Table 9-13: Major Toxicities of Cancer Drugs by Organ System

Toxicity	Common Offending Drug / Class
Peripheral neuropathy	Vincristine Cisplatin Bortezomib
Hypersensitivity reactions	Rituximab, cetuximab Cisplatin/carboplatin
Cardiomyopathy	Anthracyclines: • Doxorubicin • Daunorubicin HER2 antibodies: • Trastuzumab • Pertuzumab
Pulmonary fibrosis	Bleomycin
Skin rash	EGFR inhibitors: • Cetuximab • Panitumumab Immune checkpoint inhibitors, including: • Pembrolizumab • Nivolumab • Ipilimumab

CYTOTOXIC CHEMOTHERAPY

Alkylating Agents

Cyclophosphamide is used to treat **B-cell lymphoma** (as part of R-CHOP, a drug regimen that also includes rituximab, doxorubicin, vincristine, and prednisone), **breast cancer**, and some **leukemias**. Like temozolomide, it can cause nausea, vomiting, and myelosuppression. It can cause hemorrhagic cystitis when used in high doses.

Temozolomide is used to treat **brain cancer**. Side effects include nausea/vomiting and myelosuppression; severe liver toxicity can also occur. Monitor blood counts and liver function during treatment.

Anthracyclines

Doxorubicin (Adriamycin), **daunorubicin**, and **idarubicin** are antitumor anthracycline antibiotics used to treat many malignancies, including **breast cancer**, lymphomas, acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), **soft tissue sarcoma**, and **ovarian cancer**. Doxorubicin in its liposome form is used to treat **Kaposi sarcoma**, **ovarian cancer**, and multiple myeloma. Potentially irreversible cardiomyopathy can occur; risk is dose dependent. Monitor with echocardiograms.

Antimetabolites

Methotrexate (MTX) is a folate antimetabolite used in several malignancies, including **breast cancer**, **head and neck cancer**, leukemias, and lymphomas. To minimize toxicity, follow high-dose MTX with leucovorin “rescue” and monitor drug levels. MTX toxicities include myelosuppression, mucositis, diarrhea, renal dysfunction, and acute cerebral toxicity.

Pemetrexed is used to treat **NSCLC**, **non-squamous cell lung cancer**, and **mesothelioma**. Pemetrexed can cause skin rash and mucositis. Vitamin B₁₂ and folate replacement are necessary to avoid excess toxicity.

Pyrimidine Analogs

5-FU is a pyrimidine analog used to treat **colorectal cancer**, **breast cancer**, and **other GI malignancies**. The most common toxicities include myelosuppression, mucositis, photosensitivity, diarrhea, and hand-foot syndrome.

Capecitabine is another agent in this class and sometimes is used for colon and breast cancer.

Gemcitabine is also a pyrimidine analog. It is used to treat **pancreatic**, **lung**, **breast**, **bladder**, and **ovarian cancers**. Like other antimetabolites, gemcitabine is myelosuppressive; it also can cause pneumonitis, flulike symptoms, and skin rash.

Taxols

The **taxol** chemotherapy agents include **docetaxel**, **cabazitaxel**, and **paclitaxel**. Taxols prevent cell division by inhibiting microtubule formation. These drugs are used to

treat breast, bladder, and metastatic castration-resistant prostate cancer. Side effects include myelosuppression, edema, nail bed changes, and peripheral neuropathy.

Platinums and Platinum Analogs

Carboplatin, like cisplatin, is a platinum analog that causes DNA damage. It is used for ovarian, **testicular**, **lung**, **head/neck**, **bladder**, and **endometrial cancers**. Compared to cisplatin, it has less nausea/vomiting, nephrotoxicity, peripheral neuropathy, and ototoxicity. Carboplatin has a stronger myelosuppressive effect; its main toxicity is thrombocytopenia. Hypersensitivity (e.g., anaphylaxis) can develop after multiple doses of any platinum drug (including cisplatin and oxaliplatin).

Cisplatin (*cis*-diamminedichloroplatinum [CDDP]) is a platinum analog used to treat **testicular**, **ovarian**, **bladder**, **head/neck**, and **esophageal cancers**. It can cause severe nausea/vomiting, as well as renal, peripheral nerve, and ototoxicity. (See carboplatin, above, for comparison.)

Oxaliplatin is another platinum agent. It has superior activity in **colorectal cancer** when combined with 5-FU. Similar to carboplatin, it produces less nephrotoxicity, nausea, and vomiting than cisplatin. However, it can cause peripheral neuropathy that is exacerbated by exposure to cold temperatures. Additionally, hypersensitivity can develop after multiple doses.

Vinca Alkaloids

Vinblastine and **vincristine** are vinca alkaloids, which are antimicrotubule agents used to treat **lymphomas** and **testicular cancer**. Peripheral neuropathy can occur.

Vinorelbine has activity in **breast** and **lung cancers**. Myelosuppression is common.

Topoisomerase Inhibitors

Etoposide inhibits topoisomerase II, a DNA replication enzyme. It is used to treat **testicular germ cell tumors**, **SCLC**, **gastric cancer**, and lymphomas. Myelosuppression is common. Secondary AML can occur.

Irinotecan inhibits topoisomerase I, another enzyme involved in DNA replication. It is approved for the treatment of **metastatic colorectal cancer**. Irinotecan can cause 2 different forms of severe diarrhea: an early form treated with atropine and a later form that requires antimotility agents and aggressive fluid administration.

Miscellaneous

Bicalutamide is a nonsteroidal antiandrogen used to treat **prostate cancer**. Monitor for hepatotoxicity.

Bleomycin is an antitumor antibiotic that causes cytotoxicity by inducing breaks in DNA. It is used to treat Hodgkin disease and **germ cell tumors**. Pulmonary toxicity can be life threatening and irreversible; check pulmonary function tests before and during treatment. Fever is common.

Eribulin (Halaven) is a nontaxane antimicrotubule drug that is used to treat patients with metastatic **breast cancer** who have had failed previous chemotherapeutic regimens. Neutropenia can be a dose-limiting toxicity.

TYROSINE KINASE INHIBITORS

The tyrosine kinase (TK) inhibitors prevent cell proliferation by blocking a variety of cell-signaling pathways. These agents have antiangiogenic and/or antiproliferative properties.

Imatinib (Gleevec) was the first TK inhibitor. It blocks the initiation of the BCR-ABL1 pathway and is used in chronic myelocytic leukemia (CML) and **GISTs**. **Dasatinib** (Sprycel) and **nilotinib** (Tasigna) are other TK inhibitors used to treat **CML**. All can cause edema and nausea.

Vemurafenib targets the BRAF tyrosine kinase. It is approved for metastatic **melanoma** with the *BRAF V600E* mutation. Ironically, although it is a treatment for melanoma, it can cause cutaneous squamous cell cancers (another form of skin cancer).

Alectinib is a TK inhibitor targeting anaplastic lymphoma kinase (ALK) and the RET receptor tyrosine kinase, inhibiting tumor growth and angiogenesis. It is used to treat **ALK-positive metastatic NSCLC**. Serious toxicities include hepatotoxicity and pneumonitis. Other drugs in this class include **crizotinib**, **ceritinib**, and **brigatinib**.

Sorafenib targets multiple intracellular kinases, including VEGF receptor (VEGFR), Raf kinase, PDGFR- β , KIT, FLT-3, and RET. It is used to treat **renal cell cancer** and **hepatocellular carcinoma**. Patients may develop arterial thromboembolism, hypertension, hypothyroidism, and diarrhea. Other agents in this class include **sunitinib**, **pazopanib**, **lenvatinib**, **axitinib**, and **cabozantinib**. In addition to treating renal cell cancer, sunitinib is effective for **gastrointestinal stromal tumors (GISTs)**, pazopanib is effective for **sarcomas**, and cabozantinib is effective for **medullary thyroid cancer**.

Erlotinib (Tarceva) is an oral TK inhibitor that targets EGFR. It is used in **lung cancers that express a mutation in the EGFR** and in **refractory lung cancer**. It can cause an acne-like rash. Other agents include **osimertinib** (Tagrisso), **gefitinib**, and **afatinib**.

OTHER TARGETED SMALL MOLECULE INHIBITORS

Temsirolimus and **everolimus** are analogs of sirolimus that inhibit the mammalian target of rapamycin (mTOR). Both are approved for **advanced renal cell cancer**. Everolimus also is used to treat **metastatic breast cancer** and **NETs**. Adverse effects include mucositis, hyperglycemia, and hyperlipidemia.

BIOLOGICS — MONOCLONAL ANTIBODIES

Trastuzumab (Herceptin) is a monoclonal antibody directed at human EGFR 2 (*HER2*) on the surface of the

breast cancer cell. It is exciting because its development was based on knowledge of the molecular biology of the breast cancer cell: *HER2* is an oncogene associated with an increased likelihood of distant metastases. It is also used in *HER2*-expressing **metastatic gastric cancer** or **gastroesophageal junction cancer**. Infusion-related flu-like symptoms and urticaria are common. Cardiotoxicity can occur, especially when used with doxorubicin. Check echocardiogram (to monitor left ventricular ejection fraction) before and during treatment. Pertuzumab is another agent in this class.

Bevacizumab (Avastin) is a monoclonal antibody directed against the VEGFR, preventing tumor-associated angiogenesis. It is U.S. Food and Drug Administration (FDA) approved for **metastatic colorectal cancer**, **glioblastoma**, **nonsquamous NSCLC**, and **metastatic renal cell cancer**. Notable toxicities include bleeding, thrombosis, hypertension, and proteinuria.

Cetuximab (Erbix) is a monoclonal antibody against EGFR; it is FDA approved for **refractory colorectal cancer** and metastatic or recurrent **head and neck cancer**. It has activity in other cancers that express EGFR. It can cause an acne-like rash, and infusion reactions. **Panitumumab** is another agent in this class.

BIOLOGICS — IMMUNE CHECKPOINT INHIBITORS

Checkpoint proteins found on many normal immune cells and on many tumor cells inhibit T-cell immune responses. The binding of a checkpoint protein on the cell surface with the checkpoint receptor on the T cell stops the T cell from killing the cell. This is great for our normal cells; however, we want to destroy the tumor cells. Blocking the binding of the checkpoint protein with the T-cell checkpoint receptor allows the T cell to kill the tumor cell.

Quite a few immune checkpoint proteins have been discovered but the 2 most extensively studied that now have FDA-approved monoclonal antibody inhibitors block **PD-L1**, **PD-1**, or **CTLA4**. PD-L1 (programmed death ligand 1) is found on normal cells and on many tumor cells and PD-1 is the T-cell receptor for that ligand. Note: Ligands are small signaling molecules on cell surfaces that bind with receptors. There are a couple of ligands that bind to T-cell receptor CTLA-4 (cytotoxic T-lymphocyte-associated protein 4), with the same effect.

Monoclonal antibodies to PD-1 and to PD-L1 have shown efficacy against multiple cancers, including, but not limited to, lung, renal, head and neck, urothelial, breast, esophagogastric, colon, and hepatocellular cancers; melanoma; and Hodgkin disease. This class of immunotherapy has radically changed the treatment of patients with cancer, demonstrating:

- efficacy in a wide variety of tumor types and
- potential for long-term, durable responses, even in metastatic disease.

Unfortunately, these agents do not focus solely on tumor cells and cause widespread excessive activation of the immune system. This can cause very serious immune-related adverse events (IRAEs) with nearly every organ system. Examples include hypothyroidism, pneumonitis, nephritis, hypophysitis, skin toxicity, adrenal insufficiency, and neuritis. If severe, these autoimmune toxicities are treated with high-dose corticosteroids.

Pembrolizumab (anti-PD-1), **atezolizumab** (anti-PD-L1), **avelumab** (anti-PD-L1), **durvalumab** (anti-PD-L1), and **nivolumab** (anti-PD-1) are humanized (“zu”) or fully human (“u”) monoclonal antibodies.

Ipilimumab was the 1st checkpoint inhibitor approved by the FDA. It is an anti-CTLA-4 monoclonal antibody used to treat **metastatic melanoma** and **renal cell cancer**. IRAEs are common.

ENDOCRINE THERAPIES

Prostate cancer and estrogen receptor-positive (ER+) breast cancer often respond to endocrine therapy, alone or in combination with chemotherapy or targeted therapy.

Abiraterone is an antiandrogen and a 17- α -hydroxylase inhibitor (blocks androgen synthesis) used to treat metastatic castration-resistant prostate cancer (**mCRPC**). Major side effects include edema, hypertriglyceridemia, and transaminitis. Give with low-dose prednisone to prevent mineralocorticoid excess syndrome. **Enzalutamide** is an androgen receptor antagonist that is also effective for mCRPC.

Leuprolide and **goserelin** are luteinizing hormone-releasing hormone agonists used to treat **prostate cancer** by causing medical castration. Androgen deprivation often causes weight gain, fatigue, muscle loss, diminished libido, and hot flashes. In addition, cardiac events and accelerated bone loss can occur. Men on this therapy should be counseled on cardiac risk factors and monitored for osteoporosis.

Tamoxifen is a selective ER modulator. It has both agonistic and antagonistic effects on the ER in different tumors and is a primary therapy for **ER+ breast cancer**. It may also be used for breast cancer prevention in high-risk individuals. Rare, but potentially serious, side effects of tamoxifen can include ocular (e.g., cataracts, retinal disease), uterine malignancies, and thromboembolic disease. Tamoxifen use is a risk factor for **endometrial cancer**.

Anastrozole and **letrozole** are nonsteroidal aromatase inhibitors, which inhibit endogenous estrogen production. They are used for **HR+ breast cancer** in postmenopausal women. Arthralgias and hot flashes are common. Monitor for osteoporosis.

MAIN SIDE EFFECTS OF CHEMOTHERAPEUTIC AGENTS

Know all the following.

Mucositis, painful ulceration of the oral and esophageal mucosa, is common in patients receiving

chemotherapy. It is usually self-limited but can lead to dehydration and can be a source for infection.

Alkylating agents and **procarbazine** are very toxic to the germinal cells of the testes; **MOPP** (mechlorethamine, vincristine [**Oncovin**; the other brand name is Vincasar PFS], procarbazine, prednisone), a previously used treatment for Hodgkin lymphoma, caused **permanent sterility** in > 90% of males > 25 years of age.

Alkylating agents can cause **leukemia**.

Bleomycin can cause irreversible pulmonary fibrosis.

Vinblastine: **Myelosuppression** is dose limiting.

Vincristine: **Neurotoxicity** is dose limiting. Virtually all patients lose deep tendon reflexes, develop paresthesias of the digits, and, over time, develop muscle weakness—especially of the quadriceps in adults. Taxanes, cisplatin, oxaliplatin, bortezomib, and thalidomide also commonly cause peripheral neuropathy.

Cisplatin causes Mg^{2+} wasting, neurotoxicity, nephrotoxicity, and severe nausea/vomiting.

Anthracyclines can cause dose-dependent **cardiomyopathy**. **Trastuzumab** also causes cardiomyopathy.

Taxanes, **monoclonal antibodies**, and **carboplatin** cause significant infusion-related **hypersensitivity** reactions.

Anthracyclines, **mitomycin**, and **nitrogen mustards** are vesicants. Extravasation can lead to severe skin and tissue damage that may require surgical intervention. Consider central IV access in these agents.

EGFR inhibitors (e.g., cetuximab, erlotinib) commonly cause an **acne**-like skin rash.

Many targeted **biologic agents** (e.g., bevacizumab, sorafenib, sunitinib, axitinib, pazopanib) can increase the risk of **vascular** events and **hypertension**.

Thalidomide and **lenalidomide** cause severe birth defects (e.g., limb malformations) and are contraindicated in pregnancy.

USE OF GROWTH FACTORS

Anemia, thrombocytopenia, and leukopenia are common in cancer patients, occurring either as a result of the underlying disease process or as a side effect of chemotherapy. Hematologic growth factors are sometimes indicated to treat these cytopenias.

Erythropoietin is sometimes used for the treatment of anemia. Erythropoietin has 2 forms: epoetin (Epogen, Procrit) and darbepoetin (Aranesp), which is slightly longer acting than epoetin. Remember to maintain adequate iron stores (transferrin saturation > 20% and ferritin > 100 ng/mL [224.7 pmol/L]) with oral or IV iron, as needed. Erythropoietin is indicated for the treatment of the following:

- Anemia with hemoglobin (Hgb) < 10 g/dL in patients undergoing chemotherapy with **palliative**

intent. Remember that there is a risk of thrombosis, especially if hemoglobin is > 12 g/dL.

- Anemia of chronic kidney disease with Hgb < 10 g/dL
- Anemia in HIV-infected patients taking zidovudine (ZDV)

Erythropoietin should **not** be used in anemia due to cancer (without chemotherapy) or in patients with anemia undergoing chemotherapy with **curative** intent, because it may worsen survival. Consider red blood cell transfusion when the Hgb is < 7 – 8 g/dL (0.7–0.8 g/L) or when symptoms of anemia (e.g., dyspnea, fatigue) occur.

Thrombopoietin agonists (romiplostim [Nplate] and eltrombopag [Promacta]) are approved for the treatment of chronic immune thrombocytopenia purpura (ITP) that has an insufficient response to corticosteroids or IV IgG.

Granulocyte colony-stimulating factor (G-CSF) is indicated for the treatment of the following:

- Neutrophil recovery after treatment for AML or after bone marrow transplant
- Mobilization of stem cells for use in stem cell transplantation
- Neutrophil recovery after myelosuppressive chemotherapy regimens (does not improve survival but does decrease the number of days of hospitalization due to febrile neutropenia)
- Severe chronic neutropenia (cyclic, congenital, or idiopathic)

There are 2 forms of G-CSF: filgrastim (Neupogen, Zarxio) and pegfilgrastim (Neulasta), which is longer acting.

RADIATION THERAPY (RT)

RT is an effective cancer treatment that kills cells with ionizing radiation. Cancer cells and normal cells are killed in the treatment field. Mechanisms include:

- External beam—outside the treatment area
- Brachytherapy—next to or inside the treatment area
- Intraoperative—at the time of surgery
- Targeted radionucleotide—radionucleotides decay at specific locations (e.g., thyroid)

RT can effectively treat certain cancers with or without chemotherapy. Treatment type and course are recommended by the radiation oncologist based on multiple factors, including tumor type, location, and size. The treatment is tailored to be as effective as possible while sparing surrounding tissue.

Side effects in the acute setting are most often localized to the treatment area, including local edema and injury to organs (e.g., head and neck radiation may result in mucous membrane sores). Monitor patients for late side effects (e.g., coronary artery disease and cardiac valve disease after breast radiation), which are most often caused

by damage to adjacent organs/tissue. More information on second cancers is included under [Recurrent and Second Cancers](#) on page 9-40.

TUMOR LYSIS SYNDROME

PREVIEW | REVIEW

- Rasburicase is used in the management of which condition?

Tumor lysis syndrome is a metabolic derangement caused by the release of cellular components into the blood after rapid lysis of malignant cells. It can occur spontaneously in cancers with a high cell turnover (e.g., Burkitt lymphoma), in response to cytotoxic therapy or radiation if a large tumor burden is present, or if the cancer is highly sensitive to treatment (e.g., NHLs, ALL, AML).

Lysis results in **hyperuricemia** +/- acute kidney injury (AKI) due to uric acid precipitation in renal tubules. Malignant cells have high levels of phosphorous—rapid release of phosphate stores can cause hyperphosphatemia and hypocalcemia. Calcium phosphate then can precipitate in the kidneys, also contributing to kidney injury. K^+ release causes hyperkalemia. Clinical manifestations of tumor lysis include arrhythmias, AKI, and seizures—and sometimes death. With the advent of effective preventive measures (described below), tumor lysis syndrome has become less common. Aggressive treatment with IV fluids is used for both prevention and treatment of tumor lysis syndrome. In extreme cases, hemodialysis can be a lifesaving treatment.

Allopurinol prevents the formation of new uric acid but does not decrease pretreatment uric acid levels. It can also increase serum levels of the relatively insoluble purine precursor, xanthine, which can precipitate in the kidneys and cause obstructive uropathy.

Rasburicase (recombinant urate oxidase) oxidizes uric acid to the more soluble allantoin, which decreases uric acid levels and avoids the risk of the xanthine precipitation seen with allopurinol. Use this drug in patients at moderate-to-high risk of tumor lysis syndrome, particularly those with hyperuricemia prior to treatment.

Prophylaxis should be tailored to the patient's risk for tumor lysis syndrome. Risk is determined by the type of malignancy and tumor burden. All at-risk patients should receive IV hydration. Moderate-risk patients should receive hydration plus allopurinol. In both groups, uric acid levels should be monitored and rasburicase added if hyperuricemia develops. High-risk patients should receive prophylaxis with hydration plus rasburicase.

FEBRILE NEUTROPENIA

Febrile neutropenia is a common and potentially life-threatening complication of myelosuppressive cancer therapy. Fever is defined as a single temperature of $\geq 100.9^{\circ}\text{F}$ (38.3°C) or as $\geq 100.4^{\circ}\text{F}$ (38.0°C) over 1 hour. Neutropenia is defined as an absolute neutrophil count < 500 cells/ μL (0.5×10^9 cells/L). Risk of serious infection increases with both severity and duration of neutropenia.

Initial evaluation includes:

- History and exam, focusing on potential sites of infection
- Blood cultures, chest radiography or high-resolution chest CT, CBC with differential, serum electrolytes and creatinine, liver function studies, urinalysis, and urine culture
- Rapid administration of broad-spectrum empiric antibiotics

The initial antibiotic choice for most patients includes IV agents with *Pseudomonas* coverage, such as cefepime or piperacillin/tazobactam. Add vancomycin if there is a high risk for gram-positive infection. Add antifungal agents if there is a persistent fever after 4–7 days on empiric antibiotics. Selected lower-risk patients can be treated as outpatients with oral ciprofloxacin and amoxicillin/clavulanic acid.

Increasing use of myeloid growth factor agents with chemotherapy (e.g., filgrastim, pegfilgrastim) has decreased the incidence of morbidity associated with febrile neutropenia.

For more information on febrile neutropenia, refer to the [Infectious Disease](#) section.

CANCER SURVIVORSHIP

PREVIEW | REVIEW

- Which cancer drugs are most strongly associated with the development of second cancers? Which types of cancer do they cause?
- What technique can be used to prevent infertility from radiation therapy?

OVERVIEW

As cancer screening and survival after treatments continue to improve along with the aging of the population, treating cancer survivors becomes an increasingly important topic. Surveillance for recurrence and development of second cancers often falls to primary care providers. Managing the effects of the cancer or its treatment (e.g., neuropathy, infertility), as well as the psychosocial and financial burdens incurred, are important aspects of survivor care.

RECURRENT AND SECOND CANCERS

Cancer recurrence can be local or metastatic. As patients return to the care of their primary physician, it is the physician's job to know the surveillance recommendations for the patient's specific cancer. This is often obtained from the medical oncologist. Multiple variables—including cancer type, location, and stage—influence these recommendations.

Treatment for cancer (drugs or radiation) can increase the risk of developing a second cancer. Leukemia related to alkylating agents, topoisomerase inhibitors, and platinum agents can occur several years after treatment. The risk of solid organ cancer is increased after treatment with alkylating agents. Tamoxifen is associated with later endometrial cancer. RT also can increase the risk of a second cancer, although lower treatment doses reduce that risk. RT of childhood cancers can increase lifetime second-cancer risk.

Some malignancies are associated with a higher risk of a second cancer regardless of treatment. A 2016 study of > 2 million cancer patients found an 8.1% risk of second cancer (most common second cancer sites: prostate, breast, lung, colon, rectum, bladder, uterus, kidney, melanoma, and NHL). Monitor all cancer survivors closely for recurrence or second malignancy. Counsel patients regarding lifestyle habits, including stopping smoking, to help lower their cancer risks.

TREATMENT COMPLICATIONS

Neuropathy can develop with certain cancer drugs (see [Table 9-13 on page 9-35](#)) during or after treatment. Chemotherapy-induced peripheral neuropathy is dose related and cumulative. Symptoms during chemotherapy treatment are often treated by dose adjustment or medication change. The antidepressant duloxetine has shown some benefit in pain control after treatment. Gabapentin and tricyclic antidepressants are often used but with limited success.

Infertility can be an unfortunate complication of cancer treatment with chemotherapy, radiation, or surgery. Multiple variables affect the patient's fertility and should be considered prior to treatment. Patients may wish to preserve embryos, oocytes, or sperm prior to initiating therapy. Gonadal shielding in RT is beneficial in preserving fertility.

Cardiovascular complications in cancer survivors include constrictive pericarditis (after RT to the chest), dilated cardiomyopathy (after chemotherapy with doxorubicin or daunorubicin), and reduced ejection fraction with or without heart failure (after trastuzumab).

PSYCHOSOCIAL AND FINANCIAL BURDENS

Regularly screen cancer survivors for depression and other mental health issues. These patients can experience fatigue, insomnia, sexual dysfunction, and pain as a result of their cancer or its therapy. These symptoms can often be treated.

Financial burdens can persist long after cancer diagnosis and treatment. Keep this in mind when treating cancer survivors, and refer them to outside resources if indicated.

As the number of cancer survivors continues to grow, there are increasing resources available, including national (e.g., American Cancer Society) and local organizations with information and resources for patients and health care providers.

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Rheumatology

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INTRODUCTION

Rheumatology is a subspecialty with an incredibly broad scope of practice. Rheumatologic disorders encompass > 100 diseases and conditions.

Table 10-1 on page 10-2 broadly summarizes the frequently seen clinical and serological characteristics of some of the more common rheumatologic illnesses.

LABS

PREVIEW | REVIEW

- Which 2 ANA subtypes are specific for a diagnosis of systemic lupus erythematosus?
- Anti-U1-RNP is a very sensitive indicator for excluding which rheumatologic disorder?
- Which rheumatologic disease is associated with a positive c-ANCA and anti-PR3?
- Name 2 diseases that are p-ANCA+ and anti-MPO+.
- Name 2 diseases that consume complement during a flare.
- Other than rheumatoid arthritis (RA), a positive rheumatoid factor (RF) is seen with which other diseases?
- Which antibody test is more specific than RF for RA?

OVERVIEW

What you learn here will enable you to make better sense of lab references later in this section.

Remember: No **single** blood test makes any rheumatologic diagnosis. For example, antinuclear antibodies (ANAs) are positive in many nonrheumatologic diseases and even in healthy individuals. The key is whether the test results correlate with the clinical picture.

The most important aspect of interpreting a test result is to understand the sensitivity and specificity of the test. **Sensitivity** takes into account only those who **have** the disease. Given that a group has disease, sensitivity answers what percent tests positive. A negative result on a highly sensitive test “rules out” disease because the false-negative rate is very low. **Specificity** takes into account only those who do **not** have the disease. Given patients with no disease, it evaluates what percent tests negative. Positive results in highly specific tests help “rule in” disease because the false-positive rate is very low. Sensitivity and specificity are discussed in greater detail in the [General Internal Medicine](#) section.

ANTINUCLEAR ANTIBODY (ANA)

ANAs are autoantibodies that attack components of the nucleus. They are found in many autoimmune disorders. The most common ANA tests use:

- Indirect immunofluorescence (IIF)
- Enzyme-linked immunosorbent assay (ELISA)

IIF is more sensitive and is considered the gold standard for screening. Results of IIF are reported as a dilution or titers (e.g., 1:320) when positive.

Titers show the dilution at which the antibodies become undetectable. It is shown in doublings: 1:40, 1:80, 1:160, 1:320, 1:640—so, the higher the titer, the more antibodies in the serum.

The ANA is positive if the titers are > 1:80. The higher the titer, the greater the likelihood that an autoimmune disease is present. ANA titers do not correlate with disease activity. Therefore, once documented positive in a patient with known lupus or other rheumatic disease, the ANA should **not** be ordered again as there is no utility in monitoring the titers.

Some rheumatologic diseases that are ANA+:

- Drug-induced lupus (DIL; 100%)
- Systemic lupus erythematosus (SLE; 98–100%): Note that ANA-negative lupus is rare, so ANA is very useful for ruling out SLE!
- Mixed connective tissue disease (MCTD; 93–100%)
- Limited cutaneous systemic sclerosis and diffuse cutaneous systemic sclerosis (lcSSc, dcSSc; 60–90%)
- Sjögren syndrome (48–70%)
- Polymyositis/dermatomyositis (PM, DM; 60%)
- Rheumatoid arthritis (RA; 40%)

Example of ruling in as opposed to ruling out: The ANA is positive in almost all patients with SLE (high sensitivity). The ANA also is positive in many other diseases (low specificity). Therefore, a negative ANA test is helpful for ruling out SLE; however, a positive test is poor for ruling it in.

No longer used are the ANA patterns. While they provided some information, they did not identify the specific antibody present, nor were they specific for any particular disease.

We now use specific subtypes of ANA tests, which identify these autoantibodies far more precisely than with fluorescent staining.

When the ANA is positive and you suspect a specific rheumatologic disease, order the more specific antibody subtypes (ANA profile). Know which diseases are associated with specific subtypes (Table 10-2 on page 10-3). Again, the general ANA test is **not** specific enough to diagnose any disease, only to rule one (i.e., SLE) out.

The American College of Rheumatology (ACR) emphasizes avoiding broad testing of autoantibodies. Instead, the choice of autoantibody testing should be guided by

Table 10-1: Rheumatic Diseases and Commonly Associated Features

Disease	Common Features*	Autoantibody/Lab Association
SLE	Photosensitive rash (i.e., malar, discoid), oral/nasal ulcers, alopecia, arthritis, serositis (pleural or pericardial effusions), immune-mediated cytopenias, glomerulonephritis, neuropsychiatric disease	ANA is almost always positive. Other antibodies may be present: anti-dsDNA, anti-Smith, anti-RNP, antiphospholipids, and anti-SSA/SSB; some have low C3/C4 levels.
Antiphospholipid syndrome	Arterial/venous thrombosis and recurrent spontaneous abortions (It can be a primary disease or associated with SLE.)	Modest-to-high titers of IgG/IgM† for aCL and/or β_2 GP and/or presence of LAC; antibodies are present on two separate occasions at least 12 weeks apart.
Rheumatoid arthritis	Chronic symmetric polyarthritis‡, nodulosis. Extraarticular manifestations include ILD, scleritis/episcleritis, and vasculitis.	RF/anti-CCP antibodies (Not all RA patients are seropositive.)
Sjögren syndrome	Xerostomia (dry mouth), parotitis keratoconjunctivitis sicca (dry eyes), extraglandular manifestations such as a complex array of PNS/CNS symptoms, ILD, association with lymphoma/MALTomas	ANA, SSA (Ro)/SSB (La) antibodies (not all patients with Sjögren syndrome have these antibodies), RF, elevated LFTs
Seronegative SpA	AS (inflammatory hip/back pain); PsA (psoriatic arthritis), IBD-associated arthritis (IBD, arthritis§); reactive arthritis (history of recent GI/GU infection). Other manifestations: uveitis, enthesitis, sacroiliitis, and dactylitis	HLA-B27 is present in many with spinal disease (Seronegativity refers to negative rheumatoid factor.)
Systemic sclerosis (a.k.a. scleroderma)	Sclerodactyly (tight skin), Raynaud phenomenon, telangiectasias, esophageal dysmotility, ILD, pulmonary hypertension, renal crisis in diffuse disease	Anticentromere antibody (in limited cutaneous SSc), anti-Scl-70 antibodies and ANA (in diffuse disease)
Inflammatory myositis	Proximal muscle weakness subacutely (+/- distal weakness with IBM) with elevated muscle enzymes +/- typical skin findings with DM (e.g., heliotrope rash, shawl sign, Gottron papules, psoriasis-like scalp), cutaneous calcinosis	ANA, antisynthetase antibodies (anti-Jo-1), anti-SRP antibodies, anti-Mi-2 antibodies
Systemic vasculitis	Multisystem organ involvement; features include chronic renal disease +/- glomerulonephritis, fever, respiratory failure (+/- DAH), rash (esp. palpable purpura), abdominal pain, neurologic process (i.e., mononeuritis multiplex in PAN or EGPA), and arthritis.	c-ANCA/anti-PR3 antibodies are specific for GPA; p-ANCA/anti-MPO antibodies less specific (EGPA, MPA, IBD)¶
aCL = anticardiolipin ANA = antinuclear antibody ANCAs = antineutrophil cytoplasmic antibodies anti-CCP = anti-cyclic citrullinated peptide anti-dsDNA = anti-double-stranded DNA anti-MPO = anti-myeloperoxidase anti-PR3 = anti-proteinase 3 anti-RNP = antiribonucleoprotein	anti-Scl-70 = antitopoisomerase I anti-SSA/SSB = anti-Sjögren syndrome Types A/B AS = ankylosing spondylitis β_2 GP = β_2 -glycoprotein C3 = complement C3 C4 = complement C4 CNS = central nervous system DAH = diffuse alveolar hemorrhage DM = dermatomyositis EGPA = eosinophilic granulomatosis with polyangiitis GI = gastrointestinal	GPA = granulomatosis with polyangiitis GU = genitourinary HLA = human leukocyte antigen IBD = inflammatory bowel disease IBM = inclusion body myositis ILD = interstitial lung disease LAC = lupus anticoagulant LFTs = liver function tests MALT = mucosa-associated lymphoid tissue MPA = microscopic polyangiitis
		PAN = polyarteritis nodosa PNS = peripheral nervous system PsA = psoriatic arthritis RA = rheumatoid arthritis RF = rheumatoid factor SLE = systemic lupus erythematosus SpA = spondyloarthropathy SRP = signal recognition particle SSc = systemic sclerosis

* These are broad, common features of disease and do not include all the encountered disease manifestations.

† Excludes IgA antibodies—not included in the assessment for antiphospholipid syndrome due to lack of consistency in laboratory analysis of these antibodies.

‡ This refers to an inflammatory arthritis only (not arthralgias).

§ Obtain tissue biopsy for confirmation whenever possible.

Table 10-2: Antinuclear Antibody Subtypes and Disease Associations

Specific Autoantibody	Associations
Anti-dsDNA	Specific for SLE; an indicator of disease activity for many but not all SLE patients (similarly to serum complement C3/C4 levels) and identifies SLE patients with potential for significant renal disease. Some patients have active SLE with normal anti-dsDNA and serum complement levels, so it is important to trend these values when available to determine whether these are relevant disease activity markers for each individual SLE patient. Absent in classic drug-induced SLE; sometimes develops in patients treated with TNF inhibitors.
Anti-Smith	Specific for SLE
Anti-SSA (Ro)	SLE, neonatal SLE, Sjögren syndrome, and sometimes myositis. Usually not found in SSc; passively transferred from mother to baby → neonatal lupus and congenital heart block. HLA-DR3 is associated with SSA.
Anti-SSB (La)	SLE and Sjögren syndrome; sometimes found in patients with +SSA. Also passively transferred from mother to baby → neonatal lupus and congenital heart block.
Anti-U1-RNP	Sensitive for MCTD and can be positive in SLE (although if anti-U1-RNP is positive in the setting of anti-Smith or anti-dsDNA, the patient has SLE and not MCTD).
Antihistone	Drug-induced lupus (DIL) and SLE; mainly used to assess for DIL caused by procainamide, hydralazine, chlorpromazine, and quinidine.
Anticentromere	Limited cutaneous SSc (formerly CREST); identifies increased incidence of pulmonary arterial hypertension and improved survival.
Anti-RNA polymerase III	Increased risk for the development of scleroderma renal crisis
Anti-Scl-70 (topoisomerase I)	Diffuse cutaneous SSc; identifies increased incidence of interstitial lung disease and reduced survival.
Antisynthetase	Anti-Jo-1: a type of antisynthetase antibody; associated with myositis, identifies increased incidence of interstitial lung disease, associated with mechanic's hand rash Anti-SRP (signal recognition protein): associated with cardiomyopathy; identifies patients with myositis refractory to treatment Anti-Mi-2: associated with classic dermatomyositis and good response to treatment.

the specific disease under consideration. The ACR also recommends in their Choosing Wisely initiative that ANA subserologies should not be ordered without a positive ANA and a clinical suspicion of immune-mediated disease.

Specific Subtypes of ANA Testing

Anti-dsDNA antibodies and **anti-Smith (anti-Smith)** antibodies are **very specific** but **not sensitive** for **SLE**. Because it is so specific (~ 99%), a positive IIF anti-dsDNA is a very strong marker for SLE (IIF test is much more specific than ELISA). The anti-dsDNA levels are also a good marker of disease activity, especially renal disease, in some (but not all) patients with SLE. It is important to trend the anti-dsDNA levels when available (and to note if the levels were elevated during a period of known SLE activity) to determine whether this is an accurate disease activity marker for that particular SLE patient. You cannot assume that a patient's SLE disease is quiescent based on a normal anti-dsDNA level without trending these levels.

Anti-U1-RNP is **very sensitive** for mixed connective tissue disease (MCTD). However, it is **not specific** for the disease because it also is seen in SLE and other connective tissue diseases. Because it is so sensitive, the **absence** of the anti-U1-RNP **excludes MCTD**. A patient who has a positive anti-U1-RNP with either a positive anti-dsDNA and/or anti-Smith antibody, in conjunction with appropriate

clinical features, is more likely to have SLE than MCTD. Anti-U1-RNP and anti-dsDNA often are seen together because they bind to related antigens known as **epitopes**. An epitope (a.k.a. antigenic determinant) is the part of an antigen recognized by the immune system. The term epitope can be used to describe the antigenic component of a cell.

The **antiribosomal P protein** antibodies are **specific** but have poor sensitivity for **SLE**. They are found in ~ 15–20% of patients with SLE. Rarely, are they found in any other autoimmune diseases or in healthy controls. This is a good test to use when the diagnosis of SLE is not certain. Do not confuse antiribosomal with antiribonucleoprotein antibodies (not the same)!

Antihistone antibody is seen both in SLE and **DIL**, and it is especially sensitive (> 95%) for DIL. So, a negative test helps exclude DIL.

Anti-Scl-70 (a.k.a. **antitopoisomerase I**) is specific for diffuse cutaneous SSc. A positive ELISA test showing > 5× normal limit strongly supports the diagnosis of diffuse SSc (but not limited cutaneous SSc). It is associated with progressive skin involvement, pulmonary fibrosis, pulmonary hypertension, scleroderma renal crisis, and a higher mortality. Note that lower levels of anti-Scl-70 positivity are seen in 25% of SLE patients. This is possibly due to cross reactivity of dsDNA with this ELISA test.

SSA (Ro) and SSB (La) antibodies originally were identified in patients with Sjögren syndrome and SLE. They since have been described with other connective tissue diseases, such as inflammatory myositis, RA, and primary biliary cholangitis (PBC; previously known as primary biliary cirrhosis). These antibodies are not specific or sensitive for Sjögren syndrome and SLE but, very importantly, women with Ro/SSA (with or without concurrent La/SSB) antibodies are at an increased risk of having a child with neonatal lupus erythematosus (more under [SLE and Pregnancy](#) on page 10-21).

ANTINEUTROPHIL CYTOPLASMIC ANTIBODY (ANCA)

ANCAs are autoantibodies against antigens in the **cytoplasm** of **neutrophils**. ANCAs often are associated with vasculitis, but they are seen in other diseases as well ([Table 10-3](#)).

Table 10-3: ANCAs

IF ANCA	ELISA	Disease
c-ANCA	Anti-PR3+	GPA
p-ANCA	Anti-MPO+	MPA EGPA Pauci-immune RPGN Anti-GBM disease Drug-induced; e.g., PTU, methimazole, hydralazine, minocycline, levamisole contaminated cocaine
	Anti-MPO-	Crohn disease Ulcerative colitis Chronic active hepatitis Primary sclerosing cholangitis Primary biliary sclerosis, PAN

ANCAs = antineutrophil cytoplasmic antibodies
EGPA = eosinophilic granulomatosis with polyangiitis
GPA = granulomatosis with polyangiitis
IF = immunofluorescence
MPA = microscopic polyangiitis
RPGN = rapidly progressive glomerulonephritis
PTU = propylthiouracil

It is thought that disease may be caused by the ANCA antibodies stimulating the release of lytic enzymes from neutrophils.

2 ANCAs are identified by their immunofluorescence pattern:

- 1) **c-ANCA**: Antibodies are diffuse in the cytoplasm.
- 2) **p-ANCA**: Antibodies are perinuclear.

ANCAs are also divided based on ELISA testing of targeted antigens:

- 1) Proteinase 3 (anti-PR3; PR3 ANCA), the antigen that causes the c-ANCA finding
- 2) Myeloperoxidase (anti-MPO; MPO ANCA), the antigen that causes p-ANCA finding

Immunofluorescence (IF) results are not highly specific (there is a subjective component to the interpretation of IF patterns). As such, use caution when interpreting either a positive c-ANCA or p-ANCA result without the more specific ELISA results. ELISA tests screening for antibodies to PR3 or MPO and have higher specificity and higher positive predictive value than the IF patterns to which they correspond. Both the IF and ELISA tests are often done at the same time.

Note that IF c-ANCA with ELISA anti-PR3 positivity is very specific for **granulomatosis with polyangiitis** (GPA).

p-ANCA is less helpful because this IF pattern is nonspecific, as seen in [Table 10-3](#).

If a patient is anti-MPO+ with vasculitic symptoms, think:

- Microscopic polyangiitis (MPA)
- Eosinophilic granulomatosis with polyangiitis (EGPA)
- Pauci-immune rapidly progressive glomerulonephritis (RPGN)
- Antiglomerular basement membrane (anti-GBM) disease
- Drug-induced ANCA-associated vasculitis

Think ANCA-associated vasculitis (AAV) as GPA, EGPA, and MPA. Drug-induced AAV is caused by the antithyroid drugs propylthiouracil (PTU) and **methimazole**.

In summary:

- c-ANCA+ plus anti-PR3+: Think GPA.
- p-ANCA+ plus anti-MPO+: Think MPA, EGPA, pauci-immune RPGN, anti-GBM, and drug-induced ANCA-associated vasculitis.

The sensitivity and specificity of these antibody tests are **not** high enough for them to be used for **screening**. Pretest probability of the disease in question is important; consider before ordering ANCAs.

COMPLEMENT SYSTEM

The complement system is comprised of a variety of small proteins that function to enhance or “complement” the action of antibodies and phagocytic cells. It has 3 pathways: classical, lectin, and alternative. Through these different pathways, they ultimately perform the same functions:

- Building and activating the C5b-9 membrane attack complex
- Inducing more inflammation with anaphylatoxins C3a, C4a, and C5a
- Opsonizing target cells with C3b

Remember: All complement pathways take place on the cell membrane of the pathogen and the end point of all complement activation is the formation of the C5-C9 membrane attack complex (MAC), which, yes, attacks this membrane!

Hypocomplementemia is seen in **SLE**, **vasculitis**, RA, cryoglobulinemia, and infective endocarditis.

There is more on the complement pathways in the **Allergy & Immunology** section. Note: Complement components are decreased in cases of a **genetic** deficiency, consumption during complement activation, or **underproduction**—as in eclampsia or **HELLP** syndrome (hemolysis, elevated liver enzymes, and low platelets).

Know causes of low complement levels:

- **C2** or **C4**—usually a genetic allele deficiency
- **C3** is consumed with any activation of the complement pathway (classical or alternative).
- **C4** is consumed only with activation of the classical pathway (as with SLE).
- **CH50** assay measures total hemolytic complement of the classical pathway and requires **all** components (C1–C9) of the classical pathway for a normal result. A low level occurs with a significant complement deficiency and indicates the need for further testing of individual complement component levels.

The CH50 assay is most useful as a screening tool for disease states resulting in hypocomplementemia. A low CH50 prompts you to order the individual complements listed above. For example, patients with recurrent or severe *Neisseria* (meningococcal or gonococcal) infections may have terminal complement deficiency (C5–C9). C5–C9 make up what is known as the membrane attack complex.

Patients with SLE may have low C3 and C4; **C3** is a more sensitive index of disease activity in **SLE**. Therefore, normalization of individual complement levels and CH50 also is useful to follow disease activity. Be mindful that not all patients with active SLE have hypocomplementemia. It is important to always **trend** the serum complement levels over time to determine whether C3 and/or C4 are **reliable** markers of disease activity for each individual patient.

RHEUMATOID FACTOR (RF) AND ANTI-CYCLIC CITRULLINATED PEPTIDE (ANTI-CCP)

RF is an autoantibody that binds to the Fc region of IgG. RF and IgGs form immune complexes that contribute to the disease process. RF is positive in 80–85% of patients with RA, which makes it a fairly sensitive test for RA; however, it is not specific because a positive RF is seen in other diseases, including chronic lung disease, chronic hepatic diseases, chronic infections (e.g., tuberculosis, HIV, viral hepatitis), Sjögren syndrome, SLE, infectious endocarditis, and hematologic malignancies.

The anti-cyclic citrullinated peptide (**anti-CCP**) antibody is highly specific for RA (specificity ~ 97%) and portends a poorer prognosis. The presence of **both** RF and anti-CCP antibodies is associated with more aggressive RA and extraarticular manifestations (e.g., rheumatoid nodule, rheumatoid lung/interstitial lung disease).

MAJOR HISTOCOMPATIBILITY COMPLEX (MHC) — HUMAN LEUKOCYTE ANTIGENS (HLAs)

HLAs are the human version of the MHC. There are 3 classes of HLAs:

- **Class I** are found on all nucleated cells and platelets and interact with **CD8** or T suppressor cells, which results in either cell-mediated killing or suppression of the MHC Class I presenting cell.
- **Class II** are found on antigen-presenting cells such as B cells, macrophages, and dendritic cells, as well as some activated T cells, and these interact with **CD4** or T helper cells leading to antibody production to or phagocytosis of the antigen that was presented.
- **Class III** include several cytokines and several complement compounds.

HLA-B27

The HLA-B27 antigen is typically found in patients with **seronegative spondyloarthritis**, a group of disorders that include ankylosing spondylitis, reactive arthritis, psoriatic arthritis, arthritis/spondylitis associated with inflammatory bowel diseases, and idiopathic uveitis. However, this antigenic marker has limitations when positive because 7–8% of the non-Hispanic white population in the U.S. carry this haplotype without any disease. (HLA-B27 prevalence is lower in other ethnic groups.) Therefore, interpret its presence cautiously with each patient (Table 10-4).

Table 10-4: Incidence of HLA-B27

Ankylosing spondylitis	90%
Reactive arthritis; typically, secondary to GU/GI infections	60–80%
Reactive arthritis	50%
Uveitis	50%
Rheumatoid arthritis, osteoarthritis, rubella arthritis	10%
Healthy non-Hispanic white population	7–8%

Although it does not cause reactive arthritis, *Klebsiella pneumoniae* has an enzyme that cross-reacts with the HLA-B27 test.

HLA-DR2, -DR3, and -DR4

HLA-DR2 and -DR3 are associated with SLE. HLA-DR4 antigens are associated with severe RA.

Other HLA Associations

Other important general HLA associations to know:

- **HLA-B5701** is strongly associated with abacavir hypersensitivity reaction. See the **Infectious Disease** section.
- **HLA-B51** is associated with Behçet disease.

- **HLA-DQ2/DQ8** is associated with celiac disease. See the [Gastroenterology](#) section.
- **HLA-B5801** is associated with a higher risk for allopurinol hypersensitivity syndrome in individuals of Korean, Han Chinese, or Thai descent.

For more information on HLAs, see the [Allergy & Immunology](#) section.

ERYTHROCYTE SEDIMENTATION RATE (ESR) AND C-REACTIVE PROTEIN (CRP)

ESR, a marker of plasma viscosity, and CRP, a group of proteins involved in innate immunity, are the most common acute phase reactants (APRs; inflammatory markers) used in clinical medicine. They are most helpful in determining disease **activity** and **response to therapy**.

Unfortunately, they are of limited diagnostic utility. Although they are sensitive markers of inflammation in general, they are **not** specific for any particular disease. Diagnostically, they are most helpful in **ruling out** inflammatory disease, especially when the pretest likelihood is low to moderate. Note that an extreme elevation of the ESR (> 100 mm/hour) is almost **always** a hallmark of serious underlying disease, most commonly malignancy, infection, or vasculitis.

THE JOINTS

PREVIEW | REVIEW

- Compare and contrast noninflammatory, inflammatory, and septic joint fluid ([Table 10-5](#)).
- Describe gout crystals and their birefringence.
- Describe calcium pyrophosphate (pseudogout) crystals and their birefringence.

SYNOVIAL FLUID (SF) ANALYSIS

The SF provides nutrition for the joint as well as lubrication to reduce friction upon movement of the joint. In a normal, healthy joint, only a minimal amount of SF (~ 3 mL in knee) is necessary for function. Note there are 2 main types of synoviocytes: **Type A** cells are phagocytic and **Type B** cells provide lubrication (hyaluronic acid). Nutrition is provided by the blood vessels and lymphatics, located next to the synoviocytes. Excessive accumulation of this SF (a.k.a. an **effusion**) can occur during a disease process and/or trauma. This effusion is readily accessible by performing an **arthrocentesis**.

After aspirating SF, document the fluid's color, clarity, and viscosity and send the sample for cell count and differential, crystal analysis, and culture and sensitivity with Gram stain (the **3 Cs**). Glucose and protein can be ordered if you have enough fluid to send (in a normal joint, values should be similar to serum).

Common indications for SF analysis include suspected septic arthritis (this usually presents as a monoarticular arthritis), unexplained joint effusions, or suspected crystal-induced arthritis (SF analysis is the gold standard to establish a diagnosis of crystal-induced arthritis).

SF results are divided into 5 main classifications based on cell count findings ([Table 10-5](#)):

- **Type 1:** normal
- **Type 2:** noninflammatory
- **Type 3:** inflammatory
- **Type 4:** septic
- **Type 5:** hemorrhagic

Normal and noninflammatory fluids are clear to light yellow with normal viscosity. Inflammatory and septic fluids are cloudy or purulent with low viscosity. Hemorrhagic fluid from a traumatic aspiration shows bright red blood; however, with pigmented villonodular

Table 10-5: Classification of Synovial Fluid Analysis

Joint Fluid	WBC (μL)	Color	Viscosity	Disease Associations
Type 1: normal	< 200	Clear	High	No disease state
Type 2: noninflammatory	0 to 2,000	Usually light yellow	High	OA, trauma, neuropathic joints, hypertrophic osteoarthropathy, mycobacterial infection
Type 3: inflammatory	2,000 to 100,000	Light yellow to cloudy yellow	Low	RA, crystal-induced arthritis (e.g., gout, pseudogout), SLE, scleroderma, a seronegative spondyloarthropathy (i.e., reactive arthritis, ankylosing spondylitis, psoriatic arthritis, IBD-associated arthritis), sarcoidosis, viral arthritis, poststreptococcal arthritis, mycobacterial or fungal infection
Type 4: septic	15,000 to > 100,000*	Turbid yellow to green	Low	Bacterial, mycobacterial, or fungal infection (although sometimes crystal-induced arthritis can cause WBC > 100,000 cells/μL)
Type 5: hemorrhagic	200 to 2,000	Bright to dark red	Variable	Trauma, PVNS, bleeding diathesis, tumor

IBD = inflammatory bowel disease
 OA = osteoarthritis
 PVNS = pigmented villonodular synovitis
 RA = rheumatoid arthritis
 SLE = systemic lupus erythematosus
 WBC = white blood cell

*Partially treated infections or low virulence organisms account for the lower part of the range.

synovitis (PVNS), trauma, or malignancy, brown or dark red fluid often is seen. Viscosity in hemorrhagic fluid is variable based on the condition that caused the effusion.

SF viscosity refers to the thickness of the fluid as a result of hyaluronic acid. It is measured by the length of the fluid's string once expelled from the needle. Normal viscosity has a string sign of 2–2.5 cm. Fluid with low viscosity drops like water from the needle. Conditions that disrupt hyaluronic acid production or increase its breakdown cause low viscosity fluid (e.g., inflammatory states, infections).

The white blood cell (WBC) count in SF also determines if the fluid is inflammatory or noninflammatory. Inflammatory fluid has WBC > 2,000 cells/mm³. Because the WBC count and glucose level in aspirated SF decreases rapidly with time, be mindful to analyze the fluid shortly after aspiration. Glucose is reduced in septic joints. Protein is increased in inflammatory joints.

Send SF cultures for typical and atypical organisms (e.g., gonococcal, mycobacterial/fungal organisms) to identify the microorganism and antibiotic resistance patterns. On occasion, septic arthritis and crystal-induced arthritis occur simultaneously, so it is standard to send studies for both. If SF cultures are negative, and you still suspect infection, consider synovial tissue biopsies, which have higher yield for these organisms. Remember: A negative Gram stain does not necessarily rule out bacterial infection, so empiric antibiotics are recommended while awaiting culture and sensitivity results in a patient suspected of having septic arthritis.

You need as little as 1 drop of fluid for crystal analysis. Use a microscope with polarizing filters and a quarter-wave plate (a.k.a. a **red compensator**) to evaluate for monosodium urate (MSU) and calcium pyrophosphate dihydrate (CPP) crystals. MSU crystals cause gout. CPP crystals cause calcium pyrophosphate deposition (CPPD) disease. Both types of crystals have 2 colors (blue and yellow); hence, they are termed birefringent. The crystals are identified, however, by their color when they are **parallel** to the microscope's red compensator. If the crystals are yellow when parallel to the compensator, they are negatively birefringent. If the crystals are blue when parallel to the compensator, they are positively birefringent.

MSU (**gout**) crystals are **yellow** when parallel to the compensator (**negatively** birefringent), and they are **needle-shaped**. (Helpful hint: The double Ls in "yellow" look like 2 parallel needles.)

Gout is confirmed by the presence of these MSU crystals and with inflammatory joint fluid (> 2,000 cells/μL). During an acute gout attack, you only need to see a single MSU crystal phagocytosed by a neutrophil (or 3 extracellular MSU crystals) to make the diagnosis of gout.

CPPD is confirmed by the presence of **rhomboid-shaped**, **positively** birefringent (**blue** when parallel) CPPD crystals on polarized light microscopy, along with inflammatory joint fluid (same parameters as mentioned above with gout). It is worthwhile to note that CPPD crystals are

sometimes very weakly birefringent and more difficult to visualize compared to MSU crystals. Also note that crystals dissolve if the sample sits too long; therefore, get the fluid analyzed ASAP!

IMAGING STUDIES

Besides lab testing, imaging studies are important in the assessment of skeletal and rheumatic diseases. **Weight-bearing knee films** are the initial diagnostic tests of choice for nontraumatic knee disorders (rheumatoid arthritis or osteoarthritis) because weight bearing allows a more realistic evaluation of the joint space. Characteristic radiographic features such as bone erosions, joint space narrowing, hypertrophic changes, juxtaarticular demineralization, and periostitis are just some of the many findings seen on plain radiographs.

Diagnostic **ultrasound** imaging of the joint for signs of synovitis is increasingly being used because of its low cost, noninvasiveness, and lack of irradiation.

Magnetic resonance imaging (**MRI**) may be needed to clearly visualize all the components of soft tissues such as cartilage, ligaments, tendons, and synovium.

Computed tomography (CT) imaging has fallen out of favor for joint evaluation due to high radiation exposure. However, consider ordering a CT in patients who require a more detailed exam, generally for bone disorders, but who have contraindications to MRIs (e.g., pacemakers).

GENETIC COLLAGEN DISORDERS

The inherited disorders of collagen encompass several different diseases, many of which cause hypermobility (e.g., Marfan syndrome, Ehlers-Danlos syndrome, homocystinuria). Defects in fibrillin (Marfan syndrome) or in Type 2 or Type 11 collagen (Stickler syndrome) are well defined; different proteins are responsible for these syndromes.

The following are the ones to remember.

Marfan syndrome: Yearly echocardiograms to monitor the heart valves and the aorta are required. Ghent nosology is a scoring system with 7 criteria to aid in the diagnosis of Marfan syndrome. Some of the clinical features include:

- 1) Long limbs (outstretched arm length > height)
- 2) Pectus excavatum (sternum dips inward [a.k.a. funnel chest]) or pectus carinatum (sternum protrudes outward [a.k.a. pigeon chest])
- 3) Aortic aneurysm/dissection
- 4) Ectopia lentis (lenses displaced **upward**)
- 5) Aortic and mitral valve problems (See more in the **Cardiology** section.)
- 6) Wrist sign (Surrounding the wrist with a grip, the thumb overlaps the little finger.)
- 7) Thumb sign (The thumb inside the closed fist is not completely covered.)

Ehlers-Danlos syndrome: variable skin hyperelasticity and joint hypermobility. Joint hypermobility syndrome is diagnosed by using the Brighton criteria and the Beighton score. Hypermobility as defined by the Beighton score includes hyperextension of fingers, elbows, knees, and the ability to touch palms to the floor with knees extended. Diagnosis is made when 2 major, 1 major and 2 minor, or 4 minor Beighton criteria are met:

- Major criteria
 - Beighton Score of ≥ 4
 - Arthralgias longer than 3 months in ≥ 4 joints
- Minor criteria
 - Score of ≥ 1
 - Arthralgias ≥ 3 months in ≥ 1 joint or back pain
 - Dislocation or subluxation of a joint
 - ≥ 3 overuse injuries involving tenosynovitis or bursitis
 - Marfanoid features
 - Abnormal skin (e.g., stretchy, striae)
 - Eyes (e.g., drooping lids, myopia)
 - Varicose veins, rectal or uterine prolapse

There are several classifications of Ehlers-Danlos syndrome:

- Classic type: includes most severe form (hyperextensive and easily scarred fragile skin with hypermobile joints, hernias with prolapse)
- Hypermobility type: Manifestations are predominantly joint; skin changes not as severe as in classic form.
- Vascular type: Manifestations are predominantly skin (not joint); predilection for rupture of large vessels and viscera.
- Several other rarer types

Osteogenesis imperfecta is due to defects in procollagen genes. Features include:

- Osteoporosis
- Multiple bone fractures
- Varying degrees of blue sclera
- Lucent (brittle) teeth
- Hearing loss

Pseudoxanthoma elasticum: autosomal recessive and involves skin (easy bruising), blood vessels, and eyes. The main problem is recurrent UGI bleeds because the elastic media of blood vessels is affected. Classic findings include a cobblestone appearance of the skin with yellow papules and plaques resembling plucked chicken skin on the neck/axillae and angioid streaks on funduscopy exam.

RHEUMATOID ARTHRITIS (RA)

PREVIEW | REVIEW

- How long is the typical morning stiffness in rheumatoid arthritis (RA) vs. osteoarthritis?
- What are the essential classification criteria for RA?

- Which part of the spine is sometimes involved in RA? Which parts are not involved?
- What is the preferred type of intubation in a patient with RA?
- What is the leading cause of death in RA?
- Name pulmonary manifestations of RA.
- What is Felty syndrome?
- Which disease-modifying antirheumatic drug (DMARD) is recommended by the American College of Rheumatology as 1st line for all moderate-to-severe cases of RA?
- Know which medications used to treat RA are relatively safe and not safe during pregnancy.
- What follow-up is required in patients treated with hydroxychloroquine?
- Which DMARD causes hypoglycemia and may lead to a reduction in dose of diabetic medications?
- Which DMARD causes reversible infertility in men?
- Which DMARD and biologics cause hyperlipidemia?
- What are representative drugs for each category of biologic DMARDs?
- Which biologic is associated with gastrointestinal perforations and diverticulitis?
- Name some serious complications of the various biologics.
- Which biologic decreases the effectiveness of oral contraceptives?
- Which live virus vaccines are avoided in patients treated with biologics?

OVERVIEW

The worldwide prevalence of RA is ~ 0.5–1%, and there is a greater incidence in women than in men with a female-to-male ratio of 3:1. The typical age of onset is 40–50 years. Etiology of RA is multifactorial and basically unknown. There is a low concordant incidence of RA in identical twins, but RA does seem to have some genetic basis (~ 10% of patients have a 1st degree relative with RA; higher concordance in identical twins than in fraternal twins).

RA is a heterogeneous disease with various human leukocyte antigen (HLA) polymorphisms, resulting in anything from mild joint involvement to severely erosive joint deformity. Genetic haplotypes, such as HLA-DR and HLA-DQ, have been associated with more aggressive disease.

Other lab results associated with aggressive disease include rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP). See Labs on page 10-1. Seropositivity refers to the presence of RF or anti-CCP. ~ 60–80% of patients are seropositive. The presence of RF or anti-CCP portends a poorer prognosis.

In RA, disease occurs with **inflamed synovium** (Type A and B synovial cells are increased). In the chronic phase, this inflamed membrane of granulation tissue (**pannus**) stimulates the release of cytokines, which leads to cartilage destruction, bone erosion, and an inflammatory synovial fluid. The common cytokines are:

- Interleukins (especially **IL-1**, **IL-6**, and **IL-17** **interferons**)
- Colony-stimulating factors (**CSF**)
- **Growth factors**
- Tumor necrosis factor (**TNF**; also important when considering treatment for RA)

DIAGNOSIS

To diagnose RA, get a good history, assess physical signs and symptoms, and follow up with the appropriate lab and imaging studies.

Symmetrical small joint involvement (e.g., hands, wrists) is the hallmark of the disease. However, the knee is the most common single joint initially involved in RA. If a patient with inflammatory knee arthritis presents with a swollen calf, suspect a ruptured Baker cyst (a.k.a. popliteal cyst) causing **pseudophlebitis**. These can occur with inflammatory processes. Occasionally, a Baker cyst causes extrinsic venous compression simulating a deep vein thrombosis.

Signs and symptoms of RA include **> 1 hour** of morning stiffness/pain that improves with activity. RA patients are prone to fatigue, low-grade fever, anorexia, and weight loss. Remember: Noninflammatory, mechanical joint diseases such as OA cause < 30 minutes of stiffness and pain becomes worse with activity.

RA usually presents as a chronic (> 6 weeks), symmetric, polyarticular inflammatory arthritis with involvement of small joints more than with large joints. Pay attention to duration of joint symptoms, as certain viral arthritides (e.g., parvovirus), poststreptococcal arthritis, crystal-induced arthritis, and reactive arthritis (after a GI/GU infection) can present similarly, except that they present with a more acute/subacute arthritis and they usually last < 6 weeks.

RA has specific involvement of the hands—especially the metacarpophalangeal (MCP; **Figure 10-1**) and proximal interphalangeal (PIP) joints in a symmetrical pattern. The distal interphalangeal (**DIP**) **joints are spared!** Physical deformities occur in patients with advanced disease and can include:

- Boutonnière and swan-neck deformities
- Zeta thumb deformity
- Ulnar deviation
- MCP subluxation
- Flexion contractures of the elbows
- Piano key sign (distal radioulnar joint instability)



Figure 10-1: Rheumatoid arthritis of the metacarpophalangeal joints

Source: James Heilman, MD

In some patients, RA causes joint destruction. Some radiographic findings of this destruction include:

- Periarticular osteopenia
- Joint erosions
- Radiocarpal/Ulnocarpal joint space narrowing
- Intracarpal joint space narrowing
- Carpal bone fusion
- Symmetric joint space narrowing of other joints (e.g., radiohumeral joints, knees)

Joint symptoms of RA are intermittent (15–30%) or daily and constant. If occurrence is intermittent, it is a variant of RA known as **palindromic rheumatism**. Patients who present this way can be labeled falsely with etiologies such as gout, until the correct diagnosis is made. Most patients with palindromic rheumatism progress to chronic RA.

Uncontrolled or progressive RA has a poor prognosis. Poor prognostic indicators of RA include:

- Presence of **HLA-DR4** (HLA-DRB1*0401 has been associated with erosions and extraarticular disease.)
- High-titer **RF** or **anti-CCP** antibodies
- Elevated acute phase reactants (ESR and CRP)
- Multiple joint involvement (> 6)
- Constitutional symptoms (e.g., fever, weight loss)
- Radiographic evidence of erosive disease (**Figure 10-2 on page 10-10**)
- Extraarticular disease (e.g., rheumatoid nodules, vasculitis, lung involvement)

An increased ESR or CRP is helpful when assessing the degree of joint inflammation, but remember that these are nonspecific markers of inflammation. Interpreting them relies on correlation with clinical findings. Many patients have elevated ESR and/or CRP levels with their arthritis. However, some patients with active inflammatory arthritis may have normal or only mildly elevated inflammatory markers. It is important to always trend the ESR and CRP over time to determine if these are accurate markers of disease activity for the patient.



Figure 10-2: X-ray of rheumatoid arthritis of the hand
Source: Martin Steinhoff, MD

From this, remember the following classification essentials often used as a surrogate for diagnosis. Seropositive RA is diagnosed when all of the following are present based on some of the 2010 ACR/EULAR classification criteria for RA:

- inflammatory arthritis (from 1 to 10 joints, small joints weighted heavier than large),
- positive RF or anti-CCP,
- increased ESR or CRP (usually, but not always, elevated), and
- duration > 6 weeks.

Antibodies play a prominent role in the ACR/EULAR criteria for RA. A high titer of either RF or anti-CCP contributes 3 of the 6 points required for the diagnosis.

Exclude other causes of chronic inflammatory arthritis such as systemic lupus erythematosus (SLE), Sjögren syndrome, SSc myositis, sarcoidosis, seronegative spondyloarthritides, and systemic vasculitis, as well as crystalline arthritis.

Seronegative RA is diagnosed when patients meet other ACR/EULAR RA criteria but lack both RF and anti-CCP. These patients tend to have less severe disease than that seen in antibody-positive patients. See the complete 2010 ACR/EULAR RA classification criteria at this website: rheumatology.org.

Cervical Spine Subluxation in RA

Patients with long-standing, seropositive RA (particularly those with active disease and extraarticular

manifestations) are at the highest risk for developing cervical instability at the atlantoaxial articulation (C1–C2). Both atlantoaxial and subaxial (below C2) joints may be involved.

While patients can be asymptomatic, suspect cervical (C1–C2) involvement when a patient with RA complains of ≥ 1 of the following:

- 1) Recurrent occipital headaches
- 2) Neck pain
- 3) Limited neck range of motion
- 4) Weakness of the upper extremities
- 5) Paresthesias of the hands and feet

If these symptoms are present, order cervical spine x-rays with flexion and extension views. If there are neurologic deficits on exam or if plain films suggest subluxation, MRI of the cervical spine is the most valuable test to visualize the spinal cord and potential cord compression due to the RA pannus. Untreated cervical subluxation with cord compression causes significant morbidity and mortality (myelopathy progresses rapidly); therefore, treat urgently. Therapy in these cases is surgical and involves different strategies for cervical spine stabilization, including occipitocervical fixation.

In RA patients scheduled to undergo endotracheal intubation, it is mandatory to evaluate for cervical instability. Acute subluxation, which may occur with extension of the neck for intubation, causes spinal cord compression or vertebral artery compression—leading to quadriparesis or sudden death. Fiberoptic intubation is preferred over direct laryngoscopy to avoid neck extension.

The thoracic, lumbar, sacral spine, and the sacroiliac joints are usually **spared** in RA (in contrast to ankylosing spondylitis and psoriatic arthritis). Again, RA does **not** present as lumbar spine pain. If you see a patient with RA and spine pain, think about the myriad other potential causes of spine pain (e.g., compression fractures, infections) and **not** a flare of RA.

RA also can affect the cricoarytenoid joints and cause hoarseness, sore throat, and/or neck pain. Suspect temporal mandibular joint (TMJ) involvement when patients with RA complain of jaw pain.

Extraarticular Manifestations of RA

Remember: RA is a systemic disease. Extraarticular manifestations occur and are more common in the presence of RF and anti-CCP antibodies (seropositive RA). Know these extraarticular manifestations of RA:

- Cardiac:
 - Pericarditis (with effusion or thickening) and myocarditis
 - Rheumatoid nodules on the valves
 - Atherosclerosis: 3× increased risk of atherosclerotic cardiovascular disease (i.e., sudden death, MI). Coronary artery disease is the leading cause of death.

- Renal (all very **rare**):
 - Drug-related renal disease (usually NSAIDs and analgesics)
 - Amyloid renal disease occurring late in RA
- Lungs (males more than females): Rheumatoid arthritis-associated interstitial lung disease (RA-ILD), exudative pleural effusions, diffuse interstitial fibrosis, and intrapulmonary rheumatoid nodules are the major pulmonary manifestations.
 - RA-ILD
 - Exudative pleural effusion with low glucose (< 30 mg/dL [1.67 mmol/L]) and pH (See the **Pulmonary Medicine** section for more discussion on exudative vs. transudative effusions.)
 - Diffuse interstitial fibrosis and intrapulmonary rheumatoid nodules; when caused by mine dust in an RA patient, it is called **Caplan syndrome** or **rheumatoid pneumoconiosis** (mine dust pneumoconiosis).
- Vasculitis:
 - May resemble polyarteritis nodosa and cause nail-fold infarcts and splinter hemorrhages
 - Necrosis with ulceration may occur, especially over the **malleoli**.
- Nerves:
 - Mononeuritis multiplex, which may manifest as foot or wrist drop
 - Carpal and tarsal tunnel syndromes
 - Cervical myelopathy
- Eyes:
 - Episcleritis
 - Scleritis
 - Sicca syndrome
- Skin:
 - Rheumatoid nodules occur in 25% and indicate potential for more severe disease. These nodules usually appear on extensor surfaces; they also may be found in the lungs and on heart valves.
- Blood and lymphatics:
 - Anemia of chronic disease: Remember that not all anemia in RA is due to anemia of chronic disease. Often, RA patients are on NSAIDs for pain control, so the possibility of a subtle NSAID-induced GI bleed should be on the differential diagnosis for anemia in RA. In patients with overlap syndromes (particularly SLE), consider also autoimmune hemolytic anemia as a cause of anemia.
 - Neutropenia (< 2,000/μL; seen in **Felty syndrome** and large granular lymphocyte [**LGL**] syndrome)
 - Increased risk of lymphoma (particularly in long-standing, untreated active disease)

Felty syndrome consists of the classic triad of RA, **splenomegaly** (the spleen is “felty”), and **neutropenia**. These patients usually have long-standing active disease associated with high titers of RF and subcutaneous rheumatoid nodules. They suffer increased mortality from infections. Treatment: methotrexate, cyclosporine A, corticosteroids, granulocyte colony-stimulating factor (G-CSF), biologics,

and, if needed, splenectomy. If splenectomy is ineffective, the prognosis is poor. Felty syndrome is encountered rarely today because therapies for RA have improved disease control drastically.

TREATMENT

Drugs used to treat RA are categorized (Table 10-6) as:

- Nonsteroidal therapies (e.g., NSAIDs, Cox-2 inhibitor)
- Synthetic disease-modifying antirheumatic drugs (sDMARDs), traditional and small-molecule types (See Table 10-7 on page 10-12.)
- Biologic DMARDs (biologics; see Table 10-8 on page 10-15.)
- Other immunosuppressants (i.e., azathioprine, cyclosporine A, cyclophosphamide, minocycline, doxycycline, glucocorticoids)

Table 10-6: Drugs Used to Treat RA

NSAIDs	Nonselective (e.g., ibuprofen, naproxen, nonacetylated salicylates) and selective (e.g., COX-2 inhibitor [celecoxib])
Biologic DMARDs	Anti-TNF biologics, non-TNF biologics
Synthetic DMARDs	Methotrexate, leflunomide, hydroxychloroquine, sulfasalazine, tofacitinib, upadacitinib
Less commonly used synthetic DMARDs	Azathioprine, cyclosporine A, cyclophosphamide, minocycline, doxycycline, glucocorticoids

Studies have shown that 70% of patients with active, polyarticular RF-positive disease develop joint damage or erosions within 2 years of onset. Furthermore, it is well described that patients with untreated, seropositive, erosive arthritis have a higher risk for extraarticular manifestations and disability leading to joint deformities and interference with activities of daily living.

Early diagnosis and **early aggressive therapy** to allow patients a chance at remission are the aims of treatment. The goal is to initiate DMARD monotherapy therapy within 3 months of symptoms and titrate drugs (add additional DMARDs or biologic agents) to attain low disease activity or remission. Methotrexate (**MTX**) is the preferred initial monotherapy for most patients with early active RA.

Consider biologics if a patient has moderate or high disease activity despite traditional DMARD therapy. Make a switch in biologic therapy if the patient has poor response to treatment or adverse reactions (though insurance also may play a role in this!).

Know that NSAIDs and systemic glucocorticoids are used for more immediate control of pain and serve as a bridge in therapy while the DMARDs/biologics achieve full effect (this can take up to 3 months).

NSAIDs

NSAIDs are part of the initial treatment—unless there is a history of gastritis, peptic ulcer disease, chronic kidney disease, or recent myocardial infarction. NSAIDs help to decrease inflammation and joint swelling. They **do not alter the course** of the disease. NSAIDs are used in conjunction with DMARDs to help control pain.

For patients with aspirin (ASA) allergy, use nonacetylated salicylates such as salsalate or choline magnesium trisalicylate. These agents may have less GI toxicity; however, they can be less effective for pain control.

What about the COX-2 inhibitors? Selective COX-2 inhibitors, like other NSAIDs, inhibit cyclooxygenase-2. However, unlike other NSAIDs, they do **not** inhibit cyclooxygenase-1. As of 2020, the only FDA-approved COX-2 inhibitor available in the U.S. is celecoxib, which is approved for treatment of RA, OA, ankylosing spondylitis, and acute pain (and adjunctive for familial adenomatous polyposis).

The antiinflammatory effects of COX-2 inhibitors are comparable to other NSAIDs, with possibly reduced GI irritation and ulcer development.

Other benefits of selective COX-2 inhibitors:

- No effect on platelet function, so bleeding time is unchanged
- Less risk of bleeding in anticoagulated patients
- Less likely than other NSAIDs to precipitate bronchoconstriction in patients with aspirin-induced asthma

The **problem** with **all NSAIDs** (including selective COX-2 inhibitors) is that they increase the risk for adverse cardiac events such as MI, stroke, heart failure, and sudden cardiac death in some patient groups. **Do not use NSAIDs** in patients with a recent history of **MI** or coronary artery bypass graft (**CABG**).

Additionally, patients who are allergic to sulfa appear to have a high risk of rash with COX-2 inhibitors.

Know these important drug interactions: NSAIDs and **lithium** have common excretory pathways; therefore,

check lithium levels periodically if a patient is receiving both medications. ASA slows the breakdown of **oral hypoglycemics**; decrease dosage of these when given with ASA.

Synthetic DMARDs

General Characteristics

Synthetic DMARDs (sDMARDs) are the **foundation of RA treatment**. They are chemicals and are not derived from human or animal cells/proteins. In the 1940s, the only available sDMARDs were gold, penicillamine, and sulfasalazine (SSZ). These drugs helped, but gold and penicillamine caused a lot of side effects. Only SSZ remains in frequent use because newer sDMARDs, along with biologic DMARDs, have been developed, which have fewer side effects and greater efficacy. The following is a list of common sDMARDs used to manage RA and other rheumatic diseases:

- Commonly used:
 - Methotrexate (MTX; preferred initial treatment)
 - Leflunomide (LEF)
 - Hydroxychloroquine (HCQ)
 - Sulfasalazine (SSZ)
 - Tofacitinib
 - Upadacitinib
- Less commonly used:
 - Azathioprine (AZA)
 - Cyclosporine A (CYA)
 - Cyclophosphamide (CYP)
 - Mycophenolate mofetil (MMF)

Only the most commonly prescribed sDMARDs recommended by the 2015 ACR clinical practice guidelines will be reviewed. See [Table 10-7](#).

Methotrexate (MTX)

MTX is the **preferred initial DMARD** given for RA. It works by inhibiting dihydrofolate reductase, an important enzyme in folate metabolism. **Because it has the**

Table 10-7: Synthetic Disease Modifying Antirheumatic Drugs (sDMARDs)

Drug	Class	Approved Use	Side Effects
Methotrexate	Antimetabolite	RA, P, SLE, Crohn disease/UC, lymphomas	Pneumonitis, cytopenias, abnormal LFTs, infections, reactivation of hepatitis B, mucosal ulcers, intestinal perforation
Leflunomide	Antimetabolite	RA	Pneumonitis, hepatotoxicity, cytopenias, infections, GI
Hydroxychloroquine	Antimalarial	RA, SLE	Retinal toxicity, neuromyopathy, hyperpigmentation, hypoglycemia
Sulfasalazine	Antibiotic/ Antiinflammatory	RA, AS, Crohn disease/ UC	Cytopenias (check G6PD before prescribing), abnormal LFTs, oligospermia (reversible with discontinuation)
Tofacitinib Upadacitinib	Small-molecule JAK inhibitor	Refractory RA	Infections (particularly shingles), hyperlipidemia, cytopenias, TB reactivation, abnormal LFTs

AS = ankylosing spondylitis
G6PD = glucose 6 phosphate dehydrogenase
JAK = Janus kinase
LFTs = liver function tests
MTX = methotrexate

P = psoriasis/psoriatic arthritis
RA = rheumatoid arthritis
SLE = systemic lupus erythematosus
TB = tuberculosis
UC = ulcerative colitis

most **predictable** benefit and is usually **well tolerated**, the 2015 ACR updated clinical practice guidelines recommend methotrexate (MTX) as the initial DMARD for patients with moderate-to-severe RA without poor prognostic features. The ACR recommends MTX as the main DMARD when combination therapy is used in those with poor prognostic features. Some patients begin to improve within 6 weeks. MTX is administered orally, subcutaneously, or intramuscularly 1×/week and often is combined with other agents to maximize disease control. Contraindications to using MTX include pregnancy, moderate-to-advanced renal disease, chronic liver disease, heavy alcohol use, and parenchymal lung disease (relative contraindication).

MTX is an abortifacient (and has been used explicitly for this purpose), which emphasizes the importance of:

- Pregnancy counseling/pregnancy testing prior to initiating therapy
- Ensuring women of child-bearing age are using adequate birth control if sexually active
- Stopping therapy immediately if pregnancy is suspected

Female patients should be **off MTX for at least 1 ovulatory cycle, preferably 3 months** before attempting pregnancy; male patients should be off MTX for at least **3 months** before attempting to get their partners pregnant.

Common side effects and complications of MTX include:

- Alopecia
- Gastrointestinal (e.g., nausea, vomiting, diarrhea, mucositis)
- Bone marrow suppression leading to **pancytopenia, even at low doses**
- Increased liver transaminases (AST/ALT)
- Skin nodules (It can be difficult to distinguish these from RA nodules; they are diagnosed when MTX is withheld and nodules improve.)

Other serious, but **less common**, reactions include:

- Increased susceptibility to opportunistic infections
- Severe hepatotoxicity (follow AST/ALT)
- Nephrotoxicity (follow creatinine)
- Pneumonitis/Pulmonary fibrosis

Methotrexate pneumonitis is **not dose related** and usually occurs within the 1st year of therapy. Clinical presentation is variable but is typically a **subacute** presentation with a nonproductive cough, dyspnea, and fever. Imaging may reveal:

- diffuse interstitial infiltration on chest x-ray (CXR), **or**
- diffuse ground-glass opacities with traction bronchiectasis, **and/or**
- ill-defined centrilobular nodulosis on high resolution computed tomography (HRCT).

Often, bronchoscopy with bronchoalveolar lavage (BAL) is necessary to rule out infections, which also mimic the presentation of methotrexate pneumonitis. Order **pulmonary**

function tests in patients with symptoms of dyspnea or a history of COPD—pay attention to a low carbon monoxide diffusing capacity (DLCO), which can indicate interstitial lung disease or fibrosis.

Treatment includes immediately stopping the MTX, along with a tapering dose of glucocorticoid. Patients usually respond **very well** to this therapy and improve within days to weeks.

Before prescribing MTX, order CXR and baseline labs (e.g., CBC, CRP, ESR, comprehensive metabolic profile [CMP], viral hepatitis B and hepatitis C serologies). Monitor patients receiving MTX regularly. The ACR guidelines recommend a CBC and CMP every 4 weeks for the first 3 months of therapy, then every 12 weeks thereafter. Monitor labs more frequently if clinically indicated.

Monitoring renal function is important because most of MTX is excreted unchanged in the urine. Chronic renal disease from any cause leads to accumulation of the drug and increased toxicity. While patients are on therapy, ask them about relevant symptoms (e.g., nausea, abdominal pain, cough, shortness of breath, fever) to ensure there is no toxicity. Consider adjusting the dose of MTX in patients with chronic renal disease. Also, certain drugs may inhibit renal excretion of MTX (e.g., penicillin, sulfa antibiotics); therefore, hold or reduce the MTX dose while patients are receiving these antibiotics.

Folate supplementation, known as **leucovorin rescue**, reduces the risk for MTX side effects, including bone marrow suppression, pneumonitis, elevated LFTs, and oral ulcers. Note that coadministration of sulfa drugs, which are antifolate agents (e.g., trimethoprim/sulfamethoxazole [TMP/SMX]), increases the risk of these side effects.

Leflunomide (LEF)

LEF is another DMARD approved for treating RA. It is a pyrimidine antagonist and is used as an **alternative DMARD** in patients **unable to take MTX**.

Side effects of LEF are very similar to MTX. **Hepatotoxicity** is 1 **major side effect**. Avoid prescribing the drug in patients with preexisting liver disease. Diarrhea, alopecia, weight loss, cytopenias, renal dysfunction, interstitial lung disease, peripheral neuropathy, and infections are other possible side effects.

For patients on LEF, order the same baseline screening labs and monitoring tests as MTX.

Important: LEF has an extremely long half-life and is **teratogenic**. LEF is contraindicated in pregnancy and unsafe for lactation; therefore, screen for pregnancy prior to initiating therapy in women of child-bearing age. For women contemplating pregnancy, discontinue the drug and treat the patient with cholestyramine 8 g PO tid for 11 days to eliminate the drug. Verify leflunomide plasma levels are < 0.02 mg/L (0.02 µg/mL) by two separate tests at least 14 days apart. If plasma levels are > 0.02 mg/L (0.02 µg/mL), more cholestyramine treatment is needed.

Hydroxychloroquine (HCQ)

HCQ is used for mild RA disease activity (and is commonly used for systemic lupus erythematosus [SLE]). It is **safe in pregnancy**. The main side effect of HCQ is **retinopathy**. The usual risk is considered to be 1/5,000 patients after prolonged use. If renal or hepatic dysfunction occurs, the risk of retinopathy rises greatly. Patients started on HCQ need a baseline ophthalmologic evaluation to serve as a reference point and to evaluate for existing retinopathy. The 2016 American Academy of Ophthalmology guidelines recommend annual exams in an average-risk patient after 5 years of continuous HCQ use. If a patient has risk factors, screen annually after the baseline eye exam.

Risk factors for HCQ retinal toxicity include:

- > 60 years of age
- Doses > 400 mg/day or > 5 mg/kg/day actual body weight
- Medication use > 5 years
- Use of tamoxifen
- Underlying retinal disease or maculopathy
- Renal or hepatic dysfunction

Routine CBC and CMP should be obtained every 3–6 months.

HCQ can cause **hypoglycemia by increasing insulin levels**, which in diabetic patients may require adjustments to their diabetic regimens.

Less common, but recognized side effects include neuro-myopathy and skin hyperpigmentation.

Tobacco use reduces the efficacy of HCQ.

Sulfasalazine (SSZ)

SSZ is typically used in combination with another DMARD. SSZ also is used to treat inflammatory bowel disease (IBD). In RA, the **sulfapyridine** portion of the molecule produces effects; in IBD, the 5-amino salicylic acid (5-ASA or mesalamine) portion is the effective component. The most common side effects are sulfa-allergic reactions (rash), nausea, vomiting, diarrhea, and abdominal pain. SSZ causes a reversible oligospermia in 80% of male patients. SSZ has no effect on female reproduction, but it does inhibit the absorption and metabolism of folic acid. Give pregnant patients on SSZ supplemental folic acid. Cytopenias and abnormal liver tests do occur; monitor with periodic CBC and LFTs. The 5-ASA component can cause Reye syndrome in patients vaccinated with the varicella vaccine (because it is a live virus vaccine). Check G6PD levels in patients at increased risk for G6PD deficiency (e.g., African descent males, Mediterranean descent males).

Tofacitinib and Upadacitinib

Newer RA therapies are focused on medications inhibiting intracellular signaling involved in T-cell activation,

proinflammatory cytokine production, and cytokine signaling. Tofacitinib was the 1st oral small-molecule inhibitor to be approved for RA. It is also referred to as a JAK-3 inhibitor because it works by inhibiting Janus protein kinases-3 (JAK-3), which is important in the JAK/STAT signaling pathway. Later, it was found also to inhibit JAK-1 (but the reference to JAK-3 remains). Tofacitinib has good efficacy for treating RA, including patients who have already failed synthetic and biologic DMARDs. Side effects to know about this drug: significantly increased risk for shingles, hyperlipidemia, and cytopenias (e.g., leukopenia, neutropenia, anemia). One way to remember the side effect of anemia is to recall that other JAK inhibitors, such as ruxolitinib, are being used to treat polycythemia vera.

In 2019, the FDA approved upadacitinib, a 2nd generation JAK-1 selective oral medication, for use in RA.

Biologic DMARDs

See [Table 10-8](#) for a synopsis of the biologic DMARDs currently FDA-approved for RA and other inflammatory diseases. Biologic DMARDs are made with animal, microbial, or human “biological” proteins, in contrast to synthetic DMARDs, which are made from chemicals. The biologics have opened a new era in RA treatment because they are **highly selective** in their targets, yielding better efficacy with improved response profiles. They are designed to inhibit specific components of the immune system that regulate inflammation. Biologics also have a role in the treatment of many other immune-mediated inflammatory illnesses aside from RA. They are categorized as those that inhibit tumor necrosis factor (**anti-TNF**; TNFi) or those that target other pivotal sites in the immune system that trigger inflammation, known as **non-TNF** biologics.

There is an organization called International Nonproprietary Names (INN) that names generic drugs and they determined some initial rules on naming biologic drugs. Up until recently, any drug that ends with -mab is a **monoclonal antibody** and, of these, any drug that ends with:

- -ximab is a chimeric antibody (part mouse, part human; Fc or more replaced with human proteins),
- -zumab is a humanized animal antibody (virtually all the antibody is human except for parts of the variable region that bind to the antigen bin), and
- -mumab is a fully human antibody.

Additionally, they added a 2–3 letter infix to just before the above suffix to specify the target of the drug researchers had in mind during development. But know that in 2017 the INN decided to no longer add suffixes on the names of biologic drugs that refer to the source of antibody. They will keep the target infix though. Examples of target infixes are:

- -ci- for circulatory system
- -li- for immune system

Table 10-8: Biologic Disease Modifying Antirheumatic Drugs (DMARDs)

Drug	Class	Approved Use	Side Effects
Infliximab Adalimumab Golimumab Certolizumab pegol 1	TNF inhibitors RA, P, AS	RA, P, AS, Crohn disease/ UC	Infections (shingles is common) Malignancies (lymphomas, skin cancers) Drug-induced lupus Possible exacerbation of PML Reactivation of TB and/or hepatitis B, hepatitis C Heart failure Infusion/injection site reactions Demyelinating neuropathies such as MS and CIDP
Tocilizumab Sarilumab	IL-6 antagonist	Refractory RA	Infections, hyperlipidemia, cytopenias Diverticulitis/GI perforation Infusion reactions, abnormal LFTs, drug interactions (increase cytochrome p450 activity and decrease effectiveness of CYP3A4 substrate drugs, such as oral contraceptives, atorvastatin)
Anakinra	IL-1 antagonist	Refractory RA, CAPS	Infections (Do not combine with TNFi.) Neutropenia, injection site reaction
Rituximab	Monoclonal Ab to CD20 surface Ig	Refractory RA (with MTX), NHL, CLL, GPA, MPA	Serious infections (including PML) Infusion reactions (Stevens-Johnson, TEN) Severe mucocutaneous reactions Hepatitis B reactivation
Abatacept	CTLA-4/Co- stimulation inhibitor	Refractory RA	COPD exacerbation Infections (Avoid combining with TNFi due to increased risk for infection.)

MTX = methotrexate

NHL = non-Hodgkin lymphoma

P = psoriasis/psoriatic arthritis

PML = progressive multifocal leukoencephalopathy

RA = rheumatoid arthritis

SLE = systemic lupus erythematosus

TB = tuberculosis

TEN = toxic epidermal necrolysis

TNFi = tumor necrosis factor inhibitor

UC = ulcerative colitis

- -ne- for nervous system
- -de- for endocrine
- -fu- for fungus
- -ba- for bacteria

Note: Biologic DMARDs have an FDA **black box warning** label due to serious adverse effects, such as opportunistic infections, progressive multifocal leukoencephalopathy (PML), reactivation of tuberculosis, hepatitis B and hepatitis C, and increased risk of malignancies such as lymphoma. Also, **never** combine 2 biologics together due to the higher risk of severe infections.

Anti-TNF Biologics (a.k.a. TNF- α Inhibitors)

Infliximab, **adalimumab**, **certolizumab**, and **golimumab** are monoclonal antibodies that bind and inactivate tumor necrosis factor (TNF- α), an important mediator of the inflammatory response in RA. **Etanercept** is a soluble TNF receptor that is linked to IgG1 and also binds and inactivates TNF. TNF agents may cause a greater risk for infections (e.g., tuberculosis, herpes zoster, pneumonia). The TNF inhibitor (TNFi) drugs are approved for a variety of indications, including RA, psoriasis, psoriatic arthritis, ankylosing spondylitis, and inflammatory bowel disease.

For RA, these agents are most beneficial when **combined with MTX** and have been shown to halt and possibly heal erosive damage.

TNF inhibitors can cause drug-induced lupus. Other side effects include injection site/infusion reactions, infections, CNS demyelination, and worsening heart failure (HF). They are not recommended for patients with New York Heart Association (NYHA) Class III/IV heart failure and an ejection fraction $\leq 50\%$ because they **may worsen HF** symptoms and increase morbidity.

The impact of TNF inhibitors on the development and course of malignancies is not completely understood. A large-scale review of RA registry data did **not** find an increased risk for lymphoma or solid tumors in patients on TNF inhibitors; however, risk for **nonmelanomatous** skin cancer is increased in patients receiving TNFi compared to those receiving conventional sDMARDs. One exception to this: TNFi + thiopurine (e.g., azathioprine) = increased risk for hepatosplenic T-cell lymphoma (especially in children with IBD requiring these drugs).

Non-TNF Biologic DMARDs

Tocilizumab is an interleukin-6 (IL-6) antagonist and is indicated for patients who are refractory to traditional DMARDs and/or TNF inhibitors. Side effects include bone marrow suppression, GI perforations and diverticulitis, renal/liver toxicity, hyperlipidemia, and infections.

Tocilizumab decreases the efficiency of oral contraceptives. Give patients receiving tocilizumab an alternative means of birth control.

Anakinra (an **IL-1** antagonist) is used for RA disease refractory to MTX. However, it is anecdotally much less effective than other biologic DMARDs and requires a daily injection, so it is prescribed infrequently to treat RA.

Rituximab is an **anti-CD20** antibody directed against **B cells**, believed to play a role in antigen presentation and production of autoantibodies and inflammatory cytokines. It is **used in combination with MTX** to treat RA in patients who are refractory to TNF inhibitors. Serious side effects include toxic epidermal necrolysis (TEN), tumor lysis syndrome, and serious infusion reactions (e.g., hypotension, bronchospasm, acute respiratory distress syndrome, myocardial infarction). In addition, there have been case reports of PML associated with rituximab; suspect this in a patient who had received rituximab with new-onset central nervous system conditions such as ataxia, confusion, or slurred speech with an abnormal MRI.

Abatacept is a selective **T-cell** costimulation inhibitor. In head-to-head trials, its efficacy is comparable to the TNF inhibitors with a favorable safety profile. There is a precaution that this drug may exacerbate COPD.

Non-TNF biologics have a similar risk of infections as other biologic therapies. As a general rule, do not administer biologic therapies to patients with suspected serious infections or anticipated major surgery (typically 2–4 weeks prior to surgery depending on the half-life of the drug). Infections range from mild (e.g., upper respiratory tract viral infection) to very serious and life-threatening (e.g., pneumonia, sepsis, reactivation of hepatitis B, tuberculosis, fungal and other opportunistic infections). The following are tips to minimize the risk of infection in patients receiving biologic DMARDs:

- Screen for hepatitis B, hepatitis C, and tuberculosis prior to initiating therapy.
- Vaccinate patients with flu vaccine, pneumonia, and other vaccines per 2013 Infectious Diseases Society of America (IDSA) guidelines for the immunosuppressed.
- Avoid live attenuated vaccines.
- Suspend biologic therapy during the perioperative period for anticipated major surgery.

Know: Avoid live attenuated vaccines in patients on biologics, prednisone > 20 mg/day, MTX > 25 mg/week, and azathioprine > 3 mg/kg/day per the 2017 CDC Advisory Committee on Immunization Practices (ACIP) guidelines. The live vaccines most relevant to clinical practice are MMR, varicella, and attenuated zoster (Zostavax) vaccines. There is an inactivated recombinant shingles vaccine (Shingrix) which is safe for patients on immunosuppressive therapy.

Other Immunosuppressants

Azathioprine (AZA)

AZA has shown benefit for RA but is much more commonly used in **systemic lupus erythematosus** and **inflammatory bowel disease**. The drug's main side effects include bone marrow suppression, N/V, diarrhea, and hepatotoxicity.

It is important to understand AZA's metabolism. It is 1st metabolized to 6-mercaptopurine (6-MP) by the liver. AZA and 6-MP are inactive prodrugs. 6-MP is then metabolized by 3 different pathways into 3 active metabolites:

- 1) Thiopurine methyltransferase (**TPMT**) converts 6-MP to 6-methylmercaptopurine (**6-MMP**). It is the main metabolic pathway for 6-MP. This enzyme is defective in 11% of the population! The FDA recommends screening for genetic TPMT deficiency prior to starting AZA.
- 2) Hypoxanthine phosphoribosyltransferase (**HPRT**) starts the conversion of 6-MP to 6-thioguanineanthine (**6-TG**).
- 3) Xanthine oxidase (**XO**) converts 6-MP to 6-thiouric acid (**6-TU**).

Bone marrow suppression from high **6-TG** levels can occur in patients on AZA and who either have defective TPMT or take a xanthine oxidase inhibitor (e.g., allopurinol, febuxostat). In patients on an XO, decrease the dose of AZA by at least 1/2 and monitor CBCs and LFTs closely.

Hepatotoxicity from high **6-MMP** levels can occur if patients on AZA have decreased effectiveness of HPRT.

Cyclosporine A (CYA)

CYA is a calcineurin inhibitor. It works by inhibiting T-cell production of IL-2. It is beneficial for inflammatory joint, skin, and eye conditions. CYA exerts synergistic effects when added to MTX.

CYA side effects include **renal toxicity** and hypertension. Monitor creatinine and blood pressure closely.

CYA has several drug interactions with medications such as HIV protease inhibitors, statins, and colchicine.

Cyclophosphamide (CYP)

CYP is an alkylating agent. It works by disrupting DNA replication; hence, it is useful in treating malignancies and aggressive autoimmune diseases such as vasculitis, lupus nephritis, and severe rheumatoid disease. However, the toxicity of the drug limits its use. Risks for secondary malignancies, infertility, infections, and bone marrow suppression are associated with the drug.

Minocycline and Doxycycline

These drugs are **not FDA-approved for RA**. They have demonstrated efficacy as DMARDs in some patients with

early disease or low disease activity. These drugs work by inhibiting metalloproteinases. With newer therapies for RA available, these agents are not used frequently. Additionally, they are both teratogenic and are contraindicated in women who are pregnant or who plan to become pregnant.

Glucocorticoids

Low-dose oral prednisone (≤ 10 mg/day or equivalent) and joint injections of glucocorticoids are useful for relieving symptoms of RA. Data suggest that systemic glucocorticoids have disease-modifying properties (e.g., prevent joint damage), but standard practice is to use as little as possible for the shortest duration to prevent long-term side effects of which there are many. Side effects may include weight gain, infection, osteoporosis, easy bruising, adrenal insufficiency, diabetes mellitus, peripheral edema, hypertension, and insomnia. As the DMARDs are started and the inflammatory arthritis improves, glucocorticoids are tapered off slowly.

Perioperative Considerations

Many patients with rheumatic diseases require surgery at some point in their lives. Therefore, knowing what to do with their medications, before and after surgery, is crucial for mitigating infection and avoiding complications.

In 2017, the ACR established **guidelines for the perioperative management** of antirheumatic medications in patients with rheumatic diseases undergoing an elective procedure. Note that rheumatic patients with total hip arthroplasty and total knee arthroplasty are at increased risk for prosthetic joint infections.

Summary of recommendations:

- 1) DMARDs: Continue these medications through surgery.
- 2) Biologics: Stop medications prior to surgery and schedule the surgery at the end of the dosing cycle. Resume medications at 14 days if no postoperative complications have occurred.
- 3) For SLE: Adjustment of medications depends on the severity of lupus at the time of surgery.

Pregnancy Considerations

Balancing the risks of medication given during pregnancy with the risks of not treating active inflammation is a delicate task.

Note:

- The majority of organogenesis occurs in the 1st trimester.
- Active inflammation in the mother creates a hostile environment for the fetus.

The following are general recommendations for managing pregnant women who have active inflammatory arthritis:

- HCQ and SSZ are safe during pregnancy. Both have been used safely in breastfeeding mothers, but a few reports of bloody stools or diarrhea in infants whose mothers are on SSZ have arisen. Make sure the pregnant patient is taking folic acid while on SSZ.
- TNF inhibitors are generally considered safe in pregnancy. Consider stopping TNF inhibitors at 30 weeks of gestation due to risk for infection and placental transfer of the drug. Interestingly, certolizumab (a pegylated TNFi) has lower rates of placental transfer due to its size as a result of the pegylation.
- Minimize use of steroids during pregnancy due to risk for cleft palate, premature rupture of membranes, low birth weight, endometritis, chorioamnionitis, and early-onset neonatal sepsis. If required, prednisone < 10 mg/day is used for short durations.
- Azathioprine and cyclosporine A also are used in pregnancy.
- Avoid methotrexate, leflunomide, and cyclophosphamide.
- NSAIDs may be used during the 1st and 2nd trimesters of pregnancy (avoid NSAIDs during the 3rd trimester due to risk for premature closure of the ductus arteriosus).
- The effects of non-TNF biologics (e.g., tocilizumab, abatacept, rituximab) and small molecule DMARDs on pregnancy are not fully known.

SYSTEMIC LUPUS ERYTHEMATOSUS (SLE)

PREVIEW | REVIEW

- Characterize the pattern of arthritis in systemic lupus erythematosus (SLE).
- What are the patterns of skin rashes in SLE?
- A patient with SLE presents to the emergency department with chest pain. What are the most likely etiologies?
- Which autoantibody is associated with the development of glomerulonephritis?
- Which classifications of SLE kidney disease require treatment with cytotoxics?
- What hematologic abnormalities are seen in SLE?
- What are potential complications of chronic corticosteroid treatment in patients with SLE?
- A pregnant woman with SLE has SSA (Ro) and SSB (La) antibodies. What abnormality can occur in her fetus?
- How do you tell the difference between pre-eclampsia in a pregnant lupus patient vs. lupus glomerulonephritis?

- Which drugs classically cause drug-induced lupus (DIL)?
- Which autoantibodies are usually present and absent in DIL?

MANIFESTATIONS

SLE is the prototypic autoimmune disease. It ranges from mild rash, arthritis, and fatigue to severe, life-threatening manifestations (i.e., renal, pulmonary, CNS). SLE primarily affects women of childbearing age. Prognosis is worse in males, African Americans, Asians, and Hispanics. Virtually any organ system is affected.

Joints

Lupus arthritis is inflammatory and nonerosive. Presentation of arthritis is any of the following:

- Symmetrical or asymmetrical
- Oligoarticular or polyarticular
- Affecting large and/or small joints

If deformities occur, the most common is **Jaccoud arthropathy**. The deformities appear like boutonnière deformities of rheumatoid arthritis (RA); however, with SLE, these deformities are easily reducible (hands look normal when you stretch out the joints; RA hands do not yield to pressure). In addition, x-rays of the hand do not show bony erosions. Note that some SLE patients may have concomitant RA (lupus-RA overlap, a.k.a. “rhupus”); in these cases, severe joint deformities, nodules, and erosions may occur.

Skin and Mucous Membranes

All lupus rashes are photosensitive and can occur even when the weather is cloudy.

Classification of lupus rashes:

- Chronic cutaneous lupus erythematosus (**CCLE**), i.e., discoid lupus erythematosus (**DLE**): Hyperpigmented edges may be raised; frequently causes central scarring/atrophy with destruction of melanocytes and hair follicles (**Figure 10-3**). This skin finding may be present in **SLE** as well as the variant skin entity of DLE. Individuals with DLE have only a 5% chance of developing SLE and typically have a milder disease course devoid of significant renal manifestations.
- Acute cutaneous lupus erythematosus (**ACLE**) and **SLE**: erythematous, concentrated on sun-exposed areas—malar rash (“butterfly”) that spares nasolabial fold; (**Figure 10-4**)—forehead, upper chest, neck, ears, upper extremities, and back that flares with systemic disease
- Subacute cutaneous lupus erythematosus (**SCLE**): annular rash. This rash can be seen with Sjögren syndrome as well; patients can have negative ANAs with +Ro/La. Certain medications may bring out this rash, including calcium channel blockers.
- Other rashes: tumid lupus, chilblains lupus, urticaria, vesicles, lichen planus



Figure 10-3: Discoid rash with discoid lupus erythematosus (DLE)

Source: Seth Berney, MD



Figure 10-4: Malar rash of acute cutaneous lupus erythematosus (ACLE)

Alopecia is common, typically nonscarring, and presents as patches of hair loss or diffuse hair loss.

Aphthous (mucosal) ulcers are usually painless and can occur in the nasal passage as well as the oropharynx.

Lung

Lung disease in lupus manifests as pleuritic chest pain +/- effusion (most common), alveolar infiltrates, pneumonitis (with subsequent fibrosis and pulmonary arterial hypertension), or as alveolar hemorrhage—a medical emergency that carries a 50% mortality rate!

Heart

The Framingham Offspring Study revealed that **women 35–44 years of age with SLE have a 50-fold increase in myocardial infarctions (MI)**. Premature coronary artery disease (CAD) is thought to be due to chronic inflammation and steroid use, both of which accelerate atherosclerosis.

Other cardiac involvement found in SLE patients includes pericarditis (most common), myocarditis, and **Libman-Sacks** endocarditis (sterile fibro-fibrinous vegetations that mimic infectious endocarditis and are commonly associated with antiphospholipid antibodies). CAD is the most common cause of death

in patients with SLE. Remember: In a patient with lupus who presents to the ED with chest pain, the top differential diagnoses include MI, pericarditis, pleuritis, and pulmonary embolism.

Kidney

Glomerulonephritis is a major cause of morbidity and mortality in SLE patients. The presence of anti-dsDNA antibodies is associated with glomerulonephritis and the nephrotic syndrome. For additional information on lupus nephritis, refer to the [Nephrology](#) section.

African Americans with lupus are more likely than Caucasians to develop aggressive renal disease. Once lupus nephritis develops, lifetime recurrences are likely.

Lupus renal disease is heralded by an active urine sediment: **proteinuria** (usually > 500 mg/day or nephrotic > 3.5 g) and microscopic **hematuria**. Always perform a urinalysis on any patient whom you suspect has SLE, even if a serum creatinine is normal.

Kidney disease is staged by the International Society of Nephrology (ISN) and the Renal Pathology Society (RPS). This replaced the World Health Organization (WHO) classification system. These classifications organize renal disease according to chronicity and activity level. Although the classification system focuses on glomerular disease, know that systemic lupus also affects the tubules and vasculature.

ISN/RPS classification/treatment of glomerulonephritis in SLE:

- **Class 1:** minimal mesangial (no immunosuppressive treatment)
- **Class 2:** mesangial proliferative (no immunosuppressive treatment)
- **Class 3:** focal proliferative; < 50% of glomeruli (**glucocorticoids** and **cytotoxic drugs**)
- **Class 4:** diffuse proliferative; ≥ 50% of glomeruli (**glucocorticoids** and **cytotoxic drugs**)
- **Class 5:** membranous (**glucocorticoids**, **cytotoxic drugs**, and angiotensin-converting enzyme [ACE] inhibitor or angiotensin receptor blocker [ARB] to decrease proteinuria)
- **Class 6:** advanced sclerotic; ≥ 90% sclerotic glomeruli (no treatment; disease irreversible)

Combinations of the above stages can occur. The letters A and C also are listed as subcategories to reflect whether the changes are “active” or “chronic.” Chronic renal changes correlate with a poor response to treatment and worse prognosis.

Important: Treat Class 3 and 4 diseases aggressively with **cytotoxic drugs** (cyclophosphamide versus mycophenolate mofetil) and glucocorticoids to prevent end-stage kidney disease, which develops within 2 years in untreated patients. Other medications used to manage lupus nephritis include calcineurin inhibitors (e.g., tacrolimus, cyclosporine), azathioprine, and rituximab.

Prescribe ACEIs or ARBs for any proteinuria near or > 500 mg/day. The goal blood pressure to minimize kidney damage is < 130/80 mmHg.

Note: Membranous nephropathy often is associated with nephrotic syndrome, hyperlipidemia, and thrombophlebitis as a complication. Consider anticoagulation and statins in these patients.

Blood

Immune mediated cytopenias are common and include leukopenia (specifically lymphopenia), thrombocytopenia, and hemolytic anemia. Know that headache + thrombocytopenia + microangiopathic hemolytic anemia + acute kidney injury in a SLE patient suggests thrombotic thrombocytopenic purpura (TTP). Mortality is high if unrecognized and untreated! Plasmapheresis is indicated. See more about TTP in the [Hematology](#) section.

Neurologic Issues

Neuropsychiatric lupus encompasses cognitive/behavioral changes (most common), headaches, psychosis, mood changes (e.g., depression), aseptic meningitis, cerebritis/encephalitis, organic brain syndrome, seizures, chorea, and strokes. Even severe abnormalities may clear rapidly with aggressive management. Cerebrospinal fluid **may** be normal, despite severe symptoms; **but** elevated protein or WBCs (mostly lymphocytes) are usually seen in patients with cerebritis. MRI of the brain may show scattered areas of increased signal intensity, suggesting a vasculopathy or vasculitis. Evaluate all neuropsychiatric lupus patients for infection, including lumbar puncture, particularly if immunosuppressed. Inflammatory markers may be helpful in distinguishing infection when very elevated (e.g., ESR > 100 mm/hour). Know that **anti-Smith**, **anti-neuronal**, and **antiribosomal P protein** antibodies are associated with CNS disease. Neuropsychiatric testing is useful for following improvement or decline in neurocognition.

DIAGNOSIS

The American College of Rheumatology (ACR) SLE classification criteria were validated in 2012 when the Systemic Lupus International Collaborations Clinics (SLICC) developed lupus criteria. For the purposes of this review, only the ACR criteria will be discussed in detail. Remember: Classification criteria are designed to enroll a homogenous patient population into clinical trials. They are not diagnostic criteria; however, they are a helpful guide to aid in diagnosis.

The following are the ACR diagnostic criteria in SLE presented in the **SOAP BRAIN MD** mnemonic. ≥ 4 of the following meets criteria:

- Serositis: pleuritis, pericarditis
- Oral ulcers: usually painless

- Arthritis: nonerosive
- Photosensitivity
- Blood disorders: 1 or all blood lines suppressed (pancytopenias), hemolytic anemia
- Renal disease: proteinuria, RBC casts (Biopsy-proven lupus nephritis with a +ANA meets criteria even with no other symptoms present.)
- Antinuclear antibodies
- Immunologic phenomena (e.g., +anti-dsDNA; anti-Smith [Sm] antibodies, anticardiolipin [ACL] antibodies)
- Neurologic disorder: seizure or psychosis
- Malar rash
- Discoid rash

The ANA is the **most sensitive** test for SLE (99% of patients with active disease have a positive test); however, it has **very poor** specificity. There are some cases of ANA-negative lupus, but they are rare.

The serum CH50 is a useful screening tool because it tests all complement components (C1–C9) and can be helpful in working up “ANA-negative” lupus patients. The drawback with CH50 is that individual complement components can be decreased 50–80% and CH50 can still be normal.

Some (but not all) SLE patients have decreased complement components during disease flares, especially C3 and C4. Many rheumatologists follow C3 and C4 levels if it has been determined that they reflect disease activity. As mentioned previously in the lab discussion (see [Complement System on page 10-4](#)), it is important always to trend the serum complement levels over time to determine whether C3 and/or C4 levels are reliable markers of disease activity for the patient.

Anti-dsDNA and anti-Sm in high titers are **very specific** for SLE, but they have low sensitivity. Be careful as you are with using the C3 and C4 as markers for disease activity and remember that not all SLE patients are positive for dsDNA antibodies. However, if the dsDNA or Sm antibody titers trend with disease activity, then these can be useful to follow. Never check anti-single-stranded DNA. The ESR and CRP are markers of inflammation; these are nonspecific and may be normal even in the setting of very active lupus activity.

In summary, while working up a case of possible SLE, 1st do an ANA. If negative, SLE is almost always excluded. If the ANA is positive, and there are clinical symptoms (e.g., arthritis, nephritis, serositis) of disease, proceed with further testing. This includes antibodies for anti-dsDNA, anti-Smith, anti-SSA/SSB, antiphospholipid antibodies, lupus anticoagulant, and serum C3 and C4 levels.

PROGNOSIS

10-year survival of SLE is ~ 90% if patients receive optimal treatment. **Elevated anti-dsDNA** and **low complement**

levels indicate **worse prognosis**, with increased risk for nephritis. Patients with SLE are also at higher risk for infections (due to immunosuppression), malignancy (especially lymphoid), osteoporosis (secondary to glucocorticoids), premature death from CAD (from disease inflammation and glucocorticoids), and thrombotic events due to antiphospholipid antibody positivity.

TREATMENT

UV light exposure, tobacco, and stress exacerbate SLE. Avoid surgery during active disease and encourage sunscreen to protect against the ultraviolet-sensitive rash. Note that sunburn releases self-antigens detected by the immune system and triggers a chain reaction to cause a systemic flare! Tell your patients to use at least SPF 30 sunblock and reapply frequently. Strongly encourage tobacco cessation. Tobacco use accelerates and exacerbates lupus disease activity. Tobacco use also decreases the efficacy of hydroxychloroquine (HCQ).

There are 4 drugs approved by the FDA for the treatment of SLE:

- 1) Low-dose aspirin
- 2) Glucocorticoids
- 3) HCQ
- 4) Belimumab

However, many immunosuppressive drugs have been used off-label to manage the disease effectively, including methotrexate (MTX), azathioprine (AZA), mycophenolate mofetil (MMF), and cyclophosphamide (CYP). Because of the varying presentations of the disease, and the fluctuation of disease activity, designing drug studies to meet FDA standards has been challenging.

Treatment of SLE is individualized and focuses specifically on the organ system(s) affected. Place all patients with any degree of disease activity on HCQ (unless contraindicated). Aside from improving joint and skin disease, HCQ has other benefits. Data support the following benefits of HCQ in lupus patients:

- Decreases the risk for disease flares
- Decreases overall morbidity and mortality
- Decreases risk for neonatal lupus and congenital heart block
- Decreases thromboembolic events (e.g., MI, strokes)
- Improves glucose tolerance and insulin resistance

The following is a strategy to manage lupus:

- In **mild** disease affecting skin/joints, use hydroxychloroquine.
- For **moderate** disease activity (e.g., inflammatory arthritis, cutaneous disease, pleuritis), **add** MTX, AZA, leflunomide, belimumab, or MMF.
- In **severe** or life-threatening disease (e.g., lupus nephritis, alveolar hemorrhage, CNS involvement), CYP, MMF, rituximab, IVIG, and plasmapheresis have been used.

A note on belimumab: This drug was approved by the FDA in 2011—the 1st biologic drug approved for SLE in over 40 years! It is an antibody directed against the B-lymphocyte stimulator (BLyS) protein. It decreases the amount of abnormal B cells, which are hypothesized to be a mechanism of action in lupus. The drug is used to treat **mild-to-moderate** lupus activity (e.g., mucocutaneous, musculoskeletal, hematologic manifestations); it is not indicated for severe disease (e.g., renal, neurologic involvement). Like rituximab, belimumab sometimes causes progressive multifocal leukoencephalopathy. It can also cause depression.

Use high-dose glucocorticoids **only** for patients with severe disease and major organ involvement. Fatigue and alopecia may improve as well. Low-dose maintenance corticosteroids (< 10 mg daily or every other day) are required frequently to control symptoms and prevent flares. Remember: Up to 1/3 of SLE patients on chronic glucocorticoids develop avascular necrosis of the hip/knee/humerus! NSAIDs are useful as adjunctive therapy for pain; be careful in patients who have active renal disease because NSAIDs may make worse renal function. Also, avoid NSAIDs in patients on steroids due to risk for GI bleeds.

SLE AND PREGNANCY

Patients with SLE have a higher incidence of failed pregnancies. Pregnancy is not advised until disease has been quiescent for **≥ 6 months**. Risk of pregnancy complications (flares or fetal problems) is much greater if disease is active (especially renal manifestations) or if the mother has **anti-dsDNA** or **antiphospholipid** antibodies.

Women with antiphospholipid syndrome and a history of recurrent miscarriages are treated with heparins (low-molecular-weight or unfractionated) plus low-dose aspirin to decrease the incidence of miscarriage. Patients with antiphospholipid antibodies are also at increased risk for **HELLP** syndrome (a variant of preeclampsia with hemolysis, elevated liver enzymes, and low platelets).

Neonatal lupus: In fetuses/infants of mothers with SLE who have SSA (Ro) and SSB (La) antibodies, these antibodies may cause disease. Manifestations include cutaneous lesions, hepatitis, hematologic abnormalities, hydrocephalus, and congenital heart block, which is a feared complication. The risk for congenital heart block is 1–2% if the mother is Ro/La antibody positive; this risk increases to 15% in subsequent pregnancies. Congenital heart block begins as early as the 2nd trimester (see [Table 10-2 on page 10-3](#)). For these patients, begin serial fetal echocardiograms at ~ 16–18 weeks of gestation. If you detect cardiac abnormalities, systemic steroids (fluorinated steroids such as dexamethasone cross the placenta) may help, but some infants require a pacemaker. Know that the risk for congenital heart block and neonatal lupus is decreased with HCQ.

Measure baseline complement levels, anti-dsDNA, SSA/SSB, and a 24-hour urine protein before or very early in the pregnancy. Manage flares during pregnancy with glucocorticoids. Refer pregnant women with systemic lupus to a high-risk obstetrician (and pediatric cardiologist, if appropriate).

Sometimes, distinguishing a **lupus flare with renal involvement** from **preeclampsia** is difficult because both present with increasing proteinuria, hypertension, lower extremity edema, deterioration in renal function, and thrombocytopenia. With lupus flares, SLE disease activity markers also may be abnormal (high dsDNA Ab titer, low complements), serum uric acid is normal (< 5.5 mg/dL [327.17 μmol/L]), and urine sedimentation may be active (red cell casts, high number of red and white blood cells). These changes are not seen in patients with preeclampsia. Note that in normal pregnancy, complement levels increase.

DRUG-INDUCED LUPUS (DIL)

Drugs with the highest risk for DIL are **procainamide**, **hydralazine**, and penicillamine. Other drugs linked with DIL are chlorpromazine, propylthiouracil, isoniazid, phenytoin, TNF inhibitors, minocycline, selective serotonin reuptake inhibitors, proton pump inhibitors, and thiazide diuretics. Think about DIL in any patient who develops constitutional symptoms (e.g., fever, arthritis), serositis, and/or rash while taking any of the above drugs. DIL can develop at anytime while taking the drug; not only when starting a new drug. ANA is positive and **antihistone antibody** is generally positive (Remember: SLE patients can have antihistone antibodies, too!). In contrast to other types of lupus, C3 and C4 are usually normal, anti-dsDNA is typically negative (with the exception of DIL due to TNF inhibitors), and there is not commonly kidney or CNS involvement.

DIL can be a tough diagnosis to make. Ideally, you find:

- a positive **ANA** with **antihistone** antibodies and
- a history of exposure to 1 of the above **drugs**.

However, some drugs such as minocycline and hydralazine have a positive ANCA instead of antihistone antibody.

Sometimes you confirm the diagnosis only in retrospect by observing complete resolution of symptoms after discontinuing the drug.

Treatment: Symptoms usually **resolve** within 4–8 weeks after stopping the offending agent, but the ANA may remain positive for months to years. NSAIDs and anti-malarials may be useful. Corticosteroids work well; however, they are rarely needed.

SERONEGATIVE SPONDYLOARTHRITIS

PREVIEW | REVIEW

- What are common features of seronegative spondyloarthritides?
- "Sausage-shaped digits" are seen in which arthritides?
- "Bamboo spine" is typically associated with which disease?
- How does a patient with AS present?
- Which organisms are associated with reactive arthritis (ReA)?
- What is the classic triad of findings seen in ReA?
- What are the patterns of arthritis seen with psoriatic arthritis (PsA)? Name some other associated features.
- Which PsA medication has been known to increase suicidal thoughts in PsA patients?
- Which PsA medication has been known to exacerbate overlapping inflammatory bowel disease?
- Acute onset of psoriasis in men having sex with men should make you think of what disease?

OVERVIEW

"Spondylo-" means spine. Seronegative spondyloarthritides are a group of inflammatory spinal arthritides that are negative for both rheumatoid factor and ANA. These arthritides have been categorized as axial or peripheral, depending on which manifestation is primary in the presentation. These include:

- Ankylosing spondylitis (most common)
- Reactive arthritis
- Psoriatic arthritis
- IBD-associated arthropathy

Seronegative spondyloarthritides share some common features (to varying degrees depending on the disease):

- Predilection for the spine and sacroiliac (SI) joints (if plain films are nonspecific or negative, then obtain MRI of SI joints)
- **Enthesitis** (inflammation at the insertion site of a ligament, tendon, or joint capsule)
- Asymmetric, large-joint oligoarthritis, usually of the lower extremities
- Dactylitis ("sausage-shaped digits")
- Circinate balanitis
- Uveitis or iritis
- Bowel inflammation
- Genitourinary (GU) inflammation (i.e., urethritis, balanitis)

- Skin lesions (i.e., keratoderma blennorrhagicum, psoriasis)
- Association with recent GU or GI infections
- Variable association with the human leukocyte antigen (HLA)-B27

Enthesitis on the finger leads to the appearance of dactylitis (**sausage-shaped digits**) common in **reactive** arthritis and **psoriatic** arthritis. Note: The nail bed is also an enthesis; onycholysis (separation of the nail from the nail bed) is also associated with enthesitis in these diseases!

Again, sacroiliitis and thoracolumbar and sacral spine inflammation do **not** occur in rheumatoid arthritis (RA)! **Dactylitis** is common in the spondyloarthropathies; not in RA. When the sausage-shaped digit is combined with pitted nails, the diagnosis is psoriasis!

ANKYLOSING SPONDYLITIS (AS)

Ankylosing means "fusing," while spondylitis means "inflammation of the spine." "Early" ankylosing spondylitis is referred to as nonradiographic axial spondyloarthritis as abnormalities in the SI joints can be found on MRI, but would not be present on x-ray. AS is a systemic disease, which is marked by ascending axial inflammation. If left untreated, it leads to eventual spinal and SI joint fusion resulting in a radiographic "**bamboo spine**" (Figure 10-5). Symptoms and upper body involvement increase with age. Patients have significant morning stiffness/pain that **improves** with activity. **Most adults** with AS have symptomatic painful **sacroiliitis**; however, mild stiffness is the only complaint for some patients.

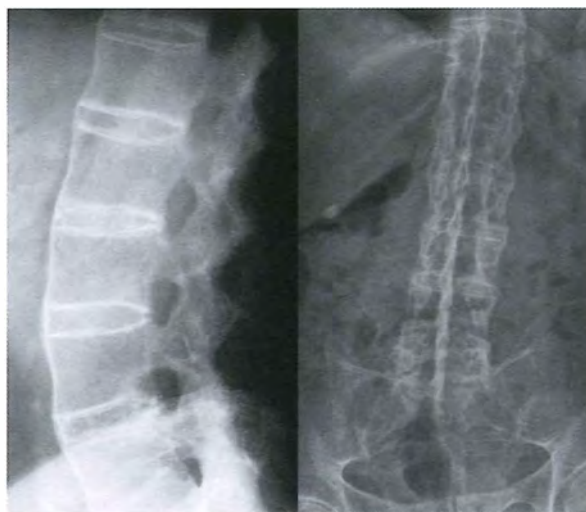


Figure 10-5: Ankylosing spondylitis (bamboo spine)
Source: Seth Berney, MD (left); Steven Fruitsmaak (right)

Usual onset is in young adulthood with a peak age of onset between 20 and 30 years of age. It affects men more than women. Teens eventually diagnosed with AS may present with **lower extremity** large-joint oligoarthritis and have a 90% incidence of **HLA-B27**-positive antibodies.

There is only a 60% occurrence of AS in identical twins, so environmental factors also play a role.

Extraarticular manifestations of AS include:

- Iritis/Uveitis (most common extraarticular manifestation)
- Conjunctivitis
- Ischemic heart disease
- Aortic insufficiency/Aortitis
- Apical pulmonary fibrosis
- IgA nephropathy

Iritis or uveitis may precede sacroiliitis and usually would present as unilateral eye pain, photophobia, and increased lacrimation. Anyone with suspected uveitis should see an ophthalmologist immediately. The uveitis associated with spondyloarthritis is typically an anterior uveitis where most of the inflammation is localized in the anterior chamber of the eye, whereas sarcoidosis can affect any portion of the uvea including anterior, intermediate, posterior, or panuveitis. Conjunctivitis may be mild and bilateral; progressive burning and eye irritation are prominent features. Asymptomatic apical pulmonary fibrosis is a late and rare manifestation. Decreased spinal mobility can cause pulmonary restriction. IgA nephropathy is associated with AS; suspect it in any patient with AS who develops an active urine sediment. Send these patients to a nephrologist for evaluation and a possible renal biopsy.

Diagnosis

Inflammatory back pain has different characteristics than other causes of back pain (e.g., disc disease). First, understand what “regular” mechanical back pain looks like. **Mechanical** back pain is typically characterized by the following:

- The patient often is obese, sedentary, and otherwise out of shape.
- There is a physical trigger. (“Doc, I was lifting this box, and it felt like I **pulled** something.”)
- Pain often is radicular and maximal at onset.
- Pain gets better with rest.
- Red flag and systemic signs are absent—by definition! (See [Low Back Pain on page 10-66](#).)

Classic **inflammatory** back pain is completely different, as follows:

- The patient can be young and otherwise in good shape.
- There is no known physical trigger (except if antecedent infection was present in cases of reactive spondyloarthropathy).
- There is no radicular pain.
- The patient complains principally of **stiffness**, particularly prolonged **morning** stiffness.
- The pain can awaken them at night.
- The pain gets better with physical activity.
- Extraarticular manifestations often are present (if you take a stellar history!).

A helpful clinical tool used in the physical examination of an adult with inflammatory signs of low back pain is the **Schober test**. This test assesses lumbar spinal mobility. Although it is **not** specific for AS (it can be abnormal in patients with degenerative disc disease), it is a sensitive measure in detecting limited spinal mobility. Elevated inflammatory markers (ESR and CRP) also are helpful tools (in conjunction with the history and physical exam—never on their own) to determine the presence and degree of inflammatory arthritis.

Plain radiographic films in AS show a symmetrical form of sacroiliitis. SI joint fusion and ascending spinal calcification resulting in the bamboo spine deformity may be absent for up to 10 years after onset of symptoms. **MRI is more sensitive and shows marrow edema in the bones adjacent to the SI joints**. Regardless, plain radiographic changes often are not seen at the time of diagnosis. The clinical and laboratory evaluations are most important in patients with early symptoms.

HLA-B27 testing is generally done. Because of the high sensitivity (> 90%), a **negative** HLA-B27 test can be useful in excluding AS in patients. Keep in mind, however, that African Americans with AS have a lower incidence of HLA-B27 positivity, so a negative HLA-B27 test does not exclude disease in all patients. HLA-B27 may be positive in reactive arthritides, so it is not specific to AS. See [Table 10-4 on page 10-5](#).

Treatment

Maintaining spinal function and pain control is the goal and in addition to pharmacologic agents, treatment will include stretching exercises, posture training, and **proper pillow positioning during sleep**. (Sometimes, no pillow is best.)

The 2019 Update of the ACR/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network guidelines recommends:

- All patients should be on a regular exercise program.
- NSAIDs are 1st line therapy.
- In patients with disease refractory to NSAIDs, use a TNF inhibitor.
- In those with concomitant iritis or IBD, use a monoclonal TNF inhibitor (in other words, do not use etanercept because it is not beneficial in IBD patients).
- Antiinterleukins can be utilized if other therapies fail or if there is an inadequate response to other therapies.

The antiinterleukins: Secukinumab or ixekizumab (IL-17 inhibitors) and ustekinumab (IL-12/IL-23 inhibitor) are approved for the treatment of AS. Secukinumab also can be used in psoriatic arthritis.

Note also that patients with **peripheral** disease may respond to sulfasalazine and methotrexate (these agents are not helpful for axial disease). If the diagnosis is made early, the prognosis is generally good, but > 20% of patients have progressive, disabling disease.

DIFFUSE IDIOPATHIC SKELETAL HYPEROSTOSIS (DISH)

DISH (a.k.a. Forestier disease) is a condition confused frequently with AS because of its radiographic appearance. It is a **noninflammatory** disease of unknown etiology, which that causes ossification of the ligaments of the spine, as well as peripheral enthesopathy.

Patients also can have peripheral involvement with evidence of hyperostoses on extensor surfaces (large bony extrusions; [Figure 10-6](#)). Patients with DISH are rarely symptomatic; the diagnosis typically is made as an incidental finding. Patients who are symptomatic with back pain symptoms usually are treated with simple analgesics. Furthermore, DISH occurs primarily in men > 50 years of age, does not affect the SI joint, and is **not** associated with **HLA-B27**. Inflammatory markers (ESR and CRP) typically are normal in DISH; they may be elevated in AS. DISH is associated with diabetes mellitus, obesity, and hyperinsulinemia.



Figure 10-6: Diffuse idiopathic skeletal hyperostosis (DISH)

Classic x-ray findings in DISH include **flowing** linear calcification anterior to the spinal ligaments predominantly in the thoracic region, unlike the ascending bamboo spine from the lumbar region in AS, spanning at least 4 contiguous vertebral bodies with preservation of disc spaces. The word “flowing” is used because these calcifications have the appearance of someone **pouring candle wax** in front of the vertebrae.

Treatment of DISH is mainly supportive with NSAIDs and physical therapy.

REACTIVE ARTHRITIS (ReA)

The **most common** cause of acute, nontraumatic arthritis in a person < 50 years of age is ReA, which is an **immunologic reaction** to a **recent infection** elsewhere in the body, typically **GU** or **GI** infections.

Common causes of reactive arthritis are a **GU** infection from *Chlamydia trachomatis* and **GI** infections due to *Salmonella*, *Shigella*, *Yersinia*, *Campylobacter*, and *Clostridioides difficile*. GI causes of ReA affect men and women equally, but GU causes predominantly occur in men (with a ratio of 9:1). ReA also is seen in those with common viral illnesses (e.g., enterovirus) and HIV infection. The arthritis typically develops within 2 months after the infection and may persist for several months or years. The responsible organism is usually not identified.

The classic triad of **urethritis**, **conjunctivitis**, and **asymmetric oligoarthritis** is seen in < 1/3 of patients. While

ReA is the most common cause of an acute nontraumatic arthritis, it is a very uncommon cause of a spondyloarthritis. Ankylosing spondylitis is more common.

ReA most usually presents as an **asymmetric**, mono- or oligoarticular arthritis of the lower extremities. Enthesitis is common and characteristic, especially at the insertion points of the **Achilles tendon** and the **plantar fascia**. Axial spine pain is not a common feature; however, it occurs in ~ 20% of patients. Thus, the categorization of ReA as a spondyloarthritis.

Extraarticular manifestations are common and include:

- Keratoderma blennorrhagicum
- Circinate balanitis
- Mucocutaneous genital lesions
- Mouth ulcers
- Conjunctivitis
- Iritis

Keratoderma blennorrhagicum classically presents as papules/pustules with central erosion and characteristic crusting on the palms and soles; it can be indistinguishable from pustular psoriasis ([Figure 10-7](#)). Circinate balanitis presents as an erythematous pustular or plaque-like lesion on the glans or shaft of the penis.



Figure 10-7: Keratoderma blennorrhagicum
Source: CDC

Diagnosis

Diagnosis can be tough because the inciting infection often is resolved when the arthritis presents. This is especially true of the enteric pathogens. DNA amplification for genital *Chlamydia* is recommended in patients who have no obvious cause in their history because *Chlamydia* infections can be asymptomatic, even in males. If a peripheral joint is swollen, arthrocentesis is recommended to exclude bacterial infection and crystalline arthropathies. Of note, the synovial fluid culture in ReA should be negative. If the culture is positive, then by definition it is an infectious arthritis and not reactive. HLA-B27 testing may be positive but is not specific; consequently, it is not helpful.

Treatment

NSAIDs are recommended for initial treatment. Use systemic steroids short-term in patients who have refractory peripheral arthritis. For severe or disabling disease, use sulfasalazine or methotrexate. TNF inhibitors are used rarely and only in extreme refractory cases.

The use of antibiotics to treat ReA has been controversial. Molecular evidence of bacterial DNA has been demonstrated in synovial fluid in cases of *Chlamydia*-related ReA. A major clinical trial demonstrated that a 6-month combination course of doxycycline + rifampin or a 5-day course of azithromycin + 6 months of rifampin was shown to be effective therapy in some patients with long-standing, chronic *Chlamydia*-induced ReA.

Put ReA at the top of your list for any patient < 50 years of age who develops a **subacute, asymmetric large-joint arthritis** in the setting of a recent GI or GU infection. Quiz patients about any recent illnesses, especially diarrhea, urethritis, or sexually transmitted infections (typically during the prior **2–4 weeks**); also ask about viral infections and conjunctivitis.

INFLAMMATORY BOWEL DISEASE — ASSOCIATED ARTHROPATHY

Inflammatory bowel disease (IBD)-associated arthropathy occurs in ~ 20% of patients with IBD and clinically manifests in 2 forms, axial and peripheral. The peripheral arthritis presents as either:

- 1) Asymmetric oligoarthritis of the lower extremities
- 2) Symmetric polyarticular arthritis of the hands

Asymmetric oligoarthritis of the lower extremities occurs with flare-ups of **IBD**, followed by **complete** remission of the peripheral synovitis as the bowel disease improves. The peripheral arthritis involves only a few joints in the lower extremities.

Patients also can present with symmetric polyarticular arthritis of the hands, as seen in rheumatoid arthritis. However, recall that spondyloarthropathies are seronegative (i.e., negative ANA, RF, anti-CCP). This form of arthritis can be independent of inflammatory bowel activity.

Axial skeleton involvement (~ 20%) may be clinically and radiographically indistinguishable from **ankylosing spondylitis** and runs a course **independent** of the bowel disease—symptoms do not worsen or improve in response to IBD flares or improvements. **HLA-B27** is present in 50–75% of patients who have **IBD with spondylitis**.

Extraarticular manifestations such as erythema nodosum, pyoderma gangrenosum, aphthous ulcers, and uveitis also can parallel the flare-ups of IBD.

Therapy for IBD (e.g., sulfasalazine, corticosteroids, azathioprine) may help to control the peripheral joint symptoms and extraarticular manifestations. Anti-TNF agents are helpful in treating both peripheral joint and spinal symptoms.

PSORIATIC ARTHRITIS (PsA)

PsA is seen more frequently in patients who have more symptoms than just the rash of psoriasis. 20–30% of patients who have nail pitting, onycholysis (separation of the nail from the nail bed), and “oil spots” (brownish discoloration under the nails) also develop joint disease; whereas, only 7% of patients who simply have rash develop arthritis. Psoriasis is typically a silvery, scaly rash on an erythematous base. Look for psoriasis on the extensor surfaces of the elbows, on the knees, behind the ears, along the hairline, along intertriginous areas, and on the umbilicus. Nail pitting is very specific for PsA (Figure 10-8).



Figure 10-8: Pitted nail as seen in psoriatic arthritis
Source: ACR

Joint involvement in PsA has varying presentations:

- **Symmetric polyarthritis:** Looks like rheumatoid arthritis (RA); can involve the PIPs, MCPs, and knees.
- **Asymmetric arthritis** (e.g., oligoarthritis): Usually involves large joints like the knees, ankles, and wrists; typically, < 3 joints are affected.
- **Spondylitis:** Presentation is similar to ankylosing spondylitis (AS) with inflammatory back pain, but x-rays show an **asymmetric** sacroiliitis (unlike AS and IBD-related spondylitis, where x-rays show a **symmetric** sacroiliitis).
- **DIP arthritis:** Looks like osteoarthritis (OA), but there is evidence of nail psoriasis.
- **Arthritis mutilans:** There is severe resorptive destruction of the joints.

Patients with PsA sometimes present with > 1 pattern of joint involvement. For example, a patient with asymmetric oligoarthritis may also have spondylitis. Imaging is sometimes helpful to distinguish PsA from other forms of arthritis. Hand radiographs may show a classic **periostitis** or a “**pencil-in-cup**” deformity, which refers to psoriatic erosions that appear as narrowed ends of phalanges inserting into the expanded end of the adjacent phalanx. Contrast this with the erosions seen in inflammatory OA, where the classic finding is “gull wings” (a.k.a. seagull erosions; Figure 10-9 on page 10-26).

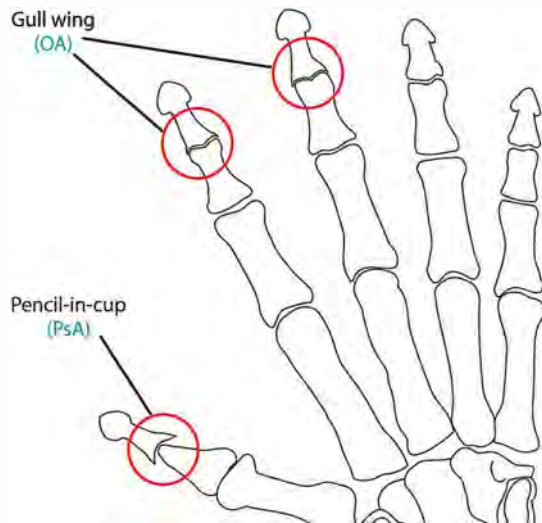


Figure 10-9: DIP deformities in PsA and OA

Treatment: NSAIDs are 1st line therapy for PsA and are used to control pain and inflammation. In patients with symmetric or asymmetric arthritis, treatment is very similar to RA, with methotrexate and leflunomide being the predominant DMARDs used in patients with disease refractory to NSAIDs. Anti-TNF agents are reserved for patients with spondylitis and for those with moderate-to-severe arthritis failing to improve with DMARD and NSAID therapy. Paradoxically, there has been a growing number of reports showing an increase of psoriasis in RA patients treated with anti-TNF drugs. The rash resolves with topical steroids or the discontinuation of anti-TNF therapy.

Several drugs are approved for the management of psoriasis and PsA, including:

- **Ustekinumab**, an IL12/23 inhibitor
- **Apremilast**, a PDE4 inhibitor
- **Secukinumab** or **ixekizumab**, IL-17 inhibitors
- **Tofacitinib**, a Janus kinase (JAK) inhibitor

Apremilast can cause diarrhea, nausea, and vomiting within the 1st few weeks of use in some patients; it typically resolves within a few weeks. Apremilast also can cause weight loss, and if significant enough, the drug has to be discontinued. Know that apremilast can make depression worse. Any patient with depression on this medication should be advised to report any increase of depressive symptoms or thoughts of suicide.

Secukinumab or ixekizumab, the IL-17 inhibitors, can exacerbate IBD, which itself can overlap with other seronegative spondyloarthritides, such as PsA.

Avoid antimalarial drugs (e.g., hydroxychloroquine), lithium, and β -blockers in PsA because they often exacerbate the skin disease. Additionally, **avoid systemic corticosteroids** because their withdrawal often leads to a severe, life-threatening form of pustular psoriasis. Other conditions that exacerbate psoriasis include skin trauma, sunburn, viral infections, and streptococcal pharyngitis. Note that severe or abrupt onset of psoriasis in men having sex with men is a reason to check for HIV/AIDS.

OSTEOARTHRITIS (DEGENERATIVE JOINT DISEASE)

PREVIEW | REVIEW

- What is the pattern of joint involvement in osteoarthritis (OA)?
- Which joints typically are spared in primary OA?
- Which joints of the hand are affected in primary OA?
- What are the diagnostic criteria for hip OA? Knee OA?

Osteoarthritis (OA; degenerative joint disease) is, by far, the most common form of arthritis. It is either primary (idiopathic) or secondarily associated with other types of inflammatory arthritis such as gout and pseudogout. It is unclear whether the OA or the crystalline arthropathy comes first. OA also arises after joint damage due to hemochromatosis, trauma, rheumatoid arthritis (RA), or neuropathic joints related to diabetes. OA pain characteristically is made worse with weightbearing and excessive activity. It has an insidious onset (unlike inflammatory arthritides such as gout and RA).

The joint damage of OA is classically noninflammatory and nonerosive (although there is a rare erosive variant of OA), asymmetric, and without calcium deposition in the cartilage (chondrocalcinosis). The most commonly affected joints are the 1st carpometacarpal (CMC-1) joints of the hands and carpometatarsal joints of feet, 1st interphalangeal joints, knees, hips, and the cervical and lumbar spine. Involvement of the ankle, wrist, and elbow is very rarely due to OA. If a patient's symptoms include swelling of 1 of these 3 rare areas, consider pseudogout, gout, RA, or other types of inflammatory arthritis—not OA!

Remember: Morning stiffness usually lasts < 30 minutes in patients with OA (as opposed to inflammatory arthritis which typically lasts > 1 hour).

OA of the hands: Changes most often affect the distal joints. The proximal interphalangeal (PIP) joints and distal interphalangeal (DIP) joints present with classic enlargements called **Bouchard (PIP)** and **Heberden (DIP) nodes** (Figure 10-10). Controversy exists whether the nodes result from osteophyte formation or development of small cysts around the joints. The enlargement of the hand joints is typically asymmetric, hard, and bony; **not** soft and spongy, as with inflammatory arthritis (Figure 10-10). Occasionally, these DIP and PIP nodes become inflamed and very tender, mimicking the inflammatory joint disease of psoriatic arthritis (PsA).



Figure 10-10: Heberden nodes

Remember: PsA has dactylitis and often nail involvement; inflammatory OA does not (see [Psoriatic Arthritis \(PsA\) on page 10-25](#)). Erosive OA is another term for inflammatory OA. X-rays reveal evidence of erosions at the DIP joints, where seagull wings are classic findings. The carpometacarpal (CMC-1) joints at the base of the thumbs can be involved. “Squaring” of the CMC-1 joint is a common physical finding.

OA **rarely** affects metacarpophalangeal (MCP) joints. When it does, consider hemochromatosis or previous trauma causing a secondary OA.

To review: Remember that OA involves the DIPs and PIPs, but not the MCPs, which is seen in RA ([Figure 10-11](#))!

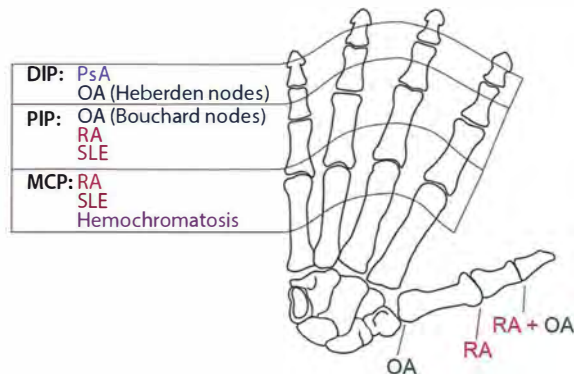


Figure 10-11: Hand joints affected by rheumatologic diseases

Diagnosis of hand OA is supported when there is pain in the hands with 3 of the following clinical criteria (sensitivity 94%; specificity 87%):

- 1) Bony enlargement of ≥ 2 DIPs/PIPs of 2nd and 3rd fingers and CMC-1 joint (usually bilateral)
- 2) Bony enlargement of > 2 DIPs
- 3) < 3 MCP swellings
- 4) Deformity of 1 of the 10 DIPs/PIPs

Treat initially with topical NSAIDs or capsaicin cream, then oral NSAIDs. Intraarticular joint therapy is not routinely recommended.

Shoulder OA: Primary OA in the shoulder is rare unless repetitive use of the joint or trauma is the contributing factor, which is much more common in the **acromioclavicular** (AC) joint than in the glenohumeral joint. AC joint arthritis pain usually is localized over the AC joint, while the pain in glenohumeral arthritis can be anterior in the shoulder or nebulous and ill-defined. Early OA appears normal radiographically and only later shows joint space narrowing and osteophytes. Treat as you would all cases of OA, with education and nonnarcotic analgesics. Surgery is not common and is the last resort.

Hip OA: Hip osteoarthritis presents as increased pain with use that is relieved with rest. The maximum point of pain intensity is localized to the groin, a feature that distinguishes hip joint pain from trochanteric bursitis, in which pain is localized to the lateral aspect of the hip. In some cases, the pain radiates to the knee and presents as knee

pain rather than hip pain. Exam usually does not reveal any erythema, warmth, or swelling; however, decreased range of motion and crepitus of the hip might be obvious.

Diagnosis of hip OA is supported by hip pain and 2 of the criteria below (and exclusion of other diagnoses):

- 1) ESR < 20 mm/hour (which typically supports a diagnosis of a noninflammatory arthritis)
- 2) Femoral or acetabular osteophytes on radiograph
- 3) Joint space narrowing on radiograph (with superior migration of the femoral head)

Using these criteria for hip OA has an 89% sensitivity and a 91% specificity. Standing or weight-bearing radiographs of the hip are used to show joint space narrowing $\pm$ subchondral sclerosis $\pm$ osteophytes ([Figure 10-12](#)). In patients with typical clinical features and abnormal radiographs, no further imaging is necessary.



Figure 10-12: OA of left hip with joint space narrowing

Treat patients with education (weight loss) and non-narcotic analgesics. Exhaust conservative measures (especially weight loss, physical therapy, and use of assist devices such as canes) before referral for total hip arthroplasty.

Knee OA: Pain usually is made worse with prolonged weight bearing and is characterized as a deep ache superior to the patella or deep inside the knee joint. Pain described as medial and inferior to the joint is more likely to be from pes anserine bursitis. Remember: Pain from hip OA can radiate to the knee.

Plain radiographs of weight-bearing views of the knee(s) commonly show asymmetric joint space narrowing (medial more than lateral), eburnation, subchondral sclerosis, and osteophyte(s) formation ([Figure 10-13 on page 10-28](#)).

Suspect knee OA when pain and several of the following features are included:

- Typically, ≥ 50 years of age
- Obesity
- Morning stiffness < 30 minutes
- Bony enlargement (especially if < 40 years of age)
- Knee malalignment: hallux varus (bow-legged) more common than hallux valgus (knock knees)

- Crepitus upon knee flexion
- Noninflammatory synovial fluid (WBCs 200–2,000/ μ L)
- Labs: ESR < 20 mm/hour
- Osteophytes on radiograph

The more of these features a patient has, the more confident you are of an OA diagnosis. Clinical criteria alone are ~ 90% sensitive and specific (higher with labs and radiographs).



Figure 10-13: OA with joint space narrowing and osteophytes
Source: James Heilman, MD

Treat knee OA with education (weight loss and exercise) and/or NSAIDs (topical or oral). Tramadol alone, or in combination with NSAID or celecoxib, is helpful for refractory pain. Acetaminophen is no longer 1st line treatment for OA but is an alternative to the therapies mentioned above. Patients taking maximum dose acetaminophen therapy (4 g/day) should be counseled to avoid other medications containing acetaminophen. Chronic or high-dose acetaminophen raises the risk of hepatic injury. Minimize long-term opiates, especially in the elderly. Lateral wedge insoles to treat OA of the medial compartment of the knee have not been proven effective.

Intraarticular **glucocorticoids** are useful in patients who are unable to tolerate NSAIDs, who receive inadequate analgesia from acetaminophen, and/or who have only 1 or 2 painful joints. Limit intraarticular steroid injections to no more than 3–4 per year.

Viscosupplementation with intraarticular injection of **hyaluronic acid** has been used with uncertain efficacy. These injections are very expensive; some institutions and insurance companies do not support their use given lack of proven efficacy. Despite this, some rheumatologists still try hyaluronic acid injections because they are usually very well tolerated (very rarely will patients develop a postinjection flare that resembles an acute inflammatory arthritis).

Alternative forms for treating OA, such as glucosamine, chondroitin sulfate, fish oils, and acupuncture, have been controversial. The American College of Rheumatology (ACR) 2019 OA management guidelines do **not** recommend glucosamine or chondroitin in the management of OA of the knee or hip. However, chondroitin is conditionally recommended for hand OA.

Preliminary results demonstrated that mesenchymal stem cell-based therapy is encouraging in reducing pain and improving the function of OA. Larger trials are ongoing.

There is no cure for OA. Therefore, if the patient does not respond to the above therapies and their pain interferes with their daily functioning, joint replacement is indicated.

CRYSTAL DEPOSITION ARTHRITIDES

PREVIEW | REVIEW

- At what age does acute gout usually present?
- What is the diagnostic procedure of choice for diagnosing gout?
- Characterize monosodium urate (MSU) crystals under a polarizing microscope. How many must be present to diagnose gout?
- How do you treat a gout flare in a single joint? Multiple joints?
- What is the goal serum uric acid level in a patient who has no tophi present and who has had > 1 attack of gout per year?
- What is the goal uric acid level in a patient who has tophi present?
- Can urate-lowering therapy for the chronic treatment of gout be initiated during treatment of an acute gout flare?
- Which genetic marker predicts increased risk of allopurinol-induced severe cutaneous adverse reaction? Name 3 ethnic groups this occurs in.
- Which drugs need the dose adjusted downward if a patient takes allopurinol?
- What medication cannot be used as monotherapy for gout due to the risk of renal insufficiency?
- Which diseases are associated with calcium pyrophosphate deposition (CPPD)?
- Inflammatory arthritis of which joints should make you think of CPPD disease?
- What do CPPD crystals look like under polarized light?
- What do hydroxyapatite arthropathy crystals look like under polarized light?

OVERVIEW

Crystalline arthropathies are due to the deposition of microscopic crystals, typically into joints; however, they also can deposit into other tissues such as muscles, tendons, and some internal organs (e.g., the kidneys). This arthritis often presents as an acute, hot, painful, and swollen joint(s), but chronic forms do exist. Diagnose crystalline arthropathies by performing an arthrocentesis and analyzing the synovial fluid under polarized light microscopy to visualize the crystals. Recall the discussion under [Synovial Fluid \(SF\) Analysis on page 10-6](#). Send all synovial fluid with a suspicion of an inflammatory, crystalline, or septic picture for culture and sensitivity because there have been reports of concomitant bacterial infection. When in doubt, always treat with empiric antibiotics while awaiting the results of synovial fluid analysis (3 Cs: cell count with differential, crystal analysis, culture and sensitivities with Gram stain).

Within this topic, the most common forms of crystalline arthritis will be discussed: gout, pseudogout (a.k.a. calcium pyrophosphate deposition [CPPD] disease), and hydroxyapatite arthropathy.

GOUT

Etiology

Gout is caused by an excess of uric acid in the serum with deposition of monosodium urate (MSU) crystals into joints, causing recurrent bouts of acute arthritis and, ultimately, chronic arthropathy. Crystals also can accumulate in tissues, causing tophi and kidney stones.

Acute gout can present after sustained hyperuricemia; however, for unknown reasons, up to 2/3 of patients with hyperuricemia never develop gout. **Middle-aged** men are affected more than women, and the incidence of gout among men increases with aging. Risk for gout increases in females at menopause because estrogen had a protective effect due to its uricosuric properties.

The following have been linked to gouty arthritis:

- Increased uric acid production:
 - Diet: high purine foods (cause excess uric acid production; alcohol, many fish and shellfish, excess fatty meats and dairy, red meat, turkey, anchovies, sardines, and some organ meats like liver)
 - Diet: high fructose consumption (especially soft drinks)
 - Leukemia
 - Hemolytic anemia
 - Tumor lysis syndrome (See more in the [Oncology](#) section.)
 - G6PD
 - Psoriasis
 - Exercise

- Decreased renal excretion:
 - Starvation/Dehydration
 - Trauma, surgery
 - Alcohol (again!; causes overproduction and underexcretion)
 - Drugs: especially thiazide and loop diuretics, nicotinic acid, low-dose aspirin, tacrolimus, cyclosporine, ethambutol
 - Comorbidities: chronic kidney disease, hypertension, DM/DKA, renal disease, hyperlipidemia, and obesity

Of all causes of gout, underexcretion accounts for 90%; only 10% are caused by overproductions.

Note that **most** patients with hyperuricemia never develop gout flares, tophi, or nephrolithiasis!

Hyperuricemia is either **primary**, in which case it is usually permanent, or **secondary**, usually a result of comorbid diseases or drugs.

To determine whether a patient is an underexcretor or an overproducer, measure the amount of uric acid in the urine over 24 hours. **Underexcretors** have low-to-normal 24-hour urine uric acid levels in the setting of increased serum levels (or < 600 mg); **overproducers** often have > 800 mg per 24 hours.

Definitely obtain serum and urine uric acid levels in **premenopausal females** and in **males < 25 years** of age who develop acute gout. (The hyperuricemia often is hereditary, and many get kidney stones.) Also, check these levels if you intend to prescribe a **uricosuric** agent (probenecid), to ensure that the patient's increased rate of elimination does not result in stone formation (i.e., in an overproducer). In **most other** cases, these levels are not checked because they do not result in a change in management.

Gout presents in various phases based on the following clinical categories:

- Asymptomatic hyperuricemia
- Acute arthritis
- Intercritical periods (between flares)
- Chronic tophaceous gout (with chronic gouty arthropathy)
- Uric acid stones, urate nephropathy

Presentation

Acute gouty arthritis classically presents as an acutely tender and swollen joint that may occur at night and awaken the patient from sleep. Pain reaches maximum intensity within the first 24 hours and self-resolves within a few days to several weeks. In 50% of patients, the initial attack occurs in the 1st metatarsophalangeal (MTP) joint of the **great toe** (termed **podagra**). The **knee** is the next most commonly affected joint. In the early stages of gout, the patient is completely asymptomatic between attacks (intercritical period), which is a useful clue to help

distinguish gout from other arthritides if the diagnosis is in question. Chronic tophaceous gout usually develops after years of acute gout or elevated uric acid levels.

Acute polyarticular gout is much less common. It is more often seen in patients with myelo- or lymphoproliferative disorders (e.g., leukemias), post-organ transplant, CKD, and other long-standing disease.

Diagnosis

Diagnosing a gout flare: Work up swollen red joint of unknown cause or suspected gout flare by tapping the joint and doing an analysis for crystals, a Gram stain, and a C+S. The Gram stain and C+S are to rule out a septic joint. Synovial fluid from a hot gouty joint usually shows WBCs $> 2,000/\mu\text{L}$ with a predominance of neutrophils. In contrast, septic arthritis has WBC $> 50,000/\mu\text{L}$. MSU crystals are **needle-shaped** and are **strongly negatively birefringent** under polarized light microscopy. Negatively birefringent crystals are yellow when parallel to the color compensator (always indicated by an arrow on the image). To be diagnostic, you need to see only 1 intracellular MSU crystal within a neutrophil or ≥ 3 extracellular MSU crystals. See [Figure 10-14](#).



Figure 10-14: Uric acid crystals under polarized light with red compensator (arrow indicates angle of the polarizer)
Source: Bob J. Galindo

It is important to know that a rapid decrease or, less commonly, an increase in uric acid level is thought to precipitate gouty attacks. The uric acid level **does not** correlate with an attack of acute gout. Often, patients have normal or low levels when acute gouty arthritis is present. Conversely, an elevated serum uric acid **does not confirm** the diagnosis of gout, but it does indicate patients who are **at risk**. As serum uric acid levels increase to $> 9\text{--}10\text{ mg/dL}$ ($535\text{--}595\text{ }\mu\text{mol/L}$), incidence of gouty attacks increases to 5% per year.

Workup for gout during intercritical periods is the same as during a flare—with synovial fluid analysis as discussed above. Virtually all intercritical patients have MSU crystals in their affected joints and $\sim 70\%$ have them when on urate-lowering therapy (ULT).

Treatment of Gout Flares

NSAIDs, glucocorticoids, or oral colchicine are all appropriate 1st line antiinflammatory agents for gout flares. Know that the earlier any treatment is initiated, the better the response.

Treat the acute attack with ice packs, and consider intraarticular glucocorticoids if only 1 or 2 joints are involved and suspicion of infection is low. Use NSAIDs or colchicine if multiple joints are involved and there are no contraindications.

NSAIDs: Traditionally, indomethacin has been the choice NSAID for the treatment of gout, but any NSAID, including a COX-2 inhibitor, works.

Colchicine is equally effective as NSAIDs and has less GI irritation. The recommended dose is lower than previously recommended. Give $1.2\text{ mg} \times 1$ dose, then 0.6 mg 1 hour later, followed by prophylactic doses as needed. Side effects of colchicine are nausea, vomiting, and diarrhea; however, myopathy and bone marrow suppression can be seen with long-term use, especially in patients with advanced CKD. Do not use colchicine in end-stage renal disease or in those with renal impairment and on CYP3A4 inhibitors (i.e., clarithromycin, protease inhibitors, voriconazole) because levels of colchicine may rise to toxic or even fatal levels. IV colchicine is no longer available in the U.S. because of its toxicities.

Glucocorticoids are also equally effective but are especially useful for patients when NSAIDs or colchicine are contraindicated or ineffective. Either local steroid injections or systemic therapy are effective; however, 1st you **must** exclude a concurrent infection.

Prednisone or methylprednisolone is used commonly as monotherapy or in combination with colchicine. Note that combining steroids with NSAIDs is not done because it increases the risk of gastric toxicity.

IL-1 inhibition with either anakinra (see [Table 10-8 on page 10-15](#)) or canakinumab (approved in Europe) is being studied to manage acute gout attacks.

Chronic Treatment

The goal of therapy is to prevent subsequent gout attacks by reducing the uric acid burden. Chronic treatment of gout includes dietary and lifestyle modification and urate-lowering therapy.

Dietary/lifestyle modifications: Avoidance of precipitants, including the foods and drugs mentioned under [Etiology on page 10-29](#), may not be practical or may be followed poorly. Counsel patients on low-purine diets, such as avoiding organ meat, red meat, high-fat dairy, bacon, seafood, and limiting alcohol and high-fructose corn syrup, which reduce the frequency of acute gout attacks, but which may not be effective in the long term in lowering uric acid levels (e.g., decline $\sim 1\text{ mg/dL}$ [$59.5\text{ }\mu\text{mol/L}$]). In addition, many patients do not adhere to dietary

modifications. The best diet is simple caloric restriction with an emphasis on complex carbohydrates (in lieu of processed simple sugars). The goal is to effect weight loss, which does lower the incidence of gout.

Initiate **urate-lowering therapy (ULT)** with patients with any of the following:

- ≥ 1 Subcutaneous tophi
- Recurrent gout flares ($> 2/\text{year}$)
- Radiographic evidence of gouty damage such as marginal erosions due to interosseous tophi (Figure 10-15)
- Uric acid kidney stones or 24-hour urine uric acid level $> 1,000 \text{ mg/day}$ (But do not use a uricosuric drug.)

Drug choice for initial treatment: **Allopurinol** is the most strongly recommended ULT, even in patients with severe CKD. Febuxostat is an alternative.

The goal of ULT is to reduce the serum uric acid level to $< 6 \text{ mg/dL}$ ($356.9 \mu\text{mol/L}$), which is below the saturation point of monosodium urate. Know this! When serum uric acid levels are $< 6 \text{ mg/dL}$, urate crystals are reabsorbed from the joint and tophi, resulting in reduction in frequency of gout flares. Patients with tophi and more severe disease benefit from an even lower serum uric acid level ($< 5 \text{ mg/dL}$ [$297.4 \mu\text{mol/L}$]).

Administer **concomitant antiinflammatory prophylaxis therapy** whenever you put the patient on ULT. Use the same antiinflammatory drugs used for gout flares (e.g., colchicine, NSAIDs, prednisone). Continue prophylactic therapy for at least 6 months after the uric acid goal is achieved if tophi are present (3 months if there are no tophi).

Maximum dose of febuxostat is 80 mg/day (although dosages of 120 mg/day of febuxostat are available in Europe).

According to the 2020 ACR guidelines, patients with **recurrent** attacks do not have to wait for 2–3 weeks after the resolution of a gout flare before starting ULT. They can begin ULT during the flare as long as they receive daily antiinflammatory prophylaxis against flares.

The 2020 ACR guidelines conditionally recommend that ULT (usually allopurinol; for chronic treatment) can be initiated during the treatment of an acute gouty flare rather than wait for complete resolution—given that the patient agrees, is compliant with meds, and does not confound the two therapies (one for acute treatment, the other for chronic). This is a new recommendation; previously



Figure 10-15:
Tophaceous gout
Source: Hellerhoff

resolution from the acute flare was achieved before starting ULT. The main benefit is simply being able to start therapy earlier. As recommended in this and previous guidelines, if the patient is on ULT at the start of a flare, it is not stopped.

Drugs for Gout — In Depth

Xanthine Oxidase Inhibitors (XOIs)

1st line ULT drugs are the XOIs, which include **allopurinol** and **febuxostat**. These agents reduce serum uric acid levels in both underexcretors and overproducers. Remember: Underexcretion of uric acid is the most common cause of hyperuricemia.

Allopurinol is the most commonly prescribed XOI and is the most strongly recommended over all other ULT drugs when initiating therapy, even in those with severe CKD! It is cheap and effective. Common side effects include nausea, vomiting, and diarrhea.

Allopurinol hypersensitivity syndrome (**AHS**) can occur, ranging from a maculopapular drug rash to severe cutaneous adverse reaction (**SCAR**) such as toxic epidermal necrolysis (**TEN**)/Stevens-Johnson syndrome (**SJS**), and **DRESS** syndrome (drug rash with eosinophilia and systemic symptoms). Allopurinol-induced SCAR is very strongly associated with HLA-B*5801 (80–100% of those affected have HLA-B*5801!). Ethnic groups with this marker are Han Chinese (majority population of China, Taiwan, and Singapore), Korean, Thai, and Africans. In the U.S., prevalence of HLA-B*5801 = Asians (7.4%), African Americans (3.8%), Hispanics and Caucasians ($< 1\%$).

TEN/SJS are variations of the same disease, with TEN being far more serious. The main manifestation is confluent epidermal necrosis with minimal associated inflammation. Diagnosis is determined by the degree of skin involvement:

- $< 10\% = \text{SJS}$
- $> 30\% = \text{TEN}$
- 10–30% = SJS/TEN overlap

Normal starting dose of allopurinol for gout is 100 mg/day, increased weekly until the target uric acid level of $< 6 \text{ mg/dL}$ is attained or a maximum dose of 800 mg/day is reached. Maintenance dose is usually 400–600 mg/day in divided doses. Patients with CKD are at greater risk for developing AHS, especially that with the maculopapular drug rash. All patients with CKD are started at 50 mg/day and it is tapered up very slowly.

Remember, with XOIs (e.g., allopurinol) the dose of **azathioprine** or **mercaptopurine** must be decreased by 66–75%. Monitor labs carefully because metabolism of these drugs is inhibited by XOIs and can lead to increased drug toxicity such as bone marrow suppression. XOIs also interfere with theophylline metabolism.

Febuxostat is useful in patients who cannot tolerate allopurinol. Hypersensitivity and severe skin reactions also have

been reported with febuxostat. Use it cautiously (or not at all) in patients with a documented hypersensitivity reaction to allopurinol. Compared to allopurinol, febuxostat:

- is much more expensive,
- causes a faster decrease in uric acid,
- has a similar side effect profile, and
- has no need to adjust dosage for GFR < 30 mL/minute.

Uricase

Uricase is an enzyme that oxidatively degrades uric acid to soluble allantoin, which is readily excreted. Humans and higher primates lost uricase expression during the course of evolution.

Pegloticase, a pegylated recombinant mammalian uricase, is approved by the FDA for use in refractory tophaceous gout. The drug has less immunogenicity, but infusion reactions and anaphylaxis remain concerns. Check G6PD levels prior to initiating therapy; in addition, obtain uric acid levels prior to each infusion of pegloticase. A rising uric acid level indicates impending adverse infusion reaction.

Rasburicase is a uricase approved for tumor lysis syndrome and helps to reduce tophi burden in patients with chronic tophaceous gout. However, the drug is not approved by the FDA for gout because it is highly antigenic and has poor tolerability and sustainability.

Uricosuric Agents

Uricosuric agents inhibit urate transporter 1 (URAT1) to increase uric acid renal clearance; however, these agents are **rarely used** due to poor adherence.

Probenecid requires multiple daily doses and ingestion of > 1 gallon (3.8 L) of water per day to prevent uric acid renal stones. It is considered a 2nd line agent in underexcretors who are resistant/intolerant to XOIs.

Avoid probenecid in patients:

- Who have a 24-hour urine uric acid level > 700 mg
- With history of renal stones
- With tophi
- With renal insufficiency where GFR ≤ 30 cc/minute or Cr > 2 mg/dL (152.5 μmol/L) because the drug is ineffective given its mechanism of action

While the efficacy of probenecid therapy is limited, the 2020 ACR guidelines still recommend adding low-dose probenecid to an XOI if needed to reach the target uric acid goal.

Lesinurad is another URAT1 inhibitor approved by the FDA to treat gout in those who have not reached target uric acid levels with an XOI alone. Unlike probenecid, lesinurad is not to be used as monotherapy due to risks of worsening renal insufficiency and kidney stones; thus, it must be used in combination with an XOI. Lesinurad is not used with a creatinine clearance < 45 mL/minute.

Gout Pearls

Know the following!

- Low-dose aspirin (e.g., ≤ 325 mg/day) interferes with urate excretion. High-dose aspirin (e.g., ≥ 1–3 g/day) causes uricosuria. Therefore, aspirin at commonly used doses interferes with uric acid excretion.
- Differential diagnosis for acute monoarticular joint swelling = infection vs. crystalline vs. fracture/trauma.
- Gout can cause fever.
- Premenopausal women rarely get gout. (Estrogen is uricosuric.)
- Older women may present with polyarticular pseudo-rheumatoid crystalline arthritis (gout or pseudogout that presents similarly to rheumatoid arthritis [RA]). So, think of gout or pseudogout in the older woman who looks like she has suddenly developed RA. Always look for crystals in joint fluid!
- Gouty joint radiographs may have a characteristic erosion with an overhanging edge, termed marginal erosion or “rat-bite” erosion caused by a tophus.
- Acute gout + joint infection is uncommon but should never be missed.
- **Losartan** has uricosuric effects and lowers uric acid levels slightly.
- Goal serum uric acid is < 6 mg/dL (356.9 μmol/L); for patients with **tophi**, the goal serum uric acid is < 5 mg/dL (297.4 μmol/L).
- Prescribe antiinflammatory prophylaxis while lowering uric acid to prevent flares.

CALCIUM PYROPHOSPHATE DEPOSITION (CPPD) DISEASE

CPPD disease (a.k.a. pseudogout) is a condition in which CPPD crystals cause **acute attacks of mono-, oligo-, or polyarthritis**, with radiographic evidence of chondrocalcinosis (calcium in the cartilage) and subsequent damage to joints. There is a subset of patients with osteoarthritis (OA) who have **asymptomatic deposition** of crystals in joint cartilage (visible only on radiographs). Most CPPD is idiopathic and occurs in patients > 65 years of age who have underlying joint damage from OA or trauma.

When you see CPPD in a patient < 50 years of age, consider these predisposing conditions:

- Primary hyperparathyroidism
- Hemochromatosis
- Hypothyroidism
- Hypomagnesemia
- Hypophosphatemia

Checking serum iron, total-iron binding capacity (TIBC), ferritin, TSH, calcium, and intact-PTH are appropriate to screen for these conditions in patients found to have CPPD.

Chondrocalcinosis is calcification of cartilaginous tissue and is a hint to underlying CPPD, so think of this diagnosis

if you see obvious calcifications in the cartilage on a radiograph (particularly in the triangular fibrocartilage area of the wrist or in the knee [Figure 10-16]). If the presentation is of an acute arthritis, the arthrocentesis usually reveals an inflammatory joint fluid (WBCs > 2,000 cells/ μ L) with an excess of neutrophils, some of which contain CPPD crystals.



Figure 10-16: Chondrocalcinosis of wrist and knee

CPPD arthropathy typically affects the **knee**. Other joints commonly affected by CPPD include wrists, **2nd** and **3rd** MCPs, **shoulders**, **elbows**, and **ankles**. Recall from the osteoarthritis (OA) topic that we said OA rarely involves these joints! If your patient has **wrist** synovitis in the face of OA, think 1st of CPPD—not OA only! Also think of CPPD when chondrocalcinosis is visible on radiographs of the wrists or MCPs.

Arthrocentesis establishes a diagnosis of CPPD. The synovial fluid demonstrates intracellular crystals that are blunted, rhomboid, and weakly positively birefringent under polarized light microscopy. (Crystals are light blue when parallel to the polarizer.) These crystals can be intra- or extracellular. See examples of extracellular CPPD crystals in Figure 10-17. Remember: Uric acid crystals are needle-shaped and are strongly negatively birefringent (bright yellow when parallel to the compensator). Be able to distinguish uric acid and CPPD crystals from photomicrographs (based on color) and from descriptions of the crystals.

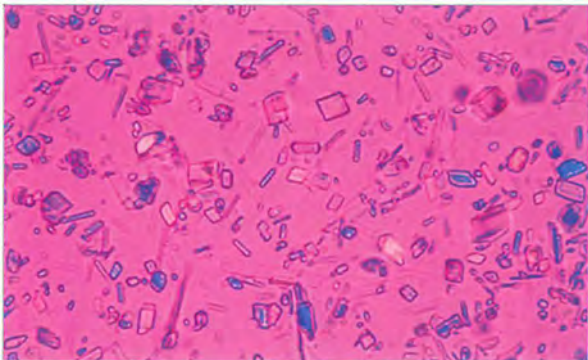


Figure 10-17: CPPD crystals, rod, or rhomboid

CPPD crystals dissolve and change their birefringence when stored > 12–24 hours, so analyze the fluid **immediately**. Urate crystals are much less likely to dissolve. If the fluid cannot be examined within a few hours, refrigerate it to slow the decomposition of crystals and white blood cells.

Management of acute CPPD arthritis is extrapolated from gout data and is essentially identical to the treatment of acute gout. 1st line therapy is joint aspiration and NSAIDs

and/or intraarticular glucocorticoid administration. Colchicine is used; however, it may be less effective. Use systemic glucocorticoids if patients have refractory disease or are unable to take NSAIDs/colchicine. Low-dose colchicine also is used as prophylaxis for acute attacks, but supporting data are not robust. There are no drug equivalents to XOIs in CPPD disease that can reduce the burden of crystals in the joints. However, in patients with some of the associated metabolic conditions, treatment of the underlying disease may decrease the number of attacks. This does not appear to be the case with hemochromatosis as phlebotomy does not change the joint calcification or symptoms.

Again, look out for the patient with wrist arthritis who also has Bouchard (PIP) nodes and Heberden (DIP) nodes consistent with OA. Think of CPPD and screen for hemochromatosis, hyperparathyroidism, and hypothyroidism in patients < 50 years of age.

HYDROXYAPATITE ARTHROPATHY (HAA)

HAA is also known as basic calcium phosphate arthropathy or calcium apatite deposition disease. Hydroxyapatite is the primary mineral in bone and teeth. Abnormal accumulation may occur idiopathically, in hypercalcemic/hyperparathyroid states, in damaged tissues, and in scleroderma and dermatomyositis. Crystal arthropathy in dialysis patients is sometimes due to HAA, and both CPPD and HAA are associated with OA. The shoulder is the most commonly affected joint.

Think about HAA in **elderly** patients (especially **women**) who have a **destructive** arthropathy of the shoulders (“**Milwaukee shoulder**”), hips, knees, and/or hands with noninflammatory and sometimes hemorrhagic synovial fluid (with increased mononuclear cells) and **no** visible crystals. The affected joint may be unstable, may have crepitus, and feels cool to the touch. Radiographs show calcification in and around the joints +/- erosions, depending on how bad the disease is.

Arthrocentesis confirms the diagnosis of HAA with identification of the HAA crystals in the joint fluid. Unlike urate and CPPD crystals, these crystals are very small, nonbirefringent, and are seen only by electron microscopy or light microscopy with special staining (using alizarin red).

Treatment for acute HAA is the same as for acute CPPD. For dialysis patients, controlling serum phosphorus levels helps prevent flares.

INFECTIOUS ARTHRITIDES

PREVIEW | REVIEW

- What is the typical cell count in the synovial fluid of a septic joint? What type of cells are they?
- What common pathogens are associated with septic joints?

- What is special about the approach to diagnosis of gonococcal arthritis compared to traditional septic joint workup?
- How do you diagnose gonococcal arthritis?
- What are presenting features of Whipple disease? What organism is involved?
- What is the most sensitive joint fluid test to diagnose tuberculous arthritis?
- What test is used to confirm a parvovirus B19 synovitis?
- What are the Jones criteria for acute rheumatic fever?
- What is the typical presentation of chikungunya-associated arthritis?
- How do you diagnose Lyme arthritis?

SEPTIC ARTHRITIS

Healthy joints are sterile. If they become infected, it is from the migration of bacteria from another portal of entry. Damaged or prosthetic joints are often the most susceptible to infection. Patients who are immunocompromised also are prone to septic arthritis. Always

culture the areas suspected as the portal of entry, in addition to the synovial fluid, to increase the yield of a positive culture.

Septic arthritis usually presents as an acute monoarticular (rarely oligo- or polyarticular) inflammatory arthritis, occurs from **seeding** during bacteremia, and is associated with **fever** and a warm, swollen joint (Table 10-9). In most cases, synovial fluid aspiration reveals a WBC count > 50,000 cells/μL (and often > 100,000 cells/μL) with neutrophil predominance, and Gram stain and culture are frequently positive. An indolent course with inflammatory fluid and negative Gram stain suggests mycobacteria, fungi, or Lyme arthritis.

Know these septic joint associations and portals of entry that allow dissemination of the bacteria (Table 10-9):

- *Staphylococcus aureus* and *Streptococcus viridans*—usual causes (60–70%) of septic native joints in adults, especially in rheumatoid arthritis (RA) patients; portal of entry: skin, wound infection
- Adolescents and young adults—*Neisseria gonorrhoeae* (most common cause of infectious arthritis in this age group!) often with concomitant *Chlamydia trachomatis*. Remember that synovial WBC counts may be in only the 10,000 cells/μL range; portal of entry: oropharynx and genitourinary tract.

Table 10-9: Microbial Causes of Septic Arthritis

Host	Bacteria	Port of Entry	Pearls
Adolescents, young adults	<i>Neisseria gonorrhoeae</i>	Oropharynx, GU tract	WBC in joint usually lower than typical septic joint. Can be 10,000 cells/μL. <i>Chlamydia</i> can coexist; joint cultures commonly negative, so culture oropharynx and GU areas to increase yield.
Children, adults	<i>Staphylococcus aureus</i> <i>Streptococcus viridans</i>	Skin/Wound infection	Accounts for 2/3 of all septic native joint arthritis
Children, adults	Anaerobes <i>Eikenella</i> spp.	Human bites	<i>Eikenella</i> is 1 of the AACEK* organisms and can cause endocarditis.
Children, adults	<i>Pasteurella</i> spp.	Animal bites	Cat bite wounds
Sickle cell patients	<i>Staphylococcus aureus</i> <i>Salmonella</i> spp. <i>Pneumococcus</i> spp.	Hematogenous	Infection can precipitate a sickle cell crisis.
Patients with prosthetic joints	<i>Staphylococcus aureus</i> Coagulase-negative <i>Staphylococcus</i>	Hematogenous, local wound infection	Loosening of prosthesis is concerning for infection.
Injection drug users	<i>Staphylococcus</i> <i>Streptococcus</i> Gram-negative bacteria (esp. <i>Pseudomonas</i>)	Hematogenous	Predilection for axial joints, sternoclavicular, sacroiliac joints
Patients with many comorbidities	Gram negatives Group A streptococci, <i>Pneumococcus</i> , <i>Staphylococcus</i>	Respiratory, hematogenous	Obtain blood cultures as well.
Immunosuppressed patients	Mycobacteria Fungus	Hematogenous, local wound infection, respiratory	Infection is indolent, chronic; synovial fluid may be bloody and noninflammatory.
Fisherman, aquarium hobbyist	<i>Mycobacterium marinum</i>	Local wound infection	Cultures may be negative from synovial fluid; need culture from mucosal surfaces.

*AACEK: *Aggregatibacter aphrophilus* (formerly *Haemophilus aphrophilus*), *Aggregatibacter actinomycetemcomitans* (formerly *Actinobacillus actinomycetemcomitans*), *Cardiobacterium hominis*, *Eikenella corrodens*, *Kingella kingae*

- Sickle cell anemia—*Salmonella* and *Pneumococcus*, but *Staphylococcus* is still most common; portal of entry: bloodstream due to asplenia.
- Human bites—anaerobes and *Eikenella*
- Animal bites—*Pasteurella multocida*
- Extensive comorbidities—gram negatives, group A streptococci, *Pneumococcus*, and *Staphylococcus*
- Indolent, chronic infection with noninflammatory fluid (+/- bloody)—mycobacteria, fungus, or a noninfectious cause
- Injection drug users—*Staphylococcus*, *Streptococcus*, gram negatives (especially *Pseudomonas*); predilection for axial disease (e.g., sternoclavicular, sacroiliac joints)
- Prosthetic joints—*Staphylococcus aureus* or coagulase-negative *Staphylococcus*; loosening of the prosthesis is very concerning for infection.

Risk factors for septic arthritis include a history of diabetes mellitus or immunosuppression, as well as a history of preexisting joint disease in the affected joint (e.g., osteoarthritis, gout, neuropathic arthropathy). Patients almost always present with an acute monoarticular (sometimes oligoarticular) arthritis. Fever, joint warmth, erythema, tenderness, and limited range of motion are typical findings on physical exam. As mentioned earlier, synovial fluid aspiration reveals a WBC count > 50,000 cells/ μ L (and often > 100,000 cells/ μ L). **Gram stain** of the joint fluid commonly shows WBCs and organisms. Synovial fluid cultures grow the organism most of the time; about half of the time, blood cultures also are positive.

It is critical to obtain blood cultures and perform arthrocentesis **before** administering empiric antibiotics. Septic arthritis is a true medical emergency, given the high risk of irreversible joint destruction without timely therapy; this is why you begin empiric antibiotics before culture results are available.

Treatment for septic arthritis includes systemic antibiotics targeted to the Gram stain result: nafcillin or vancomycin for gram-positive cocci; broader coverage for gram negatives, *Pneumococcus*, and *Gonococcus* if no organisms are seen; and antipseudomonal coverage if injection drug use is suspected. It may be necessary to repeatedly **drain** the joint. Patients who do not improve with antibiotics and repeated aspiration should undergo surgical lavage and/or arthrotomy.

Gonococcal Arthritis

Gonococcal arthritis deserves special mention as it is frequently a topic on exams. **Pregnancy** and **menstruation** are predisposing factors for disseminated gonorrhea. Patients with deficiency of **terminal complements C5–C9** or MAC components are also at high risk. Presentation is fever, migratory polyarthritis, **tenosynovitis**, and dermatitis (**red papules** that become pustular). Gonococcal joint infection is **always** from

dissemination, but you might have missed the clinical signs/symptoms during dissemination. Remember to consider this diagnosis in the adolescent patient with knee pain.

In gonococcal arthritis, arthrocentesis often reveals a WBC count > 50,000 cells/ μ L, but it can be as low as 10,000–20,000 cells/ μ L. Joint cultures are usually sterile and blood cultures are positive in < 50% of cases.

Know that in disseminated gonorrhea, you culture all mucosal surfaces that can be harboring the organism (i.e., cervix, rectum, and oropharynx in women; urethra, rectum, and oropharynx in men), in addition to any skin lesions, joint fluid, and blood. Adequate cultures require direct plating of the specimen on Thayer-Martin ("chocolate") agar at the bedside because *N. gonorrhoeae* is a relatively fragile organism, susceptible to temperature changes, drying, UV light, and other environmental stresses. First, go to the lab and get your special media before you do an arthrocentesis. Then, squirt some of the joint fluid directly onto the chocolate agar plates as well as sending the fluid for Gram stain and culture and sensitivity. The test of choice in the diagnosis of disseminated gonococcal infection is by molecular testing using the nucleic acid amplification test (NAAT), a form of polymerase chain reaction on a specimen of blood or synovial fluid, or a swab from a skin or genital lesion. This provides the greatest yield in providing a diagnosis but offers no information on sensitivity or resistance to an antibiotic, so obtain both NAAT and cultures.

PROSTHETIC JOINT INFECTIONS

Most prosthetic joint infections tend to involve the knee and hip sites. These infected joints often have a more subtle presentation, loosening of the joint, and radiolucency around the implant. In addition, there may be a sinus tract communicating with the infected implant. Surgical management requires the need for a 2-step treatment plan with infectious disease subspecialty involvement (remove prosthesis, then proceed with a 4- to 6-week course of pathogen specific antibiotics).

Patients who have prosthetic joints but need to undergo procedures (e.g., dental, urologic) are at risk for developing transient bacteremia and seeding of their joints. However, there is no evidence to recommend routine antibiotic prophylaxis in patients with prosthetic joints undergoing invasive dental, GU, or GI procedures.

WHIPPLE DISEASE

Whipple disease is a rare and chronic bacterial infection caused by *Tropheryma whippelii*. Predominantly, it affects Caucasian, middle-aged men (with a male-to-female ratio of 4:1) and causes recurrent episodes of **nondestructive** seronegative inflammatory arthritis that predominantly affects large joints (e.g., knee). It also is commonly associated with **GI** manifestations including diarrhea, malabsorption, weight loss, fevers,

lymphadenopathy, skin hyperpigmentation, and neurologic findings. Myocarditis is rare. The main neurologic symptom is memory loss due to a slowly **progressive dementia**. Oculomasticatory myorhythmia (convergent-divergent nystagmus with concomitant masticatory contractions) is **pathognomonic** for Whipple disease. Importantly, the joint manifestations usually precede other symptoms by ≥ 5 years, providing a critical window for diagnosis and treatment. Those are a lot of systems to remember. Basically, think about Whipple disease in Caucasian, middle-aged men with diarrhea, fat malabsorption/weight loss, memory loss, and a long history of recurring episodes of inflammatory arthritis.

The 1st diagnostic test is small bowel biopsy. Take 7–10 specimens and submit for periodic acid-Schiff (PAS) stain, PCR, and immunohistochemistry (if available). If these results are negative, test specimens from other parts of the body that are involved using the same studies.

Treatment usually requires parenteral antibiotics (e.g., ceftriaxone) initially to ensure CNS penetration, followed by oral therapy, such as double-strength TMP/SMX $\times$ 1–2 years! Recurrences are common. Whipple disease is also discussed in the **Gastroenterology** section.

TUBERCULOUS ARTHRITIS

Typically, tuberculous arthritis presents as an **indolent chronic monoarthritis** (months to years). Hip and knee joints are most commonly affected. The arthritis is either an expression of primary tuberculosis (TB) or a site of reactivation. Most patients do **not** have associated active pulmonary TB. Remember: Immunosuppressive agents, particularly TNF inhibitors, are risk factors for reactivation TB.

A positive TB skin test in a patient with a chronic joint effusion is a strong indication for a TB workup. As with pulmonary TB, TB skin tests are not always positive in people with infection, so do not let a negative test dissuade you from the workup if you suspect TB based on the history or other data.

Joint fluid may show inflammation (average WBCs = 20,000 **mononuclear** cells/ μ L). Know that acid-fast smears and cultures of the synovial fluid are useful if positive, but their sensitivities are not great ($< 40\%$). The most sensitive joint fluid test is **NAAT** (nucleic acid amplification test), a highly sensitive and rapid test.

As with pleural TB, **biopsy** of the synovium for pathology and culture is the gold standard (80% sensitivity, 100% specificity). Pathology shows caseating granulomas, lymphocytes, and giant cells with caseation.

Treatment is the same as for active pulmonary TB: isoniazid, rifampin, pyrazinamide, and ethambutol $\times$ 2 months until you get the organism and its sensitivities. Then, narrow therapy to 2 drugs $\times$ 4–7 more months (6–9 months total). Treat longer if the patient is HIV+.

OTHER ARTHRITIDES ASSOCIATED WITH INFECTION

Viruses and bacteria sometimes cause a true **infection** of the joint (septic arthritis) or a **reactive** (immunologic) arthritis.

We will discuss 3 common arthritides caused by infections: parvovirus B19 synovitis, acute rheumatic fever, and poststreptococcal reactive arthritis.

Parvovirus B19 Synovitis

Parvovirus B19 is 1 of the more common causes of **non-bacterial synovitis** in adults. Think about parvovirus B19 when you see a young adult female with a history of exposure to school-aged children, who presents with symmetric synovitis of the **hands** (mimicking rheumatoid arthritis [RA]) and **macular rash** (75%). The synovitis has been present for 2–4 **weeks** (unlike RA > 6 weeks), and she may even describe a recent “slapped cheek” rash in the children. Again, the history of exposure to sick children 1–2 weeks prior to the arthritis alerts you to the possibility of parvovirus B19 as the cause of **hand** arthritis. The diagnosis can be confirmed by the presence of IgM against parvovirus B19. Be aware that during this time frame, the patient also can test false positive for other autoantibodies such as RF and ANA. Thus, it is important to detect the presence of IgM parvovirus B19. Treatment is with NSAIDs. Symptoms usually resolve in a couple of weeks.

Note other causes of nonbacterial synovitis: rubella, mumps, acute hepatitis B (oligoarthritis/arthralgias associated with maculopapular rash, fever, and urticaria before jaundice), chronic hepatitis C, and enteroviruses.

Acute Rheumatic Fever (ARF)

ARF is a rare immunologic complication typically occurring 2–3 weeks after a previous group A streptococcal infection. Polyarthritis is 1 of the World Health Organization’s criteria for diagnosis. Consider ARF in adolescents and young adults (rare after 30 years of age) who fulfill the Jones criteria for diagnosis.

The Jones criteria (2 major, or 1 major and 2 minor) in the setting of recent group A streptococcal infection are sufficient for a diagnosis. If the patient has chorea alone, you need to evaluate for possible ARF.

Jones **major** criteria—**CCEPS**:

- Carditis (cannot include minor: prolonged PR interval)
- Chorea
- Erythema marginatum (pink macules with central clearing, usually on the trunk)
- Polyarthritis (typically migratory)
- Subcutaneous nodules (painless)

Jones **minor** criteria:

- Fever
- Arthralgias
- Elevated ESR and/or CRP
- Prolonged PR interval (cannot include major: carditis)

Treatment is with 1.2 million units of IM penicillin × 1 dose or oral penicillin for 10 days, then monthly prophylactic penicillin for years.

More information on ARF can be found in the [Cardiology](#) section.

Poststreptococcal Reactive Arthritis (PSRA)

PSRA is considered a separate entity from acute rheumatic fever (ARF) and from typical HLA-B27-associated reactive arthritis. Onset of PSRA is within a shorter period of 10 days of group A streptococcal infection unlike ARF. Patients may present with prolonged or recurrent arthritis that is additive (rather than migratory). There is a **bimodal** distribution: childhood and middle age. Incidence of developing carditis is low. There is little consensus on treatment—aspirin, NSAIDs, and steroids are used. The role of antibiotics is controversial.

CHIKUNGUNYA

Chikungunya virus is an arbovirus transmitted by mosquitoes. Commonly seen in Africa, Asia, and India, the virus spread to Europe in 2007 and to the U.S. in 2014. The disease manifests as abrupt onset of fever followed by headaches, rash, and severe joint pain. The joint symptoms can be debilitating and may last for a few days or years. Use NSAIDs, low-dose steroids, and DMARD therapy to manage the arthritis.

LYME ARTHRITIS

Remember: Endemic areas for Lyme disease include the northeast and north central parts of the U.S., as well as the Pacific coast, particularly northern California. Lyme arthritis is a late manifestation of Lyme disease. It occurs in 50% of untreated patients, manifesting from a few months to 1–2 years after the disease-causing tick bite.

True Lyme arthritis is an intermittent or persistent, **asymmetric**, monoarticular or **oligoarticular** arthritis, usually affecting only 1 or a small number of large joints most commonly the knee. Up to 50% of patients never have evidence of early Lyme disease: erythema migrans, carditis, cranial nerve abnormalities, peripheral neuropathies, mononeuritis multiplex, or meningoencephalitis. A small number of patients actually develop destructive, erosive arthritis. See the [Infectious Disease](#) section.

Diagnose Lyme arthritis using a serum **ELISA** test for anti-*Borrelia burgdorferi* IgG. The IgM ELISA test is not appropriate because arthritis represents a late manifestation (thus, IgG is more appropriate), and these IgM tests

often are falsely positive. Do **not** do any further testing if the IgG ELISA test is negative as a **negative** test excludes Lyme as the cause of arthritis.

False-positive Lyme ELISA serology is caused by many diseases, including systemic lupus erythematosus, rheumatoid arthritis, Rocky Mountain spotted fever, and other spirochetal diseases (syphilis and leptospirosis), and is seen at a high rate in healthy controls. So, order a **Western blot** as a confirmation test in patients with a +IgG ELISA.

Although the test is not readily available commercially, DNA amplification is useful on synovial fluid. The rate of false positives is high; do not order this test unless the patient has a positive IgG ELISA and Western blot. The DNA can persist in the joint long after adequate treatment; hence, a positive PCR test does not identify whether disease is active or treated. Antibody testing of synovial fluid is not helpful.

Treat Lyme arthritis **without neurologic involvement** with a course of oral doxycycline or amoxicillin for **28 days**; then reassess. If pregnancy is a concern, the recommended alternative medication is a macrolide (erythromycin) or amoxicillin.

Persistent synovitis after oral antibiotics is treated with NSAIDs and observation, as occasionally the inflammation takes weeks to improve. If the patient still has synovitis after oral antibiotics and a period of NSAIDs and observation, retreatment with **another 28 days** of oral doxycycline or amoxicillin is appropriate. Ceftriaxone can be used for 14–28 days in patients who do not improve at all after the initial oral regimen.

When Lyme arthritis is treated with ceftriaxone × 28 days or 2 regimens of oral antibiotics, the patient is **definitively treated**. Any further symptoms/inflammation should be treated conservatively by a rheumatologist. Options include NSAIDs, hydroxychloroquine, and intraarticular steroids.

Know that a patient with Lyme **arthritis** who has **neurologic involvement** (except for isolated Bell's palsy) should undergo a lumbar puncture and be considered for treatment with **intravenous ceftriaxone**, instead of oral antibiotics.

Some patients with persistent symptoms, which are indistinguishable from chronic fatigue syndrome or fibromyalgia, receive the diagnosis of “chronic Lyme disease,” but know that **definitive data do not exist** to support this claim. Some prefer the term “post-Lyme disease syndrome.” As such, it is inappropriate to treat any form of Lyme disease with prolonged oral or intravenous antibiotics. In very rare circumstances, a patient with late neurologic involvement may require an additional 1 month of parenteral ceftriaxone after the 1st month of treatment, but do not give a patient more than two 28-day parenteral regimens. Multiple months of oral or parenteral antibiotics, and antibiotics, which are ineffective against the organism (e.g., azithromycin, tetracycline, tinidazole, rifampin, atovaquone/proguanil HCl, artemisia), are not considered standard of care by the Infectious Diseases Society of America.

LESS COMMON ARTHROPATHIES

PREVIEW | REVIEW

- What are the characteristic clinical features and lab findings for adult-onset Still disease?
- Does hemochromatosis initially affect large or small joints?
- What is the characteristic hand x-ray finding for hemochromatosis?
- What is the most common cause of a neuropathic joint?
- Which conditions are associated with hypertrophic pulmonary osteoarthropathy?

OVERVIEW

This topic discusses joint diseases associated with systemic illness. Although they are less commonly seen, they are extremely important to know.

ADULT-ONSET STILL DISEASE (AOSD)

AOSD is an uncommon illness. It occurs with a bimodal distribution: teens to young adults and middle-aged individuals. Onset > 60 years of age is unusual. A similar disorder, called systemic-onset juvenile arthritis, is more commonly seen in children < 16 years of age. It presents with a distinctive evanescent (fleeting or vanishing), macular, **salmon-pink** rash that coincides with a daily (quotidian) high-spiking fever and significant leukocytosis (Yamaguchi criteria). The coincidence of a rash that appears with the fever and disappears at defervescence is a big clue to the diagnosis. Include AOSD in the differential diagnosis of fever without a source.

Mild oligoarthritis develops in most patients. Joint fluid is inflammatory (average WBCs = 13,000 cells/ μ L). Other signs/symptoms include sore throat, lymphadenopathy, splenomegaly, myalgias, arthralgias, and serositis. Some patients may progress to a destructive polyarthritis, and their joints actually fuse (especially the wrists); however, this is uncommon.

Associated lab abnormalities include:

- Anemia of chronic inflammation (or anemia of chronic disease)
- Reactive thrombocytosis
- Increased ESR or CRP
- Liver transaminase elevations
- Very high serum ferritin levels (> 10 $\times$ normal) are **strongly** associated with this disease and correlate with more severe **disease activity**.

Initial treatment for mild disease includes NSAIDs, but most patients **ultimately require systemic steroids**.

Methotrexate and other DMARDs are often used to manage mild-to-moderate disease. Patients refractory

to oral DMARDs respond well to IL-1 inhibitors such as canakinumab, recently approved by the FDA for the treatment of AOSD. Tocilizumab, an IL-6 inhibitor, has shown promise in managing this disease. TNF inhibitors may be used for chronic joint-predominant disease.

HEMOCHROMATOSIS ARTHRITIS

~ 20–40% of patients with hemochromatosis develop arthritis; in many, the arthritis is the presenting symptom. Typically, this happens in patients > 50 years of age.

The monthly menstrual cycle acts as a form of phlebotomy. Women with hemochromatosis may not have a manifestation of calcium pyrophosphate deposition (CPPD) disease until after menopause. So, consider hemochromatosis in **postmenopausal** women with a history of chronic OA joint pain and swelling.

The arthritis **1st** affects small joints. Think of hemochromatosis when you see synovitis of the **2nd** and **3rd** MCPs. Later, larger joints (e.g., knees, ankles, shoulders) are affected. The synovial fluid is sometimes **noninflammatory** (a big clue to help you distinguish this arthritis from the inflammatory ones that also affect the MCPs such as rheumatoid arthritis). The morning stiffness of this arthritis also is commonly < 30 minutes; x-rays show narrowed joint spaces.

Hand x-rays show **hook osteophytes** on the radial side of the **2nd** and **3rd** MCPs; erosions are not seen, unlike in RA. Other hand joints look like idiopathic osteoarthritis with joint space narrowing and subchondral sclerosis; chondrocalcinosis may be present.

Remember that **CPPD** occurs in association with hemochromatosis in ~ 50% of patients with the arthritis. So, you also may see chondrocalcinosis on radiographs and/or weakly positive birefringent crystals in the synovial fluid.

Treating hemochromatosis with phlebotomy may help other manifestations of disease, but **not the arthropathy**. Treat chronic joint disease with acetaminophen and NSAIDs. Intraarticular steroids and NSAIDs can be used for acute CPPD arthritis flares. Hemochromatosis is easily screened by iron studies. An elevated iron saturation level (iron/total iron-binding capacity [TIBC] of > 45%) or elevated ferritin level (> 89 ng/mL [200 pmol/Lng/mL]) suggests the diagnosis. See more on hemochromatosis in the **Gastroenterology** section.

NEUROPATHIC ARTHROPATHY (NEUROPATHIC JOINTS)

We used to call these **Charcot** joints. Neuropathic joints are destroyed via 2 proposed mechanisms:

- 1) Repeated trauma secondary to loss of pain sensation and/or proprioception
- 2) Autonomic dysfunction that leads to regional hyperemia, osteoclastic stimulation with active bone resorption

Diabetes mellitus is the most common cause.

Joint findings are **similar** to **severe OA** with osteophytes except that erosions also can occur. The metatarsophalangeal, tarsal, and talar joints are most typically involved, and radiographs confirm the diagnosis (**Figure 10-18**). Bony fragments, reminiscent of the trauma, often are seen floating in the joints on radiographs. To try to repair the damage, bone becomes overgrown, known as **periostitis**, and noninflammatory joint effusions develop. Eventually, the joints become **unstable** and **lax**. Think about this diagnosis in a diabetic patient with a horrific-looking joint (especially the foot) and minimal associated pain.

Treat joints with stabilization and focus on treating the underlying disease.



Figure 10-18: Neuropathic arthropathy with multiple dislocations and fractures

Source: J. Terrence, Jose Jerome

HYPERTROPHIC PULMONARY OSTEOARTHROPATHY (HPOA)

Think about HPOA when you see **polyarthritis**/joint effusion in a smoker who also has **clubbing** of the fingers. HPOA is either primary or familial, but it is most often associated with lung malignancies, usually non-small cell carcinomas (termed secondary HPOA). We do not know the mechanism for this condition, but it is associated with periosteal bone formation, joint effusions (due to synovial proliferation and inflammation), and clubbing (due to effects on connective tissue).

The bone changes can be associated with **dull, aching** pain that is **intense when you apply pressure** to the arms and legs. The arthropathy is commonly slight and appears noninflammatory (effusion WBCs < 500 cells/ μ L). Hands generally are not part of this presentation, other than clubbing!

In early stages, radiographs show periosteal bone growth adjacent to radiolucencies, especially in the diaphysis of the long bones. Later, irregular cortical thickening appears, mostly over metaphyses. Use imaging to look for an intrathoracic malignancy, especially lung cancer. Infectious etiologies also are seen in this syndrome, including bronchiectasis, lung abscess, and tuberculosis. If the cause is a lung infection, the arthropathy and clubbing usually disappear after antibiotics.

Remember: Think HPOA in the patient with **polyarthritis** (similar to rheumatoid arthritis), **clubbing** of the fingers and toes, and **periostitis** of the long bones. When you see this triad, evaluate the patient for **lung cancer**.

OTHER CONNECTIVE TISSUE DISEASES

PREVIEW | REVIEW

- Characterize the typical patient who develops primary Raynaud phenomenon.
- Which drugs **exacerbate** Raynaud phenomenon?
- Mixed connective tissue disease has features of which diseases?
- What is a typical presentation of Ig4-related disease?
- What is the treatment for Ig4-related disease?

RAYNAUD PHENOMENON

Primary Raynaud phenomenon most commonly begins in **young women** within a few years following menarche and is not associated with any rheumatologic disease. In ~ **90%** of young **women** with Raynaud phenomenon, the condition is primary (idiopathic) and without any significant sequelae. Raynaud phenomenon can cause a net-like or lacy macular rash known as **livedo reticularis** (**Figure 10-19**).



Figure 10-19: Livedo reticularis

Secondary Raynaud phenomenon is typically more severe and occurs in association with **connective tissue** diseases, and with certain prescription and illegal **drugs**. It is present in most scleroderma patients; it also is seen frequently in rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), Sjögren syndrome, mixed connective tissue disease (MCTD), primary biliary cholangitis, and dermatomyositis.

Common drugs that may exacerbate Raynaud phenomenon include:

- Serotonin agonists (e.g., triptans, β -blockers, ergots)
- Chemotherapeutic agents (e.g., bleomycin, vinblastine, cisplatin)
- Sympathomimetics (e.g., decongestants, clonidine, cocaine, methamphetamines)

Smoking decreases digital blood flow and must be avoided.

Raynaud phenomenon is defined and manifested as a sequential, **tricolor** change of the fingers and/or toes that occurs as a result of vasoconstriction with exposure to cold or emotional stress—even the stress of going to the doctor can elicit the response in some patients. Fingers and/or toes blanch or turn **white** (as a result of vasoconstriction); when cyanosis due to decreased oxygenation occurs, the digits turn **blue** (Figure 10-20); finally, with vasodilation upon rewarming, the digits flush **red** (white $\rightarrow$ blue $\rightarrow$ red). Patients may still have Raynaud phenomenon even if they do not have the classic triphasic color changes. Digits may turn white, then flush red without becoming blue. If rewarming and vasodilation do not occur, the digits are prone to necrosis. Paresthesias, pain, and clumsiness may be associated with the vasospastic episode. **Fingertip ulcerations** are an indicator of associated rheumatologic disease because ulcerations rarely occur in primary Raynaud phenomenon.



Figure 10-20: Raynaud phenomenon

The following suggest **secondary** Raynaud phenomenon: male, > 30 years of age, asymmetry of findings, **fingertip ulcerations**, coexistent vascular or autoimmune disease, and abnormal nail-fold capillaroscopy.

Nail-fold capillaroscopy is the diagnostic test of choice to confirm suspicion of **secondary** Raynaud phenomenon in an autoimmune disease. Abnormal, **dilated**, and tortuous capillaries at the nail fold are a microvascular abnormality defining secondary Raynaud phenomenon. This test is normal in primary Raynaud phenomenon. Other autoimmune rheumatic diseases, such as systemic sclerosis, also have abnormal nail-fold capillaries.

Nail-fold capillaroscopy is a simple test done in the office. Apply clear water-based lubricant over the proximal nail

folds (i.e., skin adjacent to cuticle), and examine them with an ophthalmoscope set at a diopter of 40.

Treatment includes avoiding the cold and drugs that cause vasoconstriction. Smoking/tobacco use exacerbates the disease. Initial treatment includes calcium channel blockers, α -blockers, and transdermal nitroglycerin. Consider phosphodiesterase-5 (PDE5) inhibitors (e.g., sildenafil, tadalafil, vardenafil), prostacyclin analogs (e.g., iloprost), and endothelial receptor antagonists (e.g., bosentan) in patients who fail initial treatment.

Localized digital sympathectomy is limited to patients who have failed medical treatment and who continue to experience ischemia or are at risk of losing a digit. If stress triggers an episode, relaxation techniques may be helpful.

Do not confuse **acrocyanosis** with Raynaud phenomenon. Acrocyanosis is distinguished by **persistent** blue/cyanotic fingertips/toes and the absence of pain.

Thromboangiitis obliterans (a.k.a. Buerger disease) also resembles Raynaud phenomenon. Thromboangiitis obliterans is a vasculitis characterized by recurring progressive inflammation and thrombosis of small and medium arteries and veins of the hands and feet in association with **tobacco** use. Claudication and ischemia with digital necrosis are common. Smoking cessation is the mainstay of treatment.

MIXED CONNECTIVE TISSUE DISEASE (MCTD)

MCTD patients have signs of **several** diseases including systemic lupus erythematosus (SLE), polymyositis, and systemic sclerosis; however, the signs are mixed together. Typically, MCTD presents with arthritis/arthralgias and RP. Patients may present with a mild myositis and/or serositis, as well as swollen hands. Lung involvement with either interstitial lung disease or pulmonary hypertension are the most severe complications. This disorder predominantly affects women more than men, with a female-to-male ratio of 9 to 1.

Anti-U1-RNP is the autoantibody to remember. High titers are associated with MCTD, and it has a **sensitivity approaching 100%**, so a **negative** result essentially **rules out** MCTD. Although SLE also may have anti-U1-RNP, MCTD usually does not have antibodies against dsDNA, Smith, SSA (Ro), or SSB (La). Therefore, it is unusual to see severe renal or CNS involvement with MCTD. If severe renal or CNS involvement is present, think SLE instead. Treat MCTD with steroids initially, and later convert to steroid-sparing agents (e.g., methotrexate, hydroxychloroquine). Alter treatment based on the clinical features.

Ig4-RELATED DISEASE

Ig4-related disease is systemic and is typically seen in middle-aged and older men. Its pathogenesis is due to a lymphoplasmacytic infiltrative disease in a storiform pattern of fibroblasts with Ig4-positive plasma cells.

Symptoms mimic malignancies, infections, allergies, and autoimmune diseases.

Presentations include a localized mass, retroperitoneal fibrosis, lymphadenopathy, autoimmune pancreatitis, aortitis, and sclerosing sialadenitis (inflammation and sclerosing of salivary glands).

Diagnose with elevated serum IgG level and biopsy of affected organs. Treat with prednisone, but rituximab has shown the most benefit in these patients so far. There may be a risk for malignancy in these patients, especially gastrointestinal and non-Hodgkin lymphoma.

ANTIPHOSPHOLIPID SYNDROME (APS)

PREVIEW | REVIEW

- What are the features of antiphospholipid syndrome?
- Which antiphospholipid antibodies are the most pathogenic?

APS is either primary and idiopathic, or it is secondary and associated with another disease (usually SLE), drugs, or an infection. It is characterized by the presence of at least 1 antiphospholipid antibody (repeated at a time interval of at least 12 weeks apart), along with either the findings of vascular thrombosis or those of pregnancy morbidity listed here:

- ≥ 1 of the antiphospholipid (APL) antibodies:
 - Lupus anticoagulant (LAC)
 - Anticardiolipin Ab (IgG or IgM in medium/high titer)
 - Anti- β_2 -glycoprotein-1 (anti- β_2 GP-1) Ab (IgG or IgM at any titer)

Plus, either of the following:

- Vascular thrombosis: venous (deep venous thrombosis and/or pulmonary embolism) and/or arterial clots (e.g., stroke, myocardial infarction)
- Pregnancy morbidity presenting as:
 - Miscarriage of a normal fetus at ≥ 10 weeks of gestation
 - Birth of ≥ 1 premature babies at < 34 weeks of gestation because of eclampsia/preeclampsia/placental insufficiency
 - Multiple miscarriages (≥ 3) at < 10 weeks of gestation

Because other conditions are associated transiently with APL antibodies but not the syndrome, the antibodies must be present on 2 separate occasions at least 12 weeks apart for diagnosis of APS. Note that APL antibodies cross-react with serologic tests for syphilis, causing false-positive results.

While not included as criteria for diagnosis, other findings seen with APS include:

- Livedo reticularis
- Sterile cardiac vegetations (Libman-Sacks endocarditis)
- Thrombocytopenia
- Prolongation of the partial thromboplastin time (PTT) caused by LAC (Mixing studies are done on plasma to differentiate factor deficiency from factor inhibitor.)

In a mixing study, the patient's plasma is mixed 50:50 with normal plasma. If the patient's prolonged PTT is due to factor deficiency, the mixing with normal plasma will provide the missing factor and correct the problem. If the PTT initially corrects and then again prolongs after the mixing study, the coagulopathy is most likely secondary to a clotting factor inhibitor.

Patients with APS are actually hypercoagulable, despite appearing to be anticoagulated (elevated PTT) from a laboratory standpoint!

LAC, high-titer anti- β_2 GP-1 Ab, and anticardiolipin IgG antibodies tend to be the most pathogenically associated with thromboembolic events and/or fetal wastage. Patients with elevated levels of APL antibodies, but without clots and/or fetal wastage syndrome, are treated prophylactically with aspirin 81 mg/day.

Catastrophic APS is a rare variant that carries a 50% mortality and manifests as multiorgan dysfunction secondary to numerous thromboses. Treatment includes anticoagulation, glucocorticoids, and plasma exchange.

Acute treatment of APS: Acute clots are treated with anticoagulation—usually low-molecular-weight heparin (LMWH).

Chronic treatment of APS: Treat the underlying disease if APS is secondary. Anticoagulation is commonly given. Use lifelong anticoagulation to treat primary disease. Give warfarin to maintain the INR at 2.0–3.0. Adding hydroxychloroquine is beneficial as well—the drug has antithrombotic effects.

Newer direct oral anticoagulants (e.g. apixaban, rivaroxaban, dabigatran) are not recommended as evidence has shown them less effective than warfarin for clot prevention with higher rates of recurrent strokes. In patients unable to tolerate warfarin or LMWH, they may be considered; however, the patient should be informed of their reduced benefit.

Give patients with a history of pregnancy-related morbidity LMWH and aspirin 81 mg/day prophylactically for subsequent pregnancies. Do not give warfarin to pregnant patients because it is teratogenic, can damage the CNS, and can cause fetal hemorrhage.

For more on APS during pregnancy, see the Women's and Men's Health section.

SJÖGREN SYNDROME

PREVIEW | REVIEW

- Sjögren syndrome patients are at increased risk for what kind of malignancy?

Sjögren syndrome is caused by a CD4+ T-cell lymphocytic infiltrate that destroys the exocrine glands (lacrimal and salivary glands), resulting in decreased secretions from these glands.

Sjögren syndrome occurs commonly in **women**. Patients typically present with xerostomia (dry mouth), keratoconjunctivitis sicca (KCS; dry eyes), fatigue, and/or parotid gland enlargement/inflammation. Extraglandular problems are common, including arthralgias, fibromyalgia, peripheral neuropathy, and interstitial lung disease. The majority of patients have concomitant fibromyalgia. Occasionally, patients present with only extraglandular manifestations (e.g., arthralgias, peripheral neuropathy, interstitial lung disease) and without any features of dryness mentioned above.

Some patients also have subacute cutaneous lupus erythematosus (see [Skin and Mucous Membranes on page 10-18](#)), purpura, and interstitial nephritis, with Type 1 (distal) renal tubular acidosis. These findings resemble systemic lupus erythematosus clinically, but not serologically.

Patients have at least some of the following autoantibodies:

- SSB (La): 50%
- SSA (Ro): 65%
- Rheumatoid factor (RF): 70%
- ANA: 80%

Be aware that many **medications** commonly cause xerostomia such as opiates and many psychiatric medications, including antidepressants. Review medications in anyone who presents with xerostomia for which you are considering a diagnosis of Sjögren syndrome.

In 2016, the American College of Rheumatology (ACR) published new criteria for Sjögren syndrome. Important points of these recommendations include:

- The diagnosis of Sjögren syndrome is given to all who have ≥ 1 symptom of ocular or oral dryness and have a score ≥ 4 when the weights from the criteria below are summed:
 - Labial salivary gland biopsy showing presence of focal lymphocytic sialadenitis (FLS) with focus score ≥ 1 focus/4 mm² (Weight 3)
 - Positive serum anti-SSA and/or anti-SSB (Weight 3)
 - Ocular surface staining (OSS) score ≥ 5 in ≥ 1 eye (Weight 1)
 - Schirmer test ≤ 5 mm/5 minutes in ≥ 1 eye (Weight 1)
 - Unstimulated whole saliva flow rate ≤ 0.1 mL/minute (Weight 1)

Interestingly, only ~ 15% of patients who have Sjögren syndrome do **not** have sicca symptoms. In addition, dry eyes/mouth symptoms do **not** show statistically significant association with serum anti-SSA/B, an OSS score ≥ 3 , or the presence of FLS.

Follow these patients for persistent lymphadenopathy, since there is up to a 40-fold increased risk of **B-cell lymphoma**! Patients with Sjögren syndrome and *Helicobacter pylori* infection are at high risk for mucosa-associated lymphoid tissue lymphoma (**MALToma**). Dental health is important in these patients. They are at high risk for dental caries and periodontal disease.

Remember: Children born to mothers with SSA and SSB antibodies (but especially SSA) are at risk for **congenital heart block** and **neonatal lupus** (which presents as a subacute cutaneous lupus rash).

Treatment is **symptomatic**:

- Wetting agents
- Parasympathomimetic and muscarinic agonists (pilocarpine and cevimeline) help with dryness.
- Punctal plugs for the eyes
- Cyclosporine eye drops
- Lifitegrast (a lymphocyte function-associated antigen 1 antagonist) eye drops
- Consider autologous serum ophthalmologic drops for extreme cases of KCS.
- Antimalarial agents help with arthralgias, fatigue, and rashes.

Glucocorticoids and other immunosuppressants do not improve the sicca symptoms in patients with Sjögren syndrome. Use is reserved for patients who have extraglandular disease such as peripheral neuropathy or lupus-like features.

Because the majority of patients with Sjögren syndrome have concurrent fibromyalgia, managing fibromyalgia is an important aspect of managing them.

SYSTEMIC SCLEROSIS (SSc) / SCLERODERMA

PREVIEW | REVIEW

- Which autoantibodies are associated with diffuse cutaneous systemic sclerosis (SSc)? With which complication are the antibodies associated?
- What are the key features of limited cutaneous SSc?
- Abnormal nail-fold capillaries are seen in which type of SSc?
- Which lung manifestation is often the cause of death in patients with SSc?
- What are the preferred drugs to treat scleroderma renal crisis?

OVERVIEW

Scleroderma is the term used to describe shiny, hard, thickened skin. This clinical feature may be limited to a specific anatomic location, or it may be associated with a series of systemic findings. The term systemic sclerosis (SSc) is used to describe this disease because it emphasizes the potential for sclerosis to involve internal organs.

SSc is either diffuse or limited in its expression depending on the extent of skin involvement. The general rule is: If skin is involved above the elbow and the knee (approaching or involving the torso), **diffuse** systemic sclerosis is present; if skin involvement starts at the fingertips and extends up to the elbow (or from the toes to the knee), then **limited** systemic sclerosis disease is present. The face can be involved in both diffuse and limited disease. Limited forms (80%) are more common than diffuse forms (20%).

ANA is positive in $\geq 95\%$ of those with SSc (titers are often strongly positive).

TYPES OF SYSTEMIC SCLEROSIS

Diffuse Cutaneous SSc (dcSSc)

In dcSSc, skin thickening is diffuse and is more likely than limited cutaneous SSc (lcSSc) to be associated with multiorgan involvement.

30% of patients with dcSSc are **anti-Scl-70** (antitopoisomerase I) antibody positive. The antibody is associated with development of **interstitial lung disease (ILD)** and **reduced survival**. The other antibody associated with dcSSc is anti-RNA polymerase III. It is associated with a much higher risk of scleroderma renal crisis, but a lower risk of ILD when compared to those with anti-Scl-70 antibodies.

dcSSc has a wide range of presentations based on which organs are affected. These patients are much more likely to develop **ILD**, **cardiac** disease, and **renal** disease than those with lcSSc. Pulmonary hypertension also can occur secondary to ILD. Scleroderma renal crisis is a medical emergency and occurs almost exclusively in patients with dcSSc, typically within the first 5 years of diagnosis.

Usually, dcSSc progresses within the first 5 years, after which no new organ systems are affected (although the initially affected organ systems continue to deteriorate). After this 1st explosion of disease, the skin typically begins to atrophy and loosen up, except for the hands. Know that the extent of skin disease in dcSSc is a marker for the severity of visceral disease.

Limited Cutaneous SSc (lcSSc)

In lcSSc, skin thickening occurs distal to the elbows and knees and can affect the face and neck. It affects the internal organs to varying degrees. Previously, lcSSc was referred to as CREST syndrome. The **key features of lcSSc**

are well described by the acronym **CREST**, so use it as a mnemonic (not all features of CREST need to be present for diagnosis):

- Calcinosis (Figure 10-21)
- Raynaud phenomenon—secondary (See [Raynaud Phenomenon](#) on page 10-39.)
- Esophageal dysmotility
- Sclerodactyly
- Telangiectasias (skin and mucosa; Figure 10-22)

Pulmonary hypertension is more common in lcSSc, occurring in 10–15% of lcSSc patients, and is pathologically identical to idiopathic pulmonary hypertension (IPH). Unlike dcSSc, ILD does **not** occur in lcSSc.



Figure 10-21: Limited cutaneous SSc with calcinosis



Figure 10-22: Telangiectasia
Source: Klaus D. Peter

Anticentromere antibody is specific for **lcSSc** and is seen in ~ 50% of patients. Patients who are anticentromere antibody positive tend to develop more severe digital ischemia and pulmonary hypertension.

Localized Scleroderma

In localized scleroderma, skin thickening occurs in discrete circular plaques and is referred to as **morphea**. Typically, morphea affects only 1 body part. When it affects ≥ 3 places, it is called generalized morphea. Linear scleroderma occurs when there are streaks of sclerosis. Localized scleroderma is usually seen in children, but it can be seen in adults as well. Some lesions of linear scleroderma extend deeper into the affected area and cause defects in the bone and surrounding soft tissue; flexion contractures of the joint can occur. Lesions in the face have been associated with seizures, dental malformations, and facial bone deformities known as **en coup de sabre**.

Systemic Sclerosis sine Scleroderma

Systemic sclerosis sine scleroderma is a form of systemic sclerosis that affects ~ 1% of patients. It is characterized by visceral disease without skin involvement.

MANIFESTATIONS OF SYSTEMIC SCLEROSIS

Skin

Skin changes follow a progression of mucinous edema, then induration, and finally fibrosis and atrophy.

Commonly, lcSSc involves the **distal** extremities and face.

Raynaud phenomenon eventually occurs in almost all patients with both limited and diffuse types of SSc, and severe vasoconstriction is associated with digital tip ulcerations, osteomyelitis, and black fingertips. Acroosteolysis (digital tuft resorption) subsequently develops. In lcSSc, Raynaud phenomenon usually occurs several years before other manifestations. In dcSSc, Raynaud phenomenon commonly occurs at the time of other manifestations. See [Raynaud Phenomenon on page 10-39](#).

Telangiectasias (the T in CREST) occur in dcSSc, but are much more likely in lcSSc.

Skin changes in dcSSc characteristically involve **entire** extremities, chest, abdomen, and face.

Sclerodactyly is the term used to describe localized scleroderma of the fingers or toes (either type).

Abnormal **nail-fold** capillaries may occur in either type of SSc. These capillaries are reduced in number, while the remaining enlarged capillaries form visible **giant loops**. These are important because a **direct correlation** exists between degree of abnormality of the nail-fold capillaries and severity of the SSc (more on nail-fold capillaroscopy under [Raynaud Phenomenon on page 10-39](#)).

Joints

Patients with SSc can have a mild, **symmetric** (like rheumatoid arthritis [RA] and systemic lupus erythematosus [SLE]) hand stiffness +/- synovitis. Patients with dcSSc can have a **tendon friction rub**, such as at the elbow, which is considered pathognomonic for SSc. The proximal interphalangeal joints, metacarpophalangeal joints, wrists, and ankles are the most common joints involved. Juxtaarticular osteoporosis, erosions, and joint space narrowing also occur in patients with SSc. Management of SSc arthropathy is similar to RA management, usually with DMARDs.

Muscles

Patients have mild myalgias and weakness along with mild creatine kinase (CK) elevations. Occasionally, there are features similar to polymyositis (**overlap syndrome**) or the mild CK elevation may be due to myopathy or from skin tightness.

Lungs

Lung disease is the main cause of morbidity and mortality in SSc. Cause of lung death in SSc is **often pulmonary hypertension** (PH) from 1 of 2 causes:

- 1) In lcSSc, PH is caused by intimal proliferation of the pulmonary arterioles (as in idiopathic PH). Again, this is more likely in anticentromere+ **lcSSc**.
- 2) In dcSSc, there are 2 modes of developing PH: from interstitial fibrosis secondary to alveolitis and pulmonary fibrosis (i.e., ILD) and from long-standing disease, similar to idiopathic PH.

Screen all patients with SSc for lung disease with PFTs, serum brain natriuretic peptide (BNP), and high resolution CT scan. Diffusing capacity of the lungs for carbon monoxide (DLCO) is a very important test in this group. A drop in DLCO may be the 1st sign of **ILD** or pulmonary arterial hypertension (PAH). Order spirometry regularly (every 6–12 months) to monitor for a restrictive lung disease pattern. A Doppler echocardiogram is recommended for those with abnormal screening tests.

Patients are at increased risk for lung cancers, especially if they smoke.

Kidney

Only dcSSc: Before ACEIs, scleroderma renal crisis was the major cause of morbidity and mortality. Renal crisis presents within the first 5 years of diffuse disease and is associated with prior or current glucocorticoid use and anti-RNA polymerase III antibodies. Patients develop acute malignant hypertension and renal failure with a bland urine sediment. Always consider the diagnosis of dcSSc in a young female who presents with acute malignant hypertension and renal failure. Patients may even present with thrombocytopenia and microangiopathic hemolytic anemia, which mimics thrombotic thrombocytopenic purpura.

Gastrointestinal Tract

Only dcSSc: **Wide-mouthed diverticula** are pathognomonic of dcSSc. They are not seen in lcSSc.

Only lcSSc: An association exists with primary biliary cholangitis and positive antimitochondrial antibody.

Both dcSSc and lcSSc: dysmotility throughout the GI tract, but especially the **esophagus** (the **E** in CREST) and the stomach (gastroparesis), is problematic for patients. Also, as disease progresses, the lower esophageal sphincter relaxes, so patients develop severe gastroesophageal reflux disease (GERD) with a propensity for chronic esophagitis, strictures, and Barrett disease.

Mucosal **telangiectasias** may be present throughout the GI tract. Telangiectasias in the stomach can lead to bleeding and iron-deficiency anemia. This syndrome is called gastric antral vascular ectasia (**GAVE**) or “watermelon stomach” because of its endoscopic appearance.

Dysphagia, constipation, intestinal pseudoobstruction, and malabsorption also are seen in **both** dcSSc and lcSSc.

Heart

Cardiac involvement is common in SSc, and symptomatic disease portends a **poor** prognosis. Heart findings include cor pulmonale, **restrictive** pericardial disease, and conduction defects/arrhythmias. Many patients have reperfusion defects on thallium stress tests, but true coronary artery disease is frequently absent. The abnormal stress result is presumed to be due to episodic vasospasm. Diastolic dysfunction is common.

TREATMENT

Treatment is generally symptomatic and organ specific. **No** approved medicines change the course of scleroderma, but imatinib and rituximab with hematopoietic stem cell transplantation are being investigated. Also, improvements have been made in morbidity.

Note that lcSSc has a **better prognosis** than dcSSc. However, remember that these patients can get **PAH** (especially those who are antcentromere+).

Use proton pump inhibitors aggressively in SSc patients with **GERD**. For dysmotility, prokinetic agents like erythromycin may be helpful.

Treat **localized skin disease** with ultraviolet light therapy.

ILD related to SSc is a challenge to treat. There are no consistently effective therapies. Mycophenolate mofetil or azathioprine is used often as an immunomodulator, based on retrospective data showing stabilization of lung disease (as measured by pulmonary function testing) in some patients; their use has mixed results. Consider cyclophosphamide for someone with rapidly progressing lung disease (once infection is ruled out); however, since improvements may not be substantial, weigh the decision for cyclophosphamide against the very high risks associated with its administration. Lung transplant is occasionally a viable option for some scleroderma patients with lung disease.

DLCO provides the 1st indication of both ILD and PAH. Monitor DLCO regularly. Evaluate patients with a low DLCO with an echocardiogram and a high-resolution CT scan and spirometry (to check heart and ILD as causes) especially SSc patients with antitopoisomerase I (anti-Scl-70) antibody positivity. Glucocorticoids and an immunosuppressant are commonly given to treat alveolitis. Bosentan, sildenafil, or the prostacyclin analogs (e.g., epoprostenol) are options for pulmonary hypertension. Some patients require a lung transplantation.

Kidney: Patients with diffuse disease should monitor their blood pressure monthly. Every 3 months, check the urine protein to creatinine ratio and estimate the glomerular filtration rate (GFR). Proteinuria and a > 20% reduction in GFR predict renal crisis. Administering an ACEI or ARB as primary prevention of renal crisis is no longer advised; several retrospective and case-control studies

show neither benefit nor harm. Additionally, 1 prospective observational cohort demonstrated an increased risk of renal crisis in patients with a prior use of ACEIs. Also, remember that moderate-to-high doses of glucocorticoids are associated with the development of renal crisis, so avoid them (or minimize the dose) as much as possible. If **renal crisis** is going to happen, it commonly occurs within the first 5 years of disease. Blood pressure elevations signal impending renal disease and eventual renal crisis if not controlled. Start ACEIs early; they are useful even if overt renal failure develops because renal failure may be reversed with their use.

ACEI/ARB in SSc recap:

- Not advised for primary prevention of renal crisis
- Start if developing hypertension or if there is a decline in renal function.

Lastly, there is some role for allogeneic **stem cell transplant** in patients with early dcSSc without major cardiac or pulmonary involvement. There have been dramatic improvements in disease manifestations within a few years of therapy; however, transplant in these patients is associated with a significant increase in morbidity and mortality (due to infectious complications) during the 1st year after transplant.

EOSINOPHILIC FASCIITIS

Eosinophilic fasciitis causes both **scleroderma-like** and **nonscleroderma-like skin** changes in the extremities—often **sparing** the hands (typically without Raynaud phenomenon and without antibodies associated with systemic sclerosis, including antinuclear antibodies). Eosinophilic fasciitis is known to follow unaccustomed rigorous exercise or be paraneoplastic (e.g., lymphoma, myeloma).

Tender, migrating edema of the extremities or a polyarthritides of the hands may be present in some patients.

So, these 3 useful clues can help you distinguish this mimic from systemic sclerosis (SSc):

- 1) Negative ANA
- 2) Absence of Raynaud phenomenon
- 3) Nail-fold capillaries are **normal**.

The nonscleroderma-like skin changes include peau d'orange type of induration (a late feature due to thickening and tethering of the fascial layers), which often occurs on the proximal forearms and upper legs but not the distal extremities. The affected areas have a characteristic "woody" consistency on palpation.

Additionally, **unlike** SSc, most patients have a **peripheral eosinophilia**, which appears early in the disease course, and increased inflammatory markers (i.e., ESR, CRP). A full-thickness excisional skin biopsy shows an eosinophilic infiltrate and fibrosis of the subcutaneous fascia.

Eosinophilic fasciitis is occasionally self-limited, but most patients require moderate-dose corticosteroids (40 mg/day) or steroid-sparing agents (methotrexate).

INFLAMMATORY MYOPATHIES

PREVIEW | REVIEW

- Compare and contrast polymyositis (PM) and dermatomyositis (DM).
- Which subtypes of autoantibodies are specific for certain clinical phenotypes seen in PM and DM?
- Which drugs cause myopathy?
- What conditions are associated with necrotizing autoimmune myopathy?

POLYMYOSITIS AND DERMATOMYOSITIS

Inflammatory diseases of skeletal muscle include polymyositis and dermatomyositis (about equal occurrence), impacting women more than men, between 40 and 50 years of age, as well as some less-common disorders.

Inflammatory myopathies:

- Polymyositis (adult)
- Dermatomyositis (adult)
- Myositis associated with malignancy
- Juvenile polymyositis or dermatomyositis
- Myositis associated with connective tissue disease (e.g., systemic lupus erythematosus, systemic sclerosis, mixed connective tissue disease)
- Inclusion body myositis

Polymyositis (PM)

Features of PM may be found in patients with other autoimmune disorders such as SLE and MCTD. Occasionally, PM is associated with the MHC Class II HLA antigen DR3.

PM manifests as **symmetric proximal muscle weakness** +/-, in some patients, **mild myalgias**. PM (and DM) typically does not cause neuropathy, only myopathy. Weakness usually occurs 1st in the **proximal** muscles but **hips and thighs are affected more than shoulders and arms**). Presentation mimics muscular dystrophy. Many patients present with difficulty rising from a squatting or kneeling position, as well as elevated muscle enzymes (CK, aldolase, often aspartate aminotransferase [AST] and alanine aminotransferase [ALT]), and, commonly, elevated inflammatory markers (i.e., ESR, CRP). Remember: Myositis generally presents with weakness, not pain! This is an important feature in distinguishing myositis from polymyalgia rheumatica (PMR), which presents primarily

as muscle pain and not a myopathy. Further, CK is high in myositis, while in PMR, the ESR and CRP are high but CK is normal. Know how to distinguish between these 2 entities! Also know how to distinguish myositis and PMR from fibromyalgia, which has normal muscle enzymes and absent inflammatory markers (Table 10-10).

As PM progresses, dysphagia (from tongue, pharynx, and upper esophageal dysfunction), dysphonia, dyspnea (from diaphragm weakness), and cardiac/ECG changes (from myocarditis or CAD) are all possible. These require hospitalization and aggressive immunosuppressive therapy.

Dermatomyositis (DM)

DM is similar in clinical presentation to PM, but skin involvement also occurs. In some patients, the skin manifestations are quite severe—or even the sole area of involvement (amyopathic dermatomyositis).

Skin changes in DM consist of a moderate-to-deep, violaceous, papular, sometimes scaly, photosensitive rash that occurs on the face, neck (where it may be known as a V sign or a shawl sign), and extensor surfaces of the joints. There is an associated periorbital edema with a **heliotrope** rash (Figure 10-23). This rash is **violaceous** and classically



Figure 10-23: Heliotrope rash

appears on the **upper eyelids**, but it also may appear on the cheeks and forehead. (SLE's malar rash does not involve the eyelids.) Gottron papules (Figure 10-24) are flat-surfaced, reddish-to-violet, scaling papules on the metacarpophalangeal and interphalangeal joints of the fingers (these look like "cigarette-paper" crinkling of the skin over the joints). They are the most **specific** indication of DM.

Vasculitic lesions also may develop, more commonly on the extremities. A psoriatic-like rash can appear on the **scalp**. The scalp is very



Figure 10-24: Gottron papules

Table 10-10: Distinguishing Features of Myositis, Polymyalgia Rheumatica, and Fibromyalgia

Disease Features	Muscle Weakness	Muscle Pain	CPK Levels	ESR/CRP levels
Myositis (PM/DM)	+++	—	High	High
PMR	—	+++	Normal	High
FM	—	—	Normal	Normal

DM = dermatomyositis; FM = fibromyalgia; PM = polymyositis; PMR = polymyalgia rheumatica

itchy—this is 1 of the main complaints! Changes in nailbed capillaries, as discussed under [Raynaud Phenomenon on page 10-39](#), can be seen in DM (also seen with scleroderma and SLE).

Antisynthetase Syndrome

Antisynthetase syndrome is a specific presentation of PM and DM. It is characterized by very acute onset of disease with fevers, weight loss, Raynaud phenomenon, cracking and discoloration of the hands (a.k.a. mechanic's hands), polyarticular and nonerosive arthritis, and a predilection for interstitial lung disease (ILD). Anti-Jo-1 antibodies (a type of antisynthetase antibody) often are found with this presentation. The ANA is usually negative in these patients. ILD is often more significant than the myositis. The disease typically is refractory to treatment.

Another myositis-specific autoantibody is the anti-SRP (signal recognition particle) antibody. These patients have PM and often develop **cardiomyopathy**. Prognosis is poor.

Diagnosis of PM and DM

PM and DM peak between 45 and 65 years of age. The following findings help establish the diagnosis of PM and DM:

- CK is the best initial test for screening. 95% of patients have **elevated CK** levels; you also may see an increase in other muscle enzymes such as aldolase, LDH, AST, and ALT.
- Abnormal, myopathic electromyogram (EMG; increased fibrillations, decreased amplitude, and spontaneous repetitive activity) with early recruitment
- **Abnormal muscle biopsy (gold standard)**; increase the yield on biopsy by targeting an involved muscle (usually deltoid or quadriceps), or by using MRI to select an optimal site. Avoid biopsy of sites recently studied by EMG; instead use the contralateral side. Abnormalities of muscle biopsy include **lymphocytic infiltration** of myofibrils and/or blood vessels. Immunohistochemical analysis will reveal **immune complex deposition** in the areas of inflammatory infiltrate.
- Skin biopsy in DM: Biopsy of the Gottron papules or the erythroderma in regions of the shawl sign; may make the diagnosis and thereby avoid the need for muscle biopsy. Light microscopy and immunofluorescence show abnormalities at dermal-epidermal junction.
- ANAs are present in ~ 60% of patients. But know that presence of any of the more specific antinuclear antibodies (anti-Ro, -La, -Sm, -RNP) suggests that the diagnosis is **not** PM or DM, but another connective tissue disease such as SSc, SLE, MCTD, or overlap syndrome.

Know the other myositis-specific antibodies because they are associated with characteristic phenotypes:

- Anti-Jo-1: strongly associated with ILD and antisynthetase syndrome (See [Antisynthetase Syndrome](#).)

- Anti-SRP: very acute severe PM and cardiac involvement; poor response to immunosuppression
- Anti-Mi-2: classic DM with V sign and shawl sign; mild weakness and very good response to therapy
- Anti-p155/p140: strongly associated with cancer-associated DM
- Anti-MDA-5: seen in DM with skin ulcerations, palmar papules, and ILD. Some have amyotrophic DM. It has a poor prognosis.

Cancer in PM and DM

Cancer is present in 7–10% of adult PM patients and 15–20% of adult DM patients at the time of, or soon after, diagnosis of the muscle disease. There is no increased cancer risk in juvenile DM. The risk increases with age, up to ~ 30–40% in patients > 65 years of age. The patient with cancer is usually > 50 years of age and has DM more often than PM. The most common associated malignancies are ovarian, lung, pancreatic, colon, and lymphoma. Every newly diagnosed PM or DM patient must be evaluated for underlying malignancy with age-appropriate cancer screening, in addition to any specific investigations guided by the history and physical examination. The risk for cancer is highest within the first 5 years of diagnosis. Routine total body PET/CT is not recommended as a screen for cancer in **newly** diagnosed PM or DM patients.

Treatment of PM and DM

Typically, PM and DM are treated with **high-dose glucocorticoids**, which are slowly tapered while a **steroid-sparing agent** is added (e.g., azathioprine, methotrexate). 80% of patients begin to respond to the steroid within a few days to 6 weeks.

Patients with life-threatening manifestations usually receive IV pulse glucocorticoids.

Antimalarials, such as hydroxychloroquine, are helpful for the **rash** in DM.

Intravenous immunoglobulin (IVIG), mycophenolate mofetil, and rituximab also have been used to manage refractory PM and DM.

Important points on glucocorticoid use:

- Remember to prescribe **vitamin D**, **Ca²⁺**, and **bisphosphonate** therapy for those on chronic glucocorticoids (all patients—not just those with PM or DM).
- Remember and monitor for the potential side effects of glucocorticoids: steroid-induced diabetes, adrenal insufficiency, psychosis, osteoporosis, infections, and hypertension.
- Think about **superimposed steroid myopathy** in a patient with PM or DM who initially improves with glucocorticoids but subsequently develops progressive weakness despite improvement in CK levels. Treatment is to taper glucocorticoids gradually to avoid a flare in the disease.

INCLUSION BODY MYOSITIS (IBM)

IBM is the **most common** inflammatory myopathy in persons **> 50 years** of age. It occurs more typically in Caucasian men.

IBM is a more indolent disorder characterized by prominent **proximal** and **distal** muscle weakness, either symmetrical or asymmetrical. This contrasts with PM and DM, which are diseases characterized by only proximal muscle weakness and almost always symmetrical.

Common manifestations are dysphagia, which increases the risk for aspiration pneumonia, dropping of items due to weak handgrip and finger dexterity, and “droopy neck syndrome.” Focus history on possible drug exposures (e.g., antimalarials, glucocorticoids, colchicine, statins, **cocaine**, alcohol).

No lab studies are helpful except for muscle biopsy! CK may be only mildly elevated. Markers of inflammation may be absent, and no autoantibodies develop.

Diagnosis is made by a **suggestive history** in combination with a **muscle biopsy** showing red-rimmed vacuoles and filamentous inclusions.

Take patients off the precipitating drugs and give a trial of glucocorticoids. If symptoms persist, add methotrexate or azathioprine and taper off steroids. Physical and speech therapy should be implemented early in the course of disease. IBM, unlike PM and DM, is only **minimally responsive** to treatment. It has a progressive, debilitating course.

DRUG-INDUCED MYOPATHY

Lipid-lowering drugs and chronic corticosteroids are the most common drugs that cause myopathy. Illicit drugs, such as cocaine and heroin, also are causes. Additionally, antimalarials and alcohol are causes of drug-induced myopathy. **Alcohol** is the most common myotoxin and can cause acute rhabdomyolysis with very elevated CK-MM.

Statins, especially when combined with **gemfibrozil** (a fibrate), are a known cause of drug-induced myopathy. Other risk factors for statin-induced myopathy include diabetes, untreated hypothyroidism, renal/liver disease, heavy alcohol use, consumption of a large amount of grapefruit, and taking drugs that inhibit cytochrome p450 (e.g., fluconazole, cyclosporine). Patients can present with myalgias and normal CK levels. Severe muscle pain and rhabdomyolysis also can occur. Depending on severity, patients may have weakness of the proximal muscles as well. If the myopathy is severe (e.g., weakness, CK elevations $> 3\times$ normal, myoglobinuria), stop the drug. Patients usually improve when the drug is stopped.

However, a small percentage of patients with statin-induced myopathy develop an autoimmune **necrotizing myopathy** where the muscle biopsy shows significant muscle necrosis with little or no inflammation. These patients also test positive for antibodies to 3-hydroxy-3-methylglutaryl-coenzyme A reductase (anti-HMGCR).

Treatment requires immunosuppression in addition to stopping the statin. Necrotizing autoimmune myopathy also is seen with connective tissue disease, HIV, and cancers.

Glucocorticoid myopathy typically presents in 1 of 2 ways:

- 1) Chronic myopathy:
 - Chronic use of prednisone ≥ 30 mg/day
 - Proximal muscle weakness
 - Normal CK and EMG
- 2) Acute quadriplegic myopathy:
 - High-dose IV steroids
 - Severe generalized weakness
 - Elevated CK +/- myoglobinuria; abnormal EMG
 - Most commonly associated with concurrent use of neuromuscular blocking agents in critically ill patients

Consider the acute form as a possible cause of diaphragm weakness in patients who are difficult to wean from the ventilator. Glucocorticoid myopathy is an exclusionary diagnosis; patients improve when you stop the drugs and start physical rehabilitation.

Colchicine toxicity can cause neuromuscular dysfunction (i.e., myopathy, neuropathy, or combination of the 2). It **mimics** PM with proximal muscle weakness, paresthesias, and elevated CK. Suspect this in the gout patient with chronic kidney disease who is taking long-term colchicine. Remember: PM and DM cause myopathy—they do not cause neuropathy. Treatment is suspension of the drug.

NONARTICULAR RHEUMATISM

PREVIEW | REVIEW

- What are the nonpharmacologic therapies used to treat fibromyalgia (FM)?
- Which drugs are used to treat FM?

FIBROMYALGIA (FM)

FM is a hypersensitivity syndrome characterized by hyperalgesia. This **noninflammatory** disorder is associated with neurochemical imbalances that result in increased sensitivity and heightened response to painful stimuli. Women are affected more than men with a ratio of ~ 10:1. Patients often complain of diffuse myalgias, all-day stiffness, excessive fatigue, and nonrestorative sleep.

The 2016 ACR criteria for diagnosis include:

- the widespread pain index (WPI: 0–19) and
- the symptom severity (SS) scale (0–12), which is composed of 4 variables: degree of fatigue, waking unrefreshed, cognitive impairment, and general somatic symptoms.

Diagnosis of FM must meet the following criterion:

Criterion 1:

- WPI ≥ 7 and SS ≥ 5 **or**
- WPI 4–6 and SS ≥ 9 .

Criterion 2: Pain is in 4 of 5 regions (left upper, right upper, left lower, right lower, axial). Pain in the jaw, chest, and back are not evaluated as part of this definition.

Criterion 3: Symptoms have been generally present for **at least 3 months**.

Other causes of similar symptoms must be excluded. Understand that other entities (e.g., obstructive sleep apnea, hypothyroidism) cause symptomatology similar to FM, but also know that FM can coexist with other diseases.

Consider the following labs to evaluate for other disorders: ESR, TSH, CK, CBC, and liver transaminases. A sleep study may be needed to reveal sleep apnea or another cause of excessive daytime somnolence.

Patients with FM often have associated disorders including depression/anxiety, stress, history of emotional and/or physical trauma (e.g., sexual abuse), migraines, unexplained paresthesias (unsupported by EMG), and self-reported yet undetectable Raynaud phenomenon. “Symptomatic” mitral valve prolapse, irritable bowel syndrome, interstitial cystitis, and “chronic fatigue syndrome” diagnoses tend to be comorbid conditions. Remember: FM can coexist with autoimmune disorders such as SLE and rheumatoid arthritis (RA). If an RA patient is not getting better despite aggressive immunosuppression and without clinical evidence for inflammation on exam or labs, consider FM as the cause of their pain.

Nonpharmacologic therapy is the foundation of FM treatment. Stress reduction, cognitive behavioral therapy, and behavioral feedback have been shown to help reduce symptoms. Regular exercise and sleep restoration are essential components of treatment.

Pharmacologic interventions include antidepressants or combination of antidepressants (low-dose tricyclics +/- SSRIs or SNRI [serotonin and norepinephrine reuptake inhibitors]), antiseizure medications, and/or nonnarcotic analgesics. Steroids and NSAIDs are useful only for coexisting inflammatory conditions. Tramadol and acetaminophen are adjuncts for pain. Avoid opioids because they have limited efficacy and carry significant risks.

Pregabalin (antiseizure medication) is the 1st medication approved by the FDA specifically for FM. **Gabapentin**, which is **less expensive**, is a frequently used and effective treatment. Both alleviate the pain (specifically neuropathic pain).

Duloxetine and **milnacipran** are FDA-approved dual reuptake inhibitors, which block reuptake of both serotonin and norepinephrine. Adding an SSRI or a dual reuptake inhibitor to a tricyclic antidepressant is sometimes used in patients who complain of fatigue or exhaustion coupled with mood disturbances. Be aware that this combination

increases the risk of serotonin syndrome. Note that combining tramadol with an SSRI also increases the risk for serotonin syndrome.

There may be an increased incidence of suicidal thoughts in patients taking pregabalin, duloxetine, milnacipran, or tramadol.

MYOFASCIAL PAIN SYNDROME

Myofascial pain syndrome (a.k.a. regional fibromyalgia) manifests as localized myalgias or muscle spasms. Patients usually have localized tender points in the muscles. The condition is different from FM in that myofascial pain syndrome is thought to originate from the injured muscle, whereas comparable FM pain is thought to originate from an aberration in the CNS processing of pain. Whiplash and repetitive microtrauma have been associated with myofascial pain syndrome.

Massage, physical therapy, muscle relaxants, NSAIDs, and local injection of anesthetic into the tender points may be helpful.

COMPLEX REGIONAL PAIN SYNDROME (CRPS)

CRPS, previously known as reflex sympathetic dystrophy (RSD), is a form of chronic pain usually affecting a distal extremity (upper more than lower).

CRPS is divided into 2 types, both with similar signs and symptoms:

- **CRPS 1:** Previously RSD, this type accounts for **90%** of the cases and occurs after an illness or trauma in which the nerves in the affected extremity were not directly damaged. **Fracture** is the most common trigger in CRPS 1.
- **CRPS 2:** Ensues after a **direct injury** to the nerve.

In addition to pain, patients typically have sensory, motor, or autonomic dysfunction manifested by pain, hyperalgesia, edema, temperature asymmetry, muscle atrophy, decreased range of movement, or weakness. The dysfunction often appears to be disproportionate to the inciting event. In severe cases, flexion contractures may develop. Profound **osteopenia** may be seen on x-ray imaging. The diagnosis is clinical, but triphasic bone scans may be helpful in diagnosing CRPS (sensitivity is 40–60%). The most specific findings on bone scan include diffuse increased activity with juxtaarticular uptake on the delayed (Phase 3) images. Although there have been limited studies evaluating the role of MRI in diagnosing CRPS, MRI often is used to exclude other etiologies of localized pain. MRI has less sensitivity compared to triphasic bone scans.

Treat CRPS with NSAIDs, pain modifiers (e.g., tricyclic antidepressants, gabapentin), physical therapy, short course of glucocorticoids, and sympathetic nerve block (as needed). Early, aggressive therapy helps to prevent the chronic changes described above.

OTHER CAUSES OF NONARTICULAR RHEUMATISM

Other causes of myalgia: **Hypothyroidism** frequently presents with myalgias and stiffness, and usually has an elevated CK-MM. Statins also are a relatively common cause of muscle pain. Additionally, diabetes mellitus is a cause of nonarticular rheumatism.

VASCULITIS

PREVIEW | REVIEW

- What are the typical lab findings in a patient with vasculitis?
- What is a typical presentation of giant cell arteritis (GCA)? What are the atypical presentations?
- How do you diagnose GCA? What is a serious complication of GCA within the first 5 years of diagnosis?
- What biologic drug is approved for GCA that allows for more rapid tapering of prednisone?
- What are differences in the clinical presentations of myositis and polymyalgia rheumatica?
- Which viruses have been associated with polyarteritis nodosa (PAN)?
- How do you diagnose PAN?
- Which organs/tissues are commonly involved in granulomatosis with polyangiitis (GPA)?
- Which antibodies are specific for GPA?
- Why is TMP/SMX given to patients with GPA?
- Mixed cryoglobulinemia is associated with which hepatitis virus?
- How do you distinguish cholesterol atheroembolism from vasculitis?
- What are the clinical features of Behçet disease?
- What complications are seen with Behçet disease?

OVERVIEW

Vasculitis is the inflammation of blood vessel walls, which leads to narrowing, obstruction, ischemia, or aneurysm formation. The clinical presentation is protean and varies according to the histologic type of inflammation, the **size** of the blood vessels involved, and the **organs** affected. Vasculitis usually is classified by the **size of blood vessel affected** and the presence (or absence) of antineutrophil cytoplasmic antibodies (**ANCA**s). The most common ANCA-associated vasculitides are granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA).

Vasculitis is most often the result of an immune reaction caused by either **immune complex** deposition and/or

complement activation. It affects small, medium, or large vessels. Often, vasculitis is hard to diagnose because symptoms may be systemic and nonspecific.

Frequently, presenting signs/symptoms include myalgias/arthralgias, neuropathy, fever, malaise, and weight loss. Consider vasculitis in a patient with **palpable purpura** and/or **mononeuritis multiplex** (peripheral nerve damage affecting several distinct nerves in different regions of the body).

Because of the wide spectrum of symptoms, suspect vasculitis in patients with fever without a source (FWS), especially in those with constitutional symptoms such as weight loss and fatigue. Also consider vasculitis in the differential diagnosis when there is no satisfactory explanation for the following conditions: myositis, arthritis, palpable purpura (i.e., rash that does not blanch), mononeuritis multiplex manifested as foot drop, multi-system disease, glomerulonephritis, or GI, cardiac, or CNS disease.

Again, constitutional symptoms are big in vasculitis. (Rheumatoid arthritis eats at the joints and nips at the body; vasculitis nips at the joints and eats at the body.)

Typical lab findings include an **increased ESR/CRP**, thrombocytosis (the platelet count is a "poor man's sedimentation rate"), anemia of chronic disease, and hypoalbuminemia. Not all vasculitides present with elevated ESR or CRP—primary CNS angiitis may have normal ESR and CRP!

Confirm a diagnosis of vasculitis with biopsies or angiograms. Skin biopsies may not be specific enough (although polyarteritis nodosa can be diagnosed by skin biopsy in some cases). **Muscle and nerve biopsies** are very specific, but not very sensitive; however, sensitivity increases with an increase in symptoms and with EMG findings. Do a **testicular** biopsy if the patient has testicular pain and/or swelling. Sensitivity and specificity are good. **Kidney** biopsies (in a patient with systemic vasculitis symptoms) showing a necrotizing glomerulonephritis with crescent formation is virtually diagnostic for vasculitis (but can be seen in several different vasculitic-like syndromes such as lupus). Remember: Biopsy the **most involved tissue** whenever possible.

LARGE VESSEL VASCULITIS

Large vessel vasculitis includes:

- Giant cell arteritis (Remember, **polymyalgia rheumatica** can coexist.)
- Polymyalgia rheumatica
- Takayasu arteritis
- Aortitis

Giant Cell Arteritis (GCA)

GCA is part of a spectrum of systemic inflammatory diseases associated with polymyalgia rheumatica (PMR) in 50% of patients.

GCA primarily affects the carotid arteries and their branches (ophthalmic and temporal) in patients > 50 years of age (average age is 70 years of age). Women are affected more than men (with a ratio of 3:1). The disease is most commonly seen in Caucasian northern Europeans and is rare in African Americans.

Multinucleated giant cells infiltrate blood vessels arising from the aortic arch in a patchy or segmental fashion. Symptoms include temporal headache, diplopia, amaurosis fugax (i.e., sudden monocular blindness), scalp tenderness, and **jaw claudication** (characterized by pain and soreness that worsens with chewing). Jaw claudication is a very specific symptom! Untreated, 40–50% get **ischemic optic neuropathy** with unilateral irreversible **blindness** (increased risk in the setting of thrombocytosis; the risk of visual loss, transient ischemic attacks, and stroke may decrease by adding low-dose aspirin in combination with corticosteroid therapy).

GCA occasionally has a **masked** presentation—consider it in workups for **FWS**, failure to thrive, and/or **anemia of chronic disease**.

GCA also can present similarly to Takayasu arteritis, with symptoms of large vessel vasculitis (e.g., strokes, peripheral bruits, discrepant blood pressures, asymmetrically decreased peripheral pulses, peripheral claudication). Extracranial involvement in patients with GCA increases the risk of **thoracic** aortitis.

Physical examination may reveal a thickened and tender temporal artery (**Figure 10-25**) or absent temporal artery pulse (sometimes the temporal arteries are asymptomatic, particularly if disease is associated with predominantly great vessel involvement). Bruits may be present, particularly in the carotid and supraclavicular areas. Abdominal tenderness may be suggestive of aortitis.

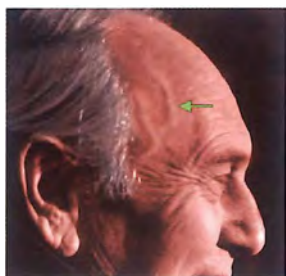


Figure 10-25: Swollen temporal artery

ESR is virtually always > 60 mm/hour in GCA. In affected patients, if ESR is not elevated, CRP usually is. While extremely rare, GCA can occur in the setting of a normal ESR and CRP. Leukocytosis and anemia of chronic disease also can occur in a patient with GCA.

The gold standard for the diagnosis of GCA is a temporal artery biopsy. Color Doppler ultrasonography (CDUS) of the temporal arteries has been studied as a means of diagnosing GCA; however, the accuracy of the test is dependent on the skills of the technician and the interpreter.

Begin glucocorticoid therapy as soon as the diagnosis is **suspected**. Do not wait for the biopsy! If you suspect GCA, treat right away to decrease the risk of vision loss. While the biopsy should be performed as early as possible, a cohort study at the Mayo Clinic shows that even

a delay of 1–2 weeks does not significantly impact biopsy results. Biopsy a **large** piece of artery (3–5 cm) and do multiple cross-sectional cuts. Even so, because of the **patchy** involvement, a negative biopsy does not exclude GCA. Bilateral temporal artery biopsies may improve sensitivity by ~ 5% compared to a unilateral biopsy; however, they are somewhat controversial.

Initial treatment for GCA is prednisone at ~ 60 mg/day. Once symptoms have resolved, the prednisone is tapered slowly, often taking up to 2 years. Relapses are common during the 1st year and require increasing the dose of steroids.

If a patient with suspected GCA develops vision loss, this is a medical emergency and requires urgent referral to an ophthalmologist (in addition to a rheumatologist). Treat this patient with high-dose IV methylprednisolone 1,000 mg/day for 3–5 days before switching to oral glucocorticoids. The FDA approved tocilizumab in 2017 to treat GCA, and patients can potentially be weaned off corticosteroids within 12 weeks of initiating therapy with this biologic. Be aware of the side effects of this medication (see biologic information under **Treatment on page 10-45**).

Follow the **sedimentation rate** because it frequently correlates with disease activity. Low-dose aspirin decreases the risk of stroke in these patients, so start this along with the steroids.

The risk for **aortic aneurysms** (usually ascending) is increased in patients with GCA. The risk is highest within the first 5 years of diagnosis. Screen for asymptomatic thoracic aortic aneurysms with chest radiographs for up to 10 years and proceed with advanced arterial screening if radiographs are concerning for aneurysm formation. Patients with history of tobacco use, hypertension, or diabetes have greater risk for aortic aneurysms.

GCA is a common exam topic. You may be given a case of an elderly Caucasian patient with shoulder aches, headache, and vision complaints. You must determine whether the patient has polymyalgia rheumatica (PMR) with GCA, other causes of retinal artery occlusion, carotid artery disease, or some ophthalmic disorder. Body pain + vision complaints in the elderly + high ESR = PMR with GCA! Also know that GCA can present as FWS or weight loss in the elderly. If you strongly suspect GCA, treat right away with high-dose glucocorticoids. If only PMR exists, then low-dose glucocorticoids suffice.

Polymyalgia Rheumatica (PMR)

PMR is a clinical syndrome classically associated with GCA and may be a milder manifestation of the same disease. 20% of PMR patients develop GCA. Conversely, in those with GCA, 50% also have symptoms of PMR or already have been diagnosed with PMR.

A PMR-like illness can be present in other conditions. Elderly-onset rheumatoid arthritis (RA) presents as a syndrome indistinguishable from PMR initially, although a significant inflammatory polyarthritis eventually

develops. (Rheumatoid factor is often negative.) Presence of FWS in a patient with PMR may indicate the development of GCA.

Think of PMR in the **older** patient with a history of **profound morning stiffness**, bilateral shoulder girdle and hip aching, and **hand swelling** (mimicking RA).

Remember: PMR **pain is out of proportion** to exam findings. PMR presents with aching and stiffness, not weakness—in contrast to myositis, which generally presents with weakness, not pain! In addition, PMR is distinguished from polymyositis by the absence of both objective weakness and elevated muscle enzymes. CK is normal in PMR even though the patient has muscle aches and feels stiff.

Sedimentation rate typically is elevated (> 50 mm/hour) but is normal in $\sim 5\%$ of patients.

Treatment: PMR responds dramatically to **low-dose** prednisone; however, it must be tapered slowly, usually over 1 year or more, for cure.

2015 ACR/EULAR guidelines say to start at the minimum effective dose (prednisone 12.5–25 mg/day), then taper in 4–8 weeks to 10 mg/day. Once remission is achieved, taper by 1 mg every month until discontinuation of glucocorticosteroids. Relapses are common, and you may need to reinstitute or increase glucocorticosteroids.

If you have an older patient with shoulder pain who improves dramatically overnight after 1–2 doses of prednisone, the diagnosis is probably PMR. Asymptomatic elevation of serum inflammatory markers does not warrant an automatic glucocorticoid dose increase; however, maintain an index of suspicion for progression to GCA in these patients.

Note: Atypical presentations of PMR or poor response to low-dose steroids can reflect a paraneoplastic process.

As with GCA, the **ESR** correlates with disease activity—follow it during treatment. If there are any signs of GCA (e.g., visual changes, headache), you **must** do a complete reevaluation immediately, including temporal artery biopsy and an increase in the prednisone dose.

Takayasu Arteritis

Takayasu arteritis (a.k.a. pulseless disease) usually involves the aorta and its proximal branches. It primarily affects **young women** (< 40 years of age), particularly of **Asian descent**. Takayasu arteritis may present initially with nonspecific inflammatory features, such as FWS (“inflammatory phase”). Then, months to years later, it may present with claudication of the upper extremities, strokes, TIAs, or renovascular hypertension with bruits (“pulseless phase”). Patients also may have Raynaud phenomenon, weak peripheral pulses, discordant blood pressures, erythema nodosum, and aortic regurgitation from dilatation of the ascending aorta.

Diagnose using conventional angiogram or magnetic resonance angiogram (MRA) demonstrating large artery

narrowing, referred to as “beading” (Figure 10-26) or “string of pearls,” and/or characteristic aneurysms. Exacerbations or recurrences of inflammation are indicated by an increase in ESR, CRP, anemia, and artery wall inflammation visible on MRA. Unlike GCA and many of the other vasculitides, tissue biopsy has essentially no role in the diagnosis of this disorder. (Trying to nick the aorta for a tissue sample = really bad idea!)



Figure 10-26: Takayasu arteritis showing areas of stenosis
Source: MedPix

Treat with glucocorticoids (main) or DMARDs. Biologics have been used to treat the acute inflammatory stage. Revascularization with angioplasty, stenting, or bypass surgery may be needed for severely stenotic arteries. Ideally, these procedures should be performed when the acute inflammatory phase is controlled. Patients may require antiplatelet or **anticoagulation** for very stenotic vessels. Takayasu arteritis tends to recur and has a guarded prognosis.

Cardiovascular disease is the major cause of death in patients with Takayasu arteritis. Strict management of cardiovascular risk factors, such as hypertension, hyperlipidemia, diabetes mellitus, and smoking, is mandatory. Remember: A patient with history of Takayasu arteritis may present with low BP in 1 arm. Check the BP in the other arm and both legs. Hypertension may be undetected and not appropriately treated in these patients!

Aortitis

Aortitis is associated with several systemic inflammatory diseases. Exam questions typically ask about the most common associations such as syphilis, endocarditis with mycotic aneurysm, GCA/Takayasu arteritis, and spondyloarthropathies. IgG4-related disease (see more under **Ig4-Related Disease on page 10-40**) is another

cause of aortitis. Know that syphilitic aortitis is a tertiary manifestation associated with aneurysm formation and valve regurgitation, but aortic dissection and rupture are **extremely rare!**

MEDIUM / SMALL ARTERY VASCULITIS

The most common and frequently tested medium/small artery vasculitides:

- Polyarteritis nodosa
- Eosinophilic granulomatosis with polyangiitis
- Granulomatosis with polyangiitis
- Microscopic polyangiitis

Of these 4, know that **polyarteritis nodosa** is the only 1 **not** associated with ANCA autoantibodies.

Review **Antineutrophil Cytoplasmic Antibody (ANCA)** on page 10-4.

Polyarteritis Nodosa (PAN)

PAN affects small to medium-sized arteries and is **strongly** associated with **hepatitis B** and **hepatitis C**. The vasculitis results in inflammation in the walls of arteries (but not capillaries or veins) with subsequent formation of aneurysms. Unlike many of the other vasculitides, the inflammation in PAN is **not** granulomatous; instead, it is marked by the accumulation of neutrophils and mononuclear cells with fibrinoid necrosis.

Classic PAN commonly affects the arteries that supply the skin, peripheral nerves, GI tract, and kidneys, but **sparing the lungs**. Symptoms of PAN include anorexia with weight loss, fevers, malaise, arthralgias, mononeuritis multiplex, CNS symptoms, abdominal symptoms, and lower extremity rashes (palpable purpura, livedo reticularis, nodules, and bullae/vesicles). The abdominal symptoms are related to mesenteric arteritis, causing infarct or perforation. Renal involvement usually presents as hypertension, mild proteinuria, and hematuria without red cell casts. **Note: PAN does not cause glomerulonephritis**; thus, the absence of RBC casts. If you suspect PAN, always order a urinalysis. The presence of glomerulonephritis suggests an alternate diagnosis and not PAN. Instead, disease affects the walls of the arteries that supply blood to the nephron. Essentially, renal ischemia is the primary pathology, with activation of the renin-angiotensin-aldosterone system and development of hypertension.

PAN affects **virtually all organ systems**, including the coronaries; however, PAN does not classically cause disease of the pulmonary arteries nor does it cause glomerulonephritis! Patients may present with pulmonary edema as a consequence of left heart failure, but PAN does not cause pulmonary hemorrhage or infarction. These tidbits help you to exclude PAN as a cause of a pulmonary-renal vasculitis. If you see a patient with a pulmonary-renal vasculitic syndrome, think

granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), or eosinophilic granulomatosis with polyangiitis (EGPA)—not PAN!

Suspect a diagnosis of PAN in a patient with **multiple diverse symptoms** such as chest pain (pericarditis), abdominal pain (mesenteric arteritis), foot drop (mononeuritis multiplex), and especially testicular pain.

Diagnosis of PAN: If there is **no** obvious **peripheral involvement** (e.g., nerve, muscle, testicle), do an **angiogram**. An angiogram of the mesenteric or renal medium-sized arteries shows diffuse, small, saccular aneurysms or stenoses in a “chain of beads” that are diagnostic. If there is **peripheral involvement**, **biopsy** the affected site. Again, biopsy the testicle(s) if pain is present. If there is mononeuritis multiplex, biopsy the sural nerve. If the kidney is affected in PAN, the involvement is in the artery, and biopsy is frequently diagnostic. (Remember: This is **not** glomerulonephritis.) Important to note: ANCA tests are usually **negative**. Test for hepatitis B infection whenever PAN is suspected. Many cases are associated with chronic hepatitis C infection as well.

PAN is a severe disease, and patients **die if not treated** (10–20% of patients survive 5 years). Treatment of PAN includes treating chronic hepatitis B and hepatitis C, if present, and giving **glucocorticoids +/- cyclophosphamide**, depending on severity at presentation. Sometimes, this treatment only slows the progression of the disease.

There is a skin variant termed cutaneous PAN that presents with ulcerating skin lesions and neuropathy as clinical features. Medium vessels are located in the deep dermis. Make sure to request that the skin biopsy (a noninvasive means for diagnosis here) includes the deep dermis and some subcutaneous fat. Systemic immunosuppression frequently is required.

ANCA-ASSOCIATED VASCULITIS

Eosinophilic Granulomatosis with Polyangiitis (EGPA)

EGPA is a necrotizing, pulmonary-renal vasculitis marked by eosinophilic granulomas. Patients **typically** have a history of adult-onset asthma **+/-** sinus disease or allergies (including allergic rhinitis and nasal polyps). Mononeuritis multiplex is particularly common (always do a detailed neurologic examination in anyone you suspect for EGPA). Glomerulonephritis is less common compared to GPA or MPA.

Labs show **peripheral eosinophilia** > 10%, p-ANCA+, and anti-MPO+.

Treatment is the same as for PAN, although many patients **respond well to glucocorticoids** alone.

Granulomatosis with Polyangiitis (GPA)

The hallmark of GPA is **necrotizing granulomas**. This is a small vessel vasculitis that commonly involves the **sinuses**, causing a **saddle nose deformity** (Figure 10-27), **lungs with cavitary nodules** (Figure 10-28), and **glomerulonephritis**. A pulmonary-renal syndrome with diffuse alveolar hemorrhage with glomerulonephritis occurs as well. Patients occasionally develop skin rashes and/or ulcerations and may have migratory large joint arthritis. Recurrent sinusitis and other upper respiratory issues are extremely common.

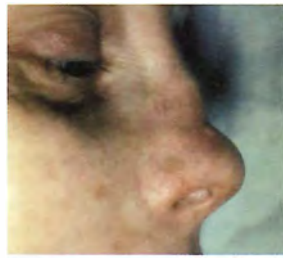


Figure 10-27: Saddle nose deformity
Source: Frederick Stucker, MD



Figure 10-28: Cavitory nodules in granulomatosis with polyangiitis (GPA)
Source: Seth Berney, MD

Typical findings on laboratory testing show elevation of ESR/CRP, reactive thrombocytosis, and anemia of chronic disease (in addition to acute kidney injury and glomerulonephritis in patients with renal involvement).

Remember the antibody tests (Table 10-3 on page 10-4).

Patients with GPA are often **c-ANCA+** and **anti-PR3+**. This helps to exclude systemic lupus erythematosus (SLE) and the other vasculitides too.

c-ANCA/anti-PR3+ is seen in > 90% of patients with **severe** GPA, but in only ~ 50% with **limited** GPA (limited typically = no renal involvement). ANCA occasionally appear in rapidly progressive glomerulonephritis and in microscopic polyangiitis, but these vasculitides are usually p-ANCA/anti-MPO+.

Confirm the **diagnosis** of GPA with tissue **biopsy** of the involved organ whenever possible. Most frequently, kidneys are the preferred biopsy site, followed by lungs

(due to their high diagnostic yield). Sinus biopsies are not done routinely because of their low diagnostic yield. Biopsied purpuric skin lesions show a nonspecific leukocytoclastic vasculitis, which is not helpful in distinguishing the various types of vasculitis.

The biopsy results of either kidney or lung show **any** or **all** of these findings:

- Small and/or medium vessel vasculitis
- Necrosis
- Granulomatous inflammation
- No complement deposition and absent immunofluorescence (rules out SLE)

GPA, like PAN, rapidly progresses to **death** without treatment. Therapy consists of high-dose glucocorticoids with methotrexate (non-life-threatening), or with rituximab or cyclophosphamide (life-threatening). Rituximab is at least equally efficacious as cyclophosphamide with less toxicity. In 2011, the FDA approved rituximab for the treatment of GPA and MPA.

In patients with mild pulmonary and renal involvement (defined as normal oxygenation and < 50% increase in creatinine), methotrexate, azathioprine, or leflunomide are treatment options.

Prescribe TMP/SMX prophylactically because of increased risk for *Pneumocystis pneumonia* (PCP) when the patient is on high-dose corticosteroids (≥ 20 mg/day), cyclophosphamide, or rituximab. It is unknown whether it is the illness itself or the immunosuppressive treatment that predisposes these patients to PCP. Preventing this lung infection may help to prevent GPA-associated lung exacerbations.

Remember: Side effects of cyclophosphamide include short-term problems such as bone marrow suppression and infection. Additionally, they include longer-term problems such as sterility, amenorrhea (higher risk for individuals > 35 years of age), bladder effects (e.g., hemorrhagic cystitis, bladder cancer), and leukemia/lymphoma. See rituximab side effects in Table 10-8 on page 10-15 and Anti-TNF Biologics (a.k.a. TNF- α Inhibitors) on page 10-15.

Microscopic Polyangiitis (MPA)

MPA is also a **pulmonary-renal syndrome**, with glomerulonephritis being much more common than pulmonary capillaritis. MPA causes a necrotizing, crescentic glomerulonephritis and can present as FWS. In contrast to GPA and EGPA, **granulomatous inflammation is absent**. GPA and MPA are referred to as **pauci-immune** vasculitides because immune complex deposition is not detected to any significant degree, unlike in SLE. MPA never has angiographic changes because it involves small vessels. Upper airway and pulmonary nodules are not typical of MPA and, when present, suggest GPA. Diagnosis is based on biopsy of affected tissue. MPA is often **p-ANCA+** and **MPO+**.

Treatment is essentially identical to GPA and, as mentioned earlier, rituximab also is approved for the treatment of MPA.

OTHER SMALL VESSEL VASCULITIDES

Other important small vessel vasculitides to remember include:

- Hypersensitivity vasculitis
- IgA vasculitis
- Cryoglobulinemia
- Antiglomerular basement membrane disease/ Goodpasture syndrome

Hypersensitivity Vasculitis

Hypersensitivity vasculitis is a small vessel vasculitis of the skin with minimal or no involvement of other organs. Skin biopsy shows leukocytoclastic vasculitis, which is a histopathologic finding characterized by polymorphonuclear leukocytes permeating through vessel walls with concomitant cellular death and debris. Although the lesions are not always palpable, the classic skin manifestation is palpable purpura ("crops" of purple **papules** or large **petechiae**), most often seen on the lower extremities (Figure 10-29).



Figure 10-29: Purpura and petechiae
Source: James Heilman, MD

~ 40–50% of hypersensitivity vasculitis cases are idiopathic, but the most common identifiable causes include:

- Drug reactions (especially β -lactams, sulfonamides, NSAIDs, diuretics, phenytoin, and allopurinol)
- Infections (e.g., viral hepatitis, β -hemolytic *Streptococcus*, HIV, endocarditis)

Other causes of small vessel vasculitis must be excluded.

Hypersensitivity vasculitis due to a **drug** reaction can occur 1–10 days after drugs are started. Keep in mind the rash may occur after the drug has already been **discontinued** (as in antibiotics). Treatment of hypersensitivity vasculitis involves treating the underlying condition, or when known, discontinuing the causative medication. In idiopathic cases, try hydroxychloroquine, dapsone, or colchicine. Use glucocorticoids for more resistant disease.

The histopathologic finding of leukocytoclastic vasculitis is also a feature of systemic vasculitis such as IgA vasculitis or cryoglobulinemia. Make sure to evaluate for other signs of systemic illness or other organ involvement (e.g., renal failure, hemoptysis, fevers, arthritis).

IgA Vasculitis

IgA vasculitis is an **IgA-mediated**, small vessel vasculitis that affects arterioles, capillaries, and venules. Organs affected often include:

- **Skin:** palpable purpura of the lower extremities
- **Kidneys:** biopsy findings identical to IgA nephropathy
- **Gastrointestinal tract:** abdominal pain and bleeding, intussusception
- **Joints:** typically, the knees and ankles

Most cases are self-limited. ~ 20% of cases have a repeat attack; 5% develop chronic IgA vasculitis. ~ 75% of cases are in children, predominantly 2–11 years of age, and 25% are in adults. Upper respiratory and streptococcal infections often precede IgA vasculitis (hence a peak in incidence during autumn and winter), but foods, medications, and insect bites have been linked to this vasculitis. IgA levels may be elevated.

IgA vasculitis is usually benign and resolves spontaneously. However, it occasionally causes renal failure ($\leq 10\%$ of adults and $< 5\%$ of children).

Confirm the diagnosis by identifying the presence of IgA deposits in the vessel wall on skin biopsy.

Treatment is generally supportive. Glucocorticoids may improve joint and GI symptoms but do not help kidney disease. Give glucocorticoids or cytotoxic agents only for life-threatening symptoms.

Cryoglobulinemia

Cryoglobulins are immunoglobulins that precipitate in a serum specimen when chilled $< 98.6^\circ\text{F}$ (37°C) and redissolve when warmed. Cryoglobulins are normally cleared by the liver. Buildup occurs with overproduction or decreased elimination from chronic liver disease.

There are 3 types of cryoglobulinemia:

Type I is least common (10–15% of patients). It is due to a single **monoclonal** antibody (IgM, IgG, or IgA) and is usually found in patients with **multiple myeloma** or **Waldenström macroglobulinemia**.

Type I does **not** have rheumatoid factor activity like Types II and III; hence, complement is not activated. Therefore, patients are typically asymptomatic until the cryoglobulin level rises high enough to cause symptoms of **hyperviscosity** such as neurologic symptoms (e.g., headache, blurred vision, vertigo, deafness, nystagmus), livedo reticularis, purpura, and Raynaud phenomenon.

Type II is most common (50–60%). It is considered a mixed cryoglobulinemia when the immune complex consists of **monoclonal IgM rheumatoid factor** attached to polyclonal IgG. **Most** patients have an associated **hepatitis C** infection. Patients who do not have hepatitis C, but who have these cryoglobulins, are considered to have “essential” mixed cryoglobulinemia.

Type III (25–30%) is similar to Type II in that it is also a mixed cryoglobulin, but Type III has immune complexes typically composed of **polyclonal IgM rheumatoid factor** and polyclonal IgG. 50% of patients have hepatitis C infection; the others usually have a chronic autoimmune disorder (e.g., SLE) or a lymphoproliferative malignancy.

A low C4 out of proportion to C3 is a clue to the presence of cryoglobulins.

Types II and III cryoglobulinemia produce similar symptoms. They both **activate complement** and frequently present with a small vessel **vasculitis**, most commonly with lower extremity purpura, glomerulonephritis, peripheral neuropathy, and hypocomplementemia. Patients may eventually get hyperviscosity symptoms as discussed in Type I.

Hepatitis C and **mixed** cryoglobulinemia (Types II and III) affect these:

- **Skin:** palpable purpura of the lower extremities
- **Joints:** inflammatory arthritis or arthralgias
- **Nervous system:** peripheral neuropathy
- **Kidneys:** membranoproliferative glomerulonephritis (MPGN). Renal failure is a poor prognostic sign.
- **Lungs:** alveolar hemorrhage (rare)

Workup: Screen for hepatitis C in anyone with suspected vasculitis or Type II/III cryoglobulinemia. If you suspect Type I disease, check a serum and urine protein electrophoresis to evaluate for multiple myeloma or Waldenström macroglobulinemia. Do **blood** cultures to exclude endocarditis. Other diseases that **mimic** this form of vasculitis include cardiac atrial **myxoma** emboli and **cholesterol** atheroembolism. Get an echocardiogram when emboli are suspected. Especially consider cholesterol atheroembolism in a patient with severe atherosclerosis who has just had an arteriogram. This

is important if the patient has hypereosinophilia (90% of patients) and/or hypocomplementemia (50% of patients). Skin biopsy of punctate lesions can confirm the diagnosis of cholesterol atheroembolism.

Types II and III cryoglobulinemia patients have low C3, C4, and CH50 (classical complement activation), and their rheumatoid factor (RF) is very high (because in Types II and III, RF is part of the immune complex). Cryoglobulin assays are difficult to perform, and false-negative rates are high. When possible, do a skin biopsy and send for histology and direct immunofluorescence (DIF), which reveal the type of immunoglobulin and complement deposition.

Treat initially with rituximab for the vasculitis caused by hepatitis C. Follow up several months later by treating the hepatitis C.

Antiglomerular Basement Membrane Disease / Goodpasture Syndrome

Antiglomerular basement membrane (anti-GBM) disease results from anti-GBM antibodies that deposit in the pulmonary and/or glomerular capillaries. The clinical presentations include a rapidly progressive glomerulonephritis without lung involvement (termed anti-GBM disease) or a rapidly progressive glomerulonephritis with pulmonary hemorrhage (Goodpasture syndrome). Goodpasture syndrome has a **bimodal** age distribution: individuals 20–30 years of age (males more than females); individuals 60–70 years of age (females more than males). Smoking has a strong correlation with alveolar hemorrhage, especially in young males.

Diagnose anti-GBM disease by measuring anti-GBM antibodies in the serum and with renal and/or lung biopsy, which demonstrates evidence of the anti-GBM antibodies on immunofluorescence (see more in the **Nephrology** section).

Note: Patients with pulmonary hemorrhage may have an increased DLCO.

Treatment involves plasmapheresis to remove circulating anti-GBM antibodies and immunosuppression with glucocorticoids and cyclophosphamide to inhibit further autoantibody formation.

Remember the pulmonary-renal syndromes (rheumatic diseases that cause **alveolar hemorrhage** and **glomerulonephritis**):

- Goodpasture syndrome
- Connective tissue disease: systemic lupus erythematosus, rheumatoid arthritis, polymyositis or dermatomyositis, Sjögren syndrome
- Systemic vasculitis: GPA, MPA, EGPA, IgA vasculitis
- Drug-induced: propylthiouracil (PTU)
- Behçet disease
- Cryoglobulinemia

BEHÇET DISEASE

Behçet disease is a unique vasculitic syndrome that affects any organ and vessels of any size and type (both arterial and venous), although it has a predilection for veins. It primarily affects young adults between 20 and 40 years of age of Middle Eastern or Asian heritage. It is rarely found in individuals with northern European heritage.

The diagnosis is made clinically because there is no pathognomonic laboratory test, although HLA-B51 and HLA-B5 have been associated with this disease. Ulcers are very painful (whereas in SLE, ulcers are typically painless).

There are 2 sets of criteria: the International Study Group (ISG; 1990) and the International Criteria for Behçet Disease (ICBD; 2006). The **earlier** set is preferred because it is used by most clinicians and is relatively sensitive and specific.

The 1990 ISG criteria are **recurrent oral ulceration** ($\times 3$ over 12 months) + 2 of the following:

- 1) Recurrent genital ulceration
- 2) Ocular lesions—uveitis or retinal vasculitis
- 3) Skin lesions—erythema nodosum or acneiform nodules
- 4) Positive pathergy test (skin prick test)

The pathergy test is fairly specific for Behçet disease; however, it is not very sensitive. The patient develops a sterile papule or ulcer 1–2 days after minor trauma, such as a needle stick. A positive pathergy test also occurs in pyoderma gangrenosum.

Peripheral arthritis is common, and patients also may develop a GI disorder that mimics Crohn disease (due to intestinal ulcerations or mesenteric vasculitis). The most serious complications include blindness, CNS disease (e.g., meningoencephalitis, cranial nerve palsies, seizures), and thrombosis or rupture of large aneurysmal vessels. In particular, if a patient with Behçet disease presents with hemoptysis, assume that they have a pulmonary aneurysm until proven otherwise.

1st line therapy for oral and genital ulcers includes topical/oral glucocorticoids. Sucralfate suspension is also an option. 1st line oral therapy is colchicine with thalidomide; the latter is reserved for more serious mucous membrane involvement given its significant side effect profile. Treat more severe disease (vascular or neurologic) with systemic glucocorticoids, azathioprine, cyclophosphamide, and anti-TNF biologic agents. Relapse is common.

RELAPSING POLYCHONDritis (RP)

RP is an inflammatory disorder of cartilage (e.g., ear, nose, larynx, trachea) and tissues rich in proteoglycans (e.g., eyes, heart valves). While RP is most often a primary disorder, it is associated frequently with other diseases, most commonly some form of systemic vasculitis, connective tissue disease, or myelodysplastic syndrome. Typically, patients are affected in their 5th decade of life; however, the disease occurs at any age.

Patients present with unilateral or bilateral ear inflammation, which mimics cellulitis, except that the ear lobe is spared (no cartilage). It also can cause arthritis, ocular disease (e.g., scleritis, iritis), hearing loss/vertigo, vasculitis (10–20%), aortic dilatation, and a valvulitis leading to aortic and/or mitral regurgitation. Skin findings are common and mimic those found in Behçet disease. These patients develop life-threatening tracheal stenosis, so do not hesitate to order a CT of the chest in anyone with this disease who complains of shortness of breath.

MAGIC syndrome is an overlap disorder (Behçet disease and RP) characterized by mouth and genital ulcers with inflamed cartilage. Suspect it in a patient presenting with hoarseness, saddle-shaped deformity of the nose, and swelling of the ear cartilage with sparing of the ear lobe.

Glucocorticoids are the cornerstone of treatment. Occasionally, steroid-sparing agents are required.

RHEUMATOLOGIC ISSUES ASSOCIATED WITH MALIGNANCY

Malignancy (more in the **Oncology** section) is associated with:

- Hypertrophic pulmonary osteoarthropathy (See more under **Hypertrophic Pulmonary Osteoarthropathy (HPOA)** on page 10-39.)
- Amyloidosis (Check with rectal biopsy or an abdominal fat pad biopsy.)
- Secondary gout (tumor lysis syndrome)
- Carcinomatous polyarthritis (Resembles rheumatoid arthritis; especially consider with breast cancer or leukemia.)
- Dermatomyositis (See more under **Dermatomyositis (DM)** on page 10-46.)

RHEUMATOLOGIC ISSUES ASSOCIATED WITH DIABETES MELLITUS

Diabetes mellitus is associated with:

- Dupuytren/Flexion contractures (see discussion under **Dupuytren Contracture (Palmar Fibromatosis)** on page 10-63) occur in poorly controlled long-standing diabetes mellitus. This and the antecedent “limited joint mobility” are known as **cheiroarthropathy**. (Cheiro- is a prefix meaning hand.)
- **Cheiroarthropathy** also may present with thickening of the skin of the fingers. (Remember that systemic sclerosis causes thickening of skin **proximal** to the metacarpals in addition to the fingers.) On physical exam, the “prayer sign” may be seen. This is the inability to press the palms together completely without a gap remaining between opposed palms and fingers.

Diabetic scleredema is due to excessive mucin deposition in the skin. It is characterized by plaques that appear on the neck, shoulder girdle, and/or upper extremities. Most of the patients are older, obese males with poorly controlled Type 2 diabetes mellitus. Often the involved skin of the upper torso, neck and shoulders becomes indurated and erythematous over a period of several years. Often, a pebbled or woody appearance may evolve. Control of the hyperglycemia does not improve the scleredema. Importantly, scleredema also is associated with infections such as *Streptococcus* and plasma cell dyscrasias; it is important to check both a serum and urine electrophoresis in anyone with this diagnosis.

- Carpal tunnel syndrome
- Adhesive capsulitis (frozen shoulder)
- Foot disorders that include neuropathic arthropathy (See discussion under [Neuropathic Arthropathy \(Neuropathic Joints\)](#) on page 10-38.)
- Osteomyelitis
- Hemochromatosis
- DISH

PAGET DISEASE

Paget disease of the bone (see the [Geriatric Medicine](#) section) is associated with:

- Osteoarthritis
- Fractures, including stress fractures
- Elevated serum alkaline phosphatase and urinary hydroxyproline (because both of these are indications of increased bone turnover)
- Osteosarcoma occurs in ~ 1%!
- High-output heart failure (See the [Cardiology](#) section.)
- Hearing loss
- Spinal cord compression
- Hydrocephalus

1st line treatment for Paget disease is bisphosphonates. Do **not** prescribe teriparatide for these patients because it is associated with osteosarcoma. Patients with Paget disease are already at increased risk for this condition.

AMYLOIDOSIS

Amyloidosis results from abnormal deposition of autologous extracellular proteins into organs and tissues, causing a disruption of function and organ enlargement. Symptoms include joint pain, shoulder pad sign, macroglossia with dysphagia, polyneuropathy, heart failure, and renal and liver dysfunction. Different types of amyloidosis have been described based on [site](#) and [pathology](#) of the lesions.

Reactive systemic AA amyloidosis (secondary amyloidosis; fibrils composed of serum amyloid A [SAA] proteins): This

is usually a long-term consequence of chronic inflammatory diseases such as rheumatoid arthritis, Crohn disease, juvenile idiopathic arthritis, autoinflammatory syndromes, malignancies, and infections. The kidneys are most commonly involved, followed by the liver and spleen. Very rarely are the heart and nervous system affected.

AL (primary) amyloidosis results from monoclonal immunoglobulin light-chain (L for light) deposition (typically, lambda light chains). This type of amyloidosis is commonly seen in patients with smoldering myeloma (e.g., monoclonal gammopathy of unknown significance [MGUS]). Any organ except the CNS can be involved. At time of diagnosis, the kidneys (66%) and heart (50%) are commonly affected.

Dialysis-associated (A β_2 M) amyloidosis is a complication from long-term hemodialysis where β_2 microglobulin is not cleared by dialysis. After ~ 5–7 years of dialysis, patients develop symptomatic lesions, often involving bones/joints (particularly the shoulder and wrist). Visceral and vascular deposits also occur (when these develop in the volar wrist, patients present with symptoms of carpal tunnel syndrome).

Senile systemic amyloidosis (ATTR amyloid): Fibrils are composed of transthyretin (amyloid deposits of transthyretin-related proteins; hence ATTR); deposition occurs in those > 70 years of age and is universal in those > 90 years of age. Typically, deposits are microvascular. However, when the heart is involved, heart failure occurs.

Biopsy of affected tissue is the gold standard for confirming the presence of amyloid. The pathognomonic finding is apple green–red birefringence when stained with Congo red dye and viewed under polarized light. Abdominal fat pad aspiration has been studied as a tool to detect senile systemic amyloidosis. It has a sensitivity of 80–90% and a specificity of 100%. Serum amyloid P (SAP)-labeled scintigraphy is useful to evaluate the whole-body burden and distribution of amyloid.

Therapy is 2-fold:

- 1) Maintenance of organ function or replacement of organ
- 2) Reduction/Elimination of fibril precursor protein (controlling the underlying inflammatory process—treating the RA)

OFFICE ORTHOPEDICS

PREVIEW | REVIEW

- Name some bursae that commonly become inflamed.
- What is the workup for acute nontraumatic arthritis?
- Compare and contrast the presentation of shoulder impingement syndrome, subacromial bursitis, and rotator cuff injuries.
- Olecranon bursitis is associated with which systemic diseases?

- How is lateral epicondylitis treated?
- Carpal tunnel syndrome affects which fingers? What about ulnar entrapment neuropathy?
- How does the pain of hip osteoarthritis differ from the pain of greater trochanteric pain syndrome (a.k.a. trochanteric bursitis)?
- Which patients are at risk for avascular necrosis (AVN) of the hip?
- Should MRI evaluation of AVN include 1 or both hips? Why?
- What intervention is used to treat a Baker cyst?
- What is the specific presentation of pes anserine bursitis?
- Name another disease that must be considered in a patient with plantar fasciitis.
- Which patients should get urgent imaging of the spine if they present with low back pain?
- What are spondylosis, spondylolysis, and spondylolisthesis?
- What are the symptoms commonly noted with lumbar stenosis?
- What is piriformis syndrome?

OVERVIEW

Know this topic **very** well! The common aspects of office orthopedics are favorite board topics.

Many rheumatologists incorporate musculoskeletal ultrasound in their practice, and this aids considerably as both a diagnostic (e.g., tendinitis, tenosynovitis, tendon tears) as well as therapeutic tool (e.g., ultrasound guided glucocorticoid injections of joints and bursae).

BURSITIS

Bursae are small fluid-filled sacs, which provide a gliding surface to reduce friction when muscles and tendons slide across bone. Healthy bursae are necessary for a smooth, frictionless surface, making normal movement painless. Bursitis is the inflammation of a bursa secondary to mechanical irritation, bacterial infection, rheumatoid arthritis (RA), gout, or pseudogout. **Bursitis** or tendinitis usually causes severe pain with any active movement of the joint—especially against resistance. **Passive** range of motion (ROM) is much less painful, or even painless.

Prepatellar bursitis (housemaid knee or clergyman knee), **olecranon** bursitis (student elbow), **trochanteric** bursitis, **subacromial** bursitis, and **pes anserine** bursitis are the most common types of bursitis encountered. Know that the knee has several bursae (suprapatellar, infrapatellar, prepatellar, and pes anserine) and that the pes anserine bursa is located on the medial aspect, just inferior to the knee. Pes anserine bursitis is described as pain +/- swelling ~ 2 cm inferior and medial to the patella. In all

locations, there is frequently a serosanguineous effusion within the bursal sac. More information on these bursitis presentations is included later in this section.

Diagnosis is usually clinical but requires exclusion of infectious bursitis if the area is inflamed and/or the patient is systemically ill, especially in patients on immunosuppressants such as patients with RA on chronic glucocorticoids. **Aspirate the fluid and send for the 3 Cs: cell count with differential, crystal analysis, and culture with sensitivities and Gram stain to determine whether infection is present.** *S. aureus* is the most common cause of septic bursitis, so if no sample is obtained for microbiology and clinical suspicion is high for infection, it may be necessary to treat empirically with an antistaphylococcal drug. Remember: Also send the fluid for crystal analysis (gout and pseudogout), as these conditions typically cause a bursitis.

Treatment consists of rest of the affected area. Glucocorticoids can be injected, provided that the bursa is not infected. Often, you can treat mild infection in immunocompetent patients with oral antibiotics. Serious infections in immunocompromised patients should be treated parenterally. Resistant, chronic cases sometimes require surgical excision of the bursa.

MONOARTICULAR JOINT DISORDERS

Joint pain can be caused by a problem within the joint, a problem with associated ligaments or tendons, or inflammation of a bursa (just discussed).

When an extremity joint is acutely swollen without a history of trauma, tap the joint and analyze for **crystals, cell count with differential, Gram stain, and culture.**

Again, remember the mnemonic for the **3 Cs: cell count, crystals, and culture.**

A word about terminology:

- Abduction = away from the midline
- Adduction = toward the midline
- Dorsiflexion = pulling the foot upward, as in taking the foot off the gas pedal
- Plantarflexion = pressing the foot down, as in pressing on the gas pedal

Note: In the following explanatory figures, the **red** highlight indicates areas of pain or tenderness.

Shoulder

True shoulder pain usually extends from the acromion to the insertion of the deltoid.

Refer to **Figure 10-30 on page 10-60** as you read this topic.

Many of the shoulder syndromes affect the glenohumeral joint and limit ROM due to pain. This is demonstrated by the **painful arc** test. In this test, the patient actively raises the arm laterally from the side to an overhead position. Pain-induced limitation of motion in the **middle** of the arc indicates a positive test.

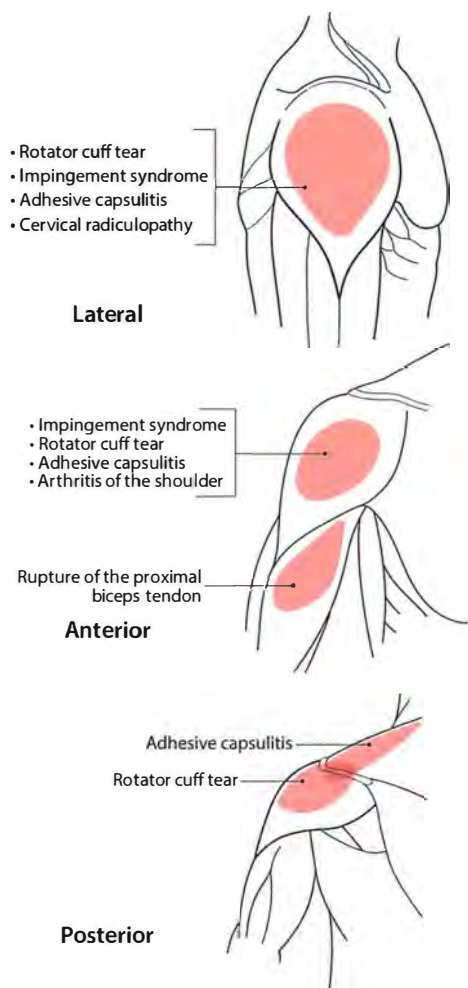


Figure 10-30: Shoulder injuries

Thoracic Outlet Syndrome (TOS)

TOS results from compression of the neurovascular structures supplying the upper extremity. Problems in the neck/shoulder cause irritation of the brachial plexus as it moves from the neck and chest cavity into the arm. Impingement of the nerves causes shoulder pain, which may be localized or may extend from the base of the neck, over the top of the shoulder, and down the arm. This pain extends into the hand and often is accompanied by paresthesias and weakness. If the vascular supply (subclavian/axillary vessels) also is affected, patients will have hand claudication +/- Raynaud phenomenon and ulcers in severe cases.

TOS has been classified into 3 categories based on etiology, symptoms, clinical presentation, and anatomy:

- 1) Arterial TOS (1%; digital ischemia, claudication, typically related to a cervical rib)
- 2) Venous TOS (2-3%; due to subclavian vein obstruction from thrombosis/scarring; upper limb swelling is common.)
- 3) Neurogenic TOS (95%; brachial plexus is compressed; paresthesia and pain in the neck, shoulder, and arm are common; symptoms are made worse with overhead motion.)

Diagnosis is difficult because the exam is usually normal unless provoked by certain maneuvers. The **elevated arm stress test (EAST; a.k.a. Roos test)** is a good test to detect neurogenic TOS. Patients abduct their arms to 90° while elbows are flexed at 90°; then they open and close their hands for 3 minutes. If they cannot maintain this position due to symptoms, the test is positive.

The **Adson test** is another common maneuver used to evaluate for vascular TOS. Locate the patient's radial pulse while the patient turns their head toward the tested shoulder. The patient then extends their neck while the examiner laterally rotates and extends the patient's shoulder with the arm straight. The patient then takes in a deep breath and holds it. The test is considered positive if there is loss of the radial pulse and reproduction of TOS symptoms. If you suspect the syndrome, do a chest radiograph (looking for cervical ribs that are sometimes a cause) and/or EMGs with nerve conduction studies to see if the brachial plexus is affected.

Treat with shoulder exercises and education about avoiding the postures that elicit symptoms. Cervical ribs are removed surgically if they are the cause.

Adhesive Capsulitis

Adhesive capsulitis (a.k.a. frozen shoulder) is most commonly seen in patients who are between 40 and 60 years of age and who typically have an underlying predisposition such as chronic bursitis/tendinitis, fracture, or rotator cuff injury. Diabetes and thyroid disease also are risk factors. However, adhesive capsulitis can occur in the absence of any apparent cause.

Diagnosis is suggested by shoulder pain, stiffness, and decreased range of glenohumeral motion in all directions. Exam shows significantly reduced ROM (< 50% of normal), both actively and passively, in all directions. Radiographs are often normal.

Symptoms usually **resolve** in 1-2 years. Physical therapy and ROM exercises are important to help patients regain their function. Intraarticular corticosteroids are occasionally used. Refractory cases may require surgery (< 10% of cases).

Impingement Syndrome

Subacromial bursa or regional tendon compression in the space between the acromion and the humeral head is called impingement syndrome. The biceps tendon (long head) and all of the rotator cuff tendons go through this area. For this reason, bicipital tendinitis and some rotator cuff injuries are often considered impingement syndromes.

Impingement typically causes pain when the patient reaches overhead or sleeps on the affected shoulder. Except in long-standing cases, strength in the shoulder is normal.

As with several other shoulder syndromes, these patients have a positive painful arc test. For diagnosis of impingement syndrome, use the following provocative maneuvers

that are more specific. If **any** of the following provocative tests elicit pain, the patient likely has an impingement syndrome:

- **Neer** test: Stabilize the scapula while passively lifting the arm in forward elevation toward the ear (forward flexion of glenohumeral joint).
- **Hawkins** test: With the patient's arm 90° forward and the elbow in flexion, internally rotate the shoulder.
- **Yocum** test: While the patient touches the uninvolved shoulder, lift the flexed elbow.

Diagnosis of impingement is **clinical**. Imaging is usually performed only when patients are refractory to therapy and require orthopedic referral.

If strength is normal, **conservative** management is best initially: rest from aggravating activities, ice, and physical therapy for 3 months. Treat the pain with a short course of NSAIDs. Consider intraarticular glucocorticoid injections if the patient does not improve quickly.

Refer for orthopedic evaluation if the patient still has pain after 3 months of therapy or if weakness/muscle atrophy is present at initial evaluation, which might suggest a rotator cuff tear.

Subacromial Bursitis

Subacromial bursitis also is called deltoid bursitis. Patients with subacromial bursitis present with pain **both** at rest and with movement. This bursitis has referred pain to the lateral aspect of the arm. Consider this diagnosis when a patient reports waking from sleep with pain in the shoulder and arm. It is often associated with a rotator cuff tear (definitely consider this if weakness is present) and impingement.

On exam, the **middle arc** of the active abduction is painful, while the extremes are painless. Several other problems cause this painful middle arc such as calcification/tear/tendinitis of the supraspinatus tendon or a fracture in the humeral tuberosity, where the supraspinatus tendon attaches. Occasionally, pain is so severe that the patient cannot accomplish any active movement, especially abduction. Passive ROM shows pain with abduction only.

Treat with ROM exercises, NSAIDs, and ice. Consider intrabursal glucocorticoid injections if infection is ruled out and the patient does not respond to more conservative measures.

Rotator Cuff Abnormalities

The rotator cuff is comprised of 4 muscles. Use the mnemonic **SITS**:

- 1) Supraspinatus
- 2) Infraspinatus
- 3) Teres minor
- 4) Subscapularis

These muscles stabilize the shoulder and allow the arm to elevate and rotate. Injuries or degeneration of the rotator

cuff are the **most common** causes of shoulder pain. Some tears, even severe ones, sometimes occur without pain—and manifest only as weakness! Consider a tear in patients with shoulder pain who play overhead sports (e.g., baseball, tennis, volleyball), have had shoulder trauma, are > 50 years of age, or have rheumatoid arthritis (RA).

Pain with **overhead** reaches and **night** pain are classic features of rotator cuff injuries. The injury sometimes causes a subacromial bursitis. This presents as anterior-lateral shoulder pain made worse with flexion and internal rotation of the shoulder (when the arm is 90° forward).

Exam of partial tears demonstrates a positive painful arc test +/- weakness. The trick here is to determine whether apparent weakness is due to pain or a true muscle tear. Remember: Patients with pain guard their shoulder. (Lidocaine injections are helpful diagnostically in this situation.) Another exam maneuver is to observe active adduction and hold the position. Patients who cannot adduct smoothly (called the **drop-arm sign**) may have a tear.

Complete rotator cuff tear is **very** debilitating. It generally involves separation of the supraspinatus tendon, but it may involve the adjacent subscapularis or infraspinatus tendons. These tendons blend with the shoulder joint capsule, and a separation of the tendons generally involves the joint capsule. This allows "communication" between the shoulder joint and the subacromial bursa. Complete tears due to chronic repetitive injury usually occur in patients > 60 years of age. Patients are unable to abduct the arm due to weakness +/- pain, except by rotation of the scapula (shrugging the shoulder). Complete tears also are caused by acute injuries from falls on an outstretched arm.

If you suspect a tear, start with plain radiographs because they sometimes show abnormalities in the positioning of the humeral head, acromion, and glenoid. MRI also makes the diagnosis, but abnormalities must be clinically correlated because many asymptomatic people have tears visible on MRI. Musculoskeletal ultrasound is also a very useful diagnostic tool to identify full and partial thickness rotator cuff tears, as well as tendinitis, tendinopathy, or tenosynovitis of the shoulder.

Treatment of most tears is conservative: rest, nonnarcotic analgesics, and physical therapy. Full-thickness tears in a healthy person are treated with surgery. Also consider surgery when conservative treatment fails.

Elbow

Olecranon Bursitis

Olecranon bursitis (Figure 10-31 on page 10-62) is due to trauma, sepsis, crystals (gout or pseudogout), or RA. Traumatic bursitis (a.k.a. **student elbow**) is caused by chronic pressure. If you suspect infection, aspirate the bursa and send the fluid for cell count, Gram stain, culture, and crystal analysis. Note: Do **not** aspirate at the vertex or point of maximal bursal distention due to risk of **persistent fluid leakage**. Instead, aspirate at an angle proximal or distal to the point of maximal distention.

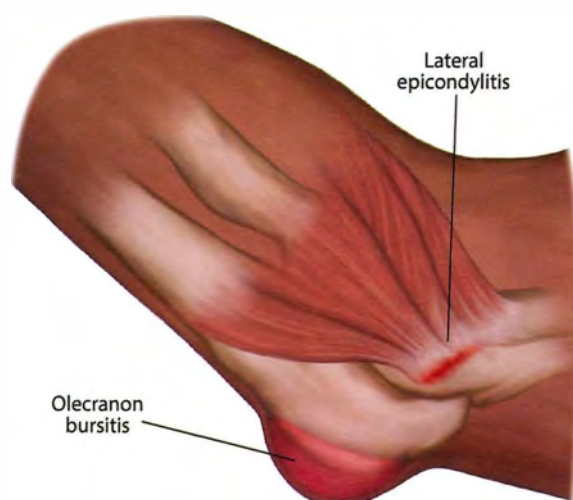


Figure 10-31: Elbow lateral view

Treat uninfected bursitis with NSAIDs or glucocorticoid injection. Treat septic bursitis with incision, drainage, and antibiotics. Use oral antibiotics for mild infections—IV is needed in cases of severe inflammation.

Lateral Epicondylitis

Lateral epicondylitis (a.k.a. **tennis elbow**; see Figure 10-31) presents with tenderness and pain well localized to the front of the lateral epicondyle of the elbow, where the extensor tendons of the forearm insert. Symptoms typically resolve spontaneously with decreased use of the elbow, although it can take ≥ 2 years.

Treatment: NSAIDs and **splinting** to reduce supination/pronation motion. Local corticosteroid injection is no longer recommended as the mainstay of treatment.

Medial Epicondylitis

Medial epicondylitis (a.k.a. **golfer elbow**) is similar to tennis elbow but involves the medial epicondyle of the elbow. Treatment is the same as lateral epicondylitis.

Wrist

Carpal Tunnel Syndrome (CTS)

CTS presents with paresthesias and dysesthesias in the **median** nerve distribution (thumb through the inside of the 4th finger) usually most bothersome during sleep. The symptoms are reproduced by tapping on the volar aspect of the median nerve (**Tinel sign**) and/or forced flexion of the wrists for 30–60 seconds (**Phalen test**). Patients often describe tingling/numbness in the middle of the night where they have to flick or shake out the hand (positive flick test).

Certain groups of patients are more susceptible, including pregnant women or those on oral contraceptives, dialysis patients, and those with arthropathy associated with wrist synovitis (e.g., RA). Hypothyroidism, diabetes, acromegaly, and amyloidosis also are associated with CTS.

Pain only in the shoulder or elbow is an atypical presentation. Nerve conduction studies aid in the diagnosis. Ultrasound measurement of the cross-sectional area of the median nerve is helpful to diagnose CTS, so consider referral to a rheumatologist who specializes in musculoskeletal ultrasound prior to ordering nerve conduction studies.

Initial treatment consists of NSAIDs and a wrist **splint** worn day and night for 3–4 weeks. Perform carpal tunnel surgical release in patients with axonal (motor) loss by EMG, persistent weakness, atrophy of the thenar eminence, or in cases refractory to conservative treatments, such as splinting or glucocorticoid injections.

Remember: Carpal tunnel syndrome causes numbness in the thumb and 2nd, 3rd, and inside of the 4th fingers, whereas **cubital tunnel syndrome** (entrapment of the ulnar nerve) causes numbness in the 4th and 5th fingers.

Ganglion Cyst

Ganglion cysts occur at any joint or tendon sheath; however, they are most commonly found on the **dorsum** of the **wrist** at the scapholunate joint. The cyst is attached to a tendon sheath or the joint capsule (Figure 10-32). There is no communication between the inside of the joint capsule and the interior of the ganglion. They are usually asymptomatic but may cause pain due to compression of a nerve or joint space. Generally, ganglia are not treated. Temporary resolution may be provided by firm pressure or aspiration. The old remedy was slamming the ganglion with the family Bible! Avoid this because it can cause an inflammatory response and recur. Definitive treatment is surgical.



Figure 10-32: Ganglion cyst

Acute Compartment Syndrome (ACS)

ACS occurs when excessive pressure builds up within an enclosed space in the body and compromises the circulation and tissue within that space. Patients can develop ACS very rapidly. Keep this diagnosis in mind in a patient with a recent cast application for fracture who presents with increased hand pain. Often the pain is out of proportion to the injury. Vascular compromise also can be evident but may be absent early. In the case of ACS caused by a cast, the treatment is immediate removal of the cast and orthopedic consultation.

De Quervain Tenosynovitis

De Quervain tenosynovitis is a chronic or subacute inflammation of the extensor pollicis brevis and the abductor pollicis longus tendons of the thumb. It is more common in middle-aged women and during the postpartum period. It is characterized by pain and well-localized tenderness over the styloid process of the distal radius. Often, it is caused by repetitive twisting of the wrist with certain motions such as wringing clothes. Although several bedside tests are used for diagnosis, the hallmark test has come to be called the **Finkelstein test** (forced ulnar motion of the wrist with the thumb adducted and clasped by the patient's other fingers), which reproduces the pain (Figure 10-33). Natural healing is very slow. Splinting, steroid injections, and NSAIDs are beneficial for milder cases. Surgery, which is curative, is reserved for patients with severe disability.



Figure 10-33: Finkelstein test

Hand

Dupuytren Contracture (Palmar Fibromatosis)

Dupuytren contracture is a flexion contracture of the fingers caused by thickening and contraction of the palmar fascia. The palmar fascia extends from the termination of the palmaris longus tendon on the wrist to the proximal and middle phalanges of the fingers. The last 2 fingers are the most frequently affected. As the contraction progresses, palpable cord-like bands on the surface of the palm are present (Figure 10-34).



Figure 10-34: Dupuytren contracture
Source: Frank C. Müller

The cause is unknown, but these contractures are associated with a positive family history, epilepsy, **diabetes**, **alcoholism**, malignancies, and recurrent occupational vibratory stimuli. Dupuytren contractures are primarily seen in Caucasian individuals, usually men.

Previously, the cornerstone of treatment was surgical, but contractures still tend to recur in young patients. In 2010, the FDA approved injectable **collagenase clostridium histolyticum** for the treatment of Dupuytren contracture with a positive cord. This medication, which contains 2 collagenases, is injected into the “cord” and provides hydrolyzing activity on the collagen, which helps reduce the degree of contraction and improve ROM.

Trigger Finger

When a finger gets stuck in flexion at the PIP joint, we call it **trigger finger** or digital tenosynovitis stenosis (Figure 10-35). It is unstuck only with strong effort or with passive movement using the other hand—which causes significant pain. There is tenderness at the base of the finger (palmar aspect). Often, a tendon nodule is felt. The cause is swelling of the flexor tendon and the opening of the flexor tendon sheath at the base of the finger. The 3rd or 4th finger is most commonly affected. Chronic tenosynovitis progresses frequently to Dupuytren contractures.

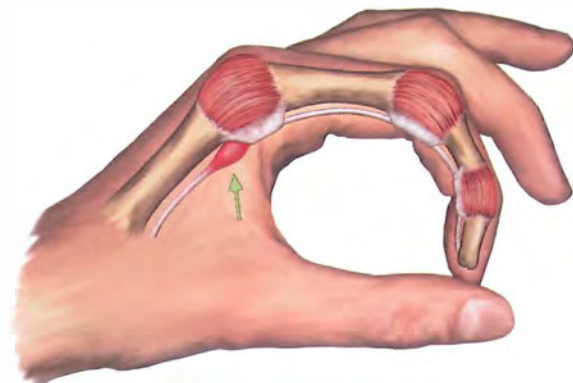


Figure 10-35: Digital tenosynovitis (trigger finger)

Splinting and local steroid injections are helpful, but a simple **surgery** is required to **cure** the condition. It consists of incising the mouth of the fibrous flexor sheath longitudinally.

Hip

Greater Trochanteric Pain Syndrome (GTPS)

GTPS (a.k.a. trochanteric bursitis and greater trochanteric bursitis) is the most common cause of lateral thigh discomfort. Patients report “hip” pain when lying on the involved side, draping the involved leg over the noninvolved limb, or bearing weight on the affected side. When asked specifically to point to the area of most intense pain, patients with bursitis point to the lateral aspect of the thigh over the greater trochanter (Figure 10-36). This helps distinguish bursa pain from true hip joint pain, which causes a point of maximum intensity in the groin or anterior-medial thigh pain.

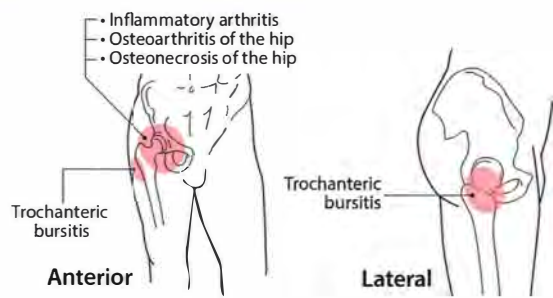


Figure 10-36: Hip injuries

NSAIDs, local heat, physical therapy, and/or glucocorticoid injections are all considered treatment modalities for GTPS depending on the patient's circumstance.

Avascular Necrosis (AVN)

AVN (a.k.a. osteonecrosis) is a poorly understood condition resulting from an impaired blood supply to the bone. The compromised blood supply is due to trauma, certain medical conditions, medications/drugs, or idiopathic disease. It affects mostly the epiphysis (ends) of the femur (affecting the hip more than knee joints), followed by the humerus. Patients on **chronic glucocorticoids** or who **abuse alcohol** have a significant risk of AVN. Medical conditions associated with AVN include sickle cell disease, pregnancy, HIV/AIDS, Gaucher disease, hypercoagulable states, pancreatitis, IBD, and systemic lupus erythematosus. Patients with femoral neck fractures or traumatic hip dislocations are especially susceptible because the blood supply to the femoral head is disrupted.

AVN is best diagnosed **early** with an **MRI** showing the classic “crescent sign” signifying subchondral collapse (when plain radiographs may still be normal; Figure 10-37). Be certain to image both hips with plain radiographs and/or MRI because the risk of **bilateral** AVN is high, even if the patient is not symptomatic in the alternate hip (Stage 0).

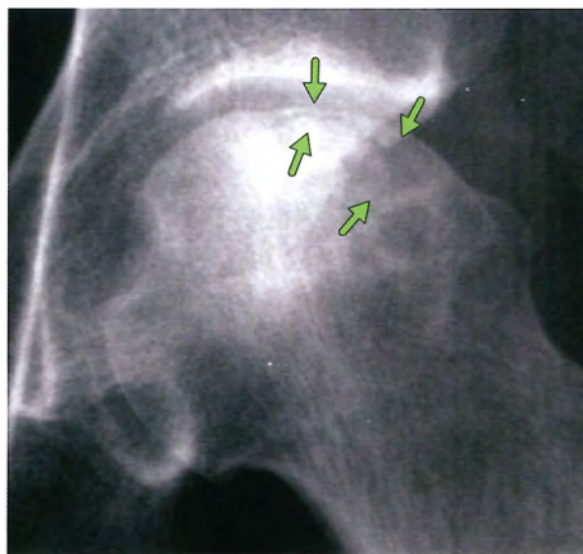


Figure 10-37: MRI of avascular necrosis of the hips

Most patients with AVN eventually need surgery. Early-stage disease can be treated with a revascularization procedure (core decompression +/- bone graft), which may eliminate the need for hip replacement. Total joint replacement is the treatment of choice for late-stage disease.

For more on AVN during pregnancy, see the [Women's and Men's Health](#) section.

Knee

Acute Knee Pain

Knee osteoarthritis is discussed under [Osteoarthritis \(Degenerative Joint Disease\)](#) on page 10-26. Acute knee pain is a common office problem (Figure 10-38). Pain often is related to trauma or overuse. A detailed history and physical is critical to diagnosing knee abnormalities. Initial treatment for most acute knee pain is **RICE**:

- Rest
- Ice
- Compression
- Elevation

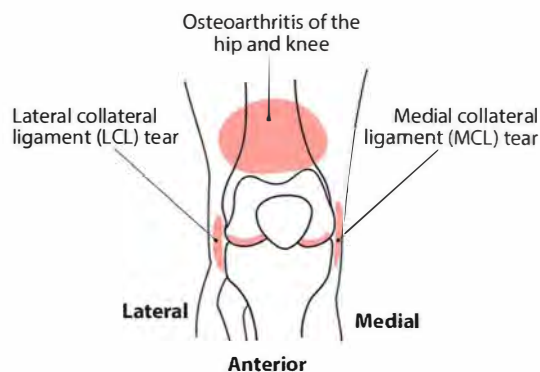


Figure 10-38: Knee anterior view

2 of the most common traumatic knee injuries are:

- **Anterior cruciate ligament tear:** The anterior cruciate ligament is a diagonal ligament that helps stabilize the knee. The mechanism of injury includes a sudden change in direction or overextension with a “pop” felt at the time of injury. ACL tear makes the knee feel unstable as well as cause pain and swelling. Exam reveals a positive **Lachman** maneuver (with the knee flexed 20–30°, the tibia is pulled forward relative to the femur; if there is > 4 mm of movement, it is considered a positive test) and a positive anterior **drawer** test (forward slide of the tibia under applied stress indicates laxity). Athletes participating in basketball, football, soccer, and skiing are especially prone to ACL tears.
- **Meniscus tear:** The menisci are fibrocartilaginous pads that help cushion the knee joint and reduce friction. The mechanism of a meniscal tear is often twisting of the knee with foot planted. A tearing sensation may be felt. There is pain over the joint line and full ROM can be limited. The **McMurray** test (extending the knee while internally and externally rotating the tibia while palpating the posteromedial aspect of the knee feeling for a “click”) is often positive.

Besides RICE, treatment for acute knee pain usually includes antiinflammatory medication, physical therapy, and sometimes immobilization. If the pain fails to respond to conservative measures, imaging with an MRI to direct further treatment is indicated.

Baker Cyst

Baker cyst (a.k.a. popliteal cyst) is a posterior herniation of the synovial cavity of the knee caused by a tense knee effusion (Figure 10-39). This forms a synovial, fluid-filled sac in the midline behind the knee or in the upper calf. A Baker cyst **commonly** occurs as a result of chronic arthritic conditions in which there is persistent synovial effusion or **meniscal tears**. If an arthritic patient with knee involvement presents with a painful, swollen calf, suspect a ruptured Baker cyst causing **pseudophlebitis**. Additionally, consider phlebitis and deep venous thrombosis (DVT).

Prognosis is usually good.

On exam, palpate the cyst in the posterior knee when the knee is partially flexed. Or, have the patient stand while you look at the posterior knee for swelling. Occasionally, a Baker cyst causes extrinsic venous compression that also simulates phlebitis. The diagnostic test of choice is an ultrasound or lower extremity Doppler, which rules out DVT and visualizes the cyst. Further imaging with MRI adds no useful information.

Treat small cysts with rest, NSAIDs, and by addressing any underlying causes. If the cyst is large or causes significant pain, perform knee arthrocentesis and then intraarticular corticosteroids. Refractory effusions may require ultrasound guided cyst aspiration and/or surgical excision.



Figure 10-39: Lateral view of Baker cyst

Prepatellar Bursitis

Prepatellar bursitis (a.k.a. housemaid knee or clergyman knee) localizes pain over the patellar bursa and is caused by kneeling on hard surfaces (Figure 10-40). Physical examination typically reveals erythema, point tenderness, and warmth of the anterior knee. If the symptoms worsen despite treatment with rest, ice, NSAIDs, +/- glucocorticoid injection, consider a bacterial infection of the bursa, which can occur without an obvious source. If in doubt, aspirate the bursa and send the synovial fluid for Gram stain, and the 3 Cs: cell count, culture, and crystals.

Pes Anserine Bursitis

Pes anserine bursitis is caused by inflammation of the pes anserine bursa, located over the **medial** aspect of the proximal tibia **2 inches (50.8 mm)** below the knee joint line (Figure 10-40). This is just proximal to the area where the 3 tendinous extensions of the gracilis, sartorius, and semitendinous muscles insert into the medial aspect of the tibial tuberosity. The symptom is pain in this area, especially when climbing stairs; point tenderness at the medial tibial tuberosity is noted on physical exam.

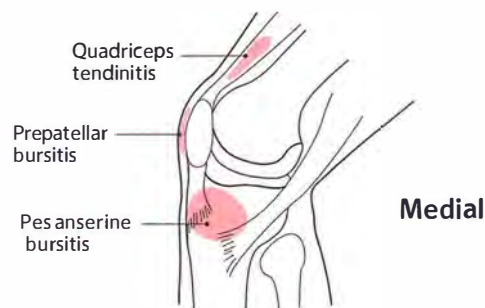


Figure 10-40: Knee medial view

Pes anserine bursitis is associated with knee osteoarthritis and obesity. Diabetes mellitus is a risk factor.

Remember to aspirate and exclude infection as a cause if there is any question about the source.

Treatment is rest and analgesics, +/- glucocorticoid injection.

Pigmented Villonodular Synovitis (PVNS)

PVNS is an idiopathic, monoarticular, benign synovial tumor that causes recurrent hemarthrosis, usually of the knee in young adults. Patients have recurrent bleeding into the knee, resulting in a darkly pigmented joint aspirate.

MRI is diagnostic with nodular intraarticular masses that demonstrate low signal intensity.

PVNS responds to synovectomy or radiation for recurrent cases.

Spontaneous Osteonecrosis of the Knee (SONK)

SONK most commonly affects the medial femoral condyle and may be the result of chronic mechanical stress or mild trauma in middle-aged and elderly individuals, especially women. Unlike secondary AVN (osteonecrosis) of the knee, SONK is typically unilateral. There is no known etiology, although it seems to be associated with osteopenia and osteoarthritis. Weight-bearing pain is present initially on the medial aspect of the knee. Symptoms often resolve with conservative management, including protected weight bearing and analgesics.

Do an MRI to exclude a tear in a meniscus.

In contrast to secondary osteonecrosis, which usually requires surgical management (i.e., arthroplasty), SONK responds well to nonoperative treatment. However, some patients ultimately may require unicompartmental or total knee arthroplasty.

Foot

Morton (Plantar) Neuroma

Morton neuroma is a benign neuroma that causes painful, burning paresthesias and tenderness in the interdigital webbing due to repeated nerve trauma. It is usually unilateral and most often appears between the 3rd and 4th toes. It is much more common in women than in men. It is thought to be related to high heels, tight-fitting shoes (e.g., ballet shoes), and people with overpronated gait. Palpation of the involved interspace produces sharp pain, which radiates frequently into the toes. Squeezing the forefoot often reproduces the patient's symptoms. Patients feel like they are standing on a pebble in their shoe. Treatment includes lowering the heel and wearing wider, soft-soled shoes with metatarsal arch support. Glucocorticoid injections may be helpful; severe cases may require surgical excision of the neuroma.

Plantar Fasciitis

This foot condition occurs most typically in individuals between 40 and 60 years of age, with increased incidence in obese patients, runners, and ballet/aerobic dancers (Figure 10-41). It is generally idiopathic, benign, and self-limiting. The hallmark of plantar fasciitis is a history of severe heel pain with the 1st few steps in the morning or after other long periods of non-weight-bearing status.

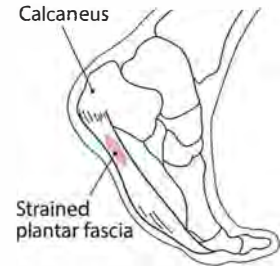


Figure 10-41: Plantar fasciitis

Radiographs are typically not necessary, but assist in excluding diseases that present similarly, such as calcaneal stress fractures and Paget disease.

Remember: Spondyloarthritides manifest with enthesitis, and the plantar fascia is a common site of involvement—keep this in mind as you do the H&P on these patients.

Treatment: rest, NSAIDs, avoidance of walking barefoot, calf stretches, shoes with arch support, weight loss, and heel inserts. Injection of mixed steroid/anesthetic is helpful in refractory cases. Avoid recurrent steroid injections because they cause fat pad atrophy.

LOW BACK PAIN

Acute low back pain is 1 of the most common reasons why patients visit their primary care doctor. There are several causes of nonspecific, acute back pain. These include a moderately prolapsed disc, catching of the synovial membrane in a facet joint, transient subluxation with ligament strain, and basic muscle strain. Certainly, worse etiologies cause low back pain (e.g., spinal stenosis, infection, metastatic cancer), so your task is to differentiate the simple causes from ones that require imaging and/or aggressive treatment.

General Approach to Low Back Pain

New guidelines regarding treatment for low back pain were issued by the American College of Physicians in 2017. Nonspecific low back pain, sometimes called lumbago, is diagnosed when the patient gives the classic history and has no red flags to suggest a more serious etiology. Use nonpharmacological treatments 1st such as heat application, massage, acupuncture, or spinal manipulation. If pharmacological treatment is required at this stage, it is recommended to use NSAIDs or skeletal muscle relaxants. For chronic low back pain failing to respond to these measures, nonpharmacological means such as physical therapy, exercise (yoga), acupuncture, biofeedback, and mindfulness-based stress reduction may be of benefit. If these interventions do not work, consider NSAIDs (1st line) and duloxetine or tramadol (2nd line). Only consider opioids as an option in those who have failed all other treatments and after you have assessed the risks and benefits of these agents with the patient.

Urgently image only those patients who have neurologic deficits, a serious underlying condition (e.g., cancer), or other red flags. The most important back pain red flags are infections (e.g., discitis, osteomyelitis, paraspinal abscesses), aortic dissection, and cancer (principally, prostate cancer and multiple myeloma—a classic presentation includes back pain, hypercalcemia, and anemia).

Treat conservatively for 1 month. Reassess with imaging reserved for refractory pain.

Underlying conditions that indicate a need for urgent MRI imaging:

- Known cancer diagnosis (Suspect a compressive myelopathy and treat with high-dose glucocorticoids if patients present with any neurologic deficits, especially motor weakness.)
- Concern for paraspinal abscess (focal pain +/- fevers; immunosuppression and/or injection drug users = higher risk)
- Multiple risk factors for cancer
- Risks for osteomyelitis: injection drug users, tuberculosis, sickle cell
- Urinary retention
- Fecal incontinence
- Progressive motor weakness
- Constitutional signs (e.g., fever, chills, weight loss)

By imaging, you are ruling out:

- Disc herniation
- Spinal stenosis
- Malignancy
- Infection
- Compression fracture

Osteoporotic compression fracture of the spine involves the midthoracic and lumbar vertebral bodies. Patients have palpable, nonradiating pain at the spinal site with sharp or dull pain exacerbated by any movement. 20% of patients will have another spinal fracture within a year. Plain films are the initial testing modality. Begin treatment with oral analgesics and physical therapy.

Muscle Strain

>50% of adults experience at least 1 episode of back strain at some time. Classic presentation is agonizing, lower back pain with a history of lifting a heavy object or making a sudden movement. Pain is increased when bending, lifting, turning, or coughing. Sometimes, initial pain is so severe that any movement of the torso is difficult.

Physical exam typically reveals guarding of movement due to pain and no true muscle weakness or neurologic deficit. Straight leg raises do not cause pain. This is a clinical diagnosis. Know that imaging does **not** assist in diagnosis of, or treatment for, muscle strain.

Most patients get better quickly (40% in 1 week; 90% in 2 months). With acute back strain, continuing ordinary activities as tolerated leads to a more rapid recovery than

bed rest. Surgery is seldom, if ever, required. Studies show that in nonemergent patients initially considered surgical candidates, conservative treatment is just as effective as surgery in the long term.

Disc Herniation

Disc herniation presents with local or radicular pain—and with weakness, if severe. Herniated discs are most common at **L5/S1** because of progressive thinning of the posterior longitudinal ligament. Central disc herniation can cause saddle pain, saddle anesthesia, and/or bowel or bladder incontinence (cauda equina syndrome); surgical consultation is needed. Classic disc pain is worse when sitting or bending and better when standing or lying down.

On exam, patients have pain when performing the **straight leg raise**. The patient's exact low back pain symptoms are elicited when they lie on their back and raise 1 leg upward (while keeping the corresponding knee straight). MRI of the spine without contrast is the test of choice for diagnosing a symptomatic herniated disc.

Long-term outcomes comparing surgery and conservative management (over-the-counter pain relievers followed by planned exercise regimen) are **equivalent**. Neurologic deficits or intractable pain are indications for surgery (i.e., microdiscectomy).

Diabetic Lumbosacral Radiculoneuropathy

An important consideration is diabetic lumbosacral radiculoneuropathy (a.k.a. diabetic amyotrophy), which is thought to be related to ischemic injury to the peripheral nervous system as a result of microvasculitis. This condition may affect even well-controlled diabetics. Patients present with an acute or subacute onset of unilateral leg pain and occasional numbness with long-term progression to proximal muscle weakness and muscle atrophy. EMG reveals characteristic findings of L2-L4 radiculopathies, with or without evidence of a distal sensorimotor polyneuropathy. There are no proven effective treatments.

Spondylolysis and Spondylolisthesis

Spondylolysis is a defect in the isthmus of the neural arch (pars interarticularis) of the 5th (rarely the 4th) lumbar vertebra. This loss of bony continuity is especially visible on the oblique view of a lumbar x-ray film showing the “collar” (break) on the neck of the “Scottie dog” (Figure 10-42 on page 10-68).

There is a hereditary component expressed as a small change in the lumbar spinal anatomy that predisposes the development of spondylolysis, which is likely secondary to a stress fracture during childhood. Patients with joint hypermobility syndrome or competitive athletes (e.g., gymnasts, figure skaters, wrestlers) with acute low back pain must be checked for spondylolysis, which often results in spondylolisthesis.



Figure 10-42: Left, normal; right, spondylosis
Source: A. Gentili, MD, et al

These patients are more susceptible to spondylolisthesis—a spontaneous subluxation (usually forward), seen best on lateral imaging of 1 lumbar vertebra over another (commonly anterior subluxation of L5 over S1; Figure 10-43). Occasionally, spondylolisthesis results in sciatica, but generally it does not affect the nerves of the cauda equina.

Plain lumbar 3-view imaging can diagnose spondylolysis and spondylolisthesis. Both are usually treated conservatively as in disc disease. However, if slippage in spondylolisthesis is > 50%, spinal fusion is recommended.

Do not confuse these terms with spondylosis, which refers to osteoarthritis of the spine.

Spinal Stenosis

Spinal stenosis (a.k.a. neurogenic claudication) is discussed in the [Neurology](#) section. The stenosis of the spinal canal in the lumbar region causes a cramping or claudication-like symptom due to nerve compression of the cauda equina. The stenosis is most often in the cervical and lumbar regions.

Typically, symptoms consist of a progressively severe, heavy, aching sensation in the lower extremities after walking or standing several minutes. Symptoms of spinal stenosis worsen with back extension (descending stairs) and improve with back flexion (ascending stairs, leaning forward on a grocery cart). This is called a neurogenic claudication (a.k.a. pseudoclaudication) and must be distinguished from ischemic claudication, which presents as pain with ambulation classically relieved with rest and is associated with obvious vascular disease on examination (e.g., bruits, lower extremity hair loss, poorly palpable

pulses). Note: We think of claudication as meaning vascular obstruction, but it comes from Latin: claudicare = to limp.

Diagnose spinal stenosis by history and physical exam. Imaging studies such as plain radiographs, CT, or MRI are indicated only for patients unresponsive to a month of conservative treatment or patients with risk factors for cancer, spinal infection, cauda equina syndrome, or neurologic disorders.

Spinal stenosis usually is treated conservatively (e.g., analgesics, physical therapy). Surgery is recommended (most commonly a decompression laminectomy) if symptoms are severe or have not responded to more conservative measures.

OTHER REGIONAL PAIN SYNDROMES

Common orthopedic complaints include pain in the buttock, sacral, and groin areas. Often, patients complain of inability to sit, stand, or ambulate. Exclude the red flags of infection and malignancy.

Sacroiliac Joint Pain

The sacroiliac (SI) joints connect the sacrum to the iliac bones. Because there is very little motion at the SI joints, they withstand a significant amount of stress when the body goes to an upright position. SI joint pain occurs when the joint is stressed (frequently referred to as SI joint dysfunction). Typically, pain presents in the buttocks; however, pain can occur in the hamstrings or lumbar region. Pain on palpation of the sacral sulcus is the most reliable indicator of SI joint pain. The iliac compression test (pain with vertical pressure directly applied to the joint) also is suggestive of SI joint dysfunction.

Causes of SI joint pain include:

- SI joint degenerative joint disease
- Spondyloarthritis (ankylosing spondylitis, reactive arthritis, psoriatic arthritis, IBD-associated spondyloarthritis)
- Infection (Consider tuberculosis in someone from endemic areas, infectious sacroiliitis in an injection drug user.)
- Pregnancy

Treat SI joint pain for noninfectious or nonspondyloarthritis conservatively, like disc pain and spinal stenosis.

Piriformis Syndrome

The piriformis muscle originates from the midsacrum and inserts to the superior surface of the greater trochanter of the femur. It serves to externally rotate and abduct the hip. Pain occurs when the muscle is inflamed and then compresses the sciatic nerve, which runs either parallel to or in the muscle belly. Suspect piriformis syndrome when pain is present in the lateral margin of the sacrum and there is reproduction of sciatica-type pain with weakness



Figure 10-43:
Spondylolisthesis L5-S1
Source: Lucien Monfils

from resisted abduction and external rotation (**Pace sign**). Patients may have difficulty sitting and on occasion demonstrate a tendency to splay the foot on the involved side when in the supine position. Physical therapy and analgesics are the mainstay of treatment.

Iliopsoas Syndrome

The iliopsoas muscle originates from the lumbar spine and inserts onto the lesser trochanter of the femur. The muscle functions as a hip flexor and external rotator. When injured, pain presents in the anterior hip and thigh or along the groin. Have the patient sit with extended knees. Iliopsoas tendinitis is suggested when pain occurs as the patient lifts the heel of the affected leg (positive **Ludloff sign**). Management is aggressive physical therapy.

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Women's and Men's Health

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WOMEN'S HEALTH

OBSTETRICS

PRECONCEPTION CARE AND FAMILY PLANNING

PREVIEW | REVIEW

- What age is considered advanced maternal age in which the risk of abnormal chromosomes increases?
- Epileptic mothers have what percentage of risk of congenital abnormalities?

Patient care prior to conception improves pregnancy outcomes. Because 50% of pregnancies are unplanned, consider pregnancy as a possibility in your reproductive-aged female patients. Use other visits (e.g., work physicals, follow-up visits) as an opportunity to address preconception issues.

The following is a preconception visit checklist:

- Genetic risks:
 - Folic acid supplementation
 - Carrier screening—ethnic background: sickle cell anemia, thalassemia, Tay-Sachs disease
 - Carrier screening—family history: cystic fibrosis, spinal muscular atrophy, fragile X syndrome, or nonsyndromic hearing loss (*connexin-26* mutation)
- Congenital infections—Screen for infectious diseases, immunize, and counsel.
- Environmental toxins, such as occupational and household chemical exposures
- Tobacco, alcohol, and prescription and nonprescription drug use
- Diseases and disorders
- Exercise and nutrition
- Domestic violence screen

Genetic Risks

Folic acid supplementation is discussed under [Folic Acid on page 11-2](#).

Maternal age ≥ 35 years is considered advanced maternal age. As women age, the risk of fetal chromosomal abnormalities, medical complications during pregnancy, and infertility increases. Counsel all women about these risks and inform them about available testing for fetal aneuploidy, which includes noninvasive prenatal testing, amniocentesis, and chorionic villus sampling. Although risk increases as women get older, everyone should be offered these available tests regardless of age.

The American College of Obstetricians and Gynecologists (ACOG) recommends screening all pregnant women for

hemoglobinopathies with complete blood count (CBC) and red blood cell indices. Carrier screening is also recommended for the following hereditary conditions:

- Spinal muscular atrophy
- Cystic fibrosis
- Fragile X syndrome (only in patients with a family history of the disease)
- Congenital hearing loss (Screen for *connexin-26* mutation in patients with congenital hearing loss.)
- Spinal muscular atrophy and cystic fibrosis (for all women contemplating pregnancy)
- Tay-Sachs disease (1:30 Ashkenazi Jews are carriers.)

Congenital Infections

Preconception screenings for HIV and syphilis are important. Include HIV enzyme-linked immunosorbent assay (ELISA) and rapid plasma reagin (RPR) testing in prenatal screening. Also include a urine culture in prenatal testing to screen for asymptomatic bacteriuria. Highly active antiretroviral therapy (HAART) during pregnancy can decrease the risk of perinatal transmission to the fetus. Consider administering hepatitis B vaccine to women at risk (although it may be given during pregnancy).

Give the live vaccines for measles, mumps, and rubella ≥ 1 month prior to pregnancy. Give the varicella vaccine ≥ 3 months prior to pregnancy. Give the influenza vaccine at any time because it can be safely administered during pregnancy.

Educate pregnant women on toxoplasmosis and the need to avoid handling cat litter, garden soil, and raw meat. See more on toxoplasmosis under [Parasitic Disease on page 11-7](#). Cytomegalovirus (CMV) and parvovirus B19 are best prevented by good personal hygiene and hand washing, especially around young children. Advise patients to avoid contact with individuals with known infections. See more on CMV under [TORCH on page 11-7](#).

Environmental Toxins

Advise women to avoid environmental toxins that can cause harm to the embryo or fetus. These include:

- Metals such as lead and mercury
- Solvents (e.g., used in dry cleaning) such as trichloroethylene, chloroform, benzene, and toluene
- Plastics in plastic manufacturing
- Pollutants and pesticides (e.g., garden sprays)
- Gases, including anesthesia and carbon monoxide
- Radiation exposure (e.g., medical use)

Tobacco, Alcohol, and Prescription / Nonprescription Drugs

Exposure to certain drugs can be harmful to the embryo or fetus. The U.S. Food and Drug Administration (FDA) categorizes drugs to try to elucidate risks. See drug information publications for further information.

Avoid the following drugs in pregnancy:

- Misoprostol, oral contraceptive pills (OCPs)
- Benzodiazepines
- Warfarin (unless patient has mechanical heart valves)
- 3-Hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors
- Megadose vitamin A
- Nicotine, alcohol
- Thalidomide
- Nonprescription drugs, such as cocaine, heroin, and marijuana

Smoking carries dose-dependent risks to the mother and developing fetus, including low birth weight, perinatal mortality, attention deficit hyperactivity disorder (ADHD), and miscarriage.

Alcohol carries risks, such as intellectual disability and growth disorders.

Medical Conditions Affecting Pregnancy

The following medical conditions can be associated with an increased risk of complications during pregnancy and of congenital abnormalities.

Diabetes: See [Diabetes on page 11-11](#).

Hypertension: See [Hypertension \(HTN\) on page 11-8](#).

Epilepsy: Note that infants of epileptic mothers have up to an 8% risk of congenital anomalies. If possible, use a single agent to control the mother's epilepsy. Many antiepileptic medications (ASMs; a.k.a. antiepileptic drugs, anticonvulsants) are teratogenic; therefore, discuss medication teratogenicity with epileptic women of child-bearing age. Do **not** stop the patient's ASM without consulting the patient's neurologist.

Anxiety/Depression: Benzodiazepines increase the risk of cleft lip, cleft palate, and withdrawal symptoms in the fetus. Discuss the risks and benefits of continuing antidepressant medications during pregnancy. Consult with the patient's psychiatrist regarding medication changes. Do not prescribe a woman of child-bearing age paroxetine. If she is already on paroxetine, consult with a psychiatrist for cross-titration of the medication to an alternate selective serotonin reuptake inhibitor (SSRI) vs. discontinuing the drug—after a discussion of risks, benefits, and alternatives during pregnancy and lactation. Consult a psychiatrist if a woman is on mood stabilizers or antipsychotics.

Exercise and Nutrition

Recommend regular, moderate exercise. Hyperthermia is associated with an increased risk of congenital anomalies. Women who are pregnant or are trying to become pregnant should avoid extremes in exercise and extremes in temperature (e.g., hot tubs).

Counsel women who are overweight (body mass index [BMI] 25 to < 30 kg/m²), obese (BMI of ≥ 30 kg/m²), or underweight (BMI < 18.5 kg/m²) on normal preconception weight.

Advise women to avoid the overuse of:

- Vitamin A (limit to 5,000 IU/day)
- Caffeine (limit to < 200 mg/day)

See [Vitamin and Nutritional Deficiencies in Pregnancy](#) for information on nutritional deficiencies.

Domestic Violence

Approximately 324,000 pregnant women are abused each year in the U.S. Domestic violence is associated with pregnancy weight gain, infection, anemia, tobacco use, stillbirth, pelvic fractures, placental abruption, fetal injury, preterm delivery, and low birth weight. Violence can escalate during pregnancy—and consequently, homicide is a leading cause of maternal mortality.

Screen for domestic violence in a private setting without any other family members present. Inform patients that this is routine assessment and is kept confidential.

VITAMIN AND NUTRITIONAL DEFICIENCIES IN PREGNANCY

PREVIEW | REVIEW

- Pregnancy requires a total of how many additional kcal?
- Neural tube defects can be reduced by taking which supplement?
- A patient with a history of a pregnancy with a neural tube defect should take how much folic acid daily?
- What is a common mineral deficiency in pregnant women who have not had prenatal care?
- How many additional milligrams of ferrous sulfate are needed in pregnancy?

Pregnancy requires only an additional 100–300 kcal/day. Although vitamin and nutritional deficiencies in pregnancy are rare in the U.S., assess the risk of nutritional deficiencies in certain populations (e.g., patients with vegan diet, pica, milk intolerance, anemia).

Encourage a pregnant woman to eat a well-balanced diet and to monitor her weight. Note that pregnancy has elevated vitamin and nutritional requirements for fetal development.

Folic Acid

The most important supplementation during pregnancy is **folic acid**. Ideally, women should start folic acid 400 mcg/day orally (PO) at least 1 month prior to conception and continue it for at least the first 3 months of pregnancy.

Neural tube defects can largely be prevented by a daily intake of folic acid 400 mcg through the preconception period. If a woman delivered a previous child with a neural tube defect, increase her daily intake to 4 mg/day.

The dose should be consumed as a separate supplement. Additionally, patients on ASMs that affect folate levels should take 4 mg/day of folic acid.

Iron

Iron deficiency is commonly seen in pregnant women who have had **no prenatal care**. Pregnant women need an additional 27 mg/day of ferrous sulfate. Anemia of pregnancy is common, and the most encountered cause is iron-deficiency anemia. The additional iron required is sufficiently provided in a daily prenatal vitamin.

Calcium (Ca²⁺)

Ca²⁺ supplementation is not routinely required during pregnancy.

Zinc

There is no requirement for zinc supplementation in pregnancy because deficiency is rare. Observational data relating zinc deficiency to adverse perinatal outcomes has been conflicting. Some studies suggest zinc supplementation can prevent congenital malformations, such as cleft lip and palate, in cases of deficiency, but this has not been proved.

Iodine

Severe maternal iodine deficiency predisposes the offspring to cretinism, characterized by severe neurological defects. The use of iodized salt and bread is recommended during pregnancy, and no supplementation is necessary.

Magnesium (Mg²⁺)

There is no requirement for Mg²⁺ supplementation, and deficiency is rare. However, deficiency can occur after gastric bypass surgery.

Vitamin A

Excess vitamin A (retinol) is associated with birth defects. Doses of > 10,000 IU/day have been associated with spontaneous abortions, cleft palate, and cardiac abnormalities. Supplemental vitamin A is not recommended for women who are pregnant. There are no reliable studies that address the risk of teratogenicity with topical retinoids.

Vitamin B₁₂

Vitamin B₁₂ deficiency can occur in vegetarian or vegan women, as well as women who have had a gastric bypass. Measure B₁₂ at the beginning of pregnancy and continue to measure monthly if there is a proven deficit. Supplementation may be needed if B₁₂ levels are low. Because breast milk of a vegetarian or vegan contains little vitamin B₁₂, these women require supplementation during breastfeeding as well.

Vitamin B₆

Use vitamin B₆ combined with doxylamine to treat hyperemesis gravidarum. A typical dose is 10–25 mg PO 3–4×/day.

DRUGS AND MEDICATIONS IN PREGNANCY

PREVIEW | REVIEW

- During which trimester is metronidazole contraindicated?
- Know [Table 11-1 on page 11-5](#).
- Are angiotensin-converting enzyme inhibitors safe in pregnancy?
- A pregnant woman has deep vein thrombosis. Which commonly used anticoagulant is not recommended?

Medications, prescriptions, and over-the-counter drugs should be used only when the benefit clearly outweighs the potential risk to mother or fetus. In 2015, the FDA replaced the former pregnancy risk letter categories (A, B, C, D, and X) on prescription drug labeling with new, more comprehensive labeling. Each drug has listed **narrative sections** titled “pregnancy,” “lactation,” and “female and males of reproductive potential.” Each section is further divided and discusses a risk summary, clinical considerations, and available data on the particular drug. Pregnancy exposure registry information is also included in the pregnancy narrative.

The following medications are considered **safe** in the treatment of common conditions in pregnancy:

- Pain/Fever—acetaminophen
- Pain/Fever—nonsteroidal antiinflammatory drugs (NSAIDs) can be used up to 30 weeks of gestation. (Avoid after 30 weeks to prevent premature closure of ductus arteriosus and oligohydramnios.)
- Antibiotics—cephalosporins, penicillins, erythromycin, clindamycin, azithromycin; additionally, avoid metronidazole and sulfonamide drugs in the 1st trimester, but they can be used during the 2nd and 3rd trimesters.
- Antivirals—acyclovir, famciclovir, valacyclovir
- Nausea/vomiting—pyridoxine + doxylamine, diphenhydramine, meclizine; 2nd line therapies—prochlorperazine, metoclopramide, and ondansetron
- Gastroesophageal reflux disease symptoms—H₂ blockers, proton pump inhibitors
- Insomnia—doxylamine, diphenhydramine
- Diarrhea—loperamide
- Constipation—docusate, bisacodyl, lactulose, magnesium hydroxide
- Anticoagulation—low molecular weight heparin (LMWH), unfractionated heparin
- Opioids—codeine, oxycodone, methadone (Note: These medications should be used for the shortest time possible to avoid neonatal abstinence syndrome.)

Know [Table 11-1 on page 11-5](#).

GASTROENTEROLOGY IN PREGNANCY

Endoscopic Workup

Esophagogastroduodenoscopy (EGD) is the test of choice to work up many gastrointestinal (GI) diseases during pregnancy to limit or preclude the use of radiation. However, only perform it if there is a strong indication, and when possible, delay it until the 2nd trimester.

Endoscopic ultrasonography (EUS) is normally used in evaluating pancreatic diseases. It can also be used to evaluate biliary duct disease. In nonpregnant individuals, endoscopic retrograde cholangiopancreatography (ERCP) is preferred, but this is best avoided in pregnancy.

Gastroesophageal Reflux Disease

Progesterone increases during pregnancy, leading to the relaxation of smooth muscle, including the lower esophageal sphincter (LES). Consequently, pregnant women are predisposed to reflux. LES pressure is also decreased by chocolate, smoking, and certain medications, especially those with anticholinergic properties. Famotidine and lansoprazole are used for refractory gastroesophageal reflux symptoms. Nonrefractory reflux usually responds to lifestyle modification such as elimination of problem foods, smaller portions, and elevation of the head of the bed. Calcium carbonate is considered a drug of choice for management of nonrefractory reflux in pregnancy, but overuse can increase the risk of milk alkali syndrome. Avoid bismuth subsalicylate due to the salicylate exposure.

Inflammatory Bowel Disease Medications

The following medications can be used for inflammatory bowel disease (e.g., Crohn disease, ulcerative colitis) and have **no** evidence of risk in pregnancy:

- Metronidazole (However, because of the lack of data, it is contraindicated in the 1st trimester.)
- Prednisone
- Sulfasalazine
- Mesalamine

Constipation

The altered progesterone and estrogen levels are the probable cause of constipation in pregnancy. First, recommend dietary modifications, such as increased fluids and fiber. If constipation persists, over-the-counter medications are indicated. The following medications are also safe to use:

- Docusate
- Bisacodyl
- Lactulose
- Magnesium hydroxide

Pancreatitis

Pancreatitis is rare in pregnancy but is treated similarly to pancreatitis outside of pregnancy. Obtain an abdominal ultrasound on the patient to evaluate for cholelithiasis. Keep the patient NPO and hydrate with intravenous (IV) fluids.

Liver Disease

Pregnancy-associated liver disease can range from mild to life threatening (for a further discussion of liver disease in pregnancy, see the [Gastroenterology](#) section). During a normal pregnancy, **albumin** levels are **lower** due to hemodilution. **Alkaline phosphatase** is slightly **elevated** from the placental source. The remaining biochemical liver tests (aspartate aminotransferase [AST], alanine aminotransferase [ALT], bilirubin, and coagulation factors) are within normal range.

Signs and symptoms suggesting liver dysfunction include jaundice, pruritus, abdominal pain, nausea, and vomiting.

Initial workup includes liver function tests (LFTs), viral hepatitis panel, right upper quadrant ultrasound, prothrombin time/international normalized ratio, CBC, and basic metabolic panel. Liver biopsy is rarely needed.

Consider the following etiologies in working up a pregnant patient with **hepatobiliary findings**:

- **Hyperemesis gravidarum** occurs in the 1st trimester. It can cause volume depletion and mild increase in AST and ALT. It usually resolves with conservative symptomatic management.
- **Intrahepatic cholestasis of pregnancy** occurs in late pregnancy (3rd trimester), and pruritus is a common symptom. It is associated with prematurity and stillbirth. Treat with ursodeoxycholic acid and early delivery (36–37 weeks).
- **Acute fatty liver of pregnancy** occurs in late pregnancy. It is a very serious condition in which there is microvesicular fat deposition in the liver (i.e., Reye syndrome), with only a modest elevation of AST/ALT/bilirubin. Patients develop coagulopathy and can progress to liver failure. It is associated with encephalopathy, hypoglycemia, preeclampsia, pancreatitis, disseminated intravascular coagulopathy (DIC), and renal failure. Prompt delivery is the primary treatment.
- **HELLP syndrome** typically occurs at 28–36 weeks of gestation, but it can occur during the 2nd trimester or postpartum. For more on HELLP syndrome, see [Hypertension \(HTN\)](#) on page 11-8.
- **Hepatitis E** (unlike hepatitis A) carries a **very high risk** for fulminant hepatitis in the 3rd trimester of pregnancy. It has a 20% fatality rate. Think of a pregnant woman traveling to Southeast Asia who contracts hepatitis E (fecal-oral transmission like hepatitis A).

Table 11-1: Frequently-Asked-About Drugs in Pregnancy

Avoid Use in Pregnancy if Possible	Effects on the Fetus	Safer Alternatives for Pregnancy (examples not all-inclusive)
ACEIs, ARBs	IUGR, oligohydramnios, stillbirth	Clonidine, labetalol, calcium channel blockers, digoxin, propranolol, procainamide
Alkylating agents	Absence of digits	
Most aminoglycosides	Ototoxicity, nephrotoxicity	Gentamicin
ASMs	Neural tube defects, cardiac defects, cleft palate, skeletal abnormalities	Levetiracetam preferred ASM
NSAIDs (e.g., ibuprofen, diclofenac, naproxen) after 30 weeks of gestation	Premature closure of the ductus arteriosus and oligohydramnios	NSAIDs are safe prior to 30 weeks of gestation. After 30 weeks, use acetaminophen.
DES	Vaginal clear cell adenocarcinoma, congenital Müllerian anomalies	
Folate antagonists (e.g., methotrexate, ASMs such as valproic acid)	Neural tube defects	Levetiracetam preferred ASM
HMG-CoA reductase inhibitor	Possible delayed fetal development	
Lithium	Ebstein anomaly	
Misoprostol	Fetal death	
Paroxetine	Ventricular and atrial septal defects, neonatal withdrawal symptoms, serotonin syndrome	Fluoxetine, citalopram, or other SSRIs
Tetracycline	Inhibited bone growth, discolored teeth	
Thalidomide	Limb effects	
Warfarin	Bone deformities, fetal hemorrhage, abortion, ophthalmologic abnormalities	Unfractionated heparin, enoxaparin (an LMWH)
TZDs	Possible IUGR, embryo-fetal toxicity (animal studies)	Metformin, insulins
Aspirin (full dose)	Premature fetal ductus arteriosus closure	Acetaminophen, low-dose aspirin
Benzodiazepines	Cleft lip and palate, neonatal withdrawal symptoms	
Bismuth subsalicylate	Premature closure of ductus arteriosus, IUGR	
Methimazole, ¹³¹ I	Fetal hypothyroidism	
Substances		
Alcohol	Fetal alcohol syndrome (most common preventable cause of birth defects and intellectual disability)	
Cocaine	Low birth weight (leading cause in developed countries), preterm birth, IUGR, placental abruption	
Smoking	Low birth weight, preterm birth, placental problems, SIDS, ADHD	
Other		
Iodine (lack or excess)	Congenital goiter or hypothyroidism (cretinism)	PTU, levothyroxine
Maternal diabetes	Caudal regression syndrome, congenital heart defects, neural tube defects, macrosomia, polycythemia, hypoglycemia	
Methylmercury	Neurotoxicity	
Vitamin A excess	High risk of spontaneous abortions and birth defects (e.g., cleft palate, cardiac abnormalities)	
X-rays	Microcephaly, intellectual disability	
ACEI = angiotensin-converting enzyme inhibitor ADHD = attention deficit hyperactivity disorder ARB = angiotensin II receptor blocker ASM = antiseizure medication DES = diethylstilbestrol HMG-CoA = 3-hydroxy-3-methylglutaryl coenzyme A IUGR = intrauterine growth restriction LMWH = low molecular weight heparin NSAID = nonsteroidal antiinflammatory drug PTU = propylthiouracil SSRI = selective serotonin reuptake inhibitor TZD = thiazolidinediones		
Adapted from: First Aid for the USMLE Step 1 2018		

PULMONARY MEDICINE IN PREGNANCY

Asthma Treatment

Treatment of asthma during pregnancy is not significantly different from asthma treatment for nonpregnant patients. It is important to minimize exacerbations and optimize control with the current medication regimen. Recommend smoking cessation because it decreases asthma symptoms, decreases hospitalizations and emergency department visits, and improves responses to treatment. Furthermore, smoking cessation is beneficial for the pregnancy because it decreases the risk of intrauterine growth restriction (IUGR), placental abruption, preterm birth, and stillbirth. Use a step-up approach for asthma control, including the use of inhaled corticosteroids and inhaled long-acting β -agonists. Use IV or PO steroids, in addition to inhaled β -agonists (albuterol) and anticholinergics, for acute exacerbations.

Budesonide is preferred in pregnancy, but all inhaled corticosteroids can be used.

Tuberculosis (TB) Treatment

Per the World Health Organization 2010 guidelines, treat a pregnant woman who has TB with standard 1st line TB drugs—with the exception of streptomycin because it causes ototoxicity and nephrotoxicity. Pyridoxine supplementation is also recommended for all pregnant or breastfeeding women taking isoniazid.

Pulmonary Embolism (PE) and Deep Vein Thrombosis (DVT)

The risk of PE and DVT, known collectively as venous thromboembolism (VTE), is increased up to 5-fold during pregnancy and postpartum. Risk factors for VTE in pregnancy include prior history of VTE, the presence of a thrombophilia, obesity, hemoglobinopathies, hypertension (HTN), and smoking.

If a DVT is suspected, the recommended diagnostic test is compression ultrasonography of the proximal veins. Patients with a PE should undergo a ventilation-perfusion scan or computed tomographic (CT) angiography. D-dimer is not recommended in pregnancy.

Treat a patient with a DVT or PE with anticoagulation. LMWH can be self-administered and requires little-to-no monitoring. Enoxaparin (a LMWH) is generally considered to be safe for both the mother and the fetus in pregnancy. The 2012 American College of Chest Physicians guidelines recommend the use of LMWH during all phases of pregnancy for prevention and treatment of VTE in women with VTE or at elevated risk for VTE (e.g., antiphospholipid antibody syndrome).

Warfarin is generally considered a contraindication in pregnancy because of its teratogenic effects. (The exception is a patient with a mechanical heart valve, for whom warfarin is the only acceptable anticoagulant.) Unfractionated heparin is an option, but it poses challenges, such as parenteral dosing and the need for frequent monitoring.

CARDIOLOGY IN PREGNANCY

PREVIEW | REVIEW

- Is an S₃ gallop normal in pregnant women?
- How is peripartum cardiomyopathy treated?
- Is electrical cardioversion possible during pregnancy?
- What do you have to rule out in a pregnant patient who presents with new-onset atrial fibrillation and pulmonary edema?

Normal Findings

An S₃ and/or a systolic murmur is normal and commonly heard in pregnant women secondary to the increased cardiac output of pregnancy. The heart rate is typically elevated, with an average increase of 10–30 bpm. Jugular venous pressure typically increases. Additionally, most pregnant women experience some pedal edema.

Cardiac Issues

Absolute cardiac contraindications to pregnancy include pulmonary arterial hypertension (PAH) and Eisenmenger syndrome. Patients with secundum atrial septal defect (ASD), aortic stenosis, or dilated cardiomyopathy must be closely watched by an obstetrician who specializes in high-risk pregnancies. Patients with significant aortic stenosis or dilated cardiomyopathy are normally kept on bed rest. Secundum ASD patients are usually not at risk for cardiac decompensation, unless they develop atrial fibrillation. Cyanotic heart disease has very high risks.

HTN in pregnancy: See [Hypertension \(HTN\) on page 11-8](#). The [Cardiology](#) section and the [Pulmonary Medicine](#) section have additional information on pulmonary HTN.

Hypertrophic cardiomyopathy (HCM) among asymptomatic women is not a contraindication for pregnancy. In women with HCM who are asymptomatic or whose symptoms are controlled with β -blockers, the β -blockers should be continued during pregnancy with increased surveillance for fetal bradycardia and IUGR. In women with HCM and resting or provokable left ventricular outflow tract obstruction (≥ 50 mmHg) and/or cardiac symptoms not controlled by medical therapy alone, pregnancy carries an increased risk for heart failure, arrhythmia, and fetal loss; refer these patients to a high-risk obstetrician.

Peripartum cardiomyopathy of pregnancy is a condition in which, at the end of pregnancy, the patient experiences heart failure signs and symptoms and is found on echocardiogram to have a left ventricular ejection fraction (EF) $< 45\%$. The etiology is unclear. Treatment for peripartum cardiomyopathy is similar to that for other forms of heart failure. β -blocker and diuretic therapy is the mainstay of treatment. Nitrates + hydralazine and digoxin can be added as 2nd and 3rd line therapy. Angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), and spironolactone are **not** recommended.

during pregnancy. Patients with a persistently low EF of < 50% (or < 25% at the time of diagnosis) are advised against future pregnancies due to the risk of heart failure progression.

Atrial fibrillation: Like secundum ASD, the initial presentation of mitral stenosis in a pregnant patient can be new-onset atrial fibrillation and pulmonary edema. The increased blood volume in pregnancy can cause a precipitous exacerbation of mitral stenosis—so consider treating all pregnant mitral stenosis patients prophylactically with digoxin. Electrical cardioversion **can** be used during pregnancy.

In a pregnant patient presenting with new-onset atrial fibrillation and pulmonary edema, rule out both **mitral stenosis** and **secundum ASD**.

Aortic dissection: The 3rd trimester of pregnancy, systemic HTN, cystic medial necrosis, bicuspid aortic valve, and coarctation of the aorta are all predisposing factors.

Valve surgery: Porcine valves (vs. mechanical valves) are often given to women of childbearing age to avoid the use of anticoagulants during pregnancy.

Controversy exists regarding the use of **LMWH** vs. **warfarin** for anticoagulation with mechanical prosthetic valves during pregnancy. Discuss the risks and benefits of warfarin (less risk of thrombosis for the mother; increased risk of defects for the infant, especially if given in the 1st trimester; increased risk of fetal bleeding throughout pregnancy) vs. LMWH (increased risk of thrombosis for the mother; decreased risk of defects for the infant). Most experts recommend warfarin in these patients.

Maternal **rubella infection** during pregnancy can cause patent ductus arteriosus (PDA), supraventricular aortic stenosis, branch pulmonary stenosis (peripheral PS), and other congenital cardiac defects. Rubella has been eradicated in the Americas.

INFECTIOUS DISEASE IN PREGNANCY

PREVIEW | REVIEW

- Should asymptomatic bacteriuria in a pregnant woman be treated?
- What is the maternal-to-fetal transmission rate of HIV without antiretroviral therapy (ART)? With ART?

Bacterial Infections

Urinary tract infections (UTIs) are typically caused by *Streptococcus agalactiae* and *Escherichia coli*. Treat with penicillins, cephalosporins, or nitrofurantoin. Ciprofloxacin is not given to pregnant women due to concerns of arthropathy developing in the fetus.

Listeria monocytogenes infections occur most often in those with **decreased** cellular immunity syndromes such as AIDS, lymphoma, and leukemia, but they are also seen

in neonates, the elderly, and **pregnant** women. The most common presentation is a woman in her 3rd trimester with a flulike illness. It is diagnosed by blood culture.

Streptococcus agalactiae, a common urinary tract pathogen, is also a cause of postpartum endometritis and bacteremia; so, suspect this in any woman who develops a **postpartum fever**!

Gonorrhea is more likely to disseminate in pregnant women. The newborn is at risk for gonococcal conjunctivitis. Antibiotic ointment is applied to the infant's eyes at birth to prevent the conjunctivitis.

Approximately 5% of pregnant women have *Chlamydia trachomatis* in their genital tract. Applying antibiotic ointment to the infant's eyes at birth does **not** prevent chlamydial conjunctivitis.

Treat asymptomatic bacteriuria in **pregnant** women, because 1/3 of cases progress to pyelonephritis without treatment.

Parasitic Disease

Toxoplasma gondii can cause congenital toxoplasmosis, which results in intellectual disability and chorioretinitis. The fetus is more likely to have a congenital infection if the disease is acquired later in pregnancy (15% in the 1st trimester; 70% in the 3rd trimester). Toxoplasmosis prior to pregnancy is generally not a concern during the pregnancy.

Viral Infections

TORCH

TORCH is an acronym for certain infections acquired in utero that are the most common causes of congenital problems. They include infections caused by:

- Toxoplasma (parasite; see [Parasitic Disease](#))
- Other (i.e., syphilis, enteroviruses, varicella zoster, parvovirus B19)
- Rubella (no longer in the Americas)
- CMV (most common viral cause)
- Herpes simplex

Previously, the “other” designation included only syphilis. Currently, enteroviruses, varicella zoster, and parvovirus B19 are included.

Varicella zoster has a slight risk of causing congenital defects. The pregnant woman with chickenpox has a 10% chance of developing severe pneumonia.

Rubella, due to a successful vaccination program, has been declared eliminated in North and South America, but it continues to be a problem elsewhere. There are still a few cases seen in the Americas, but they are imported. Rubella can frequently cause miscarriages and congenital defects, such as cataracts, heart problems, and intellectual disability. The global incidence, however, is decreasing with the use of the rubella vaccine. Worldwide, rubella incidence declined from 670,894 cases in 2000 to 14,621 cases in 2018. Congenital rubella syndrome rates are highest in Africa and southeast Asia.

CMV is **ubiquitous** and the most common cause of **con-genital** viral infection. 1–2% of all newborns have the infection in utero, but only a few have any abnormalities. These abnormalities, which range from mild neurologic problems to microcephaly, usually occur in mothers with a primary CMV infection.

HIV: Although not included in the TORCH acronym, there is a mother-to-fetus transmission risk of **30%**. However, this is reduced to < 2% with 3-drug antiretroviral therapy (ART); therefore, ensure that all pregnant women with HIV receive ART. If viral load is $\geq 1,000$ copies/mL, also give zidovudine at the time of delivery. Consider it for those with 50–1,000 copies/mL.

Zika Virus

Zika virus is a mosquito-borne (*Aedes* spp.) *Flavivirus* that causes symptoms in ~ 20% of infected patients. Zika virus is carried by the same mosquito that carries dengue and chikungunya viruses. Symptoms are milder but similar to those of dengue and chikungunya fevers, which include fever, muscle and joint pain, rash, and conjunctivitis.

In late 2015, an alarming rise in the number of infants born with microcephaly was seen in Brazil and linked to maternal Zika virus infection. This prompted the World Health Organization (WHO) to declare a public health emergency of international concern. They issued an advisory that warns pregnant women and **women considering pregnancy** against travel to high-risk areas. You can find the most current recommendations on the WHO website.

Sexual transmission of Zika virus has been reported. Recommend abstaining from sexual activity or using condoms during the pregnancy period. Women with Zika virus exposure may breastfeed.

There is no specific treatment or vaccine for Zika virus; treatment is symptomatic management.

For more on Zika virus, see the **Infectious Disease** section.

Fungal Infections

The preferred treatment for fungal infections in pregnancy is topical antifungal creams.

High-dose (400–800 mg/day) fluconazole is contraindicated in pregnancy because of associated fetal abnormalities of the cranium, face, bones, and heart. A single, low dose of fluconazole (150 mg) to treat yeast infection **can** be prescribed after the 1st trimester.

NEPHROLOGY IN PREGNANCY

PREVIEW | REVIEW

- List the 4 categories of hypertension in pregnancy.
- What are the defining features of preeclampsia?
- What are the diagnostic criteria for preeclampsia?
- What is HELLP syndrome?

Hypertension (HTN)

In normal pregnancy, blood pressure (BP) falls due to decreased systemic vascular resistance, so normal BP in pregnancy is always < 120/80 mmHg. Although the American College of Cardiology (ACC)/American Heart Association (AHA) 2017 Task Force defines HTN as BP > 130/80 mmHg, HTN in pregnancy is defined as:

- mild if systolic BP (SBP) is 140–159 mmHg and/or diastolic BP (DBP) is 90–109 mmHg or
- severe if SBP ≥ 160 mmHg and/or DBP ≥ 110 mmHg.

There are 4 categories of HTN in pregnancy:

- 1) **Chronic HTN:** preexisting HTN or HTN diagnosed **before 20 weeks** of gestation
- 2) **Preeclampsia:** new onset of HTN + proteinuria or other significant organ dysfunction **after 20 weeks** of gestation in a woman with no history of HTN
- 3) **Gestational HTN:** onset **after 20 weeks** and **no** proteinuria in a woman with no history of HTN
- 4) **Chronic HTN with superimposed preeclampsia:** worsening HTN + new-onset proteinuria after 20 weeks of gestation in a woman with history of chronic HTN

Diagnosis of Preeclampsia

Preeclampsia more commonly occurs in **primigravidas**, usually in the 3rd trimester, and resolves after delivery. However, it can present postpartum. In 2019, ACOG updated the diagnostic criteria for preeclampsia. **Proteinuria is no longer required** for the diagnosis if other signs or symptoms of significant organ dysfunction are present (see **Table 11-2**). Women with preeclampsia are considered to have **severe features** if any of the following are present:

- SBP ≥ 160 mmHg or DBP ≥ 110 mmHg
- Low platelets
- Elevated liver enzymes
- Acute kidney injury
- Pulmonary edema
- New-onset cerebral or visual symptoms (i.e., visual disturbances, severe headache, confusion, seizures)

HELLP syndrome is a severe form of preeclampsia with hemolytic anemia, elevated liver enzymes, and low platelets. **Eclampsia**, defined as generalized, tonic-clonic seizures in a woman with preeclampsia or gestational HTN, is also a manifestation of severe preeclampsia.

Risk Factors, Prevention, and Treatment of Preeclampsia

Risk factors for preeclampsia include diabetes mellitus, chronic HTN, multiple gestations (e.g., twins, triplets), chronic kidney disease, and prior preeclampsia. In 2014, the U.S. Preventive Services Task Force (USPSTF) issued a recommendation that pregnant women at increased risk for preeclampsia take **81 mg acetylsalicylic acid (aspirin) daily**. Risk of preeclampsia is reduced by **24%**! The risk of premature birth is decreased by 14% and IUGR by 20%.

Treat all **severe** HTN occurring during pregnancy (regardless of category) to at least **< 160 mmHg SBP and < 110 mmHg DBP**. Beyond this, BP treatment targets in pregnancy are controversial and not well addressed in any guidelines (remember, the JNC 8 does not discuss HTN in pregnancy). Overzealous treatment of HTN in pregnancy has the potential to cause reduced placental blood flow and low fetal birth weight. Treating to a DBP of 85 mmHg appears to be safe for the fetus and is probably a good target. Although chronic HTN is a risk factor for preeclampsia, treatment of HTN in pregnancy does **not** prevent preeclampsia (weird, but true).

Bed rest is no longer recommended for asymptomatic or mild preeclampsia—clinical trials show it does not improve outcomes. For women with symptoms or severe HTN, give intravenous magnesium sulfate to prevent seizures (eclampsia). Monitor the renal function, CBC (look for hemolytic anemia or thrombocytopenia), and LFTs. Abnormalities in any of these indicate severe preeclampsia and warrant immediate delivery, which is the only definitive treatment for preeclampsia. Ultimately, care providers often need to balance what is best for maternal health (early delivery) with what is best for the baby (postponing delivery to avoid consequences of severe prematurity).

Preeclampsia and eclampsia can occur postpartum. A woman who presents with new-onset HTN and cerebral or visual symptoms within 6 weeks of delivery has preeclampsia until proven otherwise. Monitor these women closely in an inpatient setting and treat with magnesium sulfate and antihypertensives.

Women who have had preeclampsia are at an increased risk for cardiovascular disease later in life. Regularly screen these women and treat them for modifiable cardiovascular risk factors, such as HTN, obesity, and hyperlipidemia.

Chronic HTN in Pregnancy

Review medications of women with chronic HTN who are contemplating pregnancy or are already pregnant. Discontinue ACEIs/ARBs and (usually) diuretics. BP medications may often be discontinued in pregnant women with chronic HTN that is controlled, but frequently monitor BP and symptoms. (That's right! This is the one instance where antihypertensives are actually **removed**!) Reinstitute medications if **SBP $\geq$ 160 mmHg or DBP $\geq$ 110 mmHg**.

Antihypertensive Medications in Pregnancy

Oral antihypertensives that are safe to use in preeclampsia, gestational HTN, and chronic HTN in pregnancy include:

- Labetalol (other β -blockers impair placental perfusion)
- Methyldopa
- Extended-release nifedipine
- Hydralazine

2nd line agents include diltiazem and verapamil, but watch for signs/symptoms of volume contraction, including oligohydramnios. Diuretics are generally not recommended in preeclampsia unless pulmonary edema is present. Know that the following antihypertensives are contraindicated: ACEIs/ARBs, direct renin inhibitors, and nitroprusside. ACEIs/ARBs and renin inhibitors are teratogenic; nitroprusside causes cyanide poisoning in the fetus.

Any pregnancy complicated by persistent, severe HTN (SBP $\geq$ 160 mmHg or DBP $\geq$ 110 mmHg) may require IV antihypertensives; labetalol and hydralazine are good options. Avoid rapid falls in maternal BP to prevent fetal hypoperfusion.

Table 11-2: Diagnostic Criteria for Preeclampsia

Blood pressure	SBP $\geq$ 140 mmHg or DBP $\geq$ 90 mmHg on 2 occasions at least 4 hours apart after 20 weeks of gestation in a woman with previously normal blood pressure When SBP $\geq$ 160 mmHg or DBP $\geq$ 110 mmHg, hypertension can be confirmed within minutes to facilitate timely antihypertensive therapy.
and	
Proteinuria	$\geq$ 300 mg in a 24-hour urine collection, or Protein:creatinine ratio $\geq$ 0.3 mg/mg, or Urinary dipstick reading $\geq$ 1+ (only if quantitative methods are unavailable)
or, in the absence of proteinuria, new-onset hypertension with new onset of any of the following:	
Thrombocytopenia	Platelets $<$ 100,000 μ L (100×10^9 /L)
Chronic kidney disease	Creatinine $>$ 1.1 mg/dL (97.2 μ mol/L) or doubling of the serum creatinine
Impaired liver function	AST or ALT $\geq$ 2 $\times$ normal
Pulmonary edema	Diagnosed by physical exam and chest radiograph
Cerebral or visual symptoms	Severe headache, blurry vision, scotomata, confusion, seizures
ALT = alanine aminotransferase	AST = aspartate aminotransferase

Adapted from: The American College of Obstetrics and Gynecologists Task Force on Hypertension in Pregnancy, 2019.

Systemic Lupus Erythematosus (SLE) with Lupus Nephritis

SLE with lupus nephritis: Pregnancy complicated by lupus is associated with a higher risk of maternal complications, including preterm labor, unplanned cesarean delivery, fetal growth restriction, preeclampsia, eclampsia, thrombotic events, and infections. Fetal complications include stillbirth, IUGR, and neonatal lupus syndromes. Fetuses of women with SSA (Ro) or SSA (La) antibodies are at risk for congenital heart block. Hydroxychloroquine is considered **safe** in pregnancy and should be continued.

Chronic Kidney Disease (CKD)

Patients with CKD who are normotensive with a creatinine < 2 mg/dL ($176.8 \mu\text{mol/L}$) do **not** have an increased risk of abortion or malformation, and there is **no** increase in the rate of progression of the CKD. All patients with CKD **do** have an increased risk of pregnancy-induced HTN.

As CKD progresses, a woman's fertility **decreases**. A patient on dialysis **rarely** becomes pregnant. Stable renal transplant patients usually have a great pregnancy outcome!

Renal Stones

Increased Ca^{2+} absorption and excretion occur during pregnancy. Even so, the frequency of renal stones is the same as in the nonpregnant patient. The urinary tract of the pregnant patient is dilated, and if stones develop, most pass easily.

ENDOCRINOLOGY IN PREGNANCY

PREVIEW | REVIEW

- What is the treatment for postpartum thyroiditis?
- A pregnant woman has Graves disease. What can you do to treat her?
- Which medications commonly given to patients with diabetes are contraindicated in pregnancy?
- When should pregnant women be screened for diabetes? What is the test of choice?
- What medication is used to treat gestational diabetes if diet and exercise fail to reach targets?

The Serum Osmostat

Pregnant women increase their circulating blood volume by almost 50%. This is a result of the osmotic set point resetting, causing the antidiuretic hormone to be released at a lower osmolality.

Prolactin (PRL) Levels

Estrogen directly **inhibits** dopamine outflow, so **elevated** PRL levels can be seen in pregnant patients and in those taking estrogen.

Pituitary Adenoma

About 1/3 of pituitary macroadenomas, some of which cause increased PRL levels, **enlarge** during pregnancy. Ideally, a patient should be started on bromocriptine or cabergoline prior to conceiving. If a woman is diagnosed in pregnancy and the tumor is large enough to cause symptoms, start **bromocriptine** or cabergoline at that time. Bromocriptine is considered safe in pregnancy. Caution is advised for cabergoline because there is no human data available. Consider surgery if vision is threatened.

Note: Bromocriptine and cabergoline are FDA approved for hyperprolactinemia.

Thyroid Disease

Hyperthyroidism

Treatment with ^{131}I is contraindicated in pregnancy.

Hyperthyroidism in pregnancy is uncommon and often does not require treatment. However, there are a few circumstances when treatment is necessary to prevent fetal hyperthyroidism.

Gestational transient thyrotoxicosis does not require treatment. This is normal physiology of pregnancy in which human chorionic gonadotropin (hCG) stimulates thyroid-stimulating hormone (TSH) receptors, resulting in a mild elevation in T_3/T_4 and suppression of TSH.

Subclinical hyperthyroidism (low TSH and normal free T_4) does not require treatment. Follow up thyroid labs every 4–6 weeks.

Symptomatic and/or overt hyperthyroidism requires treatment and is most commonly due to Graves disease or hCG-mediated hyperthyroidism. Treat with a β -blocker and antithyroid medication (propylthiouracil or methimazole). Patients uncontrolled on medications require thyroidectomy. Monitor the fetus to prevent fetal thyrotoxicosis.

Postpartum thyroiditis is an autoimmune-mediated process caused by thyroid peroxidase antibody. It presents with a hyperthyroid phase followed by a hypothyroid phase. This entity usually resolves within 1 year and rarely **requires** treatment. Use propranolol for significant hyperthyroid symptoms. Use replacement thyroid medication for hypothyroid symptoms or when the TSH is > 10 mU/L in asymptomatic women. It is important to follow up with thyroid function tests (TSH, FT_4 , and FT_3) every 4–6 weeks to ensure resolution and exclude Graves disease. 1/3 of patients are at risk for permanent hypothyroidism and require long-term replacement therapy.

During pregnancy, surgery may be indicated to treat **Graves disease** in patients with an associated cold nodule or relapse after radiation and in some young patients with a large goiter.

Hypothyroidism

Because pregnant hypothyroid patients' requirements increase, **always** treat them and follow their TSH levels

during pregnancy. **Increase** their dose to 50% more than the prepregnancy dose. Failure to treat maternal hypothyroidism during pregnancy can adversely affect the baby.

Polycystic Ovary Syndrome (PCOS)

See [Treatment on page 11-18](#) for the treatment of PCOS.

Diabetes

Diabetes in pregnancy is classified as follows:

Preexisting (overt) diabetes: diabetes (Type 1 or Type 2) that existed prior to pregnancy. Note that preexisting diabetes is sometimes first recognized in the 1st trimester of pregnancy.

Gestational diabetes: transient diabetes due to the increased insulin resistance of pregnancy; typically diagnosed during the 2nd half of pregnancy.

Preexisting Diabetes

In women with preexisting Type 1 or Type 2 diabetes who are planning for pregnancy, achieve strict glycemic control **before conception**. The American Diabetes Association 2019 guidelines recommend a fasting plasma glucose (FPG) < 95 mg/dL (5.3 mmol/L) and HbA1c < 6% if these targets can be achieved without significant hypoglycemia. Preconception, blood glucose control reduces fetal malformation; during pregnancy, it reduces miscarriages, fetal anomalies/death, and newborn problems. Tight glycemic control decreases the risk of macrosomia (birth weight ≥ 9–10 lb) and shoulder dystocia in the newborn (which increases as birth weight increases).

During pregnancy, a diabetic patient requires **~ 50% more** insulin due to insulin resistance from placental hormones. This increased requirement is gone **immediately** after delivery, so anticipate a reduction in insulin dosage of at least **33%** postpartum and observe the patient carefully the day after delivery. (In clinical practice, it may be prudent to cautiously lower the insulin dose to adjust for the decreased requirement.)

Insulin is the preferred agent for management of both Type 1 and Type 2 diabetes in pregnancy. In pregnancy, **avoid** the following medications commonly used in diabetes management:

- Statins
- ACEIs and ARBs
- Most oral hypoglycemics

Gestational Diabetes

Like preexisting diabetes, gestational diabetes increases the risk of preeclampsia, macrosomia, and stillbirth. Gestational diabetes usually resolves after delivery, but it can recur in subsequent pregnancies. Women with gestational diabetes have an increased long-term risk for Type 2 diabetes and cardiovascular disease.

Screen all pregnant women for gestational diabetes between 24 and 28 weeks of gestation. The initial screening test is the 50-g, 1-hour glucose challenge. If this is abnormal, proceed to the 100-g, 3-hour glucose tolerance test to make the diagnosis. Screen pregnant women at high risk for pregestational diabetes at the 1st prenatal visit. Indications for early screening include being overweight or obese (BMI ≥ 25 kg/m²) with 1 of the following risk factors: physical inactivity, 1st degree relative with diabetes, previous gestational diabetes, high-risk ethnicity, previous macrosomic infant, HTN, hypercholesterolemia, PCOS, or cardiovascular disease.

Treat gestational diabetes first with nutritional counseling and exercise. Patients should monitor blood glucose, with target fasting blood glucose of < 95 mg/dL (5.3 mmol/L), 1-hour postprandial glucose < 140 mg/dL (7.8 mmol/L), and 2-hour postprandial glucose < 120 mg/dL (6.7 mmol/L). If these targets are not achieved with diet and exercise, insulin is the 1st choice agent. Glyburide and metformin are sometimes used in women who refuse or cannot comply with insulin therapy.

NEUROLOGY IN PREGNANCY

Migraine

Treat migraines in pregnancy first with acetaminophen, acetaminophen-codeine, or butalbital-acetaminophen-caffeine. Consider NSAIDs, such as naproxen, ibuprofen, and ketorolac, prior to 30 weeks of gestation. Use triptans for moderate-to-severe symptoms.

Idiopathic Intracranial Hypertension (IIH)

Idiopathic intracranial hypertension (IIH; formerly known as pseudotumor cerebri) usually occurs in premenopausal obese women (90%) and may occur during pregnancy. See more on IIH in the [Neurology](#) section.

Seizures

Among pregnant women on ASMs, the risk of birth defects is 4–6%. However, uncontrolled seizures can cause placental abruption, early labor, and premature delivery. When the risk of teratogenicity is compared to the problems that seizures cause during pregnancy, the risk of uncontrolled seizures is **greater**.

Maintain a pregnant woman on **monotherapy** at the **lowest dose** of medication possible because the risk of malformation increases as each drug is added. Consult a neurologist to assist with any medication changes.

There is **no** “safe” ASM, but valproate is more likely to cause neural tube defects than other commonly used ASMs; avoid when possible.

The teratogenic risk of ASMs is **decreased by folic acid**. All women of childbearing age on ASMs should take 4 mg/day of folic acid.

ASMs such as phenytoin, carbamazepine, and topiramate can induce enzymes that alter the metabolism of vitamin K. However, inadequate evidence exists to determine if newborns of women taking ASMs have an increased risk of hemorrhagic complications. The American Academy of Neurology concluded in its 2009 Practice Parameter Update that there is not enough evidence to recommend for or against the use of prophylactic vitamin K to prevent bleeding in the neonate.

Carpal Tunnel Syndrome

Pregnancy can cause an **acute** presentation of carpal tunnel syndrome, which typically improves after delivery. Treat conservatively with wrist splints.

RHEUMATOLOGY IN PREGNANCY

Systemic Lupus Erythematosus (SLE)

SSA (Ro) and SSB (La) antibodies are associated with neonatal lupus and congenital heart block. General internists need to know about this risk when counseling women with lupus about pregnancy.

Patients with SLE have a **higher** incidence of failed pregnancies. Risk of pregnancy complications (flare or fetal problems) is much greater if the disease is **active** (especially renal manifestations) **or** if the mother has anti-double-stranded (anti-ds) DNA or antiphospholipid antibody syndrome (APS). Treat pregnant women with APS and a history of recurrent miscarriages with heparins (low molecular weight or unfractionated) plus low-dose aspirin—to decrease the risk of miscarriage. Heart block starting in the 3rd trimester can be seen in fetuses of mothers with SLE who have SSA (Ro) and/or SSB (La) antibodies.

If an SLE patient wishes to become pregnant and has had a recent lupus flare, **continue** the glucocorticoids and/or hydroxychloroquine. Measure baseline complements, anti-dsDNA, SSA/SSB, and a 24-hour urine protein before or very early in the pregnancy. Manage flares during pregnancy with glucocorticoids. **Refer** pregnant women with SLE to a high-risk obstetrician (and pediatric cardiologist if appropriate).

Avascular Necrosis of the Hip

Causes of avascular necrosis of the hip include pregnancy, steroid use, sickle cell disease, HIV/AIDS, alcoholism, trauma, Gaucher disease, and hypercoagulable states.

DERMATOLOGY IN PREGNANCY

Acne is more pronounced in pregnancy due to increases in progesterone. Treatment is focused on safer topical agents (i.e., erythromycin, clindamycin, azelaic acid) and avoidance of other agents known to be harmful (i.e., isotretinoin, tazarotene, tetracycline, minocycline). Also, topical benzoyl peroxide is generally not used.

Pruritic urticarial papules and plaques of pregnancy (PUPPP) is a common erythematous, pruritic papular rash that spreads outward to form plaques. PUPPP presents within the striae of the abdomen then spreads to the body, sparing the face, soles, and palms. It typically presents at around 35 weeks of gestation but can develop later in pregnancy or up to 2–3 weeks after delivery.

ALLERGY AND IMMUNOLOGY IN PREGNANCY

Persistent nasal congestion can accompany pregnancy (rhinitis of pregnancy). It is generally treated with non-pharmacological measures, including:

- Keep pets out of the room.
- Encase pillows/mattress in covers that protect against dust mites.
- Avoid outdoor activities when pollen counts are high.
- Change clothes after spending time outdoors.
- Shower to remove pollen from the hair and skin.

Intranasal steroids have not been shown to be effective.

For more information on pregnancy-related issues, see also the topics on rhinitis, vaccines, inherited immunoglobulin deficiencies, and neutropenia in the [Allergy & Immunology](#) section.

OFFICE GYNECOLOGY

ECTOPIC PREGNANCY

PREVIEW | REVIEW

- What are the risk factors for an ectopic pregnancy?
- How is an ectopic pregnancy diagnosed?

An ectopic pregnancy is the result of the implantation of a fertilized ovum in a site other than the uterus (ampulla of the fallopian tube 95% of the time). It occurs in 1–2% of pregnancies, and it accounts for 9% of all pregnancy-related deaths. Risk factors include prior history of ectopic pregnancy, history of infertility, prior tubal surgery, salpingitis, history of multiple sexual partners, ruptured appendix, advanced maternal age, smoking, and in utero diethylstilbestrol exposure. Women using an intrauterine device (IUD) or tubal sterilization for contraception are at an increased risk of an ectopic pregnancy if they become pregnant.

Presentation

Patients typically present with sudden lower abdominal/pelvic pain or 1st trimester bleeding. Bimanual cervical exam reveals adnexal tenderness and an adnexal mass. A ruptured ectopic pregnancy presents with a progression of diffuse abdominal pain, rebound tenderness, vital sign instability, and shock. The risk of rupture is ~ 30% in the first 48 hours; it then falls to ~ 5–10%.

Diagnosis

Ultrasound is indicated in all women with a suspected ectopic pregnancy to look for an intrauterine pregnancy, an adnexal mass, or free pelvic fluid. An elevated β -hCG in the absence of an intrauterine pregnancy is highly suspicious of an ectopic pregnancy.

Differential diagnosis:

- Spontaneous abortion
- Molar pregnancy
- Adnexal mass (e.g., ovarian torsion, tuboovarian abscess, cyst rupture)
- Pelvic inflammatory disease (PID)
- Appendicitis
- Pyelonephritis
- UTI
- Nephrolithiasis
- Diverticulitis
- Ulcerative colitis

No physical exam findings are specific to ectopic pregnancy because the findings can mimic those previously listed in the differential. No single serum β -hCG level is diagnostic of an ectopic pregnancy; therefore, it is necessary to perform serial serum β -hCG levels to differentiate between normal and abnormal pregnancies and to monitor resolution of ectopic pregnancy once therapy has been initiated (β -hCG decreases). Confirmed diagnosis can be made by visualization of ectopic pregnancy on ultrasound or by laparoscopy/laparotomy.

Prognosis

Spontaneous resolution occurs in 88% of ectopic pregnancies with hCG levels < 200 mU/mL and in 59% of ectopic pregnancies with hCG levels < 2,000 mU/mL. In the U.S., mortality is 0.5/100,000 live births. The recurrence rate is about 10% in women with 1 previous ectopic pregnancy, and it rises to > 25% in women with 2 previous ectopic pregnancies.

Treatment

Treatment varies depending on the presentation. Watchful waiting is an option if the patient is asymptomatic, there is evidence of spontaneous resolution, and the patient accepts the risk of rupture. Surgery or methotrexate therapy may be appropriate 1st line therapy for an unruptured ectopic pregnancy.

Give methotrexate to stable patients with a fetal crown-rump length < 4 cm and no fetal embryonic cardiac activity. CBC and comprehensive metabolic panel (CMP) are necessary prior to administering methotrexate. The following are absolute contraindications:

- Intrauterine pregnancy or breastfeeding patient
- Immunodeficiency
- Moderate-to-severe anemia, leukopenia, or thrombocytopenia

- Active pulmonary disease
- Active peptic ulcer disease
- Hepatic or renal dysfunction
- Ruptured ectopic and/or unstable patient
- Patient inability to participate in follow-up
- Sensitivity to methotrexate

Patients who receive methotrexate need serial hCG levels on posttreatment days 4 and 7. If the decrease in hCG is < 15%, give additional methotrexate.

Surgery is indicated for a ruptured ectopic pregnancy. Surgery may also be performed in stable and unruptured patients who are not candidates for or who decline methotrexate. Consult a gynecologist for all patients with suspected ectopic pregnancies.

SEXUALLY TRANSMITTED INFECTIONS (STIs)

See the [Infectious Disease](#) section for information on STIs.

VAGINITIS

See the [Infectious Disease](#) section for information on vaginitis.

PREMENSTRUAL SYNDROME (PMS)

PMS is a group of symptoms that most often start during the late luteal phase and are gone within 1–2 days of the onset of menses. The biochemistry of this dysfunction has not been established.

No single treatment has been proved to be effective, but the cause can be multifactorial, so there are many avenues of treatment to explore with each patient. You can achieve ovulatory suppression with oral contraceptives or the progestin-only pill. Other options include medroxyprogesterone acetate (MPA) and levonorgestrel implants.

Dietary changes, such as **avoiding** caffeine, salt, sugar, alcohol, and/or chocolate, can help some patients reduce or eliminate symptoms.

PREMENSTRUAL DYSPHORIC DISORDER (PMDD)

PREVIEW | REVIEW

- What are the diagnostic criteria for premenstrual dysphoric disorder (PMDD)?
- What organic syndromes can cause symptoms similar to PMDD?

PMDD is a cluster of affective, behavioral, and somatic symptoms recurring monthly during the luteal phase of the menstrual cycle. The prevalence of PMDD is between 1.8% and 8% of menstruating women. The heritability percentage of PMDD is unknown; however, heritability of premenstrual symptoms is between 30% and 80%.

Diagnosis

PMDD is diagnosed by the following *DSM-5* criteria.

At least 5 symptoms must be present in the final week before menses, improve within a few days of menses, become minimal after menses, and be observed daily for 2 cycles:

- ≥ 1 of the following mood symptoms:
 - Marked affective lability: mood swings, sudden tearfulness, increased sensitivity to rejection
 - Marked irritability, anger, increased conflicts
 - Marked depressed mood, hopelessness, self-deprecating thoughts
 - Marked anxiety or tension
- Plus ≥ 1 of the following symptoms:
 - Decreased interest
 - Difficulty concentrating
 - Lethargy, easily fatigued
 - Change in appetite, cravings
 - Hypersomnia or insomnia
 - Overwhelmed feeling or loss of control
 - Breast tenderness/swelling, joint/muscle pain
 - Symptoms that interfere with daily functioning and are not due to substances, another mental disorder, or a medical disorder

Risk factors include anxiety or depressive disorders (especially peripartum depression), increased age, stress, lack of exercise, history of interpersonal trauma, seasonal changes, and family history of PMDD.

Pathophysiology

The exact cause of PMDD is unknown. It is postulated that fluctuations in estrogen and progesterone lead to serotonin deficiency.

Workup

Exclude organic syndromes with manifestations similar to those of PMDD, including thyroid disorder (TSH), anemia (CBC), and perimenopause/menopause (FSH).

Clinical Course and Management

Onset of PMDD can occur at any point after menarche. Anecdotally, many individuals report worsening symptoms as they approach menopause. Symptoms cease after menopause, although hormone replacement can trigger the reexpression of symptoms. Treat with oral contraceptives and/or SSRIs. Combined oral contraceptives, with a 24/4 regimen and containing drospirenone or levonorgestrel as the progestogenic component, have been shown to relieve both psychological and physical symptoms of PMDD. SSRIs, while also considered a 1st line treatment, are effective for psychological symptoms only. Treat severe PMDD, unresponsive to other therapies, with gonadotropin-releasing hormone (GnRH) agonists.

CONTRACEPTIVE COUNSELING

PREVIEW | REVIEW

- The copper intrauterine device, Paragard, is effective for up to how many years?
- How frequently is the medroxyprogesterone acetate injection given?
- What is the most common of the least effective contraceptive methods?

The 2 main goals of discussing contraception are to formulate a reproductive life plan and to reduce unintended pregnancies. Discussing a reproductive life plan helps dictate which contraception type is most beneficial for the patient at that time in her life. Unintended pregnancies can result in significant depression, financial burden, poor prenatal care, and abortions.

Although there is no perfect contraception aside from abstinence, the most effective method is a personal decision for each patient. The best method for a woman depends on her individual needs, such as religious beliefs, tolerance of side effects, effects on menstruation, cost, and the ability to use a contraception properly (e.g., take an oral pill daily). Additionally, the need for or contraindication to hormones plays a large role in selecting the method.

Methods of Contraception

Contraceptive methods are divided into 3 categories:

- 1) Most effective
 - Permanent sterilization
 - Long-acting, reversible contraceptives, including IUDs and implants
 - Lowest pregnancy rate
- 2) Effective
 - OCP, vaginal ring, or patch
 - MPA injection
 - Diaphragms
 - Low pregnancy rate but dependent on patient use
- 3) Least effective
 - Condoms, spermicides, rhythm method, and pull-out method
 - Associated with a high risk of unintended pregnancies

Most effective: There are 2 types of IUDs. Both have an unintended pregnancy rate of $< 1\%$ per year. **Nonhormonal** IUDs (Paragard) contain copper, disrupt cervical mucus, and are a sperm inhibitor. They are effective for up to 10 years. **Hormonal** IUDs contain progesterone, lessen menses, thin the lining of the uterus, and inhibit sperm entry. They are effective for 3–5 years, depending on the type.

The **etonogestrel implant**, with a 0.5% failure rate, is effective for up to 3 years and is inserted in the office in the nondominant arm. It contains progestin hormone, can affect menses, and inhibits ovulation.

Effective: The most common effective method is the OCP, which has a 9% unintended pregnancy rate. OCPs are composed of estrogen and progesterone and are a hormonal ovulation inhibitor. They reduce the menstrual flow and make menses more predictable. OCPs need to be taken daily to be effective; there is typically a placebo week indicated by a lighter color at the end of the pill pack.

The vaginal ring is inserted monthly; it stays in the vagina for 3 weeks and comes out for 1 week.

The patch is changed weekly (on 3 weeks and off 1 week). Efficacy is similar to OCPs for both the ring and the patch.

MPA is an injection given once every 3 months in the office. It contains progesterone, lessens menses, and is associated with long-term, mild weight gain. The pregnancy rate is ~ 6% per year.

Diaphragms, used less commonly today, have a failure rate of about 12%.

Hormonal contraceptives with estrogen such as OCPs, the vaginal ring, and patch may also be effective in treating acne.

Least effective: The most common of the least effective methods, the condom, has a failure rate of 18%. Condoms are hormone free, available for purchase over the counter, and made of latex or nonlatex materials. **Of note, lambskin condoms do not protect against STIs.** Female condoms, withdrawal methods, and spermicides have failure rates of > 20%.

Emergency Contraception

Use emergency contraception to prevent pregnancy after unprotected intercourse. The FDA has approved ulipristal acetate (30 mg PO) and levonorgestrel (1.5 mg PO), called the “morning after pill,” for this indication. Ulipristal can be used up to 120 hours after unprotected sex, whereas levonorgestrel can be used up to 72 hours after unprotected sex. Ulipristal is prescription only but can be obtained online with an online medical consult. Levonorgestrel is over-the-counter. Levonorgestrel is not effective in women with a BMI ≥ 30 ; ulipristal is not effective in women with a BMI ≥ 35 .

Other methods of emergency contraception include specific combined progestin-estrogen pills and the copper IUD. If oral contraceptives or a copper IUD is desired for emergency contraception, refer to a gynecologist experienced in this area. No serious adverse events have been reported with emergency contraception. Typical side effects include nausea, headache, and irregular bleeding.

ENDOMETRIOSIS

Endometriosis is characterized by endometrial glands and stroma occurring outside the uterine cavity. It is a benign, inflammatory, estrogen-dependent condition. Women present with pelvic pain, infertility, or an ovarian

mass. Definitive diagnosis can be made only surgically with peritoneal biopsy. Treat with NSAIDs and OCPs. A progesterone IUD, MPA, GnRH agonist, or aromatase inhibitors are other options for treatment in patients who have failed or are not candidates for NSAIDs and OCPs. Surgical resection may be needed for refractory cases, fertility-related endometriosis, and obstructive symptoms.

OVARIAN CYSTS

Ovarian cysts are fluid-filled sacs within or on the surface of ovaries. Most ovarian cysts are asymptomatic and disappear over time. However, some can cause pain or fullness, especially those that have ruptured. Treat symptomatic cysts conservatively with pain medication, including NSAIDs. Large, symptomatic, or persistent cysts or those suspicious for malignancy may need to be surgically removed; refer these patients to gynecology. Ruptured cysts that result in hemodynamic instability require hospitalization for expectant management.

ABNORMAL UTERINE BLEEDING (AUB)

PREVIEW | REVIEW

- What test is indicated in all women with abnormal uterine bleeding (AUB)?
- What are the indications for an endometrial biopsy in women with AUB?

AUB refers to either heavy menstrual bleeding or intermenstrual bleeding. (The use of the terms dysfunctional uterine bleeding, menorrhagia, and metrorrhagia are no longer recommended.) Rule out pregnancy prior to any other workup. Address hormonal contraceptive use, which is also a common cause of abnormal bleeding.

The differential diagnosis of AUB in nonpregnant women who are not taking oral contraceptives is broad. Structural causes include endometrial polyps, adenomyosis, uterine fibroids, endometrial hyperplasia, or endometrial malignancy. Nonstructural causes include coagulopathies, ovulatory dysfunction, or infections. See [Table 11-3 on page 11-16](#) for differential diagnosis by age.

Workup

When taking a medical history, ask about bleeding patterns, pain associated with bleeding, family history of bleeding, or other bleeding problems (including gum bleeding, nosebleeds, or easy bruising). Ask about potential medications that might cause AUB, including anticoagulants, NSAIDs, or hormonal contraceptives.

Note physical signs of excessive weight, acne, hirsutism, or any acanthosis nigricans that suggest PCOS. Additionally, look for signs of a bleeding disorder, including petechiae or ecchymoses. Perform a pelvic examination, including both speculum examination and bimanual examination, to assess for cervical lesions, vaginal lesions, or uterine enlargement or irregularity. Chlamydia and gonorrhea cervicitis swabs may be obtained as well.

**Table 11-3: Abnormal Uterine Bleeding
— Age-Based Differential Diagnosis**

Patient Age (Years)	Common Diagnoses
13–18	Physiologic anovulation (immature hypothalamic-pituitary-ovarian axis) Hormonal contraceptive use Pregnancy Pelvic infections Coagulopathies
19–39	Pregnancy Structural lesions (usually polyps or fibroids) Anovulatory bleeding (usually PCOS) Hormonal contraceptive use Endometrial hyperplasia
40 to menopause	Physiologic anovulatory bleeding (secondary to declining ovarian function) Endometrial hyperplasia or carcinoma Endometrial atrophy Uterine fibroids

PCOS = polycystic ovary syndrome

Obtain a **pregnancy test**, **CBC**, and **TSH** level in all women. Order a transvaginal ultrasound to evaluate the uterus. The exception is adolescents 13–18 years of age; unless there are signs of a bleeding disorder, a pregnancy test is usually sufficient.

Perform an endometrial biopsy on **all women > 45 years of age**. Perform an endometrial biopsy on a woman < 45 years of age if she is obese, has a history of unopposed estrogen exposure, or has previously failed medical management for AUB.

Diagnosis

Diagnose structural lesions by **ultrasound**. A thickened endometrium can be indicative of an endometrial polyp, endometrial hyperplasia, or malignancy; however, this finding is nonspecific. Adenomyosis and fibroids can also be seen on ultrasound.

Diagnose coagulation disorders with laboratory testing. Among patients with suspected bleeding disorders based on history, order a CBC and coagulation studies. The most common bleeding disorder, von Willebrand disease, is diagnosed by decreased von Willebrand factor antigen or decreased ristocetin cofactor activity.

Diagnose anovulatory bleeding clinically. Anovulatory cycles are those that vary in length from one cycle to another. Patients with anovulation also do not have premenstrual symptoms, such as breast discomfort or premenstrual cramping and bloating. Further workup of anovulatory bleeding is discussed under **Anovulatory Bleeding**.

Diagnose infections, such as chlamydia or gonorrhea, with a cervical swab using culture, antigen, or nucleic acid detection methods.

Treatment

Treatment depends on the etiology of the bleeding. Treat patients with suspected anovulatory bleeding and an otherwise normal workup with combined oral contraceptives or progestins (including cyclic oral progesterone or the levonorgestrel IUD). Treat any infections with appropriate antibiotics (see the **Infectious Disease** section for treatment of STIs).

Refer patients with suspected bleeding disorders to a hematologist. Refer patients with structural lesions, including uterine fibroids or polyps, to a gynecologist.

Uterine Fibroids

Uterine fibroids (leiomyoma or myoma) are a common structural cause of AUB. They can be asymptomatic or cause heavy bleeding, dysmenorrhea, and infertility. A diagnosis can be made using a simple ultrasound. Refer suspected or symptomatic cases to a gynecologist. Some patients may require a hysteroscopy or laparoscopy for diagnosis. Management options for symptomatic fibroids include hormone therapy such as OCPs or GnRH agonists or surgery.

ANOVULATORY BLEEDING

PREVIEW | REVIEW

- What hormone is lacking in patients with anovulatory bleeding?
- What blood work should be ordered to rule out an androgen-secreting tumor?
- What is the typical treatment for an adolescent (13–18 years of age) with anovulatory bleeding?

Anovulatory bleeding is a type of AUB resulting from a lack of regular ovulation. Patients who are anovulatory have cycles that vary in length by > 10 days from one cycle to the next. Ovulatory dysfunction can result in 2 types of bleeding patterns:

- 1) Oligomenorrhea—cycles > 35 days and < 6 months apart
- 2) Amenorrhea—no menstruation for 6–12 months after the establishment of a cyclical pattern (See more on this topic in the **Endocrinology** section.)

Pathophysiology

During normal ovulatory cycles, follicular development occurs, followed by ovulation. Once ovulation occurs, the corpus luteum develops and then undergoes luteolysis. Estrogen rises during the first 1/2 of the cycle, and then progesterone rises after ovulation.

In patients with anovulation, estrogen continues to rise as no ovulation or corpus luteum development occurs. **No progesterone is secreted by the ovary**. Consequently, unopposed estrogen production leads to uncontrolled

endometrial proliferation without progesterone-induced withdrawal bleeding. The endometrium is vascular and without stromal support, leading to abnormal bleeding patterns.

Etiologies

Like AUB in general, the differential diagnosis for anovulatory bleeding is broad. The most common causes are physiologic anovulatory bleeding, commonly seen after menarche, and PCOS (see [Polycystic Ovary Syndrome \(PCOS\)](#)). Differential diagnosis and recommended diagnostic workup are listed in [Table 11-4](#).

Treatment

Treat bothersome physiologic anovulation in adolescents with combined oral contraceptives or other progestin contraceptives. Adolescents 13–18 years of age with a negative pregnancy test and signs of anovulatory bleeding can be started on hormonal treatment without any other workup. Treatment of PCOS is discussed in detail under the next topic. Hypothyroidism is treated with levothyroxine. Treat patients with hyperprolactinemia secondary to a pituitary adenoma with bromocriptine. Counsel patients with hypothalamic amenorrhea on nutrition. These women should increase their caloric intake. Give patients with primary ovarian insufficiency oral contraceptives.

Refer patients with congenital adrenal hyperplasia, 3- β -hydroxysteroid dehydrogenase deficiency, androgen-secreting tumors, Cushing syndrome, or acromegaly to an endocrinologist specializing in these disorders.

POLYCYSTIC OVARY SYNDROME (PCOS)

PREVIEW | REVIEW

- How does a woman with polycystic ovary syndrome (PCOS) present?
- The Rotterdam criteria for PCOS require how many signs of PCOS?
- What are 4 clinical features of hyperandrogenism?
- Patients with PCOS should be evaluated for which additional diagnoses?

PCOS is one of the most common endocrine disorders of women of reproductive age in the U.S., with a prevalence of 4–12%. It is characterized by menstrual dysregulation (e.g., oligomenorrhea, amenorrhea), high levels of masculinizing hormones (resulting in hirsutism and acne), decreased fertility, and metabolic syndrome. The onset is at about 16 years of age; however, syndrome recognition may be delayed as the symptoms can be interpreted as normal maturation during the few years after menarche. The etiology of PCOS is unknown but is related to excess ovarian androgen production. PCOS is associated with obesity (BMI ≥ 30 kg/m²), insulin resistance, diabetes, hyperlipidemia, fatty liver, and obstructive sleep apnea. Family history may be notable for diabetes, obesity, menstrual disorders, infertility, adrenal enzyme deficiencies, or hirsutism.

Table 11-4: Differential Diagnosis of Anovulatory Bleeding

Suspected Diagnosis	Additional Signs and Symptoms	Diagnostic Testing
Physiologic anovulatory bleeding	None except irregular menses; patient is within 3 years of menarche	None
PCOS	Hirsutism, polycystic-appearing ovaries on ultrasound	Testosterone, pelvic ultrasound
Hypothyroidism	Fatigue, weight changes, thyroid nodule, or goiter	TSH
Hyperprolactinemia	Lactation, headaches, visual disturbances	Prolactin, MRI of brain (if prolactin elevated)
Late-onset congenital adrenal hyperplasia	Hirsutism	Early-morning 17-hydroxyprogesterone
Hypothalamic amenorrhea	Disordered eating, overexercising, low body weight	LH, FSH, estradiol
Primary ovarian insufficiency	Hot flashes	FSH, estradiol
Androgen-secreting tumors	Virilization, deep voice, clitoromegaly	Testosterone, DHEA-S, urine level 17-ketosteroids Imaging of the ovaries and adrenals
Cushing syndrome	Buffalo hump, striae, hypertension	Cortisol and dexamethasone suppression testing
Acromegaly	Changes in hat and hand size, protruding jaw, impaired vision	Insulin-like growth factor
DHEA-S = dehydroepiandrosterone sulfate FSH = follicle-stimulating hormone	LH = luteinizing hormone MRI = magnetic resonance imaging	PCOS = polycystic ovary syndrome TSH = thyroid-stimulating hormone

Pathophysiology

In PCOS, the ovaries and adrenals produce excess androgens (testosterone and dehydroepiandrosterone sulfate [DHEA-S]) for unclear reasons, possibly related to peripheral insulin resistance and hyperinsulinemia. Estrogen levels are also high from peripheral aromatization of the androgens. The continuous production of estrogen decreases FSH secretion and enhances LH secretion (LH/FSH ratio > 2). The increased LH induces ovarian stromal hyperplasia and more theca cells, which in turn produce more androgens. This results in a mild increase in the levels of androgens. Marked increases in androgen levels ($2\text{--}4\times$ $>$ normal limits) should prompt a workup for ovarian or adrenal tumors. In summary, in PCOS, estrogen, androgen, and FSH levels are increased, whereas LH is decreased.

Diagnosis

The diagnosis of PCOS is based on 3 signs:

- 1) Hyperandrogenism
- 2) Oligomenorrhea (70–75% of cases)
- 3) Polycystic ovaries

The Rotterdam criteria for the diagnosis of PCOS require 2 of the 3 signs listed previously. NIH criteria require the first 2 signs and the PCOS society criteria are fulfilled if hyperandrogenism and 1 of the other signs are found.

Hyperandrogenism presents with:

- Acne
- Androgenic alopecia (i.e., male-pattern baldness)
- Male-pattern hirsutism
- Elevated levels of testosterone or DHEA-S

Other signs and symptoms of PCOS include:

- Infertility (30–70% of cases)
- Obesity and metabolic syndrome (40% of cases)
- Diabetes
- Obstructive sleep apnea

Polycystic ovaries are present when:

- at least 1 ovary has ≥ 12 follicles, or 25 follicles using more modern ultrasound techniques or
- 1 ovary has a volume of 10 mL.

Note that 65% of patients with normal ovulatory patterns have ovaries fulfilling these criteria.

See Figure 11-1 for ultrasound images of normal ovaries and ovaries with PCOS.

As adolescent females commonly have oligomenorrhea after menarche, many experts suggest that all 3 criteria (i.e., hyperandrogenism, oligomenorrhea, and polycystic ovaries) be present to diagnose an adolescent with PCOS.

In addition to hyperandrogenism, physical findings include increased abdominal adiposity (monitor BMI); cutaneous findings include skin tags and acanthosis nigricans (brown to black, velvety hyperpigmentation of the skin found on the neck, on axillae, under breasts, or on the vulva).

Additional Testing

In addition to androgen levels (testosterone and DHEA-S) and a pelvic ultrasound, perform the following tests on patients with PCOS:

- TSH, prolactin, 17-hydroxyprogesterone levels (to exclude other common causes of anovulatory bleeding such as Cushing's and congenital adrenal hyperplasia [CAH])
- 2-hour oral glucose tolerance test (screening for diabetes and impaired glucose tolerance)
- Fasting lipid and lipoprotein levels

Prognosis

Up to 40% of women with PCOS have insulin resistance, placing them at an increased risk of Type 2 diabetes and cardiovascular and cerebrovascular diseases. Screen women for Type 2 diabetes, HTN, dyslipidemia, as well as obstructive sleep apnea (given likelihood of obesity). Women with PCOS are also at an increased risk for endometrial hyperplasia and carcinoma due to chronic anovulation (resulting in continuous endometrial stimulation).

Treatment

Recommend lifestyle modifications, such as improved diet and increased physical activity, for all women with PCOS. A reduction in body weight is associated with improved pregnancy rates, improved glucose levels, and decreased hirsutism. If a patient does not desire pregnancy, treat PCOS with hormonal contraception or

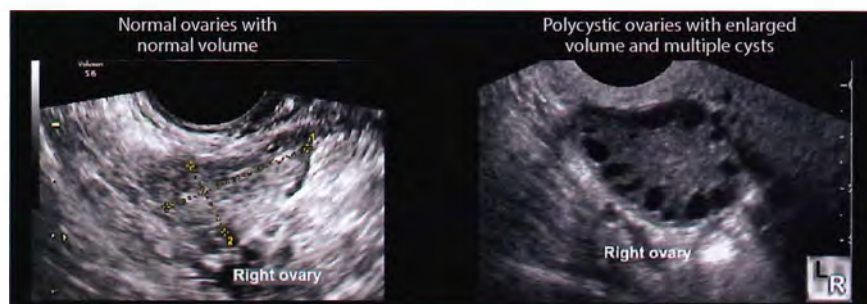


Figure 11-1: Normal vs. PCOS ovaries

progesterone medication to prevent endometrial hyperplasia, mitigate irregular menses, decrease hirsutism, and improve acne.

Use **metformin** to treat insulin resistance and obesity. Treat excessive hair with **spironolactone**. Recommend depilatory methods if the patient desires. Treat acne with topical creams. If a patient desires pregnancy, do not prescribe spironolactone.

If a patient wants to become pregnant, refer her to a sub-specialist. Infertility secondary to anovulation is typically treated with ovulation induction agents, including letrozole, an aromatase inhibitor, and clomiphene citrate, an estrogen receptor modulator.

AMENORRHEA

See the **Endocrinology** section for information on amenorrhea.

DYSMENORRHEA

PREVIEW | REVIEW

- Which hormone is released from the uterine lining that causes painful menstruation?

Dysmenorrhea, or painful menstruation, is divided into primary and secondary categories. **Primary** dysmenorrhea is the presence of recurrent, crampy pain during menstruation in the absence of an identifiable cause. **Secondary** dysmenorrhea has similar clinical features, but the symptoms are specific to a cause.

Risk factors for developing dysmenorrhea include smoking, BMI < 19 kg/m² or > 30 kg/m², history of sexual assault, and < 30 years of age. Dysmenorrhea is thought to result from painful uterine contractions initiated by prostaglandins.

Dysmenorrhea is a **clinical** diagnosis and does not have any laboratory or radiology features. To make the diagnosis, a good history and physical exam are necessary, focusing on the symptoms and complaints of the patient. It is important to exclude identifiable causes by evaluating the severity of the disease; e.g., days missed from school or work, amount of medication (e.g., NSAIDs) taken, and grading of the pain. Consider miscarriage, ectopic pregnancy, ruptured ovarian cyst, fibroids, and endometriosis as possible identifiable causes.

Nonhormonal and hormonal treatment options for dysmenorrhea include NSAIDs, OCPs, IUDs, and progesterone injectables.

PERIMENOPAUSE AND MENOPAUSE

PREVIEW | REVIEW

- What is the definition of menopause?
- What is the median age of menopause?

- Menopause prior to what age is considered primary ovarian insufficiency?
- What are the risks of the 2 most common formulations of hormone replacement therapy (HRT)?
- What hormonal treatment is given to patients who suffer from vaginal atrophy?

Menopause is defined as the permanent cessation of menses; it occurs secondary to the loss of ovarian activity. Patients are postmenopausal after 1 full year of amenorrhea, making menopause a retrospective diagnosis. The median age of menopause is 51 years. The transition to menopause is called perimenopause and occurs naturally any time after 40 years of age. Primary ovarian insufficiency, menopause prior to 40 years of age, is abnormal and occurs in approximately 1% of women.

During perimenopause, FSH levels are higher than LH levels, and both rise to even higher values than those seen during normal menstruation. The FSH rise precedes the LH rise. Persistently high FSH levels combined with 12 months of amenorrhea indicate menopause.

Symptoms and Effects of Menopause

Symptoms of perimenopause are hot flashes, mood swings, vaginal dryness, irregular periods, and lack of sexual desire. Perimenopause lasts for ~ 4 years before the final menstrual period occurs. Many women go through this time naturally and do not need medical treatment.

Hot flashes (a.k.a. night sweats) are the most common symptom reported during perimenopause. The mechanism of action is unknown. Hot flashes are described as a flush of heat that lasts up to 4 minutes starting in the chest and rising to the face. Hot flashes can persist past menopause, which is normal. They occur mainly at night and can cause sleep disturbances.

Vaginal dryness and libido: Naturally, the vagina becomes dry with the lack of estrogen as a woman goes into menopause. This can manifest as painful sex and even pain with daily walking activities. Secondary to painful sex and the changing appearance of the vagina, many women then experience a decrease in sexual desire. On exam, the vagina appears pale and raw. Wet mount may reveal parabasal cells. The introital opening narrows and the vagina becomes narrower.

With decreasing estrogen, a woman is susceptible to an increased risk of **cardiovascular disease** and **osteoporosis**. Furthermore, low-density lipoprotein increases during the menopause transition, and **bone loss** is significant.

Differential Diagnosis

The differential diagnosis for menopause includes hyperthyroidism, pregnancy, malignancy, or pheochromocytoma.

Treatment

Many patients attain menopause naturally, with no treatment needed. However, for those who do require treatment, hormone replacement therapy (HRT) is the mainstay for severe symptoms of the menopausal transition. The most substantial data we have for HRT is from the Women's Health Initiative (WHI), which was initially published in 2002, with updates in 2014.

WHI addresses 2 types of HRT: combination HRT with estrogen and progesterone or HRT with estrogen alone. Patients with a uterus need estrogen combined with progesterone, in the form of either a transdermal patch/gel/spray or a daily pill to prevent endometrial hyperplasia. Transdermal estrogen formulations are preferred over oral pills because they bypass the GI conversion of estradiol to estrone, resulting in lower triglyceride levels and clotting factors. Case-control studies show a lower risk of VTE with transdermal preparations. Additionally, vaginal rings have been used for hormone replacement and, similarly, achieve a lower risk of blood clots. Estrogen alone is prescribed in women who have had a hysterectomy.

The following are conclusions from WHI:

- **Combination HRT:**
 - causes an increase in heart disease, stroke, venous clotting, breast cancer, and gallbladder disease;
 - does not cause an increased risk for heart disease and stroke with short-term use (≤ 5 years) in younger premenopausal women (older women do have an increased risk); and
 - is used to safely treat primary ovarian insufficiency (menopause before 40 years of age) until the woman is 50 years of age.
- **Estrogen alone:**
 - causes endometrial hyperplasia and increases risk of endometrial cancer,
 - is not associated with heart disease or breast cancer risks, and
 - is only to be used in women without a uterus.

Note: In 2002, the WHI was terminated early due to trends in the data showing that HRT was actually associated with increasing rates of cardiovascular disease and breast cancer in postmenopausal women. Since the WHI, there have been more studies done to assess risk. In 2014, the American College of Obstetricians and Gynecologists released a practice bulletin, which encourages an individualized approach to the use of HRT for menopausal symptoms.

General management: For the normal woman with a hysterectomy and disruptive menopausal symptoms, give low-dose estrogen alone, generally for < 5 years. If the woman has an intact uterus, give low-dose estrogen plus progesterone, again generally for < 5 years. BRCA+ women or women who are survivors of breast cancer should not receive HRT.

Give vaginal estrogen to patients who suffer from painful sex and atrophy. Typically, these patients do not require progesterone supplementation.

Give hormonal alternatives to patients who are not candidates for or who do not want estrogen. Alternatives to hormones for the treatment of vasomotor symptoms include paroxetine, clonidine, and gabapentin; only paroxetine is FDA approved. Alternative methods, such as herbals, vitamins, black cohosh, or vitamin E, have not been proved to help ease symptoms of the menopausal transition.

POSTMENOPAUSAL BLEEDING

Perform an **endometrial assessment** (transvaginal ultrasound or endometrial biopsy) if a woman has postmenopausal bleeding:

- In the absence of HRT therapy
- After she has been on combined HRT continuously for 1 year without bleeding
- At an unexpected time during cyclic replacement

Postmenopausal bleeding is cancer until proved otherwise. If a transvaginal ultrasound reveals an endometrial thickness of ≤ 4 mm, it has a 99% negative predictive value for endometrial cancer, and endometrial biopsy is **not** indicated. If the thickness is > 4 mm, perform an endometrial biopsy because endometrial cancer cannot be excluded.

ENDOMETRIAL CANCER

Endometrial cancer is the most common gynecological cancer in the U.S. The average age of diagnosis is 61 years. Unopposed estrogen exposure is the main risk factor. Surgery is usually curative for low-risk patients. Adjuvant chemotherapy is offered to high-risk patients. See the [Oncology](#) section for more on endometrial cancer.

BREAST DISORDERS (NONCANCEROUS)

PREVIEW | REVIEW

- What is the most common infectious organism that causes mastitis?
- When during breastfeeding is mastitis most likely to occur?
- What antibiotic is used to treat mastitis?
- Cyclic breast pain typically happens how many weeks prior to menses?
- What location on the breast is cyclic pain most common?
- Does cyclic breast pain occur more commonly in larger- or smaller-breasted women?
- What are some physical signs of breast cancer?
- What is the only drug the U.S. Food and Drug Administration has approved to treat cyclic breast pain?

Mastitis

Mastitis, breast inflammation typically due to infection, frequently occurs in lactating women. Puerperal, or lactational, mastitis is caused by prolonged engorgement, oversupply of milk, infrequent feedings, or a blocked milk duct. Organisms grow in the static milk and result in infection. The most common infectious organism that causes mastitis is *Staphylococcus aureus*. If infection does not resolve, an abscess results. Although possible, it is rare that mastitis occurs in nonlactating women secondary to TB, foreign bodies, sarcoidosis, histoplasmosis, or idiopathic causes.

Pain, swelling, and redness are the typical clinical symptoms of puerperal mastitis. Mastitis is most common during the first 3 months of breastfeeding.

Diagnosis is made clinically; labs are not needed.

Therapy includes NSAIDs, cold compresses, continuance of breastfeeding, and antibiotics. Treat *S. aureus* with dicloxacillin 500 mg 4×/day. If the patient has an allergy to β-lactam antibiotics, use clindamycin. If improvement does not occur after 48 hours with antibiotic use, do an ultrasound to rule out an abscess. Differential diagnosis includes inflammatory breast cancer and breast abscess.

There is no proven prevention of puerperal mastitis; however, consistent breastfeeding, ensuring that the infant is well attached during breastfeeding, and breastfeeding for 4–6 months is recommended.

Cyclic Breast Pain

Breast pain, most commonly cyclic, is a common complaint seen in the office. Cyclic breast pain is related to the menstrual cycle and presents the week prior to menses. The location on the breast is usually in the upper outer quadrant of the breast, and the pain is bilateral. Women with larger breasts are more likely to have cyclic breast pain than are women with smaller breasts. Most cyclic breast pain resolves within 3–4 months and returns intermittently throughout a woman's lifetime. Although cyclic breast pain is not typically associated with breast cancer, it is important to evaluate whether the pain is pathological or physiological.

Include the following information in the history and physical:

- Location of the pain
- Whether the pain is bilateral
- Relation of the pain to any activity
- Recent trauma to the breast
- Whether the pain is phasic

The goal of the physical exam is to exclude any signs of a possible malignancy, such as nipple retraction, a solid mass, or bloody nipple discharge. Also examine the axillary lymph nodes for enlargement or tenderness. If a mass or signs of malignancy are observed, order a mammogram and breast ultrasound.

Most women who present with cyclic and diffuse breast pain need only a physical exam and reassurance.

Those who experience severe pain that interferes with their lifestyle may benefit from hot compresses and support bras. Danazol is the only FDA-approved drug to treat cyclic breast pain; acetaminophen and NSAIDs are also effective. Tamoxifen is rarely used due to its side effects of hot flashes, vaginal dryness, and an increased risk of blood clots. Reduction of caffeine and vitamin E have not been proved to help.

MEN'S HEALTH

BENIGN PROSTATIC HYPERPLASIA (BPH)

PREVIEW | REVIEW

- How does prostatic hyperplasia affect prostate-specific antigen levels?
- What is the initial treatment for benign prostatic hyperplasia? Which medications are commonly used for treatment?

OVERVIEW

BPH (also incorrectly called benign prostatic hypertrophy) is an enlarged prostate gland. The prevalence of BPH increases from about 10% at 30 years of age to > 80% at 85 years of age. About 15% of these patients have impaired urination. We still do not understand what causes BPH and have yet to identify any specific risk factors—except age. BPH does not increase the chance of prostate cancer.

Symptoms of BPH are secondary to urinary retention and include frequency, hesitancy, urgency, nocturia, and difficulty starting and stopping the stream, as well as reduced stream. Other diseases can also cause these symptoms (e.g., bladder cancer, cystitis) and should be considered before making a diagnosis of BPH. Know that serum prostate-specific antigen (PSA) levels increase as the prostate increases in size, so PSA screening for prostate cancer is less specific in men with BPH (more false positives).

Do the 2 definitive tests:

- 1) Digital rectal exam to palpate the prostate: A smooth, rubbery, and symmetrical gland is normal, whereas a hard, irregular, and asymmetrical gland is suggestive of malignancy.
- 2) Urinalysis to assess for hematuria (with a culture if infection is suspected)

The American Urologic Association (AUA) does not recommend serum PSA or serum creatinine in the workup of BPH, whereas the European Urologic Association does. Experts in the U.S. go either way.

TREATMENT

Treat BPH only if it significantly affects the patient adversely and/or if it causes outlet obstruction that leads to hydronephrosis or acute kidney injury.

Start treatment of symptomatic patients with **behavioral therapy**. Make sure patients know to reduce the intake of caffeine and alcohol (diuretics), stay away from fluids before bed, and attempt to urinate twice to completely empty the bladder.

Medical therapy:

- 1st line: **α -blocker** (i.e., terazosin, doxazosin, tamsulosin, alfuzosin, silodosin)
- Add a **5- α -reductase inhibitor** (finasteride or dutasteride) if needed.

The most common side effects of these medications are **postural hypotension** and **lightheadedness**. Be careful about combining sildenafil or vardenafil with these drugs because the combination worsens hypotension.

The 5- α -reductase inhibitors, which inhibit conversion of testosterone to dihydrotestosterone, take at least **6 months** to decrease prostate size and relieve symptoms. These drugs work better for large prostates and have a more durable effect. The major side effect is **impairment of sexual function** (decreased libido and delayed ejaculation). Finasteride, a type of 5- α -reductase inhibitor, can decrease microvessel density in the prostate, especially the suburethral prostate, because it reduces episodes of recurrent hematuria in patients with BPH. 5- α -reductase inhibitors **decrease serum PSA**, even in cancer patients.

Transurethral resection of the prostate (TURP) is the treatment of last resort and is used when drugs fail to work.

typically causes a gradual decrease in function over time. There is a strong age-related increase in problems with erection in men > 50 years of age: 2% of men < 40 years of age complain of frequent problems with erections, whereas 40–50% of men > 60 years of age have significant problems with erections.

The smooth muscle in the flaccid penis is in a state of tonus or contraction due to **α stimulation** by norepinephrine. Cyclic guanosine monophosphate (cGMP) and cyclic adenosine monophosphate (cAMP) are made by the norepinephrine and vasoactive intestinal peptide (VIP) pathways. This cGMP causes relaxation of the smooth muscle in the penis, which increases the inflow through the helicine artery into the erectile tissue. The swelling of this tissue causes compression of the outflow venules, resulting in a sustained erection.

Men with ED have problems with this pathway. Atherosclerosis can lead to a decrease in blood flow through the helicine artery, preventing venous compression and, therefore, an erection. Nerve damage from a stroke, spinal cord injury, or diabetes can also prevent relaxation of the smooth muscle of the penis, leading to ED.

Many men with ED can have low self-esteem and depression and fear or avoid future sexual encounters, resulting in decreased sexual satisfaction and reduced sexual desire in the individual's partner. Risk factors for acquired erectile disorder include age, smoking tobacco, lack of physical exercise, diabetes, and decreased desire. Associated factors include neurotic and submissive personality traits, depression, and posttraumatic stress disorder.

Erectile failure on first sexual attempt has been found to be related to having sex with a previously unknown partner, concomitant use of drugs or alcohol, not wanting to have sex, or peer pressure. There is minimal evidence regarding the persistence of erectile failure after the first attempt.

The natural history of lifelong ED is unknown. Most episodes of ED remit spontaneously without professional intervention, but some men continue to have episodic problems. In contrast, acquired ED is often associated with an organic cause (e.g., vascular disease) and persists.

CLASSIC CAUSES OF ED

ED can be caused by **organic** or **psychological** problems or a **side effect of medications** (25% of cases). Most causes of ED are at least partially organic.

Causes of ED:

- **Organic:** The organic causes are neurogenic, vascular, hormonal, and normal aging. Onset is usually slow, and patients present with loss of nocturnal and morning erections.
 - **Neurogenic:** The most common neurogenic cause of ED is **diabetes mellitus**. Other causes are surgical procedures (especially prostate), multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS),

ERECTILE DYSFUNCTION (ED)

PREVIEW | REVIEW

- What percentage of males by age group experience erectile dysfunction (ED)?
- What is the most common cause of neurogenic ED?
- If an exam presents a young male with ED who is on no medications, what is the most likely etiology?
- Which medications most commonly cause ED?
- What is the mechanism of action for sildenafil?

OVERVIEW

The most common type of male sexual dysfunction is ED, which is defined as the inability to achieve or maintain an erection sufficient for satisfactory sexual intercourse. It is not uncommon for men to experience brief episodes of ED, often secondary to stress, anxiety, or alcohol. However, true ED caused by a physiologic problem

Parkinson's, and other causes of peripheral neuropathy. Cyclists who spend > 3 hours/week on an upright bicycle can experience ED due to pressure that the seat places on the pudendal nerves (reducing blood flow to the cavernosal artery).

- **Vascular:** The most common vascular cause is peripheral arterial disease. Those with diabetes can also have vascular damage, compromising blood flow. Other causes are surgical procedures, inflammatory conditions, or pelvic fracture. In older men, ED is caused by vascular compromise in 50% (indicated by a low penile brachial pressure index [PBPI]). ED due to vascular compromise indicates increased risk of present and future major vascular disease.
- **Hormonal:** often accompanied by a loss of libido. Symptoms can include a gradual onset of frontal headaches or visual disturbances (space-occupying tumor); hot flashes and a decreased need for shaving (decreased androgens); fatigue + weight gain + dry skin + constipation (hypothyroidism).
- **Normal aging:** Sexual potency **does** decrease with age.
- **Psychological:** typically, **acute** onset. This is the most common cause of ED in younger patients. They continue to have nocturnal and morning erections, but libido is lost. ED is directly correlated with **depression**. Unfortunately, SSRIs used for the treatment of depression are also associated with a very high incidence of sexual dysfunction (generally delayed ejaculation).
- **Medications:** especially antidepressants (e.g., SSRIs), clonidine, spironolactone, β -blockers, and thiazide diuretics. Tricyclic antidepressants (TCAs), monoamine oxidase inhibitors, benzodiazepines, antipsychotics, antihistamines, antihypertensives, diuretics, NSAIDs, and finasteride can also cause ED.
- **Drugs of abuse:** nicotine (85% more common in smokers), alcohol, cocaine, opiates

DIAGNOSIS

Perform a thorough physical examination (rule out hernia). **Blood tests include:**

- | | |
|--------------------|-------|
| • Serum chemistry | • TSH |
| • CBC | • LH |
| • LFTs | • FSH |
| • Lipid profile | • PRL |
| • Hemoglobin A1c | • PSA |
| • Urine toxicology | • U/A |
| • Testosterone | |

Serum testosterone should be tested if there are symptoms that suggest low testosterone levels, such as depressed mood, poor concentration, memory loss, decreased libido, ED, and hypersomnolence. Testosterone levels tend to decline later in the day in younger patients, so obtain total testosterone levels in the morning and confirm the diagnosis of low testosterone with a repeat test or free testosterone level. For more detailed information about hormone levels in males, see the [Endocrinology](#) section.

Diagnostic tests include:

- Duplex ultrasound
- Penile nerve function
- Nocturnal penile tumescence (NPT)
- Penile biothesiometry
- Dynamic infusion cavernosometry and cavernosography (DICC)
- Corpus cavernosometry
- Magnetic resonance angiography (MRA)

TREATMENT

1st line treatment for ED:

- **Sildenafil citrate** (Revatio, Viagra) inhibits phosphodiesterase Type 5 (PDE5), an enzyme that inactivates cGMP. It works very well for many causes of ED, including psychogenic. Side effects are due to its vasodilatory properties—headaches, flushing, dyspepsia, bluish hue in the vision. Reports of sudden-onset sensorineural hearing loss have also been documented.
- **Vardenafil** (Levitra, Staxyn) is similar to sildenafil in mechanism, effectiveness, and side effects.
- **Tadalafil** (Adcirca, Cialis) has the same mechanism of action as sildenafil and vardenafil but with a longer half-life. Erectile function is improved for up to 36 hours. This drug is approved for daily use. One specific side effect is back pain, which often precludes its use. Tadalafil is FDA approved as a treatment for BPH symptoms when used on a daily basis, although the mechanism remains unclear.
- **Avanafil** is similar to sildenafil in mechanism, effectiveness, and side effects.
- **PDE5 inhibitors** are more likely to cause hypotension when taken with nonselective α -blockers (prazosin, doxazosin, and terazosin). Uroselective α -blockers (tamsulosin and alfuzosin) are less likely to cause hypotension. There is a risk of hearing loss with all the PDE5 inhibitors. Contraindications are any concurrent nitrates. Relative contraindications are heart failure, hypotension, unstable angina, hypertrophic cardiomyopathy (HCM), and severe aortic stenosis.
- **Yohimbine** is a naturally occurring α -blocker. It has minimal effect, but, because it is inexpensive and has minimal side effects, it is often tried on patients with a mostly psychogenic etiology. It is better than a placebo but much less effective than sildenafil.
- **Vacuum devices** work well but are clumsy to use. They are indicated only when oral therapy is contraindicated or the patient prefers them to oral therapy.

2nd line treatment for ED:

- **Alprostadil** (prostaglandin E₁) injected into the corpora cavernosa of the penis works well. It is especially useful in patients with ED due to neurologic dysfunction.

3rd line treatment for ED:

- **Penile implants:** There are various types—hydraulic, semirigid, and flexible rods. This option is normally used only for those who have failed all other therapy. The surgery can cause complications, and there is a risk of postsurgical infection. Scarring can cause erections to curve. Tissue erosion can occur. If there are no complications, penile implants are effective and patient satisfaction rates are high.
- **CBT** (individual and couples therapy) can also be beneficial.

SCROTAL MASSES (NONCANCEROUS)

PREVIEW | REVIEW

- How does ultrasound help in the diagnosis of testicular torsion?
- If surgery is done within 6 hours of symptom onset of testicular torsion, what is the success rate in salvaging the testicle?
- What are common ultrasound findings in epididymitis?
- What are common causes of acute epididymitis in younger men?
- How is acute epididymitis treated empirically?
- How does a hydrocele develop?
- On which side do most varicoceles develop?

OVERVIEW

Scrotal masses vary in origin from benign causes to surgical emergencies. Here we discuss scrotal masses of nonmalignant origin. (See the [Oncology](#) section for testicular cancer.) The anatomy of the scrotum is described in [Figure 11-2](#). See [Table 11-5](#) for a summary of scrotal masses. [Figure 11-3](#) summarizes the evaluation of a scrotal mass.

History and examination are very useful in evaluating scrotal masses. An initial assessment of pain is important. Painful masses suggest more emergent problems, such as testicular torsion or epididymitis.

TESTICULAR TORSION

Testicular torsion occurs when there is twisting of the spermatic cord within the tunica vaginalis and subsequent occlusion of the arterial blood supply to the testicle. It most commonly occurs in adolescent boys but can occur in older men as well. Torsion can lead to testicular loss (due to ischemia) within ~ 6 hours if not corrected surgically.

Presenting symptoms are unilateral scrotal pain, nausea, and vomiting. The most accurate sign of testicular torsion is an absent ipsilateral cremasteric reflex—a reflex observed in males when stroking the inner part of the

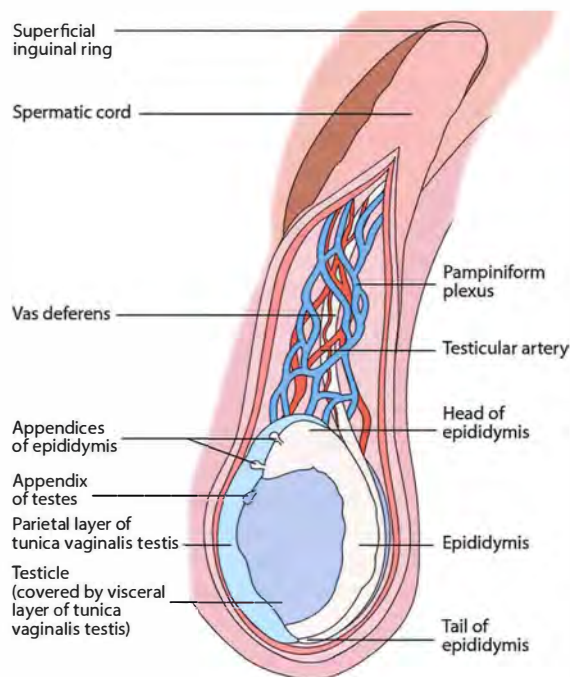


Figure 11-2: Anatomy of the scrotum

thigh results in contraction of the cremaster muscle that pulls up the testis ipsilaterally. Other signs on examination include fever, swelling of the scrotum, and a testicle that is positioned horizontally or riding higher than normal.

Patients with a suggestion of testicular torsion warrant **emergent urologic** evaluation and surgical exploration. Doppler ultrasound assists the diagnosis by demonstrating absent testicular blood flow. Time is of the essence; there is a 90% salvage rate if surgery is done within 6 hours and drops to 50% if surgery is not performed within 12 hours of symptoms.

If surgery is not an option, attempt manual detorsion. With torsion, the testicles usually twist medially so you typically **must twist laterally to achieve detorsion**. For example, when detorsing the patient's left testicle, stand in front of the patient. Using the right forefinger and thumb, rotate the testicle clockwise 180° at a time. Repeat as needed. It can take up to 4 tries because the torsion can have rotations up to 720°. Successful detorsion is made evident by immediate pain relief. Detorsing the patient's right testicle requires counterclockwise rotation. Follow up with ultrasound to ensure good vascular flow. Surgery is still required to ensure full detorsion and for bilateral testicular fixation. Keep in mind that intermittent torsion of the testicle occurs, and a patient presenting with a history of intermittent scrotal pain and swelling also requires urologic evaluation.

Torsion of a testicular appendage: Tiny pedunculated testicular appendages (appendix testis; appendix epididymis) occur in about 50% of boys. Torsion can occur in either with scrotal pain and swelling. The key finding with torsion of an appendage is the "blue dot sign," a bluish hue from the ischemic appendage over the upper part of the testicle. Once the diagnosis is confirmed (i.e., not testicular torsion!), treatment is the same for both—reassurance and pain control.

EPIDIDYMITIS

Epididymitis occurs when there is pain and inflammation of the epididymis. Orchitis is an inflammation of the testes, and it can be related to epididymitis infection that has spread to the testicles. If both the epididymis and testicles are affected, it is called epididymoorchitis.

Presenting symptoms are similar to testicular torsion. Patients present with acute-onset, unilateral scrotal pain and erythema. Physical examination reveals localized

tenderness and swelling of the affected testicle. If severe, patients can present with fever, scrotal wall erythema, and a reactive hydrocele.

Ultrasound can help differentiate epididymitis from testicular torsion. Epididymal swelling and hyperemia suggest epididymitis. Color Doppler ultrasound shows absent blood flow with testicular torsion (see [Testicular Torsion](#)) and increased vascularity of the epididymis with epididymitis.

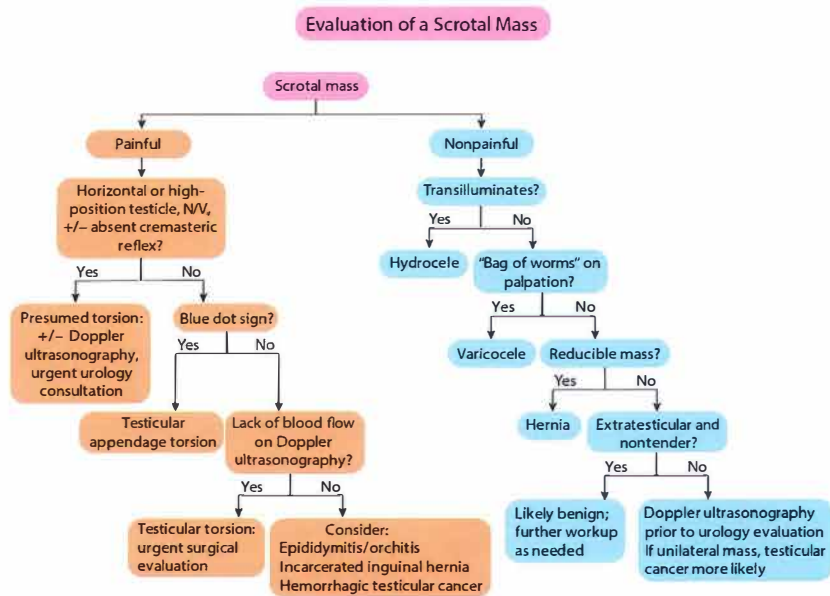


Figure 11-3: Evaluation of a scrotal mass

Table 11-5: Summary of Scrotal Masses

Cause	Presentation	Diagnosis	Treatment
Testicular torsion	Pain and swelling Possible absent cremasteric reflex Horizontal or high position of the testicle Nausea/Vomiting Fever	Clinical, with Doppler ultrasound	Orchiopexy within 6 hours, manual detorsion if surgery unavailable Bilateral orchiopexy is recommended because the contralateral testis is at risk for torsion.
Epididymitis/ Epididymoorchitis	Acute unilateral pain and swelling	Clinical, with Doppler ultrasound	Ceftriaxone and doxycycline; consider adding fluoroquinolone
Testicular appendage torsion	Acute unilateral pain Blue dot sign	Ultrasound	Pain control
Hematocele	History of trauma Pain and swelling	Ultrasound or surgical exploration	Pain control; surgery if needed
Testicular cancer	Firm, unilateral nodule	Ultrasound, tumor markers	Surgery
Inguinal hernias	Pain with bending, lifting, coughing, or straining Pain and scrotal bulge with Valsalva maneuvers	Physical examination, ultrasound	Surgery
Hydrocele	Painless scrotal swelling (Unless very large; these present with painful scrotal swelling and lower back pain.)	Transillumination, ultrasound	Watchful waiting, hydrocelectomy and aspiration, pain control
Varicocele	Dilation of tortuous spermatic veins, which look like a "bag of worms"	Ultrasound	Observation, surgery, or embolization

Urology consultation is often helpful, especially if the diagnosis is uncertain.

Acute epididymitis lasts < 6 weeks and frequently coexists with urethritis (which may be asymptomatic). **Chronic** epididymitis lasts > 6 weeks.

In younger men, acute epididymitis commonly results from STIs caused by *Chlamydia trachomatis* or *Neisseria gonorrhoeae*. Men who engage in anal intercourse (as the insertive partner) can develop acute epididymitis caused by enteric organisms such as *E. coli* and *Pseudomonas* species. As men age, urinary outflow obstructive disease (e.g., BPH) with bacteriuria can cause an acute epididymitis. Other etiologies of epididymitis include immunosuppression, surgery, and systemic illness.

TB can cause chronic epididymitis with granuloma formation, which can be bilateral. Consider TB as the cause in men with a history of TB exposure.

Gram stain of urethral secretions can demonstrate leukocytes in epididymitis, and if *N. gonorrhoeae* is the cause, intracellular gram-negative diplococci are usually present (~ 95% sensitive in the symptomatic man). Perform further testing with urine NAAT (nucleic acid amplification test; 1st choice) or culture to isolate chlamydial and gonorrheal infection.

Epididymitis is generally self-limiting and heals without complications with analgesics and rest in prepubertal boys. Treat epididymitis empirically with ceftriaxone and doxycycline, and if enteric organisms are causative, consider adding fluoroquinolone. Tailor treatment depending on NAAT or culture results. In addition to antibiotics, supportive therapy includes reduction in physical activity, scrotal support and elevation, NSAIDs/analgesics, sitz baths, and ice packs.

Refer sexual partners for evaluation. Epididymitis in the setting of HIV infection expands the differential diagnosis to include CMV, *Salmonella*, *Toxoplasma gondii*, *Ureaplasma urealyticum*, *Corynebacterium* species, *Mycoplasma* species, and *Acinetobacter lwoffii* (formerly *Mima polymorpha*).

INGUINAL HERNIA

Inguinal hernia is an extremely common disorder that occurs when fat or intestine displaces through the inguinal canal (indirect) or when there is a weak area or tear in the abdominal wall (direct). Primary symptoms are pain with bending, lifting, coughing, or straining. These same actions may lead to pushing more intestinal content down the inguinal canal, causing a visible scrotal mass that bulges or has a palpable impulse with Valsalva maneuver. If not obvious, a hernia can often be identified by placing a finger through the scrotal sac to the inguinal canal and having the patient cough. In general, treat symptomatic hernias surgically.

HYDROCELE

Hydrocele results from accumulation of serous fluid between the layers of the tunica vaginalis surrounding the testicle (Figure 11-4). Patients typically present with painless swelling of the groin or scrotum on one or both sides.

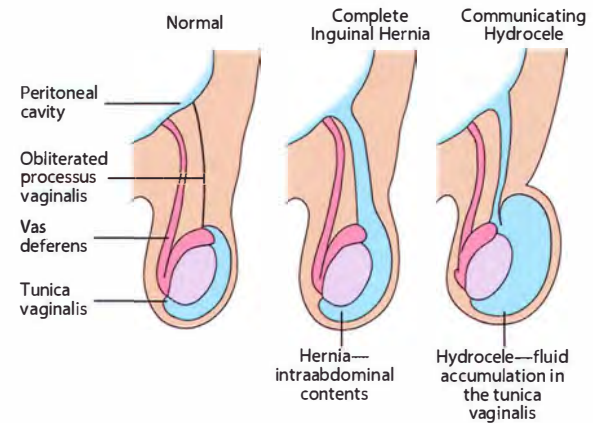


Figure 11-4: Inguinal hernia vs. communicating hydrocele

(Larger hydroceles may cause scrotal or lower back pain.)

Hydrocele result from infection, trauma, and neoplasm. Inguinal hernias may also be contributory.

Diagnose a hydrocele clinically, using transillumination. Hydroceles transilluminate well, unlike hematoceles, hernias, or solid masses.

Classic presentation is a tense, **painless**, fluid-filled swelling in the scrotum/groin that easily transilluminates. Use ultrasonography if palpation and transillumination are inconclusive.

Surgical exploration is warranted if any of the following signs or symptoms exist:

- Inability to clearly delineate or palpate the testicular structure
- Tenderness, fever, or any GI symptoms
- Shadows on transillumination

Treatment includes watchful waiting if the hydrocele is not very painful or large, or aspiration (if necessary). Hydrocelectomy is required if the hydrocele is too large or is recurrent.

HEMATOCELE

Hematocele is a collection of blood outside of the testicle but within the tunica vaginalis. It can appear similar to a hydrocele; however, it does not transilluminate, differentiating the 2 conditions. Furthermore, a hematocele is typically caused by trauma or surgery. It results in pain and swelling of the testicle. Larger hematoceles can cause distortion of the testis and may resemble malignancy. Ultrasound and MRI are useful in diagnosis. Treatment includes surgery and pain control.

VARICOCELE

A varicocele is an abnormal dilation of the spermatic veins due to an anatomical abnormality. Malfunctioning vein valves result in retrograde flow of blood into the scrotum, leading to tortuous spermatic veins. See [Figure 11-5](#) for the difference between normal and tortuous spermatic veins.

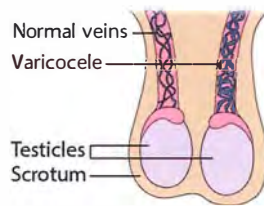


Figure 11-5: Left varicocele

A patient with a varicocele presents with complaints of dull, aching pain in the scrotum, typically on the left side. Diagnose varicoceles clinically. The scrotum feels like “a bag of worms” on palpation. Diagnosis can be confirmed with ultrasound.

Varicoceles are also a common, often reversible, cause of male infertility. Treatment options include observation, surgery, and embolization, depending on the suspected impact of the varicocele on male fertility, the patient’s age, and overall health.

SEXUAL HEALTH CONCERNS FOR WOMEN AND MEN

SEXUAL DYSFUNCTIONS

PREVIEW | REVIEW

- Which class of commonly used antidepressants can lead to sexual dysfunction in men and women?
- What mechanism of contraception can lead to sexual dysfunction in women?
- Know the prevalence of sexual dysfunctions by age and type.

OVERVIEW

Sexual dysfunctions are a heterogeneous group of disorders characterized by a clinically significant disturbance in a person’s ability to respond sexually or to experience sexual pleasure. An individual can have several sexual dysfunctions at the same time. It is important to diagnose and treat properly.

DIAGNOSTIC FEATURES

Sexual dysfunctions cause significant distress for at least 6 months and are not better explained by nonsexual mental disorder, severe relationship distress, substances, or another medical condition. They are either lifelong (since the start of sexual activity) or acquired (start after period of normal sexual activity). Sexual dysfunction is

either generalized (not limited to certain situations) or situational (only occurs with certain types of stimulation, situations, or partners).

Sexual dysfunctions for women and men include those listed in [Table 11-6 on page 11-28](#) and [Table 11-7 on page 11-28](#), respectively.

INFERTILITY

PREVIEW | REVIEW

- When should an infertility workup be considered?
- How can you tell if a woman is ovulatory?
- What lifestyle modifications have been shown to improve pregnancy rates among patients with infertility?

Infertility has many potential causes, and for many couples, both male and female factors are present. Causes of female infertility include both endocrine disorders (e.g., prolactinoma, primary amenorrhea, PCOS, congenital adrenal hyperplasia [CAH]) and gynecologic causes (e.g., endometriosis, tubal obstruction and other fallopian tube abnormalities, pelvic adhesions). Male infertility can also be caused by endocrine disorders (e.g., prolactinoma, CAH, other causes of secondary hypogonadism), but the majority are due to primary (testicular) defects in sperm production.

An infertility workup for a couple can start when a couple fails to conceive after 1 year of frequent, unprotected intercourse—6 months if the woman is > 35 years of age because time is running out! Evaluate the woman and man simultaneously when possible. Initial workup includes:

- Semen analysis (for sperm count, motility, and morphology)
- **Assessment of ovulation:** Women with regular menstrual cycles are likely to be ovulatory, and ovulation can be confirmed with a serum progesterone level on day 21 of the menstrual cycle. Women with irregular cycles should have a progesterone drawn 7 days before their presumed menses and then drawn weekly until menstruation occurs.
- Hysterosalpingogram to assess the patency of fallopian tubes and integrity of the uterus
- Assessment of ovarian reserve with biochemical testing, such as FSH and estradiol on day 3 of the menstrual cycle, and/or anti-Müllerian hormone levels

Counsel all patients, both men and women, with infertility on the following lifestyle modifications:

- Stop smoking.
- Limit or stop alcohol consumption.
- Reduce BMI to between 18.5 and 29.9, or ideally between 18.5 and 24.9.

Table 11-6: Female Sexual Dysfunctions

	Female Sexual Interest / Arousal Disorder	Female Orgasmic Disorder	Genitopelvic Pain / Penetration Disorder	Substance- / Medication-Induced Sexual Dysfunction
Definition	Persistent or recurrent deficiency of sexual desire, aversion to sexual activity, or inability to complete sexual activity with adequate lubrication	Persistent or recurrent delay or absence of orgasm	Persistent or recurrent pain during intercourse and/or fear or anxiety regarding pain during intercourse	Persistent or recurrent disturbance in sexual function secondary to an exogenous substance, a medication, or withdrawal from that substance or medication
Prevalence	10–19%	3–6%	8–22%	Unknown
Etiology	Stress Anxiety or depression Relationship issues Medication use (i.e., SSRIs, OCPs)	Stress Anxiety or depression Relationship issues Medication use (i.e., SSRIs, OCPs)	Physical conditions (numerous—e.g., endometriosis, vulvodynia, pelvic adhesions) Vaginismus Sexual abuse history	Alcohol or other sedatives Opioids Anxiolytics Stimulants
Diagnosis	Based on history	Based on history	Based on history, physical examination, and/or pelvic ultrasound	Urine or blood toxicology screen
Treatment	Stop SSRIs or OCPs Sex or couples therapy Individual therapy Flibanserin (only FDA-approved treatment for premenopausal women with female sexual interest/arousal disorder) Testosterone (used off-label) Bupropion (used off-label)	Stop SSRIs or OCPs Sex or couples therapy Individual therapy	Varies depending on etiology (broad)	Discontinue substance in question

OCPs = oral contraceptive pills

SSRIs = selective serotonin reuptake inhibitors

Table 11-7: Male Sexual Dysfunctions

	Male Hypoactive Sexual Desire Disorder	Erectile Disorder	Premature Ejaculation	Delayed Ejaculation	Substance- / Medication-Induced Sexual Dysfunction
Definition	Persistently or recurrently deficient/absent sexual/erotic thoughts or fantasies and desire for sexual activity	Difficulty obtaining or maintaining adequate erection during sexual activity	Persistent or recurrent pattern of ejaculation occurring during partnered sexual activity within 1 minute following vaginal penetration	Marked delay, infrequency, or absence of ejaculation	Persistent or recurrent disturbance in sexual function secondary to an exogenous substance, a medication, or withdrawal from that substance or medication
Prevalence	6% age 18–24, 41% age 66–74	10–25%	20–30%	1%	Unknown
Etiology	Stress Anxiety or depression Relationship issues Medication use (i.e., SSRIs) Low testosterone	Vascular disease Neurogenic etiologies (e.g., diabetes, stroke) Low testosterone	Stress Anxiety or depression Prior sexual abuse Prostatitis	Neurologic disorders Stress Anxiety or depression Prostate surgery Medication use (i.e., SSRIs, α -blockers)	Alcohol or other sedatives Opioids Anxiolytics Stimulants
Diagnosis	Based on history Testosterone level	Based on history CBC, CMP, HbA1c hepatic panel for cardiovascular, atherosclerotic, renal, and liver disease	Based on history Urinalysis	History Neurologic examination	Urine or blood toxicology screen
Treatment	Stop SSRI Sex or couples therapy Individual therapy Testosterone replacement	Treat medical issues Sex or couples therapy Individual therapy Phosphodiesterase inhibitors Alprostadil Penile prosthesis/vacuum pump devices	SSRIs Local anesthetics Individual therapy	Stop SSRIs Stop α -blockers if possible Individual therapy	Discontinue substance in question

SSRIs = selective serotonin reuptake inhibitors

All patients with infertility should be referred to an obstetrician-gynecologist or reproductive endocrinology specialist. If abnormalities are detected on the above testing, refer the patient(s) directly to a reproductive endocrinologist. Treatment of infertility depends on the cause but can include medications to induce ovulation, metformin (for PCOS), surgical procedures to fix fallopian tube obstruction, and assisted reproductive technologies (e.g., in vitro fertilization).

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Neurology

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CENTRAL NERVOUS SYSTEM (CNS): BRAIN — CORTEX

COMA

PREVIEW | REVIEW

- What is the significance of doll's eyes (i.e., positive oculoccephalic reflex)?
- Which pupil finding can be seen with uncal herniation?

OVERVIEW

Lethargy, confusion, stupor, obtundation, and coma are terms that apply to different degrees of the level of alteration of consciousness. The reticular activating system (RAS) and at least one of the cerebral cortices must be working effectively to sustain normal consciousness.

The RAS resides principally within the brainstem, so injury to the brainstem, such as from a hemorrhage, basilar artery ischemic stroke, or structural herniation affecting the pons or midbrain, can cause coma. The RAS also sends projections to the thalamus and hypothalamus (with the thalamus also being a relay center of information for the cortex). Thus, bilateral dysfunction of these structures may also cause coma.

Finally, diffuse processes affecting both cerebral hemispheres are common causes of coma. Therefore, severe metabolic derangements, toxic exposures, infection, anoxic brain injury, extensive traumatic brain injury (TBI), extensive bilateral cortical seizure, and non-convulsive status epilepticus (NCSE) all may present with coma.

APPROACH TO COMA

Neurologic Exam Findings

A thorough history and neurologic exam are necessary to establish the diagnosis and to ascertain the etiology of coma. This includes a review of underlying medical and mental health illnesses, medications, ingestions, and intoxications. Use the **Glasgow Coma Scale** to assess responsiveness of patients with cerebral trauma. However, using this scale to evaluate other etiologies of acute coma provides little insight into the localization of the anatomical dysfunction. A full comatose exam includes the following:

- Assessment of level of consciousness to see if there is any response to verbal or painful stimuli
- Cranial nerve exam (especially pupillary reaction, oculoccephalic maneuver or cold caloric testing, corneal reflex, and gag reflex)
- Evaluation of motor responses, reflexes, and observation of respiration (including specific respiratory patterns or whether the patient is breathing over the ventilator)

Vital signs, including temperature, pulse, respiratory rate, and blood pressure, can provide clues to the diagnosis, as can evaluation for nuchal rigidity and motor tone. Focal exam findings imply a structural cause of coma, while a nonfocal exam is more suggestive of a toxic-metabolic etiology.

Motor Responses

Motor responses related to cortical function include grimacing, localization of pain stimulus, and withdrawal to pain. Lack of reactivity to pain in one extremity or asymmetrical response implies a focal weakness or sensory loss. Posturing responses such as **decerebrate** and **decorticate** are subcortical responses that can help to localize the site of injury:

- **Decerebrate posturing** is a type of rigidity that occurs when the tonic labyrinthine reflex, which resists gravitational force, acts without modulation of the higher brain, causing **extension of all extremities**.
 - This posturing can be seen during either uncal or cerebellar tonsillar **herniation** (uncal transtentorial; see [Evaluation of Findings on page 12-2](#)).
 - Decerebrate posturing implies brainstem dysfunction or severe neurologic dysfunction and is a worse sign than decorticate posturing.
- **Decorticate posturing** is a type of rigidity characterized by **flexion of upper limbs** with **extension of lower limbs**. It is caused by lesions at a more rostral level (toward the nose) of injury to both corticospinal and rubrospinal tracts resulting from damage to brain areas that can include the cerebral white matter, internal capsule, and thalamus. These are **upper** motor neuron lesions. Causes include anoxic or TBI, stroke, intracranial hemorrhage, brain tumors, and encephalopathy.

With uncal herniation, patients can progress from decorticate to decerebrate posturing.

Respirations

Cheyne-Stokes respiration is a pattern of breathing in which the patient has periods of hyperventilation alternating with apnea. This pattern occurs in **bilateral** cerebral disease, **impending herniation**, and **brainstem** lesions; it can also be due to cardiac and **metabolic** causes.

Apneustic breathing is characterized by a series of slow, deep inspirations, each one held for 30 seconds or longer, after which the air is expelled by elastic recoil of the lungs, followed by an apneic pause. The rate of apneustic breathing is commonly around 1.5 breaths/minute. It is due to a lesion of the lower pons.

Ataxic breathing is very irregular and typically indicates a lesion of the medulla.

Central neurogenic hyperventilation: Lesions of the lower midbrain/upper pontine tegmentum cause

central neurogenic hyperventilation, which produces an increase in the rate and depth of respiration, resulting in advanced respiratory alkalosis.

Note that many of these patterns may not be seen in comatose patients because they often will be intubated to protect the airway. Assessment of whether a patient is breathing over the ventilator provides useful information.

Pupils

Remember that any significant asymmetry between the sizes of the pupils must be considered pathologic (Table 12-1). Carefully assess light reactivity and perform funduscopic examination to exclude papilledema, which is a sign of increased intracranial pressure (ICP).

Oculovestibular Testing

Oculocephalic (doll's eyes) and ice-water caloric testing (eyes look toward the cold) test the same vestibular-brainstem-ocular muscle pathway. The **complete absence** of eye movement in response to oculovestibular testing indicates either **severe** disruption of **brainstem** at the level of the **pons** or a profound **overdose** of sedative, anesthetic, or antiseizure medications.

Doll's eyes:

- Definition: When the head is turned, the eyes keep "looking" in the initial direction (eyes do not follow the movement of the head). Doll's eyes (i.e., a positive oculocephalic reflex) in a comatose person indicates that the brainstem is working normally. **Absent doll's eyes**, similar to no eye movement with cold caloric testing, implies **dysfunction** of the brainstem at the level of the **pons** and is a poor prognostic indicator. Generally, doll's eyes are preserved in early metabolic coma. One exception is metabolic coma due to barbiturates.
- Test for doll's eyes, which requires moving the head, only after C-spine injury is ruled out.

Reduction or absence of spontaneous **blinking** and loss of **corneal** reflexes are signs of deepening coma or brainstem dysfunction along the blink reflex arc involving afferent input from cranial nerve 5 (CN 5) and bilateral efferent input from CN 7.

Workup

Quickly obtain a CT or MRI of the brain to narrow the differential, especially when the cause is unclear.

In your workup, include CBC, electrolytes, BUN, creatinine, glucose, LFTs, ammonia level, ABGs, urinalysis, and a toxicology screen for illicit drugs.

Other tests, such as electroencephalography (EEG), are helpful in identifying NCSE, especially when there is a prior history of seizures. In one series of comatose patients in whom the cause was unknown, 8% were found by EEG to be in NCSE.

Finally, you may need to do a cerebrospinal fluid (CSF) examination (including the usual bacterial and viral tests) if you suspect meningitis or encephalitis.

Evaluation of Findings

Supratentorial coma is due to an injury of the hemisphere(s).

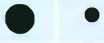
There are 2 mechanisms:

- 1) **Uncal (lateral) herniation**: An expanding asymmetric mass lesion (i.e., tumor, stroke, hemorrhage) forces the uncus through the middle opening in the tentorium. This puts pressure on the brainstem and, therefore, the RAS. Because of the course of the 3rd cranial nerve, the herniating uncus compresses this nerve, causing an enlarged pupil ipsilateral to the supratentorial lesion.
- 2) **Central herniation**: Injury to the thalamus (such as hemorrhage) results in diminished consciousness very early in its course. Later, the pupils are in midposition and become fixed. As the herniation continues, the course begins to merge with that of uncal herniation. In other words, central and uncal herniation syndromes can be differentiated early on, but later their courses merge.

Note, however, that on CT scan of the brain, horizontal shift of the pineal body can help correlate with consciousness level:

- 0–3 mm shift = Alert
- 3–4 mm = Drowsy

Table 12-1: Pupil Size in Coma

Size	Description	Cause	Examples
	One dilated, nonreactive, or sluggish pupil	Parasympathetic nerve problem	Oculomotor nerve compression from uncal herniation, aneurysm of the posterior communicating artery
	One pinpoint pupil (miosis)	Sympathetic nerve problem (Horner's)	Lateral medullary syndrome, hypothalamus injury, Pancoast tumor, carotid dissection
	Two midposition, nonreactive pupils	Parasympathetic and sympathetic nerve problem	Midbrain disruption (can affect one or both pupils), anoxia, hypothermia, anticholinergics, severe barbiturate overdose
	Two dilated, nonreactive pupils		Anoxia, hypothermia, anticholinergics, severe barbiturate overdose
	Two pinpoint, reactive pupils		Opiates, pontine destruction

- 6–8 mm = Stupor
- 8–13 mm = Coma

Infratentorial coma is due to an injury that causes destruction or compression of the brainstem. Signs of infratentorial herniation include **bilateral reactive pinpoint pupils** (due to pontine involvement) and **respiratory abnormalities**, including Cheyne-Stokes breathing, apneusis (deep gasping), and ataxic breathing. There are 3 possible causes:

- 1) Basilar artery occlusion with pontine infarction
- 2) Cerebellar infarction or hemorrhage
- 3) Posterior fossa neoplasms

Expansion of the contents of the posterior fossa forces the contents of this compartment in 1 of 2 directions:

- **Upward herniation** pushes the posterior fossa contents up under the tentorium, compressing the brainstem.
- **Downward herniation** forces the cerebellar tonsils down through the foramen magnum, compressing the medulla.

Metabolic coma has many causes including ischemia, hypoglycemia, hypothyroid (myxedema coma), thiamine deficiency (Wernicke encephalopathy), organ disease (e.g., lung [hypoxia and hypercapnia], liver [hepatic encephalopathy], kidney [uremia]), severe electrolyte derangements (such as Na^+ and Ca^{2+}), and drugs. Early in metabolic encephalopathy, patients have changes in respiratory pattern and mentation. The **pupils** are typically **reactive** until the terminal stages. Exceptions include anticholinergic toxicity and severe barbiturate intoxication, which cause fixed, dilated pupils. In addition, both hypothermia and anoxia/ischemia can cause fixed pupils of varying size. Anoxic-fixed pupillary dilatation lasting longer than a few minutes implies severe and, usually, irreversible brain damage.

COMA MIMICS

PREVIEW | REVIEW

- What is the presentation of locked-in syndrome?
- What is the definition of a persistent vegetative state?
- What is the etiology of akinetic mutism?
- What is the etiology of catatonia?
- How is brain death diagnosed? Is electroencephalography required?
- What is involved in an apnea test?

LOCKED-IN SYNDROME

Locked-in syndrome is rare and most often caused by a lesion of the **ventral pons** as a result of **basilar artery**

occlusion. The lesion commonly spares the somatosensory pathways and the ascending RAS responsible for arousal and wakefulness, as well as midbrain structures that allow the eyelids to be raised. Thus, the lesion interrupts the corticobulbar and corticospinal pathways, leaving the patient unable to speak. Osmotic demyelination of the pons following the rapid correction of hyponatremia is another possible cause.

Those with locked-in syndrome are **awake** and **aware** of the surrounding environment but only have the ability to control eye movements. Typically, they can communicate only by using eye blinks and **vertical eye movements**. (The efferent abducens nerve fibers controlling horizontal eye movements are usually destroyed.) Because the cerebral cortex is spared, an **EEG is normal**.

Some patients can recover some function, so include multidisciplinary and physical and speech therapy, pulmonary rehabilitation, and help with swallowing in patient treatment. Locked-in syndrome highlights the need to carefully assess the level of consciousness in presumed comatose patients to avoid misdiagnosis.

VEGETATIVE STATE

Vegetative state results from severe **bilateral cerebral** dysfunction, often following a period of coma. Vegetative state is often caused by **anoxic brain damage** (e.g., after cardiac arrest) and can be the final stage of progressive cortical degenerative diseases, such as **Alzheimer's** and **Creutzfeldt-Jakob's**.

These patients typically have normal sleep-wake cycles but no discernible cognitive function. Respiratory rate can increase in response to manual stimulation, and they can have automatisms, such as swallowing, bruxism, grimacing, grunting, and moaning. There is loss of sphincter control. EEG abnormalities include low-amplitude delta-frequency background activity, burst suppression, widespread alpha and theta activity, an α -coma pattern, and sleep spindles. Stimulating the patient causes minimal, if any, change in background EEG activity.

Neuropathology shows cortical laminar necrosis, which is often extensive, with a relative or complete sparing of brainstem structures (including the RAS).

Comatose patients who enter into vegetative states may recover or progress to death—normally within 2 weeks. A vegetative state that persists > 3 months is called a persistent vegetative state. Patients in a persistent vegetative state following TBI are more likely to recover than patients with anoxic injury. Up to 39% of TBI patients who are vegetative > 3 months recover consciousness by 1 year, whereas only 6% of nontraumatic patients do. After 6 months of vegetative state, 19% of TBI patients recover consciousness but only 1% of nontraumatic patients recover. Generally, within 5 years, demise occurs from pneumonia, urosepsis, or sudden death.

AKINETIC MUTISM

Patients with akinetic mutism are profoundly apathetic, although they register most of what is happening around them. They may speak normally and relate events from the recent and distant past. This state is caused by **bilateral** lesions generally of the anterior parts of the **frontal lobes**, leaving the motor and sensory pathways intact.

CATATONIA

Catatonia is a state of stupor and neurogenic motor immobility that can be caused by psychiatric states, such as schizophrenia, depression, PTSD, and drug abuse, as well as a wide range of underlying medical conditions. Patients with catatonia are unresponsive, although they preserve oculocephalic responses (doll's eyes). Some patients display a waxy flexibility of passive limb movement and hold limb postures that appear uncomfortable for long periods of time. Unusual motor mannerisms or repetitive motions, seen in a number of these patients, can give the impression of seizures. There are no signs of structural brain disease. EEG is typically normal, although it shows diffuse slowing with malignant catatonia. Treat with a trial of benzodiazepines or, in severe cases, consider electroconvulsive therapy.

BRAIN DEATH

The central features of brain death are an irreversible absence of all **cerebral** and brainstem functions, including spontaneous respiration. This regularly results from catastrophic brain damage (e.g., trauma, cardiac arrest, cerebral hemorrhage), but you need to exclude reversible causes, such as drug overdose.

Signs indicating the absence of **cerebral** function are the presence of deep coma along with the lack of spontaneous movement and motor and vocal responses to all visual, auditory, and cutaneous stimulation, as well as lack of brainstem reflexes and spontaneous respiration.

Diagnostic criteria for brain death:

- Knowledge of the preceding catastrophic event (clinical or imaging) responsible for the current status
- All possible metabolic confounders (e.g., electrolyte abnormalities) excluded
- Toxins excluded
- Core temperature > 97.0°F (36.1°C)
- Systolic blood pressure (SBP) > 100 mmHg (pressors allowed)
- Absence of brainstem function on exam, as indicated by the following:
 - Loss of spontaneous eye movements
 - Midposition of the eyes
 - Lack of oculocephalic (doll's eyes) and oculovestibular (caloric) responses

- Presence of dilated or midpoint fixed pupils (4–9 mm)
- Paralysis of bulbar musculature (no facial movement or gag, cough, corneal, or sucking reflexes)
- Absence of motor and autonomic responses to noxious stimuli
- Absence of spontaneous respiratory movements

If all the above criteria are fulfilled, carry out an apnea test.

Apnea test: Preoxygenate the patient with 100% O₂; pCO₂ should be normal. Then, disconnect the ventilator for 10 minutes and observe for respiration. A positive test occurs when there is no respiration, even with a pCO₂ > 60 mmHg or > 20 mmHg from baseline.

Diagnosis of brain death is made only by fulfilling the above clinical criteria.

Tests that can support a diagnosis of brain death (but are not mandatory except in children) include:

- Evaluation of brain blood flow
 - Angiography
 - Transcranial Doppler
 - MRA/CT angiography
 - SPECT (single-photon emission computed tomography)
- EEG

SEIZURES

PREVIEW | REVIEW

- Name some environmental triggers for seizures in susceptible people.
- What are some differences between generalized and focal seizures?
- Which test should you order if you suspect recurrent psychogenic nonepileptic seizures?
- What is the treatment of status epilepticus?
- Which drug is exclusively used to treat absence seizures?
- Which antiseizure medications (ASMs) decrease the effectiveness of oral contraceptives?
- Which ASM serum concentration is reduced by estrogens?
- Which ASM reduces the serum concentration of progestins?

OVERVIEW

Convulsion is an intense paroxysm of involuntary, repetitive muscular contractions, and it does not always have to be present during seizures. **Seizure** is preferable as a generic term because it includes all paroxysmal

electrical discharges originating in the **cerebral cortex** that cause loss of consciousness, alteration of perception or impairment of psychic function, convulsive movements, disturbance of sensation, or some combination thereof. **Epilepsy** is a history of ≥ 2 unprovoked seizures occurring at least 24 hours apart. The condition of prolonged or repetitive convulsive seizures is termed **status epilepticus** and can be life-threatening.

It is crucial to determine whether the seizures are primary (idiopathic) or secondary.

In susceptible individuals, triggers for seizures include intense emotions, strobe lighting, loud music, stress, menstruation, and lack of sleep.

Metabolic or toxic causes of seizures do not constitute epilepsy. This type of seizure can be provoked by severe or rapid metabolic derangements (e.g., Na^+ , Ca^{2+} , low Mg^{2+} , hypoglycemia); drugs, such as cocaine and amphetamines; and alcohol withdrawal (within 7–48 hours after last drink).

SEIZURE CLASSIFICATION

The 2017 International League Against Epilepsy (ILAE) changed the way seizures were classified and created a new framework with different levels for categorization, the International Classification of Epileptic Seizure. The levels are meant to provide consistency across research and clinical diagnoses and treatments. An explanation follows for [Figure 12-1](#). Refer to this figure as you read the topic discussion.

Seizure type indicates where the current seizure began in the brain: **focal** onset, **generalized** onset, or **unknown** onset—with no history of or with a new-onset seizure, this is often the only information you have. Onset locations:

- Focal onset seizure is subclassified by the patient's level of awareness (impaired or not), and whether or not there are motor symptoms at the onset.
- Generalized onset seizure is subclassified as motor or nonmotor (i.e., absence).
- Unknown onset

Epilepsy type is the 2nd level of diagnosis. It assumes that the patient has a diagnosis of epilepsy using standard criteria and testing (e.g., EEG). The patient has recurrent seizures that have been diagnosed as:

- Focal
- Generalized
- Combined generalized and focal
- Unknown

Epilepsy syndrome is the 3rd level of diagnosis. These syndromes are reliable concurrences of the above findings (e.g., seizure types, EEG patterns) with other factors such as age of onset and remission, diurnal variation, triggers, best treatment, and prognosis. Examples of syndromes with idiopathic generalized epilepsies are childhood absence epilepsy, juvenile absence epilepsy, juvenile myoclonic epilepsy, and generalized tonic-clonic seizures. There are several self-limited focal seizure syndromes that begin in childhood.

Etiology is considered from the very first seizure. These etiologies may be combined. For instance, a genetic abnormality may cause a metabolic or structural abnormality. The 6 etiologic groups are:

- 1) Infectious (most common cause worldwide; e.g., neurocysticercosis, HIV, cerebral toxoplasmosis, cerebral malaria, and congenital infections, such as Zika virus and CMV)
- 2) Structural (may be genetic or acquired; e.g., due to tumor, stroke, trauma, infection)
- 3) Genetic (based on family history, population research, or gene research)
- 4) Metabolic (most are genetic but may be acquired; e.g., cerebral folate deficiency, alcohol withdrawal)
- 5) Immune (e.g., antibody)
- 6) Unknown (cause is simply not yet known)

Comorbidities are associated with many epilepsies. There are often psychological, behavioral, and learning problems. Severe epilepsies can have motor deficits and movement disorders. Any comorbidity can cause psychosocial concern.

SEIZURE EXAMPLES

The following has 2 examples of generalized seizure (motor and nonmotor) and 2 of focal seizure (without and with impaired level of awareness):

- 1) **Generalized tonic-clonic** (previously grand mal) seizures involve both hemispheres, with resulting

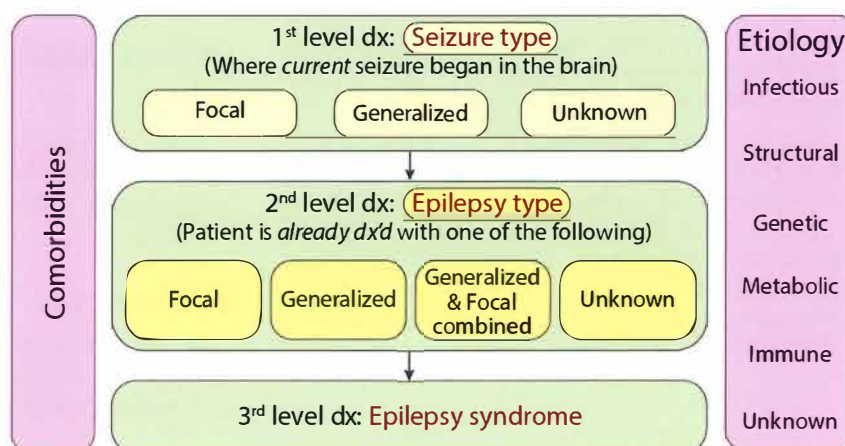


Figure 12-1: ILAE framework for seizure classification

bilateral motor involvement. Consciousness is impaired with a pronounced postictal period. These seizures can be generalized from the start, or they can be focal seizures with secondary generalization.

- 2) **Absence** (previously petit mal) seizures are a type of generalized seizure. These are nonconvulsive, generalized seizures with no aura and no postictal symptoms. The attacks occur without warning and consist of a sudden interruption of consciousness during which the patient stares and briefly stops talking or ceases to respond. They can be induced by **hyperventilating**. Absence seizures have a characteristic 3-per-second spike and wave pattern on EEG. 2/3 of affected children outgrow absence seizures.
- 3) **Focal** seizures originate in a small area of the cortex. Consciousness is preserved. The symptoms of a focal seizure depend on the region of cortex from which the event is generated. For instance, a focal seizure arising in the occipital lobe (visual cortex) can be manifested by complex visual hallucinations; e.g., spinning colorful spheres. A focal seizure affecting the motor cortex can cause focal motor convulsions. These can spread to involve more of one side of the body ("Jacksonian march") as the seizure progresses. Postictally, patients may temporarily have weakness of the affected limb.
- 4) **Focal seizures with diminished consciousness** have many causes. A common type is the temporal lobe seizure in which the preceding aura may be a hallucination or perceptual illusion. There is a period of altered behavior and consciousness for which the patient is later found to be amnesic. The motor components of the temporal lobe seizure take the form of automatisms (e.g., lip-smacking, chewing or swallowing movements, salivation, fumbling of the hands, shuffling of the feet).

Status epilepticus is the term reserved for prolonged seizure activity. Prolonged seizures lead to neuronal cell death and long-term consequences. It is considered a medical emergency. A cause can be determined about 2/3 of the time. Usual causes in adults include stroke, alcohol or other drugs, stopping or changing seizure medications, hypoxia, CNS infection, metabolic causes, tumor, and trauma.

Status epilepticus was historically defined as a seizure lasting > 30 minutes or a series of ≥ 2 seizures without regaining consciousness in between. The 2015 ILAE report on status epilepticus defined status as a generalized tonic clonic seizure ≥ 5 minutes. Most seizures last only 1–2 minutes, so when a seizure lasts ≥ 5 minutes, be aggressive with abortive treatment to avoid prolonged status epilepticus.

PSYCHOGENIC NONEPILEPTIC SEIZURES (PNES)

PNES (a.k.a. pseudoseizures) are not due to abnormal brain activity but are psychogenic. Features that suggest PNES include forced eye closure during event, pelvic thrusting, crying, awareness during a spell of bilateral convulsing, side-to-side head movements, or absence of a postictal state.

Order video EEG monitoring if PNES is suspected or when the events do not respond to treatment and the diagnosis is not clear. Prolactin levels are elevated about 10 minutes after a generalized motor seizure, but they are not elevated with PNES. Note, however, that 20% of patients with PNES also have epilepsy.

SEIZURE AURA

An aura is a perceptual disturbance that may precede a **focal** seizure. Auras do **not** occur with **primary** generalized seizures. Note that auras do occur with migraine, but all discussion here is in reference only to seizures.

Auras have various manifestations affecting the **senses**. They can be somatosensory perceptions, such as pain, numbness or tingling, or related to other senses. They can be mostly **motor**, ranging from tremors or shaking to gross motor movement. They can also be:

- Visual with lights, patterns, or seeing objects
- Auditory with voices, noises, tones, and other sounds
- Olfactory, typically with a burnt rubber smell
- Gustatory with the perception of strange tastes

Know: Auras, in the context of seizures, are used as a warning manifestation of seizure and allow the patient to take precautions. These auras are thought to be produced by **early** seizure activity.

A focal seizure can evolve into a focal seizure with diminished consciousness, and either of these can evolve secondarily into a generalized seizure. In any of these situations, the preceding seizure is also called an aura by some.

SEIZURE MANAGEMENT

History

When obtaining the history, check for alcohol or drug use, recent medication changes, head injury, sleep deprivation, diabetes, and thyroid or parathyroid surgery.

Scans and Labs

Include glucose, Na⁺, Ca²⁺, Mg²⁺, LFTs, toxicology, drug levels (i.e., lithium, phenytoin), and BUN in lab tests to evaluate for provoking causes of a seizure. Order

either an MRI with gadolinium or a CT with contrast (if MRI is contraindicated) after a first unprovoked seizure to exclude a structural abnormality; **MRI is the best neuroimaging test**. An **EEG** showing epileptiform abnormalities suggests the diagnosis of epilepsy, but a **normal EEG does not** exclude the diagnosis of a seizure disorder. Catching a seizure while a patient is hooked up to an EEG definitively distinguishes between seizure and nonepileptic causes of spells. However, typically, an EEG is obtained interictally, and one routine EEG only has a 50% sensitivity for detecting an abnormality between seizures.

Whether to start antiseizure therapy after an initial seizure depends on the following:

- Start antiseizure medication after 1 unprovoked seizure with the following, as the risk of recurrence is high:
 - An abnormal EEG
 - History of a prior neurologic injury
 - Focal abnormality on exam
 - Nocturnal seizure
 - An abnormality on MRI
- Unless a patient has a 2nd unprovoked seizure, hold off on starting antiseizure medication with:
 - Normal EEG
 - Normal MRI
 - Normal exam
 - Absence of risk factors

Remember to consider CNS infection in a patient with seizure, headache, and fever or with meningeal signs. Obtain imaging prior to lumbar puncture.

In ~ 70% of all patients with epilepsy, medications can control the seizures completely or almost completely; in an additional 20-25%, the attacks are significantly reduced in number and severity, but some may remain refractory. Epilepsy surgery and other options are available for treatment in refractory cases.

Acute Treatment of Seizures

Acute treatment of seizures: Intravenous benzodiazepines (e.g., diazepam, lorazepam, midazolam) are the drugs of choice. Phenytoin is also effective, but it takes longer to infuse. Treat alcohol withdrawal seizures acutely with IV benzodiazepines.

Typical treatment of status epilepticus in adults: Give thiamine and then 50 mL of D50 if the blood glucose level is low. Also give benzodiazepine (**lorazepam** preferred × 2 doses) followed by a loading dose of **phenytoin** or equivalent fosphenytoin for all status epilepticus patients. Fosphenytoin lacks the injection site necrosis and cardiac rhythm complications of intravenous phenytoin infusion **but** is much more expensive and can result in lower initial brain phenytoin levels (because of the time required for conversion from fosphenytoin to phenytoin). Nevertheless, the infusion

rate is 3× faster than for phenytoin; therefore, fosphenytoin is frequently used in the emergency department. Also consider IV levetiracetam or IV valproic acid for status epilepticus, particularly in patients with known generalized epilepsy; though in general, fosphenytoin is 1st line treatment.

If the patient is still seizing after the initial treatment options noted above, give a 3rd dose of lorazepam, maximize the phenytoin dose, and then proceed to a barbiturate (phenobarbital or pentobarbital) or propofol. Endotracheal intubation and ICU-level care are generally needed if seizures are not controlled by the first 2 doses of lorazepam and a dose of phenytoin.

Chronic Treatment of Seizures

Antiseizure medications (ASMs; a.k.a. antiepileptic drugs, anticonvulsants) are the mainstay of treatment, with monotherapy the preferred goal (**Table 12-2 on page 12-8**). ASMs in epilepsy are generally started after ≥ 2 unprovoked seizures but are typically used after 1 focal unprovoked seizure if EEG is abnormal or if there is a head injury history. The risk of seizure recurrence after 2 seizures is ~ 60%, and after 1 seizure the risk is ~ 35%.

The choice of ASM depends primarily on the seizure type, with additional considerations including cost, side-effect and metabolism profile, and patient preference for a dosage schedule.

Focal seizures—**almost all** available ASMs are effective in the treatment of focal seizures. The notable **exception** is ethosuximide, which only treats absence seizures and is the most effective medication for absence seizures. Other ASMs like lamotrigine and valproic acid can also treat absence seizures. Further, with few exceptions, the ASMs are equally effective. The main differences are that older ASMs are generally cheaper, whereas newer ASMs are typically better tolerated and have fewer side effects.

Generalized tonic-clonic seizures—the list of effective agents includes:

- Topiramate
- Lamotrigine
- Valproic acid
- Levetiracetam
- Clobazam
- Zonisamide

Absence seizures—the list of effective agents includes:

- Lamotrigine
- Ethosuximide
- Valproic acid

When can you **stop** the medication? This must be individualized. Risk factors include a seizure within the last 2 years, epileptiform spikes on the EEG, abnormal MRI, and a late age of onset of the seizures. Patients who are seizure-free for 2-4 years and have their ASMs gradually withdrawn have ~ 40% risk of recurrent seizures within 2 years.

Options for **intractable epilepsy** include resective surgery (best for temporal lobe epilepsy), vagus nerve stimulation (does not work as well as surgery), and the ketogenic diet (works well in children).

Driving restrictions vary from state to state and continue to evolve. The Epilepsy Foundation has updated information for your state: epilepsy.com/driving-laws.

Drug Interactions with Antiseizure Medications (ASMs)

ASMs and Oral Contraceptive Pills (OCPs)

Certain ASMs reduce the efficacy of OCPs:

- Phenytoin
- Phenobarbital
- Carbamazepine

- Lamotrigine
- Oxcarbazepine
- Topiramate

Advise women taking these ASMs to use a method of birth control other than oral contraceptives.

Oral contraceptives that contain estrogen can **decrease** the drug concentration of the ASM **lamotrigine**. Doses may need to be increased empirically. Conversely, lamotrigine can **decrease** serum concentrations of progestins (mini-pill). Thus, women on progestin-only contraceptives are at risk of getting pregnant. Counsel them to switch to alternate methods of contraception.

ASM Interactions

Phenytoin, phenobarbital, carbamazepine, and primidone are the earlier generation enzyme-inducing ASMs

Table 12-2: Notable Advantages and Disadvantages of Antiseizure Medications (ASMs)

Drug	Used to Treat	Notable Advantages / Disadvantages
Carbamazepine	Focal [†]	Good: Toxicity is uncommon. Bad: hyponatremia, leukopenia, thrombocytopenia, aplastic anemia, hepatotoxicity, teratogenic, liver inducer; reduces the efficacy of OCPs; risk of SJS in Asians with HLA-B* 1502
Clobazam	Generalized Focal	Good: broad spectrum, effective Bad: sedation, increased secretions, interacts with other medications metabolized via P450 enzymes (e.g., fluconazole, omeprazole, cannabidiol)
Ethosuximide	Absence [†] only	Bad: can cause bone marrow suppression (rare)
Gabapentin	Focal (adjunctive use)	Good: the only one with no significant drug interactions; renal clearance, so useful in those with liver disease Bad: ataxia, amnesia, limited efficacy
Lamotrigine	Focal (adjunctive use) Generalized Absence (alternative)	Good: wide spectrum, good efficacy, well tolerated in elderly patients Bad: can cause severe rash and SJS with rapid titration; OCPs decrease serum concentration of lamotrigine
Levetiracetam	Focal and generalized (monotherapy)	Good: well tolerated in elderly patients; renally excreted, so no interaction with levels of other ASMs; IV form available Bad: depression, fatigue, irritability, and personality change
Oxcarbazepine	Focal	Good: generally well tolerated, metabolized in liver Bad: SJS, aplastic anemia, angioedema, hyponatremia; reduces the efficacy of OCPs
Phenobarbital	Focal (last choice)	Bad: sedation in adults, hyperactivity in children, among other cognitive changes; teratogenic; reduces the efficacy of OCPs; liver inducer: decreases levels of carbamazepine, felbamate, lamotrigine, tiagabine, and valproic acid
Phenytoin	Generalized	Good: wide spectrum, good efficacy Bad: Gingival hypertrophy, decreases bone density, rash and SJS, interferes with efficacy of OCPs, liver inducer, and increases risk of fetal malformations. Toxic levels can induce seizure.
Topiramate Zonisamide (similar indications and side effects as topiramate)	Focal (monotherapy or adjunctive) Generalized (monotherapy or adjunctive)	Good: weight loss, headache prophylaxis if present Bad: kidney stones and increased glaucoma, weight loss, paresthesias, cognitive dysfunction; teratogenic; reduces efficacy of OCPs
Valproic acid	Generalized tonic-clonic [†] Absence (alternative) Focal (alternative, esp. if it generalizes)	Good: wide spectrum, good efficacy, IV form available Bad: GI side effects (fewer with extended release formulation); can rarely cause bone marrow suppression and hepatotoxicity/liver failure; teratogenic (neural tube defects), tremor, weight gain, hair loss; inhibits the metabolism of some antiseizure medications, such as carbamazepine, phenobarbital, phenytoin, and lamotrigine

Note: Any of the above ASMs can cause ataxia, dizziness, and somnolence.

Also of note: Overall, use of antiseizure medications confer a small increased risk of suicidal thoughts.

[†] Primary drug

ASM = antiseizure medication; GI = gastrointestinal; OCP = oral contraceptive pill; SJS = Stevens-Johnson syndrome

that stimulate a variety of **cytochrome P450** enzymes. Because many other drugs are metabolized by these enzymes, patients on enzyme-inducing ASMs often need their dosage of other medications increased.

These can affect the metabolism of each other, requiring a change of dose. One counterintuitive example: Even though phenytoin increases the metabolism of primidone, the active metabolite of primidone is phenobarbital—so you may need to decrease the primidone dosage.

Valproic acid is different from other older-generation ASMs in that it **inhibits** some of these same enzymes! Especially watch for an increase in levels of phenobarbital, carbamazepine, phenytoin, and lamotrigine.

Newer ASMs do not have the same broad inducement of enzymes. Still, some have more specific effects; for example, as discussed in **ASMs and Oral Contraceptive Pills (OCPs)**, some can increase the metabolism of OCPs.

Treatment of Seizures During Pregnancy

Know!

The background risk for birth defects is 2–3%. The goal of treatment during pregnancy is to control the seizures—uncontrolled seizures can cause placental abruption, early labor, and premature delivery. When the risk of teratogenicity is compared to the problems that seizures cause during pregnancy, the risks of uncontrolled seizures are **greater!**

Maintain a pregnant woman on **monotherapy** at the **lowest dose** of medication possible; risk of malformations increase as each drug is added.

Many ASMs are **teratogenic**. The most significant teratogens include phenytoin, phenobarbital, carbamazepine, topiramate, and valproic acid.

Valproic acid is **more likely** to cause **neural tube** defects than other commonly used ASMs and is associated with lower IQs of children exposed to this drug in utero—therefore, avoid if pregnancy is planned. The teratogenic risk of ASMs is **decreased** by **folic acid**, and thus, advise all women of childbearing age on ASMs who can become pregnant to take 1 mg of folate daily—4 mg of folic acid daily in patients taking valproic acid or carbamazepine.

Note: Physicians generally give prophylactic **vitamin K** during the last **month** of pregnancy in patients on ASMs, based on reports indicating increased bleeding in patients on ASMs. However, the 2009 American Academy of Neurology (AAN) guidelines state there is not enough evidence to recommend for or against use of prophylactic vitamin K.

For more on seizures during pregnancy, see the **Women's and Men's Health** section.

DEMENTIA

PREVIEW | REVIEW

- What is the definition of dementia?
- Which 6 domains may be impaired in patients with dementia?
- What is the definition of mild cognitive impairment?
- What is the clinical triad in normal pressure hydrocephalus?
- How is Alzheimer disease (AD) diagnosed?
- Which class of drugs is the 1st line treatment for AD?
- Which drug is used with a cholinesterase inhibitor for the treatment of advanced AD?
- What is a potential complication from the use of atypical antipsychotics in elderly patients with dementia?
- What is the most common cause of vascular dementia?
- How does the clinical presentation of frontotemporal dementia differ from that of AD?
- Is Creutzfeldt-Jakob disease (CJD) insidious or rapid?
- How do you diagnose CJD?
- What is the problem with using antipsychotic drugs to treat patients with dementia with Lewy bodies?
- What are the clinical features of Huntington disease?
- Name some features that distinguish depression from dementia.

DEFINITION

Dementia is defined as a chronic cognitive decline with or without behavioral impairment that is:

- **progressive**,
- **interfering** with normal daily functioning, and
- **not due to delirium** or an underlying **psychiatric disorder**.

Note how this definition contrasts with encephalopathy, which causes altered states of consciousness—from delirium to stupor.

WORKUP

Diagnosis of Dementia

Basic principles:

- Perform a thorough H&P that includes obtaining history from the patient and an additional informant (because history from a potentially demented patient is not always reliable).
- Perform an objective cognitive assessment using a validated tool; e.g., the Montreal Cognitive Assessment (MoCA), the Mini-Mental State Exam (MMSE).
- Evaluate for depression that can mimic cognitive decline and for other secondary (reversible) medical causes of cognitive decline as outlined under **Reversible Causes**.
- Consider detailed neuropsychological testing to fully map out affected domains of cognition to help solidify the correct diagnosis.

Dementia is diagnosed when abnormalities exist in ≥ 1 of the following 6 domains and are also progressive and interfere with daily functioning and independence:

- 1) **Learning and memory**—acquiring and/or remembering new information. Do they ask repetitive questions, lose items, or get lost?
- 2) **Executive function**—reasoning. Do they understand appropriate danger? Can they perform their activities of daily living (ADLs), such as grocery shopping?
- 3) **Perception and motor function**—assessing visuospatial orientation. Do they recognize faces and objects? Can they dress themselves? Do they get lost in their house?
- 4) **Language**—comprehension and speaking appropriate language. Do they have problems recalling common words without hesitations?
- 5) **Social cognition**—behaving normally and appropriately. Is there undue agitation, apathy, loss of empathy, or compulsive behavior?
- 6) **Complex attention**—ability to perform complex steps. Can they balance a checkbook or pay a grocery bill with cash?

Psychosis is a common feature of advanced dementia.

Mild Cognitive Impairment (MCI)

When ≥ 1 of the domains is in decline, but the impairment does not significantly impact daily functioning, the diagnosis is **MCI**. If MCI is diagnosed, obtain an assessment of functional status.

MCI can be either amnesic or nonamnesic. **Amnesic MCI** is more common. Not all patients with MCI deteriorate into dementia. MCI progresses to dementia at a rate of about 5–10% per year. Such progression is more likely in patients with a family history of **Alzheimer Disease (AD)**. Patients with amnesic MCI have memory impairment

that does not significantly impact daily living, and general cognition is intact. Those with amnesic MCI are more likely to deteriorate to Alzheimer disease.

Patients with nonamnesic MCI have impairment in ≥ 1 of the other domains (executive function, perception, language, social, or complex attention), but daily living is not impacted.

Reversible Causes

In evaluating dementia, consider the following treatable causes of impaired cognition:

- Medications
- Vitamin B₁₂ deficiency (may have associated polyneuropathy/myelopathy)
- Hypothyroidism
- Chronic subdural hematomas (consider especially in patients with alcohol use disorder, on anticoagulants, and elderly patients with a history of falls)
- Normal pressure hydrocephalus (NPH)
- Tumors, especially involving the frontal lobes
- Infection and inflammation (consider with clinical clues or a subacute, rather than indolent, decline)
 - AIDS
 - Neurosyphilis
 - Neurosarcoidosis
 - Chronic meningitis
 - Lupus cerebritis
 - Vasculitis
- Autoimmune encephalopathy (such as Hashimoto encephalopathy or paraneoplastic/autoimmune encephalitis)
- Heavy metal poisoning (e.g., arsenic, mercury, lead)

In practice, an initial medical evaluation of cognitive disturbance entails imaging of the brain (MRI preferred, if possible), as well as thyroid and B₁₂ testing. Additional lab testing, such as for syphilis or HIV, is based on risk factors. Consider a much more expanded workup based on other clinical clues or a more rapid, subacute decline in cognition (see above again for the broad differential of reversible causes of cognitive decline).

Diagnosing a specific subtype of dementia is based on a range of clinical clues and presentations.

SPECIFIC CAUSES OF DEMENTIA

Normal Pressure Hydrocephalus (NPH)

Hydrocephalus is enlargement of the cerebrospinal fluid (CSF) spaces. There are various types:

- NPH has enlarged ventricular size with normal opening pressures on LP.
- Noncommunicating (obstructive) hydrocephalus has enlarged ventricles due to a physical blockage in the small passages between ventricles—often in the aqueduct of Sylvius between the 3rd and 4th ventricles.

This is usually a congenital issue (i.e., aqueductal stenosis), but it can be acquired in adults (e.g., hemorrhage, tumor, infection). Intracranial pressure (ICP) is elevated.

- Communicating hydrocephalus has enlarged ventricles due to decreased CSF resorptive capabilities. ICP is elevated.
- Hydrocephalus ex vacuo is a compensatory enlargement of the ventricles due to atrophy of the brain substance as a result of stroke, injury, or diffuse white matter changes (e.g., from diabetes or hypertension; see [Vascular Dementia on page 12-12](#)). ICP is normal.

NPH causes the **classic triad** of:

- 1) Gradually worsening dementia
- 2) Gait apraxia (a wide “magnetic” gait, like walking on a boat)
- 3) Bladder issues (detrusor overactivity with urinary urgency/frequency and incontinence)

Patients can present with frequent falls due to gait instability. Often, the mental issues and gait problems precede the bladder control issues. NPH rarely causes headaches.

NPH can occur as a result of prior head **trauma**, acute or ongoing chronic **meningitis**, or **subarachnoid hemorrhage**.

NPH has **no** associated cerebral atrophy. The opening pressure on lumbar puncture (LP) is normal, and there is no papilledema. With early diagnosis, further neurologic deterioration can be improved, but not always sustained, with the placement of a ventricular shunt. An MRI or CT shows enlarged ventricles with normal size sulci. The course of dementia, while slowed with shunt placement, is similar to Alzheimer's.

Note that hydrocephalus ex vacuo from diffuse white matter changes can present with the **same clinical triad** as NPH.

Diagnosis: Suggestive review of symptoms and physical exam findings. There is no papilledema, and opening pressure on LP is normal. Observing the clinical response to a high-volume LP (such as pre- and postgait assessments) remains the most utilized clinical diagnosis.

Treatment for NPH is **ventriculo-peritoneal** or **ventriculo-atrial shunt**. Certain indicators help identify patients who are most likely to respond to shunting:

- NPH secondary to subarachnoid hemorrhage, acute or ongoing chronic meningitis, or head trauma
- < 6 months of symptoms
- Gait abnormality > cognitive abnormality

Dementia for > 2 years or significant white matter disease or atrophy on imaging are indicators of poor shunt responsiveness.

Alzheimer Disease (AD)

Diagnosis of AD

AD is the most common cause of dementia **after 60 years of age**. 1st degree relatives have a 4× normal risk of developing it.

AD is diagnosed when the illness is found to be **insidious**, **progressive**, and marked by impairments in **≥ 2 domains** (memory, executive functioning, perception, language, behavior, and complex attention), such that there is **significant impairment** in normal daily functioning. As with **Mild Cognitive Impairment (MCI)**, the amnesic presentation of AD is the most typical. Patients with Alzheimer's have **normal LP** parameters.

Initial signs of AD usually reflect hippocampal dysfunction, with poor immediate recall and short-term memory. Impairment of naming can also be an early sign. As the disease progresses, impairments emerge in perception, social, complex, and executive domains, reflecting dysfunction in the **parietal** and **frontal** lobes. Changes in environment (such as vacations or hospital stays) can be disorienting, and the patient may become lost on walks or while driving.

Do **not** use any of the following for a definitive diagnosis of AD:

- MRI scans that show disproportionate atrophy
- PET scans demonstrating amyloid deposition or decreased tracer uptake
- CSF tau and amyloid measurements

These biomarkers are **not specific enough**, and abnormalities sometimes are seen in patients with normal cognition or MCI only. On autopsy, Alzheimer pathology has the characteristic findings of plaques made of β -amyloid protein and neurofibrillary tangles made of tau protein but without Lewy bodies (as seen in Parkinson disease dementia).

Additionally, do **not** diagnose AD as a cause of dementia if the patient:

- has a history of significant cerebrovascular disease,
- has clinical features of frontotemporal dementia (see [Frontotemporal Dementia \(FTD\) on page 12-12](#)) or dementia with Lewy bodies (DLB; more under [Parkinson Disease Dementia \(PDD\) on page 12-13](#)),
- has evidence of another psychiatric or neurologic illness, or
- takes a medication that can cause cognitive impairment.

You must rule these out as causes of the dementia symptoms. In an elderly patient presenting with dementia without a movement disorder, the main diagnoses to consider are AD, **vascular** dementia, and **mixed** dementia (with both neurodegenerative and vascular components).

Treatment of AD

The 1st line treatment for Alzheimer's is cholinesterase inhibitors (CIs):

- Donepezil (Aricept)
- Rivastigmine (Exelon)
- Galantamine (Razadyne)

Additive drug treatment includes the *N*-methyl-D-aspartate receptor antagonist memantine (Namenda).

The **combination** of a CI + memantine appears to be better than a CI alone, especially for advanced AD.

The CIs produce a small improvement in cognition and, sometimes, in neuropsychiatric instability. Data is conflicting on their long-term effects. Not every patient benefits. Note that these drugs are for dementia only; do **not** use to treat MCI. The best results with CIs are achieved in mild-to-moderate Alzheimer's, but other types of dementia (e.g., multi-infarct and DLB) sometimes also improve. Treatment effects with these medications are modest only.

Dose escalations for each of these medications must be carried out over 4–6 weeks to minimize side effects. The main side effects are anorexia, nausea, and occasionally diarrhea or bradycardia (cholinergic symptoms). Rivastigmine is available as a patch that has fewer GI side effects and is useful in patients who will not swallow medications.

Neuropsychiatric instability in late-stage AD is common and difficult to treat. Mild-to-moderate depression in the early stages may respond to SSRIs, trazodone, or CIs; definitely avoid tricyclic antidepressants because of the anticholinergic symptoms, particularly short-term memory impairment and confusion.

Atypical antipsychotics (e.g., olanzapine, quetiapine, risperidone, clozapine) have been used to treat the agitation, insomnia, delusions, aggression, and wandering. However, in 2005, the FDA published a black box warning that these drugs can cause **increased mortality** in the elderly with dementia (any cause but especially in the elderly with DLB), and in 2017, the FDA issued a formal warning about the increased risk of associated falls and fractures. This does not mean antipsychotics cannot be used in patients with dementia. The American Psychological Association (APA) recommends only using antipsychotics in patients with dementia who have psychosis or present a danger to themselves or others. The lowest effective dose of antipsychotic should be used in patients meeting these criteria who have not responded to nonpharmacological interventions.

Vascular Dementia

Dementia with cognitive deficits associated with vascular factors (a.k.a. vascular dementia) is the 2nd most common form after AD. Vascular dementia results from infarction or ischemia of 3 major structures: large arteries, small arteries (e.g., lacunar), and small arteries in the

white matter. The Hachinski ischemic score can help differentiate vascular (≥ 7) from AD (≤ 4), and is based on several features including a history of atherosclerosis, hypertension, prior stroke, focal deficits, and rate of onset. The classic description of vascular dementia involves a stepwise decline. With each new stroke, there is a new cognitive baseline. Smaller strokes could be subclinical but still contribute to the cognitive decline.

Chronic **hypertension** is the most common cause of dementia due to lacunar infarcts and diffuse nonspecific white matter changes, which are visible on MRI. The changes result from chronic ischemia mediated by occlusive disease of small, penetrating cerebral arteries and arterioles. **Diabetes** is also a common cause of this condition.

Early symptoms include mild confusion and impairments in memory, perception, and executive functions. Marked difficulties in judgment and orientation develop later, along with dependence on others for ADLs. Neuropsychiatric symptoms (e.g., apathy, anxiety, psychosis, euphoria, depression, aggression) also develop as the deep white matter changes and infarcts accumulate. Pyramidal and cerebellar signs can be seen. With advanced disease, patients frequently present with urinary incontinence and dysarthria with or without other pseudobulbar features (e.g., dysphagia, emotional lability).

Frontotemporal Dementia (FTD)

FTD, previously Pick disease, is quite similar in presentation and course to Alzheimer's, but it is characterized by a **more rapid** and significant change in personality and behavior, often with **disinhibition**, **language deficits**, or both. Onset is in the 5th to 6th decades (relatively young, compared to Alzheimer's), and the incidence in males exceeds that in females.

Common behavioral features include apathy, disinhibition, weight gain, food fetishes, compulsions, and loss of empathy.

Cognitive testing usually reveals spared memory but impaired planning, judgment, or language. Patients often show an absence of insight into their condition.

The naming of FTD subtypes is based on their primary manifestations; e.g., behavioral variant vs. progressive, nonfluent vs. semantic. Patients with FTD have **more focal atrophy** of the frontal and temporal lobes on CT or MRI, compared with the diffuse atrophy of Alzheimer's or a medial temporal/parietal distribution with Alzheimer's.

Currently there are no effective treatments for FTDs, but the serotonin selective reuptake inhibitors and the atypical serotonergic agent trazodone have been shown to result in some behavioral improvement, mainly in irritability, agitation, depressive symptoms, and eating disturbances.

Creutzfeldt-Jakob Disease (CJD)

CJD is one of the very rare (1 per million people) **prion** diseases. Based on observations of causes, CJD is divided into **sporadic** (sCJD; most typical at 90%), **familial** (fCJD; about 10%); **iatrogenic** (iCJD; < 1%), and **variant** (vCJD). Usually, **sCJD** presents around 55–65 years of age, and we have no idea what causes it. **fCJD** has genetic associations. When you see CJD in younger patients, think either iCJD or vCJD. iCJD is caused by receipt of infected human tissues, hormones (e.g., growth hormone, gonadotropins, dural grafts, corneal or liver transplants), or exposure to contaminated surgical instruments. Current safety practices have essentially eliminated iatrogenic cases, though long incubation periods of former exposures can still present today. **vCJD** is believed to be caused by consuming cattle meat contaminated with the prion that causes **mad cow disease** (bovine spongiform encephalopathy).

Regardless of cause, CJD develops as a **rapidly progressive** dementia (weeks as opposed to years) with characteristic startle **myoclonus** (response to loud noises or startle). The early stages of the neurologic disease are characterized by changes in behavior, emotional response, and intellectual function, often followed by ataxia and visual distortions, confusion, hallucinations, delusions, and agitation. Dementia and muteness quickly follow the early symptoms. Younger patients with vCJD tend to have dementia with predominantly **psychotic** features. The disease involves the cerebral cortex, basal ganglia, and spinal cord.

The diagnostic gold standard is brain **biopsy**. Supportive studies include:

- **MRI** of the brain with diffusion-weighted images shows abnormal diffusion in thalami, basal ganglia, or the cortical ribbon (helps also to differentiate sCJD from vCJD).
- **EEG** (characteristic pattern of periodic sharp wave complexes on a diffusely slowed background)
- **14-3-3 protein** in an otherwise bland CSF (Only the National Prion Disease Pathological Surveillance Lab does this test, at Case Western, and sensitivity/specificity is < 80%.)

Creutzfeldt-Jakob disease is fatal within 1 year in > 90% of patients. There are no known treatments.

Parkinson Disease Dementia (PDD)

PD is caused by a loss of dopaminergic neurons in the substantianigra. (See [Movement Disorders on page 12-17](#).)

Dementia in PD (PDD) is common, eventually affecting as many as 80% of patients. Its frequency increases with aging and, in contrast to Alzheimer disease, primarily affects **executive functions** and **attention in its earlier stages**, with relative sparing of language, memory, and calculations until later in the disease course. When dementia precedes or develops within 1 year after the onset of motor dysfunction, it is referred to as **dementia with Lewy bodies**

(**DLB**). Neuropathology in both PDD and DLB shows Lewy bodies mixed with amyloid plaques and neurofibrillary tangles. Lewy bodies are spherical eosinophilic inclusions within the neuron ([Figure 12-2](#)).

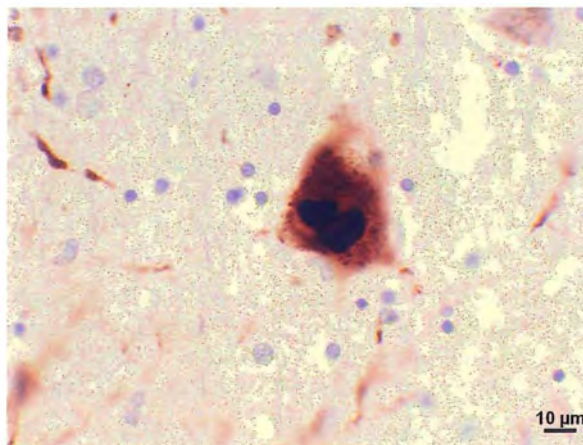


Figure 12-2: Lewy body

The core clinical features of DLB (besides dementia) are spontaneous motor features of parkinsonism (although this may not be present in every case); recurrent, vivid visual hallucinations; and prominent fluctuations of attention and cognition. Other supportive clinical features include hallucinations in nonvisual senses (e.g., tactile, olfactory, auditory), delusions, REM sleep behavior disorder (dream enactment), unexplained falls or loss of consciousness, and depression.

Both the dementia and psychosis may be at least partially responsive to acetylcholinesterase inhibitors and memantine. **Clozapine** (which spares the D₂ dopamine receptor) can be helpful. Quetiapine is another option.

Patients with DLB have poor responses to the older antipsychotic drugs that block the D₂ dopamine receptor, including haloperidol and chlorpromazine—and even to some of the “atypical” neuroleptics. With these drugs, patients have a dramatic and severe worsening of symptoms with extreme sedation, increased confusion, and postural instability (with falls). Avoid all antipsychotics other than clozapine and quetiapine in those with DLB.

As described in the Alzheimer’s topic discussion (refer to [Treatment of AD](#)), antipsychotic drugs are under an FDA **black box warning** because they are associated with an **increased risk of death** when used in elderly patients with dementia, and especially so in those with DLB.

Progressive Supranuclear Palsy (PSP)

Refer to [Progressive Supranuclear Palsy \(PSP\) on page 12-19](#) under the topic discussion of movement disorders.

Huntington Disease (HD)

HD causes both a **dementia** and a **movement disorder**. (See [Movement Disorders on page 12-17](#).) The gene responsible for HD is the *HTT* gene on chromosome 4p,

which codes for a mutant huntingtin protein that is probably toxic. (Note: The protein is spelled with an i, while the disease is spelled with an o.) It is inherited in an autosomal dominant fashion with complete penetrance. Problems commonly begin in those who are in their **late 30s**. Of those diagnosed, 7% commit suicide.

HD causes dementia, **chorea**, and psychiatric disturbances, including personality changes, depression, and **psychosis**. Memory is relatively spared. Chorea is usually the heralding symptom. The emotional disturbances and changes in personality can be so severe that they can manifest as psychosis with persecutory delusions or hallucinations.

Disease is progressive with death (typically from pneumonia) within 30 years after symptoms begin. Diagnosis is made in the setting of positive family history, clinical features, and genetic testing demonstrating the *HTT* gene.

Atrophy of the caudate nuclei on CT or MRI ("boxcar ventricles") is characteristic and correlates with deterioration in cognition. No curative medication exists, and the disease is invariably **fatal**. Tetrabenazine is effective in controlling mild **chorea**. Side effects are significant and include depression, sedation, and bradykinesia. Other symptoms can be ameliorated with antipsychotics (neuroleptics), benzodiazepines (e.g., clonazepam), and antidepressants.

Genetic counseling prior to genetic testing is available for family members but is performed only ~ 15% of the time.

Acquired Immunodeficiency Syndrome (AIDS)

AIDS is the most common cause of dementia in younger patients. Dementia affects half of all AIDS patients not on antiretroviral therapy (ART). The manifestations can be mild (minor cognitive-motor disorder) to severe (HIV-associated dementia). Impairment is related to the degree and duration of immunosuppression. Controlling the virus in a patient who has had AIDS for a prolonged period, with a low CD4 count, often does not reverse dementia.

HIV-associated dementia (**HAD**) is characterized by cognitive impairment, movement disorders, and depression. It starts with small comprehension problems and anhedonia, accompanied by tremor and gait abnormalities. Over time, patients develop slower movements with substantial cognitive impairment. Exclude opportunistic infections of the CNS (e.g., cryptococcosis, toxoplasmosis, neurosyphilis) as part of the workup.

Treatment includes treating the HIV with ART, focusing specifically on designing a regimen of medications that enter the CNS at higher levels. Also treat associated depression. See more on HAD under [Human Immunodeficiency Virus \(HIV\)](#) on page 12-22.

Depression

Some patients with **major depression** present with significant cognitive dysfunction, known as depressive "pseudodementia." One differentiating feature is that **frontal lobe** release signs (grasp, suck, rooting, and palmarmental reflexes) are common in patients with dementia, particularly if moderate or advanced, but they are not typically seen in isolated depression. Another distinction is that immediate recall is usually poor in depression (due to attentional dysfunction) but good in dementia. Patients with depression-related pseudodementia tend to be concerned about their deficits but perform rather normally on office cognitive testing, whereas patients with dementia are more often brought to attention by family members and may not have insight into their cognitive impairment.

Depression can be reactive or endogenous. Symptoms are the same for both. In endogenous depression, patients, as expected, can have an abnormal response to the dexamethasone suppression test in which the cortisol is initially suppressed, but the duration of suppression is shortened (normal is > 24 hours).

DELIRIUM

PREVIEW | REVIEW

- What are the 2 clinical hallmarks of delirium?

Delirium is an acute, and often transient, onset of altered mental status, typically within hours to days. It is most commonly seen in hospitalized elderly patients, patients in hospice units, and patients in the ICU. It increases mortality. Diagnose based on the clinical hallmarks of decreased attention span and varying states of confusion. Aim treatment at identifying any underlying cause and supportive care. The risk factors are many and include infection, restraints, older age, dementia, untreated pain, and medications (particularly benzodiazepines). Delirium is also discussed in the [Geriatric Medicine](#) section.

CNS: BRAIN — SUBCORTEX

DEMYELINATING DISEASES

PREVIEW | REVIEW

- What are 2 ocular presentations of multiple sclerosis (MS)?
- Which findings in cerebrospinal fluid are helpful for the diagnosis of MS?
- What is the treatment for an acute exacerbation of MS?
- Natalizumab can cause which neurologic disease?

- Aside from patients with AIDS, progressive multifocal leukoencephalopathy (PML) can occur in which patients?
- What are the symptoms of PML?
- What is the cause of osmotic demyelination syndrome?
- Which clinical findings are seen in osmotic demyelination syndrome?

MULTIPLE SCLEROSIS (MS)

Know all of the following! MS is a demyelinating disease of the CNS that usually begins between 20 and 30 years of age. Women are affected more often than men (about 2:1). The incidence is higher in northern latitudes, possibly because of reduced sun exposure. It is recognized that adequate vitamin D levels may have a protective effect and an important role as a modifiable nutrient risk factor. MS is a chronic condition with episodes of focal disorders of the optic nerves, spinal cord, and brain, which remit and recur over a period of many years.

The disease process is thought to be autoimmune, although no specific antibodies have been found and the disease may not always respond to immunomodulators. Infections as an etiology have not been excluded either. One theory is that there is an initial infectious insult and an autoimmune reaction acts as a secondary trigger. Another theory is that MS is a result of T-cell sensitization to myelin. A familial aggregation of MS has also been reported.

The neurologic symptoms depend on the region of brain that is affected.

There are 3 types of MS:

- 1) Relapsing-remitting (RRMS)
- 2) Secondary progressive (SPMS)
- 3) Primary progressive (PPMS)

The relapsing-remitting type (initially normal between spells but later presents with residual deficit between spells) can slowly transform into the progressive type (which classically is slowly progressive from onset). Although 85% of cases are initially RRMS, most transform to the progressive type after several years.

Patients with a 1st episode and ≥ 2 lesions on brain MRI have a 90% risk of developing MS in 10 years—as opposed to a 28% risk if no lesions are found on brain MRI.

Clinical Manifestations of MS

Paroxysmal symptoms make up the usual course of early disease (except in chronic progressive cases). Weakness or numbness in ≥ 1 limbs is the initial symptom in about 1/2 of the patients. Tingling of the extremities and tight band-like sensations around the trunk or limbs are commonly associated symptoms.

Although strict criteria are used to diagnose MS (see [Diagnosis of MS on page 12-16](#)), place MS in the differential anytime you encounter the following characteristic syndromes (especially if recurrent!).

Optic neuritis (ON) is the most common presentation of MS eye disease and the 1st manifestation in about 25% of patients. It occurs at some time in 50% of all MS patients. There is swelling of the optic disc, but with progression, the disc becomes pale. ON presents as a rapid loss of vision in one or both eyes, often accompanied by slight pain, especially on eye movement. The vision loss is usually central, but a variety of field defects can be seen. With unilateral involvement, the **Marcus Gunn pupil** (a.k.a. relative afferent pupillary defect) is typically seen. Light shone into the eye with ON produces slower and incomplete constriction of both pupils than light shone into the healthy eye. On the swinging flashlight test, when the flashlight is swung to the affected eye, both pupils dilate; however, when light is presented to the healthy eye, both pupils constrict briskly. More than 90% of these cases recover completely.

Internuclear ophthalmoplegia (INO) is caused by a lesion in the medial longitudinal fasciculus, and, although it presents as difficulty in moving the eyes horizontally, convergence is normal. (Remember that normal convergence means the patient can turn each eye inward slightly as they follow your finger to their nose, so that they continue to see a single object.) There is adduction paresis ipsilateral to the lesion, with the deficit ranging from complete medial rectus paralysis to slight slowing of an adducting saccade. Gaze-evoked horizontal jerk nystagmus is present in the abducting eye contralateral to the eye with adduction weakness. (Remember: Adduction means “toward the midline” and abduction means “away from the midline.”) Think multiple sclerosis whenever you hear of a relatively young patient being diagnosed with INO. In older patients, however, it is more commonly due to cerebrovascular disease. The presence of bilateral INO in a young adult is virtually diagnostic of MS.

Acute myelitis causes a rapidly evolving (several hours or days) symmetrical or asymmetrical paraparesis or paraplegia, ascending paresthesia, loss of deep sensibility in the feet, a sensory level on the trunk, sphincteric dysfunction, and bilateral Babinski sign (upturning big toe with firm stroking of sole of foot).

Other symptoms of MS can include generalized fatigue, nebulous sensory abnormalities (e.g., pain, paresthesias, itching, feeling of coldness or swelling, numbness [especially of the face]), vertigo/diplopia, lower-extremity motor weakness/paralysis, ataxic gait, and bowel/bladder dysfunction. Flexion of the neck may induce a tingling, electric-like feeling down the shoulders and back known as the Lhermitte sign.

Young women with bilateral trigeminal neuralgia and/or bilateral INO have MS until proven otherwise!

Dementia is not a typical feature of MS, especially in the earlier stages, but substantial cognitive impairment may

occur in some patients with advanced chronic progressive disease. If your patient presents with dementia and gait abnormalities, a more likely diagnosis is Parkinson disease, PSP, or NPH.

All symptoms of MS tend to **worsen** in the **heat**, called Uhthoff phenomenon. This is because heat increases conduction block in demyelinated pathways.

Diagnosis of MS

Diagnosis of MS is no longer based solely on the history and neurologic exam. The traditional (Posner) criteria incorporated signs and symptoms indicating 2 CNS lesions separated in **time and space** that were not caused by other CNS disease and included CSF findings. The fact that MS lesions disseminate over time and space remains an essential component of making the diagnosis: MS develops slowly over time with new lesions occurring in different parts of the brain, thereby causing different neurologic signs and symptoms. Current criteria incorporate CNS imaging as a diagnostic tool.

MRI has become an essential tool in the workup of MS. T1-gadolinium MRI shows the characteristic enhancement or “plaques” of patchy myelin loss (white matter disease) with 90% sensitivity. T2-weighted MRI shows MS lesions as hyperintense areas. Many non-MS lesions can show up as hyperintense, so the **specific location** where these lesions are found has **diagnostic weight**. Dawson fingers refer to MS lesions around the veins that radiate out from the ventricles.

The 2017 McDonald criteria consider time- and space-specific MRI findings. CSF findings are not included. MS lesions and their dissemination over **time and space** are the main diagnostic criteria:

- Time
 - Presence of asymptomatic enhancing and nonenhancing lesions
 - New T2 lesion
- Space
 - At least one T2 lesion in ≥ 2 of the 4 MS CNS regions (periventricular, juxtacortical, infratentorial, or spinal cord)

In addition, consider MRI of the spinal cord, especially if brain imaging does not reveal plaques and the patient's presentation is very suspicious for MS. The diagnostic criteria equate certain cord lesions to certain brain lesions. MRI is also essential to **rule out** conditions that can mimic MS. White matter disease due to ischemia (elderly) and vasculitis both have a very different pattern of distribution from that seen with MS.

CSF analysis is particularly useful during acute exacerbations when **IgG** immunoglobulins to **myelin** can be found in the CSF. When these globulins are processed using electrophoresis, a **few** “bands” appear; thus, the term **oligoclonal bands**. 90% of MS patients have increased

IgG index and oligoclonal IgG bands in the CSF. CSF protein and cell count is generally normal—on occasion, a small CSF lymphocytosis may be present, but it should be ≤ 50 cells/ μ L.

Evoked potentials (visual, brainstem auditory, and somatosensory evoked potentials) can help to establish the diagnosis of MS by identifying a clinically silent 2nd lesion.

So, the workup for MS includes an **MRI**, a **lumbar puncture**, and **evoked potentials**. Ultimately, the diagnosis is made using a combination of clinical history, physical exam, laboratory, and imaging data.

Treatment of MS

There is **no** cure for MS. Treatment is very specialized and managed by neurologists. As a result, general internists are expected to know that the treatment of acute exacerbations is to rule out a possible triggering infection (e.g., UTI, pneumonia), then treat with **high-dose corticosteroids** (as opposed to the myriad treatment options for both intermittent and progressive disease). If an infection, like UTI, is causing a pseudoexacerbation or worsening of old deficits, then it is sufficient to treat the infection alone. If the patient has new neurologic deficits, then treat for an inflammatory flare; if needed, an MRI with and without contrast can help clarify whether a patient is experiencing a new flare. For treatment of a flare, glucocorticoids may shorten the duration of exacerbations but do not alter the natural course of MS. Treat with IV methylprednisolone, 1 g/day for 3–5 days.

Other drugs used to treat chronic MS: **immunomodulators** (β -interferons and monoclonal antibodies), glatiramer acetate (Copaxone, Glatopa), and **other immunomodulatory drugs** such as ocrelizumab, which is the only medication approved for primary progressive MS.

Other examples of drugs include fingolimod (Gilenya) and dimethyl fumarate (Tecfidera), which are oral medication options rather than the injection therapy options with glatiramer acetate or β -interferons. Be aware that patients taking natalizumab have an increased incidence of **Progressive Multifocal Leukoencephalopathy (PML)**. For interferons, monitor CBC and LFTs every 6 months because they cause flu-like symptoms, fatigue, and depression.

PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY (PML)

PML, which affects **white (leuko)** matter only, is a progressive demyelination seen in patients with severe T-cell immunodeficiencies (e.g., HIV/AIDS), monoclonal antibodies, and chronic neoplastic diseases. An example of the monoclonal antibodies is **natalizumab**, used in the treatment of MS and moderate-to-severe Crohn disease. Natalizumab is an antibody to the

VLA-4 antigen expressed on activated T cells and monocytes. Most cases of PML of this type have occurred with the combination of natalizumab and other immunomodulators.

Other cases of PML can be seen in patients taking a number of **immunosuppressants** (e.g., rituximab, fludarabine, mycophenolate, chronic corticosteroids) for treatment of rheumatologic, hematologic, post-transplant, and inflammatory bowel diseases.

It is caused by the **JC polyomavirus**.

Symptoms are varied and typically start with abnormal mentation (personality changes and intellectual impairment) and then slurred speech. Initial symptoms can be followed by hemiparesis progressing to quadriplegia, visual field defects, cortical blindness, aphasia, ataxia, dysarthria, dementia, confusional states, and/or coma. Some patients have a predominantly cerebellar syndrome.

A definitive diagnosis can be made with **brain biopsy**. Alternatively, follow up a suggestive MRI with a PCR analysis of spinal fluid. Finding JC virus in spinal fluid is strongly supportive of PML, although sensitivity of the PCR test decreases as the immune system is reconstituted on antiretroviral therapy (ART). ART has improved mortality in patients with PML, but many patients have persistent neurologic deficits because the nerves are unable to remyelinate. Standard antiviral drugs are ineffective for treatment.

The course is subacute and progressive, often leading to death in 3–6 months.

OSMOTIC DEMYELINATION SYNDROME

Osmotic demyelination syndrome (formerly central pontine myelinolysis) occurs in patients with severe hyponatremia that is corrected too quickly with hypertonic saline. The risk increases as the following factors increase: length of time the patient is hyponatremic before correction is started, severity of the hyponatremia, and the rate of hypertonic saline infusion.

These patients can present with quadriparesis, mutism, pseudobulbar palsy, chewing and swallowing dysfunction, and/or locked-in syndrome. Paralysis is initially flaccid, but spasticity develops within a few days. For a further discussion of hyponatremia, see the **Nephrology** section.

MOVEMENT DISORDERS

PREVIEW | REVIEW

- What are the 4 motor features of parkinsonism?
- Name some common drugs used to treat Parkinson disease.

- What is a potential side effect of anticholinergic drugs when used to treat Parkinson's?
- What are the side effects of direct dopamine agonists?
- Selegiline can cause serotonin syndrome when combined with which other drugs?
- What is the clinical presentation of serotonin syndrome?
- What is a potential complication of an L-dopa dose reduction in a patient with Parkinson psychosis?
- What is the classic eye finding of progressive supranuclear palsy?
- What is the clinical presentation of essential tremor?
- What improves essential tremor?
- What causes tardive dyskinesia (TD)?
- How is TD treated?
- What is the clinical presentation of neuroleptic malignant syndrome?
- Which comorbidities are associated with Tourette syndrome?
- Which antihypertensive drug is used to treat tics in Tourette syndrome?

PARKINSONISM

Know this topic well. Parkinsonism (a.k.a. secondary Parkinson's or Parkinson syndrome) is a neurological syndrome. Parkinsonism signs and symptoms have the characteristic set of 4 motor features (the **4 Rs**):

- 1) Resting tremor
- 2) Rigidity and flexed posture
- 3) Restricted movement (bradykinesia and hypokinesia)
- 4) Loss of postural Reflexes

Resting tremors at a rate of 4–5 Hz (cycles per second) occur in the distal extremities. Tremor is usually the 1st symptom noticed. Sometimes the tremor is present with use, with dramatic worsening at rest.

Patients with parkinsonism have diffusely **increased** muscle tone, which, combined with the tremor, causes the "**cogwheeling**" seen with passive range of motion of the limbs. The rigid, flexed posture can include the entire body; ultimately, the spine, elbows, hips, and knees may become flexed. The classic hand position is flexed metacarpophalangeal joints with straight interphalangeal joints.

Hypokinesia/bradykinesia is the primary feature. With hypokinesia, the patient has decreased amplitude of voluntary movements—especially with repetitive tasks. This may manifest as micrographia (progressive reduction in amplitude of writing). Bradykinesia is difficulty initiating movement, slowness of movement, and decrease or loss of spontaneous movement (e.g., masked facies, tendency to sit motionless, decreased blinking).

Loss of postural reflexes contributes to the festinating gait; the patient walks progressively faster to remain under the forward center of gravity caused by truncal flexion. This eventually leads to falls and then to the inability to stand or walk without assistance.

There are many causes of parkinsonism. These range from Parkinson disease to drugs, toxins, metabolic disease, infections, repeated head trauma, and cerebrovascular disease.

The most common cause of parkinsonism is **Parkinson Disease (PD)**.

Many drugs can cause secondary parkinsonism. The usual culprits are:

- Dopamine-depleting drugs (e.g., reserpine)
- Dopamine antagonists, such as phenothiazines or butyrophenones
- Antiemetics, such as metoclopramide

Drug-induced parkinsonism is typically much more symmetric than PD.

Common toxins: carbon monoxide, manganese, and organic solvents. Repeated head trauma can also cause parkinsonism (punch drunk syndrome). Parkinsonism also occurs in some forms of Huntington disease (rigid form, typically seen in younger patients), frontotemporal dementia, and spinocerebellar ataxia.

PARKINSON DISEASE (PD)

The pathologic findings in PD are loss of pigmented cells in the substantia nigra of the midbrain and in other pigmented nuclei (i.e., locus ceruleus, raphe, dorsal motor nucleus of the vagus). Many of the remaining cells contain eosinophilic cytoplasmic inclusions, surrounded by a faint halo, called **Lewy** bodies.

The **motor** features of PD are caused by a dropout of dopamine-producing cells in the substantia nigra. Normally, dopamine from these cells is released in the basal ganglia, where it has a complex effect on the motor system, facilitating voluntary movement. When there is a decrease in dopamine from deterioration of the substantia nigra, the motor symptoms of PD emerge.

Diagnosis

Know! PD is a **clinical** diagnosis, and diagnosis is easy to miss in the early stages.

The core features of PD are the tetrad of:

- 1) hypo- and bradykinesia,
- 2) resting tremor,
- 3) postural instability, and
- 4) rigidity.

These are manifested as an expressionless face, slowness, and a lack of voluntary movement, resting tremor, stooped posture, axial instability, rigidity, with festinating

gait (short, shuffling, hurried steps) and turning en bloc (multiple short steps to turn around). For unknown reasons, symptoms always start on one side of the body and spread to the other side after a few years.

Consider causes of secondary Parkinson's. Look for signs that might suggest other neurodegenerative disorders, such as multiple systems atrophy, Lewy body dementia (refer to **Parkinson Disease Dementia (PDD)** on page 12-13), or **Progressive Supranuclear Palsy (PSP)**.

80% of patients with PD eventually develop dementia.

Treatment

As with MS, treatment for PD is very specialized. Focus on diagnosis, major treatments, and side effects of treatment. Staying active and **exercising** are important goals that keep patients independent as long as possible.

Drugs that stimulate the dopamine system are the mainstay of therapy to treat symptoms:

- **Levodopa + carbidopa**, with or without the catechol-O-methyltransferase (COMT) inhibitor entacapone (Comtan) or tolcapone (Tasmar)
- Nonergot direct **dopamine** receptor **agonists**
 - Ropinirole (Requip)
 - Pramipexole (Mirapex)
 - Rotigotine (Neupro skin patch)
- Amantadine
- Anticholinergics
- Monoamine-oxidase (MAO)-B inhibitors
 - Selegiline
 - Rasagiline

Treatment of Mild PD

Anticholinergics, such as amantadine, benzotropine (Cogentin), and trihexyphenidyl, are used to treat **mild** symptoms, especially tremor.

Anticholinergics can cause **altered mental status**, including psychosis, especially in patients > 70 years of age and in individuals with cognitive impairment.

Treatment of Mild-to-Moderate PD

Dopamine receptor agonists (ropinirole, pramipexole and rotigotine) can be useful as monotherapy for **mild-to-moderate** PD, but 60% of patients require adjunctive levodopa (L-dopa) after 4 years.

Know that these direct dopamine receptor agonists can cause impulse control disorders, such as **hypersexuality**, **compulsive shopping**, and **pathological gambling**.

The **MAO-B inhibitor** **selegiline** delays the need for L-dopa in patients with mild PD by ~ 9 months. There is evidence that rasagiline may also slow decompensation in early Parkinson disease. To date, however, no treatment for PD has been proven to be neuroprotective.

Know that combining selegiline with tricyclics or SSRIs can potentially cause serotonin syndrome. This problem is caused by excessive serotonergic activation of both CNS and peripheral receptors. Signs and symptoms include cognitive impairment ranging from confusion to hallucinations to coma; autonomic effects, such as hyperthermia, tachycardia, shivering, and sweating; and somatic effects, such as hyperreflexia and clonus, twitching, and tremors. Symptoms can be mild to rapidly fatal, depending on the amount of overstimulation.

Treatment of Severe PD

More severe symptoms are commonly treated with L-dopa + carbidopa. L-dopa acts as a precursor for dopamine synthesis in the basal ganglia. The carbidopa blocks conversion of L-dopa to dopamine in the periphery, a desirable effect because peripheral dopamine does not cross the blood-brain barrier. Additionally, peripheral dopamine causes side effects, such as postural hypotension and nausea. Carbidopa does not help with the central side effects of L-dopa that emerge after several years. Note that L-dopa absorption can be reduced by dietary protein.

Although L-dopa is the most effective drug for PD, its use is withheld as long as possible, especially in younger patients, to delay the onset of complications that are common with chronic use—especially dyskinesias (drug-induced involuntary movements, choreiform, or dystonic) and motor fluctuations (periods of good symptom control alternating with periods of reemergent parkinsonism).

Deep brain stimulation is an option for patients who are L-dopa responsive but continue to have motor fluctuations or dyskinesias as a side effect from L-dopa.

Direct dopamine receptor agonists (ropinirole, pramipexole, and rotigotine) and COMT inhibitors (entacapone or tolcapone) are added to reduce the overall daily dose of L-dopa, to even out the serum levels of this drug, and to provide more continuous dopamine receptor stimulation.

The older dopamine agonists (bromocriptine, cabergoline, and pergolide) can have ergot-related adverse effects, including a risk of valvular heart disease, and are no longer used in the U.S. to treat PD. Cabergoline remains available for treatment of prolactinomas.

Complications of PD therapy include the following:

- End-of-dose “wearing off” effects (due to short half-life of L-dopa)
- Unpredictable “on-off” fluctuations that are characterized by unpredictable loss of L-dopa treatment effect and dyskinesias (50% of patients after 3–5 years)
- Psychiatric symptoms develop in 30% of patients treated with L-dopa or dopamine receptor agonists. These symptoms include agitation, confusion, hallucinations, and delusions. Older patients with cognitive impairment are especially at risk. Approximately 17% of patients treated with a dopamine agonist develop an impulse control disorder.

Know that patients who develop psychosis with L-dopa treatment sometimes require a reduction or a switch in their medications to control their behavior. With the dose reduction or switch in medications, these patients are especially susceptible to development of a neuroleptic malignant-like syndrome. This syndrome is sometimes termed Parkinsonism hyperpyrexia and presents with hyperthermia, delirium, muscular rigidity, high creatine phosphokinase (CPK) level, and autonomic instability. Drug holidays are no longer used in Parkinson patients for this same reason.

PROGRESSIVE SUPRANUCLEAR PALSY (PSP)

PSP is similar to Parkinson disease in that patients have bradykinesia, abnormal gait, increased muscle tone, and later develop dementia.

The disease has its onset typically in the 6th decade of life (range: 45–75 years of age), with some combination of difficulty in balance, abrupt falls, visual and ocular disturbances, slurred speech, dysphagia, and changes in personality. Ultimately, the characteristic syndrome of supranuclear ophthalmoplegia, pseudobulbar palsy, and axial dystonia develops. Patients usually do not have a tremor.

Within 2 years, these patients develop the classic symptom of a vertical ophthalmoplegia, commonly with initial impairment of downgaze, progressing to complete ophthalmoplegia in all directions. Subsequently, patients have trouble reading, eating, and walking down a flight of stairs. There is a gradual stiffening and extension of the neck. Within another 2–3 years, they may be unable to walk because of marked imbalance.

The treatment is palliative, aimed to improve the quality of life. These patients commonly die of aspiration pneumonia due to severe dysphagia.

TREMORS

When a tremor occurs determines its type:

- Static tremors occur at rest, or when the head and extremities are held in a fixed position (termed postural tremor).
- Kinetic tremors occur during voluntary movement.
- Action tremors persist unchanged throughout voluntary movement and generally disappear at rest.
- Intention tremors occur with target-directed movement and worsen as the movement unfolds.

Exaggerated Physiologic Tremor

Most people have a usually unnoticeable physiologic tremor that has a frequency of ~ 10 Hz. This normal tremor can be aggravated by anxiety, stress, fright, hyperthyroidism, drug withdrawal states, certain drugs (e.g., SSRIs, corticosteroids, tricyclics, theophylline, β -agonists, nicotine, caffeine), and metabolic abnormalities (e.g., hypoglycemia). This tremor can also be postural or seen with action.

Essential Tremor

Essential tremor is the most common type of nonphysiologic tremor. It is often familial. In familial cases, it seems to be transmitted as an autosomal dominant trait, with variation in age at onset and severity. It affects the hands as a **postural** and **action** tremor with a frequency of 4–8 Hz. It can also be a higher frequency and affect the head and chin as a “yes, yes” or “no, no” postural tremor. There can be an associated vocal tremor. Essential tremor is typically benign but sometimes results in functional disability. Note that a postural tremor of the head is very unlikely to be due to Parkinson’s and is more often essential tremor. Parkinson tremors that affect the face commonly involve the lips, tongue, or jaw only.

The frequency of essential tremor is usually decreased transiently by drinking alcohol, and you can often diagnose an essential tremor when patients tell you that their tremor improves after an alcoholic drink. **Propranolol** and **primidone** are effective in reducing the limb tremors.

Gabapentin and topiramate reduce limb tremors a little and are 2nd line drugs. In severe cases, try botulinum toxin and deep-brain stimulation surgery.

TARDIVE DYSKINESIA (TD)

TD is mostly a result of **long-term** antipsychotic drug use or **long-term** or **high-dose** metoclopramide use. The only way to be certain to avoid TD is to keep patients off chronic antipsychotics, but this cannot be accomplished in many patients with chronic psychosis.

Some atypical antipsychotics (2nd generation drugs), particularly clozapine and quetiapine fumarate (Seroquel XR), are **less likely** to cause TD. Clozapine can cause bone marrow toxicity.

TD consists of many involuntary movements, including dystonia, chorea, athetosis, and tremor. The face, tongue, lips, eyelid, and bulbar muscles are most often involved, but you may also see neck, shoulder, and spine muscles with arching of the back.

Clonazepam is a useful benzodiazepine for patients with mild TDs and anxiety. Extract of ginkgo biloba significantly reduces TD in patients with schizophrenia. More disabling cases can be treated with tetrabenazine, a dopamine depleter or botulinum toxin. Deep-brain stimulation surgery can be used in the most severe cases.

OTHER MOVEMENT DISORDERS

Neuroleptic Malignant Syndrome (NMS)

NMS is an unusual response to antipsychotics (both typical and atypical), resulting in hyperthermia, rigidity, diaphoresis, autonomic instability, and altered mental status with a risk of rhabdomyolysis-induced renal failure. Occasionally, other drugs, such as metoclopramide and promethazine, can also cause this syndrome. Labs often show leukocytosis, electrolyte disturbances, and elevated CPK levels.

This syndrome can occur days, weeks, or months after neuroleptic treatment is begun. It carries a **mortality** rate of 15–30% if not recognized and treated promptly. Know: Patients with **Parkinson’s** who **acutely** discontinue their L-dopa therapy (or reduce dose) can develop NMS.

Treat NMS by discontinuing any offending drug; by using a direct **dopamine** agonist, such as bromocriptine or dantrolene; and by giving supportive therapy, including adequate hydration and scrupulous pulmonary hygiene. If rigidity is sufficient to affect ventilation, sedate, intubate, and paralyze the patient. Pursue electroconvulsive therapy in medically refractory patients. Patients can have recurrence of NMS if the drugs are restarted.

Hemifacial Spasm

Hemifacial spasm is a motor analog to trigeminal neuralgia. 80% of patients have a tortuous, dilated basilar artery (basilar dolichoectasia) that loops around and irritates the facial nerve! Other causes include aneurysm, acoustic neuroma, and, occasionally, **MS**.

Botulinum toxin injections are generally the best treatment. Some patients have benefitted from surgery to separate the facial nerve from direct contact with the basilar artery (microsurgical decompression). Occasionally, carbamazepine, baclofen, and gabapentin can be effective.

Tourette Syndrome

Tourette syndrome is a developmental neuropsychiatric disorder characterized by chronic (> 1-year duration) multiple motor tics and ≥ 1 vocal tics. Motor tics can be **simple** (including eye blinking or rolling, facial grimacing and head or limb jerking) or **complex** (including semi-purposeful movements, such as tapping, jumping, and copying the gestures of others [echopraxia]). Vocal tics can also be **simple** (such as sniffing, snorting, grunting, and coughing) or **complex** (including utterance of words or phrases, obscenities [coprolalia], or imitating the speech of others [echolalia]). Onset is commonly between 2 and 15 years of age. Many patients have comorbid attention deficit hyperactivity disorder (ADHD), obsessive-compulsive disorder (OCD), learning disorders, or conduct disorders.

Diagnosis is clinical and requires confirmation of both motor and vocal tics.

Milder tics and/or associated ADHD may respond to clonidine or guanfacine. More severe ADHD can be treated with stimulants, such as methylphenidate; data shows that these drugs may not exacerbate tics as previously thought, although close monitoring is necessary. Tics can also be treated with Comprehensive Behavioral Intervention for Tics (CBIT), which is a behavioral health intervention that promotes relaxation and incorporates habit reversal therapy to improve tics. Neuroleptics (dopamine antagonists) like pimozide and fluphenazine have been traditionally used to treat tics that are severe enough

to interfere with daily functioning. However cost prohibitive, tetrabenazine is gaining traction as an effective agent and has fewer side effects compared to neuroleptics. Treat focal motor tics with botulinum toxin.

Focal Dystonias

Focal or segmental dystonias are intermittent, brief, or prolonged spasms or contractions of a group of adjacent muscles that place the body part in a forced and unnatural position.

Know the following 4 focal dystonias:

- 1) Blepharospasm is bilateral, forceful, involuntary eye closure and can occur as an isolated syndrome or as part of Meige syndrome.
- 2) Meige syndrome is a combination of blepharospasm and oromandibular dystonia (involuntary jaw opening and jaw movements).
- 3) Spasmodic torticollis occurs when spasms of the neck and shoulder muscles turn the head to one side.
- 4) Writer dystonia (a.k.a. writer cramp) occurs when spasms of the hand and arm emerge with writing, limiting the ability to write legibly.

A few oral drugs may offer mild relief: benzodiazepines, baclofen, anticholinergics, and sometimes antidopaminergics. However, **botulinum toxin** is the **treatment of choice**, providing much more reliable but temporary relief when injected directly into the affected muscles. Treatment requires repeat injections every 2–5 months.

CNS: BRAIN — VENTRICLES / CEREBROSPINAL FLUID (CSF)

INFECTIONS

PREVIEW | REVIEW

- What is the classic triad of symptoms observed in patients with a brain abscess?
- What is the diagnostic test for West Nile virus encephalitis?
- What is the treatment for central nervous system toxoplasmosis?
- What is the clinical presentation of neurocysticercosis?
- Characterize the cerebrospinal fluid (CSF) of a patient with cryptococcal meningitis.
- How useful is the CSF/serum cryptococcal antigen (sensitivity/specificity) in diagnosing meningitis?

BACTERIAL CNS INFECTIONS

Acute Meningitis

Headache, stiff neck, photophobia (due to meningeal inflammation), and lethargy are typically present with acute meningitis, but thought processes usually remain intact.

Diagnose acute meningitis with analysis of the CSF. If there are focal neurologic signs, mental status change, or papilledema, do a CT before the lumbar puncture (LP). CSF latex agglutination tests are no longer recommended in the **initial** evaluation of meningitis. With suspected meningitis, start antibiotics immediately **after** the LP and blood cultures; do not wait for any LP results. Also, if the LP is going to be delayed more than 30–60 minutes, go ahead and give antibiotics immediately (before the LP)! See the **Infectious Disease** section for a full discussion on bacterial meningitis.

Neurosyphilis also is discussed in the **Infectious Disease** section.

Brain Abscess

The classic triad of brain abscess symptoms is **headache, fever, and focal neurological deficit(s)**.

Most abscesses arise from intracranial extension of cranial infections (i.e., sinuses, teeth) or after skull fracture or neurosurgical procedures. Much less often, they are due to bacteremic seeding. In adults, the most common organisms are *Staphylococcus* and *Streptococcus* species (e.g., *S. epidermidis* after a penetrating head injury), but do not forget about *Nocardia*. In the immunocompromised, consider toxoplasmosis.

VIRAL CNS INFECTIONS

CSF in Viral Encephalitis

With viral encephalitis, CSF has increased **lymphocytes**, normal to slightly increased **protein**, and normal glucose. **EEG** is almost always abnormal with diffuse slowing or **focal temporal** changes. MRI is more sensitive than CT and may show hemorrhagic changes.

Herpes Simplex Encephalitis

Altered mental status (due to parenchymal inflammation) is the hallmark of an encephalitis. Herpes simplex encephalitis is the most common type of **nonepidemic** viral encephalitis and presents with fevers, headaches, and focal seizures. In adults, it is usually due to a reactivation of the HSV-1 virus, although 25% are due to primary HSV-1 infection. HSV-2 is sexually transmitted and can cause aseptic meningitis during primary infection. HSV-2 less typically causes encephalitis but can cause polyradiculitis and myelitis. HSV encephalitis has a predilection for the temporal lobe; immunomodulators increase risk (i.e., natalizumab, TNF- α inhibitors).

Varicella-zoster virus (VZV) can also cause encephalitis, especially in the immunocompromised; and it can cause vesicular lesions that can be confused for herpes simplex.

See the [Infectious Disease](#) section for treatment of HSV and VZV.

Mosquito-Borne Arboviruses

Mosquito-Borne ARboviruses are ARthropod-BORne viruses. Mosquitoes are the main vector, but ticks, fleas, and gnats may also be carriers. Neuroinvasive disease caused by arboviruses presents as encephalitis, meningitis, or flaccid paralysis. We'll go over mosquito-borne arboviruses here.

In the U.S., the West Nile virus is by far the main cause of neuroinvasive disease. Per the CDC, there were 2,813 reported cases of arboviral infection in 2018; the breakdown of reported arboviruses was:

- West Nile virus (94%)
- La Crosse virus (3.1%)
- Jamestown Canyon virus (1.5%)
- Powassan virus (0.7%)
- St. Louis encephalitis virus (0.3%)
- Eastern equine encephalitis virus (0.2%)

West Nile virus (WNV; genus *Flavivirus*) causes fever with no neurologic symptoms in otherwise healthy patients. Encephalitis is more likely to occur in the immunocompromised and in older patients with comorbidities, such as hepatitis C, diabetes mellitus, and chronic alcohol use. West Nile encephalitis can additionally present with a flaccid paralysis. It is considered a modern-day mimicker of polio.

Flaviviruses that cause neuroinvasive disease in non-U.S. areas include the West Nile, yellow fever, Zika, and dengue viruses. Read more about these viruses in the [Infectious Disease](#) section.

Diagnosis of Viral Encephalitis

Polymerase chain reaction (PCR) DNA amplification of the herpes viruses allows for an easy, rapid, and accurate diagnosis of herpes simplex and zoster. Initiate IV acyclovir in all encephalitis patients until herpes simplex is ruled out. This is the most important management principle in encephalitis patients.

Draw acute and convalescent serum titers to diagnose most arboviruses. West Nile diagnosis requires finding antibody in spinal fluid. Enterovirus may cause encephalitis, draw PCR if indicated.

Viral Myelitis

Myelitis (focal or segmental) is infection of the spinal cord—a classic focal viral cause is poliomyelitis affecting the anterior horn cells of the spinal column. Additional focal causes are other enteroviruses (coxsackievirus and enterovirus) and flaviviruses (e.g., West Nile).

Reflexes are usually decreased and weakness is typically asymmetric with preserved sensation. Segmental viral forms of myelitis can cause a transverse myelitis (e.g., herpes simplex, varicella zoster, cytomegalovirus, Epstein-Barr). Motor weakness and sensory changes occur below the lesion. Autonomic dysfunction can also occur.

Slow Viruses and Prions

Slow viruses:

- Subacute sclerosing panencephalitis (SSPE) is caused by the measles virus. Most cases occur around 10 years of age, many years after the initial infection.
- PML (Refer to [Progressive Multifocal Leukoencephalopathy \(PML\)](#) on page 12-16 under the discussion of demyelinating diseases.)
- Prion: CJD (Refer to [Creutzfeldt-Jakob Disease \(CJD\)](#) on page 12-13.)

Human Immunodeficiency Virus (HIV)

Infection with HIV can result in dysfunction of any part of the nervous system. Patients get subacute encephalitis, vacuolar myelopathy, aseptic meningitis, and peripheral neuropathies (including mononeuritis multiplex).

HIV-associated cognitive impairment is common. It ranges from asymptomatic to mild to what is called HIV-associated dementia (HAD). In adults, it takes the form of a slowly or subacutely progressive dementia with loss of retentive memory, inattentiveness, language disorder, and apathy.

Know that the differential diagnoses for HAD includes PML, toxoplasmosis, and lymphomas.

Since the use of ART began, the incidence (new cases per year) of HAD in the U.S. has dropped by half. Patients are getting a different type of dementia post-ART; this dementia is associated more with deficits in complex reasoning and less with global impairment. In addition, even though the incidence is dropping, HAD is occurring in patients with higher CD4 counts, even in patients who have had long-term viral suppression on antiretroviral agents.

Zidovudine myopathy can be seen and has mitochondrial features on muscle biopsy.

Peripheral HIV neuropathy has 3 forms:

- 1) Guillain-Barré syndrome (GBS) or chronic inflammatory demyelinating polyneuropathy (CIDP) phenotype may be seen. GBS is seen at seroconversion, and CIDP is seen in more moderate-to-severe HIV. Usually with GBS or CIDP there is cytoalbuminologic dissociation of the CSF (high protein and normal white blood cells), but if the clinical case is consistent with GBS or CIDP and there is an unexpectedly high number of white blood cells in the spinal tap, then consider HIV.

- 2) Distal symmetric polyneuropathy is common in AIDS patients (1/3 get it). Symptoms are paresthesias of the feet and distal weakness in the legs. Treatment typically includes tricyclic antidepressants or gabapentin.
- 3) A painful mononeuritis multiplex thought to be due to focal vasculitis also occurs.

Progressive Multifocal Leukoencephalopathy (PML)

Progressive multifocal leukoencephalopathy (PML) affects white matter only. PML is caused by the human JC polyomavirus, resulting in a progressive demyelination of the CNS white matter. (Refer to [Progressive Multifocal Leukoencephalopathy \(PML\)](#) on page 12-16 under the discussion of demyelinating diseases.)

Acquired Immunodeficiency Syndrome (AIDS) Myelopathy

Advanced HIV infection can cause a vacuolar myelopathy (see [Infectious Myelopathies](#) on page 12-40) and causes progressive weakness, incontinence, hyperreflexia, and ataxia. There is vacuolation and deterioration of the dorsal and lateral spinal columns. It is found in about 50% of AIDS patients at autopsy. This myelopathy must be differentiated from B₁₂ deficiency, copper deficiency, human T-cell lymphotropic virus (HTLV), and from spinal cord compression due to some other cause, such as lymphoma.

PARASITIC CNS INFECTIONS

Toxoplasmosis

Toxoplasma gondii is an intracellular protozoan parasite that infects 30–50% of the world's population. Seropositivity ranges from 11% in the U.S. to > 80% in many warm, humid, low-altitude regions of the world. In immunocompetent hosts, initial infection is either asymptomatic or has flu-like symptoms (especially fever, headache, muscle aches, and tender lymphadenopathy), which can last from weeks to months then fully resolve. The parasite remains in the body but becomes dormant. If the infected host then becomes immunocompromised, the parasite can reactivate and cause a much more severe form of toxoplasmosis disease with brain lesions.

If a mother gets an active infection while pregnant, the child may get congenital toxoplasmosis, which can cause cognitive problems, blindness, and seizures—even later in life.

AIDS-related brain lesions: If you see **multiple ring-enhancing lesions**, the most likely cause is **toxoplasmosis**. CNS lymphoma, TB, and bacterial infections are less likely causes.

Because toxoplasmosis is a reactivation infection, patients typically have *T. gondii* IgG antibody, but not IgM antibody. But remember that many people are infected and only a few become immunocompromised, so finding a positive IgG *T. gondii* antibody is supportive of the diagnosis of

toxoplasmosis but not diagnostic. Also know that an absent toxoplasmosis IgG does not exclude toxoplasmosis as the cause of a brain lesion in a patient with AIDS.

Treat with sulfadiazine, pyrimethamine, and leucovorin. Add dexamethasone if there is midline shift or rapid deterioration.

Do a brain biopsy if there is no improvement after empiric treatment, if there is a mass effect, or if there is only 1 lesion. Relapses occur often.

Neurocysticercosis

Neurocysticercosis is the **most common worldwide parasitic** CNS infection. It is caused by ingesting food or water contaminated with *Taenia solium* (a tapeworm). It forms cysts in the brain, which initially cause no symptoms. But when the cyst walls break down several years later, it causes cerebral edema, usually with **seizures** as the 1st symptom. In some patients, a large subarachnoid or intraventricular cyst can obstruct the flow of CSF. In a more malignant form of the disease, the cysticerci are located in the basilar subarachnoid space, where they induce an intense inflammatory reaction leading to hydrocephalus, vasculitis, and stroke as well as cranial nerve palsies.

MRI is the preferred imaging modality—when worms are still viable, MRI shows multiple, nonenhancing, hypodense lesions. As the worms die, they are surrounded by edema and flair on the MRI imaging. When dead, they calcify and shrink. Support the diagnosis with *T. solium* antibody testing on serum.

Treatment of CNS infection is controversial because of the lack of randomized studies and the propensity of dying worms to cause symptoms. Most experts treat with high-dose praziquantel or albendazole +/- corticosteroids. Give ASMs to patients at high risk for seizures. Read more about neurocysticercosis in the [Infectious Disease](#) section.

FUNGAL CNS INFECTION

Consider cryptococcal meningitis when working up a progressive headache, cognitive impairment, and/or meningeal signs in patients with AIDS or on chronic corticosteroids.

CSF pressure is usually **very elevated**. Standard CSF studies can be entirely normal, so always check the **cryptococcal antigen titer** in the blood and CSF (in HIV patients, sensitivity/specificity is > 95%). In HIV-negative patients, the CSF antigen is still 93–98% sensitive.

Treat with amphotericin B deoxycholate or liposomal amphotericin B and flucytosine × 2 weeks, then change to oral fluconazole × 8 more weeks (minimum). Lower doses of oral fluconazole are used for secondary prophylaxis in immunocompromised patients. Manage elevated ICPs with daily taps to keep CSF pressure < 200 mm H₂O, or patients can lose their vision. Shunts are appropriate if daily taps are needed. Do not use mannitol, acetazolamide, or corticosteroids.

Find more about fungal CNS infections in the [Infectious Disease](#) section.

HEADACHE AND FACIAL PAIN

PREVIEW | REVIEW

- Name some triggers of migraine headaches.
- What is the main difference between migraine with aura and complicated migraine?
- Which migraine patients should not receive a triptan drug?
- Which migraine prophylactic drug causes kidney stones?
- Are cluster headaches more common in men or women?
- What are the clinical features of a cluster headache?
- How do you treat a cluster headache?
- Which agent is 1st line to prevent cluster headaches?
- What is the most common variety of headache?
- What are the high-risk factors indicating the need for a CT scan after head trauma?
- Name a risk factor that is associated with idiopathic intracranial hypertension (IIH).
- What is the clinical presentation of IIH?

OVERVIEW

The history and examination of the patient are crucial in diagnosing the type and etiology of headache, including the **quality** of pain (dull, sharp, throbbing, and constant), **location**, **duration**, **exacerbating** or **ameliorating** factors, and associated symptoms. Also important are the mode of onset of pain and variation over time. Headaches can be classified as primary or secondary, and the 1st step is to determine the classification:

- Primary headaches
 - Migraine
 - Cluster headache and other trigeminal autonomic cephalgias
 - Tension-type headache
 - Other primary headaches
 - Tend to be chronic, recurrent, and without signs of neurologic disease
- Secondary headaches
 - Headache due to hemorrhage (i.e., subarachnoid hemorrhage)
 - Headache due to head and/or neck trauma, benign intracranial hypertension, brain tumors
 - Headache due to cranial or cervical vascular disorders (e.g., carotid dissection, sinus venous thrombosis, giant cell arteritis)
 - Headache due to a substance or its withdrawal (e.g., nitrates, EtOH, caffeine)

- Headache due to infection (e.g., meningitis, encephalitis)
- Headache due to disorders of homeostasis (e.g., HTN, hyperviscosity)
- Headache of facial pain (e.g., cranium, neck, eyes, sinuses, teeth; trigeminal neuralgia; herpes zoster)
- Headache due to psychiatric disorders

MIGRAINE

Presentation

Know: Migraines are a typically unilateral, periodic pulsatile (throbbing) headaches that run in families; begin in early adult life or childhood; and tend to occur less frequently as patients get older. Migraines are more common in females. 90% of patients who present to emergency departments with recurrent headaches have migraines. These headaches are typically unilateral (~ 60%) but not consistently on the same side (unlike vascular headache secondary to arteriovenous malformation [AVM]). They last several hours, usually 4–72 hours. They are considered episodic if < 15 episodes per month and chronic if > 15 episodes per month for 3 months. Yearly, < 5% of episodic sufferers progress to chronic sufferers.

Triggers include emotional stress, certain foods (e.g., chocolate, **aged cheese**, other foods that are rich in tyramine), alcohol (particularly red wine or port), menstruation, exposure to glare or other strong sensory stimuli (including perfumes), and rapid changes in barometric pressure. In women, they often occur in the premenstrual period and can be worsened by oral contraceptives. Migraines are frequently associated with nausea, vomiting, sensitivity to smell, photophobia, and phonophobia. Movement of the head exacerbates the pain, while sleep and darkness may help lessen the pain.

Migraine with aura (previously called classic migraine) makes up 25% of all migraine headaches. It is preceded by an **aura**—most commonly visual symptoms, such as sparkling lights (scintillating scotomata) or jagged zigzag lines (fortification spectra), that move slowly across the visual fields for several minutes—and may leave scotomatous defects. Migraine auras last for 5–60 minutes with longer auras representing prolonged auras (complicated migraine) or concern for stroke.

Migraine without aura (previously called common migraine) occurs without an aura and is ~ 5× more typical than migraine with aura.

Other migraine auras (less common) include focal sensory disturbance or weakness (usually unilateral) or dysphasic speech. If sensory symptoms spread from one part of the body to another or evolve over time, they do so relatively slowly, over several minutes (not seconds, as in seizures), and not acutely as with concern for a transient ischemic attack (TIA). Importantly, the neurologic symptoms are fully reversible and followed by typical migraine headache. Rarely, migraine aura can occur without a headache (also called “acephalgic migraine” or

typical aura without headache. The first presentation of focal aura symptoms (sensory, motor, or language) should prompt neuroimaging.

Basilar migraine affects the **brainstem**. Patients are typically young women or children with a family history of migraine.

Patients with basilar migraines may experience:

- Visual phenomena that occupy **both** visual fields (temporary cortical blindness may occur)
- Vertigo
- Dysarthria
- Staggering
- **Incoordination** of the limbs
- Diplopia (“seeing double”)
- Tingling (may occur in both hands and feet and sometimes around both sides of the mouth)

These symptoms last 10–30 minutes and are usually followed by an occipital headache. In exceptional cases, coma or transient quadriplegia can develop.

Acephalic migraine (migraine without headache) can present with abnormal transient neurologic dysfunction, such as visual symptoms, focal sensory deficits, transient aphasia, or hemiparesis. These spells are stereotyped and evolve over minutes, again unlike acute symptoms from a vascular etiology.

Cutaneous allodynia is a stinging sensation that can occur during migraines. This can affect the skin, scalp, or eye (in patients that wear contacts).

Status migrainosus is characterized by multiple or virtually continuous headaches with persistent scalp tenderness, over a period of 72 hours or longer.

Diagnosis of Migraine

Diagnosis is most often done with **history** alone. For patients who present with typical migraine symptoms, **first** give a **trial of treatment** (as follows) before neuroimaging or any other studies.

Atypical symptoms, including change in headache pattern, seizure, or focal neurologic symptoms, warrant further workup, including imaging studies; the initial study is usually a head CT with and without contrast.

Acute Treatment of Migraine

Acute treatment refers to any treatment that is given **within the 1st hour** of the headache. Acetaminophen, aspirin, and NSAIDs are effective in some patients, especially if the migraine is mild and infrequent.

Triptans are the **1st line** drugs for migraine therapy. Triptans are more effective and are very safe to use even in patients with infrequent migraines. Under-dosing and less-effective drugs are associated with failure to control migraines.

The triptans:

- Sumatriptan
- Zolmitriptan (Zomig)
- Rizatriptan (Maxalt)
- Naratriptan (Amerge)
- Almotriptan (Axert)
- Eletriptan (Relpax)
- Frovatriptan (Frova)

Know the following about the triptans:

- Rizatriptan, almotriptan, and eletriptan have the highest consistent success rates.
- Rizatriptan interacts with propranolol and requires that you adjust the rizatriptan dose downward (propranolol increases the levels).
- Sumatriptan has 3 methods of delivery: injection, intranasal, and oral.
- Combination tablet of sumatriptan + naproxen works synergistically and is better than taking either agent as monotherapy.
- Naratriptan and frovatriptan have the slowest onset but the fewest side effects.

Because of the risk of inducing ischemia, do not use triptans for any of the following conditions:

- Migraine with prolonged aura (> 1 hour), hemiplegic migraine, or basilar migraine
- Cardiovascular disease (CVD) or Prinzmetal angina
- History of stroke
- Uncontrolled blood pressure (patients with BP > 160/95 mmHg were excluded from the clinical trials)

Eletriptan, frovatriptan, and naratriptan can be used with monoamine oxidase inhibitors; the others are contraindicated. All triptans should not be used within 24 hours of ergot drugs.

Instead of the triptans, IV **prochlorperazine** or **metoclopramide** in addition to intravenous fluids are effective for termination of migraine in patients who present to the emergency department with vomiting. Diphenhydramine 25 mg IV helps prevent the unusual dystonic reaction of the antiemetic.

Dihydroergotamine (DHE) can be effective in some patients, but it also must be avoided in patients with CVD, HTN, pregnancy (for more on migraine during pregnancy, see the **Women's and Men's Health** section), history of peripheral arterial disease, and liver or kidney disease. You can try narcotics; however, restrict their use to 2 days/week. You can use oral or IV corticosteroids to terminate status migrainosus, as well as IV valproic acid or IV ketorolac.

Increased use of any medication, including triptans and NSAIDs, to treat frequent headaches can incite a **rebound**, called a medication overuse headache. Instruct patients not to take analgesics more than 10 days/month. If a patient needs medication this often, then prescribe prophylactic treatment.

Prophylactic Treatment of Migraine

The American Heart Association/American Stroke Association 2014 Guidelines for the Prevention of Stroke in Women recommend **prophylaxis** for women with frequent migraines with aura if **< 55 years of age**, especially if they are taking oral **contraceptives (OCPs)**. These guidelines also recommend aggressive smoking cessation efforts in women with migraine with aura.

Generally, avoid the use of OCPs in women who have migraine with aura (increased risk of stroke). For other patients, the **frequency** of headache determines whether prophylaxis is needed; normally, the threshold is **> 2–3 headaches per month**. There is usually a lag of 2–4 weeks between the start of prophylaxis and its effect.

The following are major categories of migraine prophylaxis agents:

- **β-blockers**: Propranolol and timolol are FDA-approved for migraine, but atenolol, metoprolol, and nadolol are also used; **not recommended** in patients **> 60 years of age** and/or **smokers**.
- **Tricyclic antidepressants**: amitriptyline; side effects include oversedation, dry mouth, palpitations, orthostasis, blurry vision, weight gain, constipation, and short-term memory impairment or confusion—especially in the elderly or in those with baseline cognitive impairment.
- **Antiseizure medications**: valproic acid, topiramate. Topiramate can cause kidney stones, paresthesias, and word-finding difficulties. It also can cause weight loss, which is a positive side effect in many cases. Avoid use of these antiseizure medications during pregnancy.
- **Calcium channel blockers**: verapamil, nimodipine; may develop tolerance
- **Angiotensin-converting enzyme inhibitors** and **angiotensin receptor blockers**: lisinopril and candesartan
- **NSAIDs**
- **Botulinum toxin injection**: approved by the FDA in 2010 for refractory chronic migraine (i.e., migraine occurring **≥ 15 days/month** with headaches lasting **≥ 4 hours/day**). 31 injections are delivered into 7 specific head and neck sites. The treatment usually needs to be repeated every 12 weeks, on average.

Definitely use prophylactic agents to treat migraine with prolonged aura and basilar migraines. Relaxation techniques also may be helpful for patients to prevent headaches.

CLUSTER HEADACHE

Cluster headache is a distinct syndrome that frequently responds to treatment with oxygen. The term “cluster” is derived from the periodicity of the headaches: They can occur up to several times/day for a few weeks before remitting. Cluster headache becomes chronic in 10% of patients.

Cluster headaches are **more common in men** (5:1). They tend to occur in the 20- to 50-year-old age group. **70%** of patients find that **alcohol** triggers their headache.

The daily attacks may occur at the same hour each day (in 50% of patients). The pain is unilateral, severe (described as an “ice pick” or “hot poker”), and **peri- or retroorbital**. It peaks quickly, in 5–10 minutes, and resolves in 1–2 hours.

Another characteristic feature is nightly recurrence, about 1–2 hours after the onset of sleep or several times during the night. The cluster headache period may last 6–12 weeks, followed thereafter by complete freedom for many months or even years.

Associated vasomotor phenomena include ipsilateral blocked nostril, rhinorrhea, lacrimation, miosis, and flush and edema of the cheek that last about 45 minutes.

Patients with cluster headaches tend to be restless during attacks, as opposed to most migraine sufferers who prefer a dark, quiet room and stillness.

Treatment: The best acute treatment for cluster headaches is **oxygen**. Inhalation of oxygen at 6 L/minute × 15 minutes is usually **rapidly abortive**, acting to inhibit neuronal activation in the trigeminocervical complex. However, this is not always practical or available. Subcutaneous and intranasal triptans are effective and can be combined with oxygen; but remember, do not use triptans in patients with a history of or strong risk factors for CVD and stroke. For patients who do not get better with O₂ and cannot take triptans, octreotide and intranasal lidocaine are options.

Once a patient experiences the 1st of what will become a cluster episode, **prophylactic** treatment can be instituted. Verapamil is the drug of choice (outpatient oral titration up to 480 mg), but monitor the patient's pulse and ECG for bradycardia and heart block when titrating higher than 240 mg. Other drugs sometimes used include lithium, methysergide, prednisone, and topiramate. Use corticosteroids as acute drugs while waiting for verapamil to work. Taper off the medication once the cluster is over.

TENSION HEADACHE

Tension headache, the most common variety of headache, is characterized by pain that is chronic, bilateral, constant, nonthrobbing, **squeezing**, and devoid of migrainous or cluster features. It can be intermittent or chronic. Unlike most other headaches, it can be present throughout the day for long periods of time. The onset is slow with gradual increment in intensity, typically at the end of the day. Sleep is normally undisturbed, but headache returns upon awakening. It is more common in women. 1/3 of patients with chronic tension headaches have symptoms of depression.

Use aspirin, acetaminophen, or NSAIDs to treat acute attacks.

Consider **preventive** medication when attacks occur **> 2 days/week**—this can help prevent medication overuse, which can predispose to chronic headache. Limiting

treatment to 9 days/month (2 doses of meds/day) helps prevent this complication. Effective prophylactic drugs include amitriptyline and other tricyclics (refer to [Prophylactic Treatment of Migraine](#)) and gabapentin. Relaxation, biofeedback, and behavioral therapy are helpful in dealing with the tension that brings about the headaches.

BENIGN SEXUAL HEADACHE

Benign sexual headache (a.k.a. coital headache) occurs more often in men than women (4:1). The headache occurs either as a tension-type headache as sexual excitement increases or as a severe, throbbing headache at the time of orgasm. These headaches can persist for several minutes or hours; they are benign. If the headache does not resolve after 2 hours or is accompanied by neck stiffness, vomiting, and/or neuro deficits, rule out an underlying vascular AVM, such as an aneurysm with subarachnoid hemorrhage. Evaluate with urgent neuroimaging. Treatment with NSAIDs before sexual activity may prevent the headache.

CONCUSSION

A concussion is transient neurologic symptoms in the setting of a head trauma. It is classified as a mild traumatic brain injury (TBI), usually without structural findings on imaging. With nearly 2–4 million sport-related concussions per year, there is growing awareness and interest in this clinical condition.

Common concussion symptoms include transient confusion, amnesia, headache, dizziness/vertigo, nausea/vomiting, behavioral changes, photophobia, imbalance, and loss of consciousness.

Though transient loss of consciousness may be seen, it is not mandatory for the diagnosis. Focal neurologic findings or a seizure require a CT head to evaluate for intracranial pathology of concern, as well as other risk factors identified by the Canadian CT Head Rule study. This study identified risk factors that would merit a head CT for evaluation:

- High-risk factors
 - Failure to reach Glasgow Coma Scale of 15 within 2 hours
 - Suspected open skull fracture
 - Any sign of basal skull fracture
 - Vomiting > 2 episodes
 - > 65 years of age
- Medium-risk factors
 - Retrograde amnesia before impact > 30 minutes
 - Dangerous mechanism of injury

Most concussive symptoms resolve over hours to 7–10 days. The 2017 Berlin Concussion in Sport Group

(CISG) Consensus Statement—5th International Conference discusses the **11 Rs** of concussion:

- 1) Recognize
- 2) Remove
- 3) Reevaluate
- 4) Rest
- 5) Rehabilitation
- 6) Refer
- 7) Recovery
- 8) Return to sport
- 9) Reconsider
- 10) Residual effects and sequelae
- 11) Risk reduction

Utilize the SCAT5 tool (Sports Concussion Assessment Tool, 5th edition) for sideline field assessment after concussion. The SCAT5 is designed to be a sideline rapid assessment tool. It includes symptom evaluation and cognitive screening with orientation, memory, concentration, balance, and delayed recall testing. The score determines if a concussion was suffered. The CISG also recommends the CCMI baseline testing battery to compare cognitive differences if present.

Recovery follows a 6-day graded return to play protocol that begins with complete physical and cognitive rest followed by graded increase in activity. Rehabilitation Level 1 is no activity, and Level 6 is return to normal play. Each stage lasts a minimum of 24 hours, and only when the patient achieves full recovery at a level can you move them to the next level of activity. The minimum recovery time for return to play is 6 days.

A minority of patients have persistent concussive symptoms, termed postconcussive syndrome, that may last for months or longer. This may require symptomatic treatment for persistent migraines, anxiety/depression, and cognitive dysfunction.

Finally, some patients who have had repeated mild TBIs may develop chronic traumatic encephalopathy, which is a chronic dementia-like syndrome associated with tau deposition in the brain. There is increasing awareness of this syndrome, as well. Chronic behavioral/cognitive decline is a hallmark, but other neurologic sequelae may be seen, such as Parkinsonism, tremor, and gait disturbance.

POSTTRAUMATIC HEADACHE

Posttraumatic or postconcussion headache can occur even after a minor head injury. It can present similarly to migraine clinically; however, some have proposed that the headache is due to abnormal neurotransmission within the brain. Accompanying symptoms include dizziness, fatigue, insomnia, nervousness, irritability, and inability to concentrate. Symptomatic treatment is usually effective, and the headache often spontaneously remits. Patient reassurance is important.

GIANT CELL ARTERITIS (GCA)

GCA (a.k.a. temporal arteritis) typically occurs in patients > 55 years of age. History commonly includes a recent onset of headache. Jaw claudication, fatigue, weight loss, and low-grade fever can also occur. Up to 50% of patients have a history of polymyalgia rheumatica. Do not miss the diagnosis of GCA; if untreated, ischemic optic neuropathy can cause irreversible vision loss. Diplopia occurs in 10–15% of patients. On physical exam, look for a palpable temporal artery with associated tenderness.

The erythrocyte sedimentation rate (ESR) and the C-reactive protein (CRP) tests (for inflammation) are elevated. (So, if ESR and CRP are normal, it is not GCA.) Do a **temporal artery biopsy** if you suspect the diagnosis. Yield of bilateral artery biopsy (~ 2 inches of tissue) in expert centers is about 85%. Read more on this topic in the [Rheumatology](#) section.

TRIGEMINAL NEURALGIA (TN)

TN is neuralgia occurring in ≥ 1 branches of the 5th cranial nerve (usually V2 or V3). The 3 branches of the trigeminal nerve cover the anterior upper (ophthalmic), middle (maxillary), and lower (mandibular) areas of the face. Even though TN occurs rarely, it is one of the most common causes of facial pain. TN most often affects people > 50 years of age and women somewhat more than men (~ 1.5:1).

The pain of TN is characteristically abrupt in onset, with the most intense pain at onset. It can be extremely severe and has a shock-like or burning quality—typically in the maxillary distribution. Sporadic episodes are usually triggered by innocuous activities, such as chewing, eating, or brushing teeth.

Start treatment with antiseizure medications, such as carbamazepine, phenytoin, gabapentin, or pregabalin.

IDIOPATHIC INTRACRANIAL HYPERTENSION (IIH)

IIH, formerly known as pseudotumor cerebri, is a set of signs and symptoms—headaches, papilledema, and loss of vision—caused by **increased intracranial pressure** (ICP). IIH ordinarily occurs in obese, premenopausal women (90%) and can occur during pregnancy. It rarely occurs in children or in men.

Obesity is strongly correlated with IIH (90–95% of patients) and causal. With the increasing obesity of the U.S. population, the incidence of IIH is also increasing.

Drugs that can cause IIH include vitamin A (especially in the form of isotretinoin, used for the treatment of severe acne), tetracycline, and corticosteroids; but the condition can also be precipitated by steroid withdrawal.

Severe, irreversible vision loss is the major morbidity. It occurs in > 6% of patients and is 2× more common in men than in women. Perform magnetic resonance venography in at-risk patients to exclude venous thrombosis.

The cardinal symptom of IIH is a **morning** headache described as dull or as a feeling of pressure (90%) made worse by **coughing** or straining. There is almost always (90–100%) a **peripheral visual field loss** accompanied by blind spots that may be noticeable only with formal visual field testing. **Pulse-synchronous** tinnitus (60%) may be present. Transient visual obscurations (seconds of transient visual blackouts) can be another hallmark sign. Diplopia is less commonly seen.

On exam, papilledema is a hallmark finding. 6th nerve palsy may be obvious either unilaterally or bilaterally. CT/MRI is typically **normal**, with absence of deformity, displacement, or obstruction of the ventricular system—but may show slit-like ventricles. The CSF pressure is elevated, usually in the range of 250–450 mm H₂O. (Normal CSF pressure is generally 50–180 mm H₂O.)

Treatment of IIH includes a low-sodium, weight-reducing diet; symptomatic treatment for headaches; carbonic anhydrase inhibitors (acetazolamide); prevention of vision loss; and discontinuation of isotretinoin.

Repeat LPs, with drainage of sufficient fluid to maintain CSF pressure < 200 mm H₂O, is helpful in ~ 25% of cases.

Prednisone works acutely but is **not** recommended for chronic cases of IIH because of side effects, not the least of which is increasing ICP. Unilateral optic nerve sheath fenestration may preserve vision in the acute setting.

Consider ventriculoperitoneal (VP) shunt in refractory cases, especially if there is vision loss.

CNS: BRAIN — CORTEX, SUBCORTEX, AND BRAINSTEM

STROKE AND TRANSIENT ISCHEMIC ATTACK (TIA)

PREVIEW | REVIEW

- Which viral infection increases risk of strokes?
- In addition to exercise, smoking cessation, and control of diet, blood pressure, and lipids, which other interventions should be offered to certain patient groups in order to prevent stroke?
- Which imaging study would you do for a patient with a suspected subarachnoid hemorrhage (SAH)?
- Which imaging studies are recommended for evaluation of vasculature in patients with transient ischemic attack or stroke?
- How does a patient with an anterior cerebral artery stroke typically present?
- How does a patient with a middle cerebral artery stroke usually present?
- How does a patient with a posterior cerebral artery stroke typically present?

- What type of stroke causes lateral medullary syndrome? What is the clinical presentation of this syndrome?
- How do you distinguish a central vs. peripheral 7th cranial nerve palsy on physical exam?
- Which tests are recommended in the initial evaluation of ischemic stroke?
- What is the timeframe for prescription of tissue plasminogen activator (tPA) in patients with ischemic stroke?
- Which patients with a stroke between 3 and 4.5 hours are excluded from tPA?
- What are the recommendations for lowering blood pressure in patients with ischemic stroke who do not receive tPA?
- Why should you keep a patient with an ischemic stroke in the posterior fossa under close observation?
- What are the recommended antiplatelet regimens after ischemic stroke?
- What are the most common causes of an intracerebral hemorrhage?
- What are the recommendations for treatment of blood pressure in a patient with an intracerebral hemorrhage?
- What is the most common cause of SAH?
- If imaging for SAH is negative and suspicion is high, what are alternative tests?
- Which further evaluation is indicated in cocaine users who present with a cerebral bleed, even if they are hypertensive?
- Which patient groups are prone to subdural hematoma?
- Describe the differences between subdural and epidural hematomas.

OVERVIEW

Stroke (a.k.a. cerebrovascular accident [CVA]), after heart disease and cancer, is the 3rd most common cause of death in the U.S. The term **stroke** is applied to a sudden focal neurologic syndrome caused by cerebrovascular disease. **Cerebrovascular disease** refers to an abnormality of the brain caused by pathology of blood vessels, such as:

- **Occlusion** by embolus or thrombus
- Vessel **rupture**
- Altered **permeability** of the vessel wall
- Increased **viscosity** or other change in the quality of the blood flowing through the cerebral vessels

The primary vascular disorder may be atherosclerosis, hypertensive arteriosclerotic change, arteritis, aneurysmal dilatation, or a developmental malformation. The

secondary parenchymal changes in the brain resulting from the vascular lesion can include ischemia (especially in the penumbra or periphery of infarcted tissue), infarction, and hemorrhage.

Important risk factors for stroke include familial predisposition, age, hypertension, diabetes mellitus, smoking, hypercholesterolemia, and atrial fibrillation (A-fib). Know that a rare cause is **varicella-zoster infection**, which increases risk of ischemic and hemorrhagic strokes and transient ischemic attacks by 30%. There is an even higher risk with the presentation of herpes zoster ophthalmicus. This risk is highest within 3 weeks of the appearance of the rash.

TIA

A TIA is brain ischemia **without infarction**. When brain infarction occurs, it is termed an ischemic stroke.

Note that the latest American Stroke Association guidelines (2014) on TIA **removed** all references to **duration** of symptoms. The definition was changed because infarctions sometimes occur even when symptoms last < 24 hours, making the previous time-based definition of TIA occasionally incorrect.

COMPLICATIONS OF TIA

Patients with TIA are at risk for the following:

- Stroke
 - 10% have ischemic stroke within 3 months; 50% of this group do so within 48 hours.
- Cardiac events
 - 3% have cardiac events within 90 days.
 - Acute myocardial infarction (AMI) risk is increased.
 - Mortality in AMI after TIA is increased.

The ABCD² score estimates the risk of stroke after TIA based on demographic factors, symptoms and comorbidities ([Table 12-3 on page 12-30](#)).

The 2014 AHA/ASA (American Heart Association/American Stroke Association) guidelines recommend hospitalization within 72 hours of an event if:

- ABCD² score ≥ 3
- ABCD² score 0-2 and unable to complete workup within 48 hours
- ABCD² score 0-2 and other evidence that events were caused by ischemia

Have patients with TIA imaged within 24 hours, or ASAP after their symptoms begin, to determine if any infarction is present. Also order CT or MR angiography of intracranial and neck vessels versus carotid duplex, echocardiogram, and blood work, including chemistries, blood glucose, lipids, and CBC. Order an ECG to rule out A-fib. See more under [Evaluation of Ischemic Stroke on page 12-33](#).

Table 12-3: ABCD² Scoring and TIA Risk Stratification

ABCD ²		Factor	Point Value
A	Age	≥ 60	1
		< 60	0
B	BP	≥ 140/90 mmHg	1
		< 140/90 mmHg	0
C	Clinical	Weakness	2
		Isolated speech	1
		Other	0
D	Duration (minutes)	≥ 60	2
		10–59	1
		< 10	0
D	Diabetes	Present	1
		Absent	0
2-Day Risk of Stroke (%)		Total Score	
0	0–1		
1.3	2–3		
4	4–5		
8	6–7		

CLASSIFICATION OF STROKES

Strokes are classified as **ischemic** or **hemorrhagic**. Ischemic strokes can be thrombotic or embolic.

Ischemic strokes (87% of all strokes):

- 20% are due to large artery atherosclerosis.
- 20% are due to cardiac emboli.
- 20% are due to lacunar/small vessel infarcts.
- 5% are due to vascular disorders (e.g., vasculitis, dissection).
- 35% are cryptogenic.

Hemorrhagic strokes are of 2 main types:

- 1) Intracerebral hemorrhage (ICH)
- 2) Subarachnoid hemorrhage (SAH)

PRIMARY PREVENTION OF STROKE AND TIA

The 2014 AHA/ASA guidelines for primary prevention of stroke and TIA include:

- Treatment of blood pressure and lipids
- Smoking cessation
- Antiplatelets or anticoagulation
- Diet and exercise
- Treatment of A-fib (Read about A-fib in the [Cardiology](#) section.)

- Carotid endarterectomy if > 70% in selected patients, and if perioperative morbidity and mortality is < 6%
- Prophylaxis for migraine (Refer to [Prophylactic Treatment of Migraine](#) on page 12-26.)
- Evaluation and treatment of obstructive sleep apnea
- Screening the following for aneurysms with CTA or MRA:
 - Patients who have ≥ 2 first-degree relatives with SAH/aneurysm (But screening is **not** recommended in patients who have only 1 affected first-degree relative.)
 - Patients who have autosomal dominant polycystic kidney disease (ADPKD) and ≥ 1 relatives with ADPKD + SAH/aneurysm

IMAGING OF STROKES

A main reason to do neuroimaging is to determine whether a patient is eligible for tissue plasminogen activator (tPA), but there are other uses:

- Exclude intracranial bleeding
- Detect ischemia
- Exclude other illnesses that mimic stroke
- Image the vessels
- Assess possible viability of infarcted tissue

Imaging with CT: A **nonenhanced CT (NECT)** scan can be performed as a basic form of stroke imaging ([Figure 12-3](#)). Its main role is to rule out hemorrhage in the acute setting, though large strokes may have early ischemic signs, such as a hyperdense middle cerebral artery (MCA) sign showing the clot or sulcal blurring.



Figure 12-3: CT of intraparenchymal bleed

IV tPA can be given to patients with duration of stroke symptoms < 4.5 hours, a CT scan negative for hemorrhage, and no hemorrhagic risk contraindications.

The NECT results can be enhanced by using these important adjunct scans:

- Angiography (CTA) images contrast-enhanced blood vessels
- Dynamic perfusion studies (computed tomography perfusion [CTP]) determines perfusion of the ischemic area

When adding angiography, evaluation of source images (SI) helps to interpret the study (CTA-SI).

Imaging with MRI:

- Diffusion-weighted imaging (DWI) reduces the amount of signal return in certain tissues. It has a major role in identifying ischemic stroke, differentiating acute from chronic stroke, identifying tumor types, and assessing demyelination.
- Fluid-attenuated inversion recovery (FLAIR) is a special technique that removes CSF from the resulting images. Helps detect subtle changes in the periphery of the hemispheres and in the periventricular region close to CSF.

MRI can also be enhanced using additional imaging sequences:

- Perfusion (magnetic resonance perfusion [MRP]) assesses perfusion in cerebral ischemia and brain tumors. Most common methods use a contrast agent.
- Angiography (MRA) is a noninvasive look at the blood vessels, usually done with a contrast agent.
- Gradient-recalled echo (GRE) improves the contrast between white and grey matter.

Now that you know the abbreviations and acronyms, we'll go over which imaging to use in particular situations:

- Intracerebral hemorrhage (ICH): MRI-GRE is **equivalent** to NECT for finding blood. MRI is also better for detecting hemorrhagic transformation of ischemic stroke (occurs in about 5% ischemic CVAs).
- Subarachnoid hemorrhage (SAH): Use NECT.
- There is some data showing MRI with FLAIR is as sensitive as NECT. No matter which test you choose, a lumbar puncture (LP) is still mandatory if the CT or MRI is negative.
- Ischemia: MRI-DWI is best. CTA-SI is comparable, but it is not as good for imaging of the posterior fossa/brain stem and for discovering small infarcts. MRI is also better than NECT to detect an occluded vessel.

Unless your patient has signs and symptoms of SAH, MRI + DWI and MRI + GRE sequences (at minimum) are the best imaging for possible ischemic stroke because they both exclude ICH and identify areas of infarction—provided you can get the test without delay. Remember

that time from symptom onset > 4.5 hours precludes use of tPA (< 3 hours is best). If you cannot get an MRI in a reasonable time frame, then get a CT with CTA-SI.

CTA or MRA is recommended to evaluate the intra- and extracranial vasculature of patients with TIA or stroke symptoms. Both imaging modalities are significantly more sensitive and specific than carotid Doppler ultrasound for diagnosing extracranial vascular stenosis. Carotid ultrasound also tends to **overdiagnose** lesions and leads to unnecessary surgery in some patients, so only utilize that for screening purposes. CTA is better than MRI at identifying intracranial aneurysms.

If performing CTA or MRA does not extend the time from symptom onset beyond 4.5 hours maximum (< 3 hours is best), either is recommended as part of the **initial** evaluation of stroke because, sometimes, clotted vessels can be treated with urgent intraarterial therapy or stents. Patients with a large clotted vessel—often the MCA—do not respond as well to IV tPA as they do to direct arterial intervention (intraarterial tPA or mechanical thrombectomy options).

Although assessing viable brain tissue after infarction is one of the main purposes for imaging a stroke patient, we are still in the beginning stages of learning how to incorporate the data into treatment plans. Dynamic CTP and MRP are the leading imaging techniques.

At this point, the standard of care has been at least a CT brain to exclude hemorrhage for tPA candidacy, which can be performed urgently to assess for the IV tPA window, but advanced imaging techniques for endovascular candidacy is increasingly becoming the standard of care at stroke centers. (Find more information under [Acute Treatment of Ischemic Stroke](#) on page 12-34.)

ISCHEMIC STROKES

Thrombotic vs. Embolic Strokes

Thrombotic strokes: Atherosclerotic occlusion most commonly occurs in the internal carotid, middle cerebral, vertebral, and basilar arteries.

The initial neurologic symptoms often occur in a **slow, stepwise** progression (“stroke in evolution”). Often patients have a history of TIAs in the same distribution as the presenting symptoms of their stroke. If the patient has not had TIAs, a clear differentiation between thrombotic and embolic stroke can be difficult to detect. Other, rarer causes of thrombotic occlusion are lupus anticoagulant, polycythemia, meningovascular syphilis, dissecting aortic aneurysm, and thrombocytosis.

Embolic strokes: Neuro deficit is commonly **worst at onset**. Embolic strokes are **not** typically preceded by a TIA. Emboli from the heart, due to large particle size, usually go to the middle > posterior > anterior cerebral arteries. Emboli can also be multiple. Obtain an echocardiogram or transesophageal echocardiogram to evaluate left atrial size, valvular structure, and global ventricular function assessment.

Anterior Circulation

Anterior Cerebral Artery (ACA) Strokes

When the ACA is affected distal to the anterior communicating artery, the weakness and sensory loss primarily affect the contralateral leg.

Urinary incontinence and gait abnormalities can also be present. If the **corpus callosum** is affected, patients can develop tactile agnosia, which is an inability to recognize objects by touch.

Occlusion of the stem of the ACA proximal to the anterior communicating artery is generally well tolerated because collateral flow is provided by the contralateral ACA. When both ACAs arise from one occluded stem, there is resulting paraplegia, incontinence, lack of motivation (abulia), and frontal lobe personality changes.

Buzz phrase: The patient with **ACA** stroke typically presents with contralateral **leg weakness** that is **opposite** to the side of the stroke.

Middle Cerebral Artery (MCA) Strokes

Most MCA stem occlusions (Figure 12-4) are from **emboli**. MCA strokes result in:

- contralateral weakness (hemiplegia), which is denser if the internal capsule is involved;
- contralateral sensory loss (hemianesthesia); and
- contralateral homonymous hemianopia.

The weakness pattern follows a lateral homunculus pattern: The face and arm are more affected than the leg on the contralateral side of the body compared to the brain lesion.

If the **dominant** hemisphere is involved (the **left** side in most people, even left-handed individuals), these patients experience **aphasia**. Examples of dominant hemisphere MCA strokes and their presenting signs:

- A lesion that affects the lower part of the left frontal lobe (Broca area) causes **expressive** (a.k.a. **Broca**) **aphasia**. These patients understand language, but they have trouble forming words and sentences, so their speech is nonfluent and effortful.
- A lesion at the boundary of the temporal and parietal lobes causes a **fluent** or **sensory** aphasia, called **Wernicke** aphasia. These patients cannot comprehend written or spoken language and have errors in their spontaneous speech, often speaking in invented words, called **neologisms**.
- An extensive infarction can produce **global** aphasia, which is both expressive and sensory.

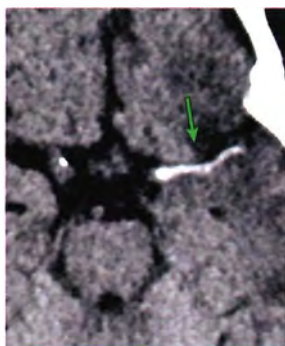


Figure 12-4: CT of MCA stroke

If the **nondominant** hemisphere is involved, patients may experience changes in spatial perception and can develop hemineglect syndrome.

With **parietal** lesions of **either hemisphere**, cortical sensory signs are often present:

- Contralateral loss of 2-point discrimination
- Failure to perceive tactile stimuli on the opposite side of the involved hemisphere when stimuli are presented to both sides simultaneously (sensory inattention)
- Inability to recognize objects through touch (tactile agnosia)
- Inability to recognize letters drawn on their palm (agraphesthesia)

If the lesion involves the frontal lobe, patients may have a gaze preference or gaze deviation—they look toward the side of the lesion for 1–2 days after the stroke.

Buzz phrase: The patient with **MCA** stroke typically presents with **face/arm > leg weakness** that is **opposite** to the side of the stroke and a **language deficit** if the dominant hemisphere is involved.

Posterior Circulation

Posterior Cerebral Artery (PCA) Strokes

PCA strokes typically occur from an embolic source.

PCA stroke syndromes can be categorized by which area of the brain is affected. The PCA supplies the occipital cortex, occipitoparietal cortex, medial temporal lobe, midbrain, and thalamus.

Depending on the area affected, there can be mild contralateral sensory loss, inability to name colors (color anomia), failure to see to-and-fro movements, inability to count objects, inability to control eye movements (oculomotor apraxia), inability to see > 1 object at a time if the dominant occipital lobe is involved (simultanagnosia), visual hallucinations, and/or memory loss.

The finding of a visual field defect can give you an idea of where the stroke is located (see Figure 12-9 on page 12-55 for reference). Visual field defects will be contralateral. You can find:

- a homonymous hemianopia with strokes affecting the medial occipital lobe,
- an inferior quadrantanopia with strokes affecting optic radiations through the parietal lobe, or
- a superior quadrantanopia with strokes affecting optic radiations through the temporal lobe.

Bilateral cortical blindness can result from simultaneous or successive PCA occlusion but may also be due to anoxia related to surgery, especially cardiac surgery. Rarely, patients with cortical blindness deny their visual defect (Anton syndrome).

If the patient has color anomia, the posterior aspect of the corpus callosum (splenium) may have been affected. Lesions that affect the dominant hemisphere's occipital

lobe (which is most commonly the left) along with the splenium of the corpus callosum cause alexia without agraphia (inability to read but able to write).

If disruption of blood flow occurs bilaterally, the memory loss is severe and persistent.

Buzz phrase: The patient with **PCA** stroke commonly presents with **visual** field defects + **color** anomia + **paresthesias** without any motor findings.

Vertebral / Basilar Artery Occlusion

Vertebral and/or basilar artery occlusion in the posterior circulation is the usual cause of **brainstem** (posterior fossa) strokes. Consider this when you see any of the following:

- Bilateral extremity motor and sensory dysfunction (quadriplegia in severe cases)
- Crossed sensory findings (e.g., right face, left arm)
- Horner syndrome
- Cerebellar signs
- Stupor and coma
- Cranial nerve dysfunction not usually seen with single hemisphere strokes, such as diplopia, pharyngeal weakness, jaw weakness, and deafness
- Crossed hemiplegias (e.g., ipsilateral cranial nerve deficit and contralateral arm or leg weakness)

Know! A vertebral stroke can cause **lateral medullary syndrome** (a.k.a. Wallenberg syndrome), which has a **mixed bag** of symptoms:

- **Ipsilateral** cerebellar signs and symptoms (due to involvement of the inferior cerebellar peduncle and cerebellum)
- Nausea, vomiting, nystagmus (vestibular nuclei)
- **Ipsilateral** Horner syndrome (due to involvement of the descending sympathetic fibers)
- **Ipsilateral** palate and vocal cord weakness (involvement of the nucleus ambiguus)
- **Crossed** sensory loss (ipsilateral face and contralateral body, due to involvement of the trigeminal nucleus and tract and spinothalamic tract, respectively)

Buzz phrases: The patient with **posterior circulation** stroke typically presents with:

- Vertigo and diplopia if due to vertebrobasilar artery, sometimes with antecedent TIA symptoms
- Lateral medullary syndrome
- Vertigo + nystagmus + nausea + ataxia (if **cerebellar**)

Single Hemisphere Strokes

Single hemisphere strokes typically do not affect paraspinal muscles or muscles of the pharynx, jaw, and forehead. If these muscles are affected, think bilateral hemispheric involvement or brainstem stroke. Remember: Upper motor neuron lesions of cranial nerve 7 do not affect eye

closure or forehead wrinkling, which helps you to distinguish clinically between a central lesion and Bell's palsy (peripheral 7th nerve involvement).

Lacunar Infarcts

Small artery disease, usually due to chronic hypertension or diabetes, can lead to small vessel occlusion with resultant necrosis of small areas of the brain. Over time, resorption of these necrotic regions causes small infarcts, or lacunae, to develop.

Although most are silent, hallmarks of **symptomatic lacunar infarcts** are:

- Pure hemiplegia (with no sensory dysfunction)
- Pure hemisensory stroke (with no motor dysfunction)
- Sensorimotor stroke
- Ataxic hemiparesis (ataxia ipsilateral to hemiparesis)
- Clumsy hand-dysarthria syndrome

Multiple bilateral frontal lobe lacunae can result in pseudobulbar palsy—emotional lability with uninhibited crying or laughter and evidence of upper motor neuron signs, such as brisk jaw jerk, hyperreflexia, and Babinski sign.

Evaluation of Ischemic Stroke

Assess the patient with a neurologic deficit like any other emergency, using the **ABCs** first: stabilize airway, breathing, and circulation.

If the patient is stable, take a good history. The **most important element is the time of symptom onset** because that determines eligibility for an IV **thrombolytic**. If the patient awoke with deficits, then the last time they remember having normal function is the time of symptom onset. Remember that complicated migraines, postictal states, and subdural hemorrhages can resemble a stroke; therefore, ask about headaches, seizure activity, and falls.

Physical exam focuses on possible sources and alternative diagnoses. Look for evidence of seizures (tongue biting), trauma, myocardial ischemia, carotid and vertebral artery bruits, heart murmurs, and arrhythmias.

The National Institutes of Health Stroke Scale (NIHSS) score is a standardized instrument incorporated as part of a physical exam at most stroke centers. The general concepts of the scale are presented in [Table 12-4 on page 12-34](#).

The NIHSS helps to quantify neurologic deficits, communicate with neurologists, possibly identify the occluded vessel, make an early prognosis, and identify a patient's suitability for thrombolytics. Patients get points for their **inability** to complete the various parts of the assessment.

Table 12-4: National Institute of Health Stroke Scale (NIHSS)*

Category		Clinical Response
Consciousness	Level	Choose a response: alert, arousable by minor stimuli, requires repeated or painful stimuli, unresponsive or reflexes only, or areflexic.
	Questions	Ask month and age; no partial credit. Aphasic and stuporous patients score 2. Intubated patients score 1.
	Commands	Ask patient to open and close eyes, then to grip and release nonparetic hand.
Gaze		Test horizontal eye movements.
Vision		Test visual fields by confrontation with finger counting.
Facial Palsy		Ask patient to show teeth or raise eyebrows and close eyes.
Motor: Arm and Leg		Test for pronator drift.
Ataxia		Perform finger-nose-finger and heel-shin tests.
Sensation		Assess for sensation or grimace to pinprick or withdrawal from noxious stimulus.
Language		Describe what is happening in a picture, name items printed on paper, and read a sentence.
Speech		Read words from a list.
Extinction and Inattention		Assess previous tests to determine if patient orients only to one side.

* For the full scale with scoring, go to www.stroke.nih.gov/documents/NIH_Stroke_Scale_508C.pdf

The AHA/ASA 2019 Guidelines for the Early Management of Acute Ischemic Stroke recommend the following immediate diagnostic tests at presentation:

- NECT or MRI of the brain (refer to [Workup on page 12-2](#)) is done to rule out hemorrhage. If negative for hemorrhage, then do a CT angiogram or MRA (if CTA is contraindicated) to evaluate vessels—but do not allow this to delay any necessary reperfusion therapy.
- Blood glucose level
- Oxygen saturation measurement
- Serum electrolytes and renal function tests
- CBC with platelets
- Prothrombin time (PT), partial thromboplastin time (PTT), INR
- 12-lead ECG +/- telemetry monitoring for arrhythmias

- Optional tests in selected patients:
 - Thrombin time (TT) and/or ecarin clotting time (ECT) or chromogenic anti-Xa assay if on direct thrombin inhibitors (but not readily available)
 - Hepatic function test
 - Toxicology and alcohol screen
 - Pregnancy test
 - Again, do an LP with CSF assessment if SAH is a concern and NECT (or MRI with FLAIR) does not show blood.
 - EEG if you suspect the patient has seizures
 - ABG if hypoxic

Acute Treatment of Ischemic Stroke

Critical Times

Always refer patients via 911 to a primary stroke center or a comprehensive stroke center.

The AHA/ASA 2019 guidelines recommend these goals:

- Door to **physician** should be ≤ 10 minutes.
- Door to **stroke team** should be ≤ 15 minutes.
- Door to **CT initiation** should be ≤ 25 minutes.
- Door to **CT interpretation** should be ≤ 45 minutes.
- Door to **drug** (≥ 80% compliance) should be ≤ 60 minutes.
- Door to **stroke unit** admission should be ≤ 3 hours.

If the stroke occurred < 4.5 hours ago and the NIH stroke scale rating is > 4, tPA is effective in decreasing severity or reversing neurologic deficits, provided that the patient fits inclusion/exclusion criteria (2019 AHA/ASA stroke treatment guidelines).

While these goals for tPA remain unchanged, the 2019 AHA/ASA stroke treatment guidelines expanded the window for mechanical thrombectomy from 6 hours to up to 24 hours in select patients. See [Endovascular Interventions](#).

Tissue Plasminogen Activator (tPA) Criteria for < 3 Hours

< 3 hours tPA inclusion criteria:

- Diagnosis of ischemic stroke causing measurable neurologic deficit
- Onset of symptoms < 3 hours before beginning treatment
- ≥ 18 years of age

< 3 hours tPA exclusion criteria:

- Minor or rapidly improving stroke symptoms
- Significant head trauma or prior stroke in last 3 months
- Symptoms suggest SAH
- History of prior intracranial hemorrhage
- Intracranial tumors or arteriovenous malformation (AVM) or aneurysm

- Arterial puncture at noncompressible site
- Infarct in last 7 days
- Recent intracranial or intraspinal surgery
- SBP > 185 mmHg or DBP > 110 mmHg
- Active internal bleeding
- Platelets < 100,000/mm³
- Anticoagulation with INR > 1.7 or PT > 15 seconds
- Used direct thrombin inhibitors or direct factor Xa inhibitor with abnormal INR/aPTT/PT/ECT/TT/Xa activity assay
- Blood glucose < 50 or > 400 mg/dL (< 2.77 or > 22.20 mmol/L)
- CT with **multilobar** infarction (hypodensity > 1/3 cerebral hemisphere)

Relative exclusions:

- Seizure with postictal deficits
- Major surgery or serious trauma in prior 14 days
- GI or GU hemorrhage within last 21 days
- AMI within 3 months

Additional tPA Criteria for 3–4.5 Hours

Inclusion criteria (3–4.5 hours):

- Diagnosis of ischemic stroke causing measurable neuro deficit
- Onset of symptoms within 3–4.5 hours before beginning treatment

Relative exclusion criteria (3–4.5 hours):

- Age > 80
- Severe stroke (NIHSS > 25)
- On anticoagulation regardless of INR
- History of both diabetes mellitus (DM) and prior ischemic stroke

Endovascular Interventions

Intraarterial fibrinolysis or mechanical thrombectomy is a consideration for patients who have contraindications to IV fibrinolytics or select patients who are eligible for an expanded 6- to 24-hour thrombectomy treatment window. Eligible patients have a high NIH score (≥ 6), low premorbid baseline, and large vessel occlusion of the internal carotid or proximal MCA confirmed by vascular imaging. These recommendations from the 2019 AHA acute ischemic stroke guidelines represent a critical change in stroke care.

Other Aspects of Acute Ischemic Stroke Care

Management that emphasizes supportive care and treatment of complications:

- Give airway support to stroke patients with reduced consciousness or airway compromise; oxygen prn.
- Monitor with telemetry for the first 24 hours after a stroke to assess for arrhythmias.
- Treat hypertension cautiously so as not to extend infarct size. If the patient meets criteria for tPA

except for BP, go ahead and treat to reduce BP to $\leq 185/110$ mmHg, then give tPA. If not giving tPA, withhold meds for BP < 220/120 mmHg and allow the patient to gradually drop their pressure on their own. If BP > 220/120 mmHg, then treat with the goal of reducing the BP ~ 15% in the first 24 hours. Recommended medications include IV labetalol, nitroprusside, and nicardipine infusion.

- Restart antihypertensives for patients with long-standing hypertension after 24 hours (if not treated already for BP > 220/120 mmHg).
- Maintain normoglycemia 140–180 mg/dL (7.77–9.99 mmol/L).
- Look for and treat sources of fever. Give antipyretics to reduce fever.

Know: In patients who are ineligible for treatment with tPA, and who are not taking anticoagulation for any other underlying disease, give 325 mg aspirin once, followed by aspirin 150–325 mg/day while hospitalized. The optimal dose is not yet clear. The risk of hemorrhagic transformation of an infarct is not high enough to offset the benefits of aspirin therapy, so **treat** all eligible patients, even if a small hematoma is present within the infarcted area. Heparin or low-molecular-weight heparin (LMWH) is generally discouraged in the acute setting of stroke due to bleed risk. Use anticoagulation with oral agents in cardioembolic settings for secondary prevention (i.e., A-fib and other subtypes, outlined in the topic discussion of **Chronic Treatment of Ischemic Stroke**). If the ischemic stroke is large, hold off starting anticoagulation for the first 1–2 weeks due to bleed risk; if the stroke size is minimal, then starting after the first 24 hours is reasonable. Of note, cardiac embolism from endocarditis is an absolute contraindication to anticoagulation because of increased risk of CNS hemorrhage.

If the stroke occurs in the **posterior** fossa, **admit** the patient for close observation. Expansion of the contents of the posterior fossa can cause either upward or downward herniation; these patients then decompensate quickly and without warning.

Chronic Treatment of Ischemic Stroke

Reduce the patient's risk factors for stroke by treating hypertension, diabetes, and lipids according to 2014 AHA/ASA national guidelines for stroke prevention, and add aspirin 50–325 mg/day.

Equally acceptable alternatives to aspirin are clopidogrel and the combination of **ASA + dipyridamole**. These provide a small amount of increased benefit compared to aspirin alone. Consider using these agents as 1st line therapy based on a financial cost discussion or if the patient has had a recurrent stroke and was already on aspirin. Use clopidogrel in patients with aspirin allergy. Know that aspirin + clopidogrel does not offer additional benefit in general and does increase risk of bleeding. Nevertheless, a specific indication for dual therapy is for the first 90 days following a stroke due to large artery intracranial disease.

Headache is a common side effect of dipyridamole, which sometimes causes patients to self-discontinue the drug. Normally the headaches can be treated symptomatically with acetaminophen.

Anticoagulate the patient who has A-fib if the patient meets guidelines. (See more on A-fib in the [Cardiology](#) section.) Newer agents are available and becoming widely utilized for anticoagulation in nonvalvular A-fib and do not require blood test monitoring (i.e., apixaban, rivaroxaban, edoxaban, dabigatran). Warfarin is still used for other indications for anticoagulation for secondary prevention, such as prosthetic valves, rheumatic mitral valves, DVT with patent foramen ovale (PFO), cerebral venous thrombosis, and LV thrombus. It is sometimes considered for low ejection fraction or extracranial dissection. Refer for carotid endarterectomy if the patient has > 70% occlusion and an expected lifespan of > 5 years and the anticipated operative morbidity and mortality is < 6%.

Blood pressure control is paramount in secondary prevention of stroke. Control of lipids, glucose, diet, and exercise remains important, as is treatment of underlying sleep apnea.

Cerebral Venous Thrombosis (CVT)

Thrombus in the cerebral venous system prevents drainage of blood flow from the brain and can have protean clinical presentations (i.e., headaches, seizures, focal deficits, altered mental status). It is 3× more common in women and is associated with OCPs, pregnancy, hypercoagulable states, infection, and previous head trauma. MRI with MR venography are the best imaging modalities. Treatment is with anticoagulation for ≥ 3 months.

INTRACRANIAL HEMORRHAGE

The primary (and spontaneous) types of intracranial hemorrhage are **intracerebral** (ICH; a.k.a. parenchymal), **subarachnoid** (SAH), and **intraventricular** (IVH). These are the causes of 10%, 3%, and 0.04%, respectively, of strokes in the U.S. (Because primary IVH is so rare, it is often considered a common finding in ICH and SAH rather than a cause of primary intracranial hemorrhage.) The secondary forms of intracranial bleed, almost always the results of trauma, are **subdural** and **epidural** hematomas.

ICH is a **parenchymal** (brain tissue) bleed and 25% present with secondary IVH. SAH flows into the subarachnoid space that surrounds the brain. 25–50% present with secondary IVH. IVH, whether, primary or secondary, is a strong contributor to early severity and complications and is, in all cases, an independent prognostic sign of a poor outcome with a mortality of 50–80%.

Intracerebral Hemorrhage (ICH)

The most common causes of ICH are **hypertension** (#1 overall), AVM rupture (#1 in children), **amyloid angiopathy** (#1 lobar ICH in older adults), and **ischemic**

strokes (especially post thrombolytics). Warfarin use is a risk factor, especially when the **INR** is > 3.

ICH due to hypertensive vasculopathy occurs from arterial rupture where small arteries branch off at a 90° angle from major intracerebral arteries. In 25%, the bleed extends into the ventricles, causing a secondary IVH, which worsens both symptoms and prognosis. See [Figure 12-5](#) for a CT of an acute intracerebral hemorrhage with leakage into the lateral ventricles.

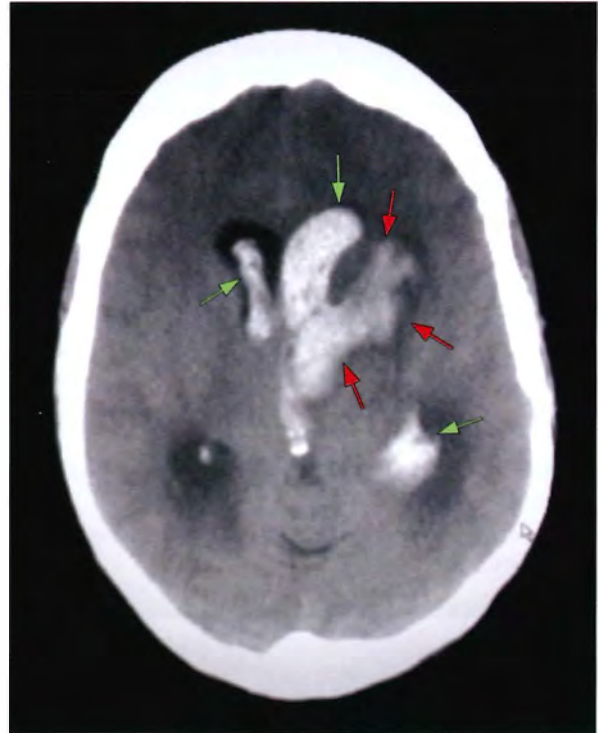


Figure 12-5: Acute ICH (red) with IVH (green)

Some patients have preexisting evidence of intermittent, small bleeds on MRI of the brain. It is possible that these MRI-visible microbleeds are indicators denoting which patients are prone to future ICH. Because the bleeding arises from small arteries, the symptoms of microbleeds typically evolve gradually but continuously.

Signs and Symptoms / Diagnosis

Intracerebral hemorrhagic stroke occurs in the following 4 areas of the brain (from **most** common site to **least** common):

- 1) **Putamen** and the adjacent **internal capsule** (50%): If the hematoma involves the internal capsule, there is contralateral hemiparesis and usually sensory loss and hemianopia. This type of hemorrhage can be difficult to distinguish from an MCA infarct (one of the reasons to do the enhanced NECT or MRI to look for blood at presentation). For central white matter of the temporal, parietal, or frontal lobes, symptoms are based on the lobe affected.

- 2) **Thalamus:** contralateral hemianesthesia without cortical sensory signs. Some motor signs may be present if the adjacent internal capsule is involved.
- 3) **Pons:** coma, pinpoint pupils, and quadriplegia. There can be decerebrate posturing bilaterally.
- 4) **Cerebellum:** acute dizziness, ataxia, and vomiting with no change in mentation and no loss of consciousness

Amyloid angiopathy is a typical cause of intracerebral hemorrhagic stroke in those > 60 years of age. The hemorrhage tends to be **lobar and subcortical** and there can be multiple instances. It rarely involves the deep structures (as does a hypertensive bleed). These hemorrhages can recur within months or years. Dementia occurs in 30% of patients. Other clinical features include acute reactive hypertension, vomiting, headache, and nuchal rigidity.

Other causes of intracerebral hemorrhage include:

- Bleeding diatheses
- Trauma
- Bleeding into a tumor mass
- Cocaine use

Treatment of ICH

Treatment includes the basic **supportive** care given to ischemic stroke patients. (Refer to [Other Aspects of Acute Ischemic Stroke Care on page 12-35](#).)

Immediately reverse any anticoagulant effects with both vitamin K and replacement of clotting factors, no matter the reasons for anticoagulation. Give protamine sulfate for any hemorrhage associated with unfractionated heparin. Also, stop any antiplatelet agents.

Control of ICP is important, and **mannitol** is usually used.

The 2015 AHA/ASA Guidelines for the Management of Spontaneous Intracerebral Hemorrhage state that acute lowering of systolic blood pressure to **140 mmHg** is safe in patients who present with SBP 150–220 mmHg. For patients who present with SBP > 220 mmHg, the guidelines state that a continuous IV infusion (e.g., labetalol, esmolol, nicardipine, enalapril) can be considered for aggressive BP lowering. Be sure to maintain frequent BP monitoring while instituting this strategy.

Emergently consult a neurosurgeon. The neurosurgeon considers clot removal depending on the site and for cerebellar hematomas > 3 cm. Surgical evacuation for supratentorial hemorrhage can also be considered in deteriorating patients. In patients with minor deficits or deeply comatose patients, surgery is generally not done. Interventional radiologists or endovascular neurosurgeons can perform coil embolization for AVMs.

ICH prognosis: Mortality in the first few days is 15–25%. At 30 days, mortality is 35–50%. Survival rate at 1 year is ~ 50%. Independent function at 1 year is attained in only ~ 20%.

Subarachnoid Hemorrhage (SAH)

SAH accounts for only 3% of strokes but has devastating consequences. **85% of SAHs result from rupture of an intracranial aneurysm.** Aneurysms are most common at the bifurcation of vessels in the **circle of Willis** or its major branches. SAH most likely occurs between 40 and 60 years of age, and it occurs in women more often than in men.

The majority occur in the anterior circulation: 40% of aneurysms affect the internal carotid artery, 35% involve the anterior cerebral artery, and 20% the middle cerebral artery. Just as with ICH but even more often (25–50%), the bleed from a SAH extends into the ventricles, causing a secondary IVH, which again worsens both symptoms and prognosis.

Nonaneurysmal causes of SAH are unusual but include AVMs, sickle cell disease, bleeding diatheses, pituitary apoplexy, trauma, cocaine abuse, and intracranial arterial dissection. Among persons with saccular aneurysms, there is an increased incidence of congenital polycystic kidneys, fibromuscular dysplasia of the extracranial arteries, Moyamoya disease, AVMs of the brain, and coarctation of the aorta.

Signs and Symptoms

Ruptures typically occur when the patient is active rather than at rest. More than 1/3 of patients report a history of **sentinel bleed** symptoms days or weeks earlier.

The characteristic symptoms of SAH are the acute **“thunderclap”** or **“worst headache of my life”** sensation in combination with **neck stiffness**. Common associated symptoms include loss of consciousness, nausea/vomiting, and photophobia. Systemic manifestations of SAH can include ECG changes of giant inverted T waves (cerebral T waves), hyponatremia, and diabetes insipidus.

The most important determinant of outcome is the neurological condition of the patient upon arrival at the hospital. 10% die before getting to hospital, 25% die within the first 24 hours. If comatose, the prognosis is poor.

Know that 1st degree relatives of patients who experience an SAH have a 2–5× increased risk of an SAH. The AHA/ASA 2014 Guidelines for the Primary Prevention of Stroke recommend aneurysmal screening (refer to [Primary Prevention of Stroke and TIA on page 12-30](#)).

Diagnosis of SAH

NECT is the best test to identify blood in the subarachnoid space. The NECT in [Figure 12-6 on page 12-38](#) shows a massive SAH in which all the white in the brain tissue is due to blood in the subarachnoid space. If the NECT shows no SAH **and no mass**, then do a **lumbar puncture**. The CT misses **progressively more** subarachnoid bleeds as time passes from initial rupture—picking up only about 50% of bleeds after 5 days. In an SAH, CSF is bloody with xanthochromic supernatant (pink or yellow tint); however, even clear CSF does not preclude the diagnosis because it may take hours after onset of the

bleed before you find red cells at the level of the spine where you draw the CSF sample. Nevertheless, most cases have many thousands of red blood cells without sufficient clearing from tube 1 to tube 4 (indicating this is not a traumatic tap). Additionally, in some cases you can have an elevation of white blood cells due to an aseptic meningitis reaction to the blood, so do not mistake that for meningitis when the primary issue could still be an SAH.

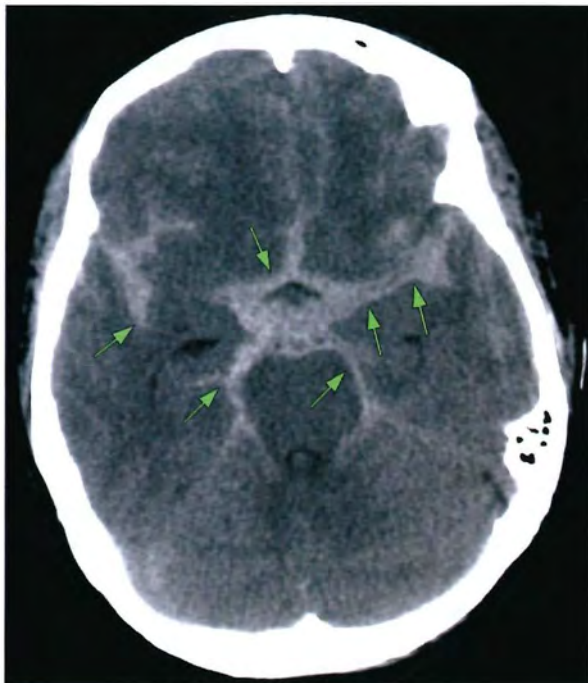


Figure 12-6: Massive subarachnoid hemorrhage

If a bleed is still suspected in the setting of a normal NECT and LP, then angiography is the procedure of choice. CTA and MRA are alternatives to the more invasive, conventional angiography.

MRA and CTA have similar sensitivity for aneurysms ≥ 5 mm, are more widely available, and can be obtained faster than conventional angiography. Due to the increased sensitivity for small aneurysms (< 5 mm), conventional angiography remains the gold standard.

Complications of SAH

After a sentinel bleed, **rebleeding** is common. The risk is highest in the first 24 hours, but the risk remains high for at least 1 month.

Vasospasm can occur in up to 70% of patients, happen most frequently **7–10 days** after the hemorrhage, and resolve 21 days after the hemorrhage. Read about treatment under the next topic discussion, **Treatment of SAH**.

Communicating hydrocephalus is the 3rd major complication. It occurs in 15–20% of patients after SAH. The likelihood of hydrocephalus depends on the volume of intraventricular and subarachnoid blood.

Seizures occur in 5–10% of patients; 2/3 begin within the 1st month after the hemorrhage, while the remaining occur within the 1st year.

Treatment of SAH

If the patient is on an anticoagulant or antiplatelet agent, stop the drug before performing any interventions. **Surgical clipping** and **endovascular coil insertion** into the bleeding vessel are the major interventions used to **prevent the aneurysm from bleeding again**. Remaining treatment focuses on preventing complications, such as calcium channel blockers to prevent vasospasm. Control of ICP and blood pressure is important as well, although recommendations are less clear-cut than with intracranial hemorrhages. Refractory vasospasm may need angiographic interventions.

Prognosis: Mortality rate in the first few days is 30%. Long-term morbidity includes cognitive defects, anxiety, depression, and sleep disturbances. Epilepsy occurs in ~ 5%. Recurrent SAH is a small but continuing risk.

Cocaine Use

Know that cocaine use can cause AVMs and aneurysms that rupture during episodes of severe drug-induced hypertension. These can cause either intracerebral or subarachnoid strokes. Evaluate all active cocaine users with an intracranial bleed with angiography.

Subdural Hematoma (SDH)

SDH is usually due to direct trauma, but deceleration forces can also cause it. Consider SDH in patients with a history of falls, blows to the head, alcoholism, a recent motor vehicle accident, and in the elderly. Subdural bleeds are usually of **venous** origin.

SDH can be acute or chronic, and each type manifests differently. In **acute** SDH, 1/2 of the patients immediately become comatose, but the other 1/2 remain lucid for a period of hours to days, after which cognition becomes gradually and progressively impaired until coma develops.

Symptoms can also be fluctuating. Other signs of increased ICP are often present (e.g., headache, nausea/vomiting, neck stiffness, gait abnormalities).

In **chronic** SDH, the trauma is often forgotten. Over a period of weeks, patients may develop headache, lightheadedness, slowness in thinking, apathy, drowsiness, unsteady gait, and occasionally seizure. Initially, they may be diagnosed as having a vascular lesion, brain tumor, drug intoxication, a depressive illness, or Alzheimer disease.

NECT is used in triage of these patients, but MRI with FLAIR is the most sensitive test. NECT in **Figure 12-7** shows a subdural hematoma with a skull deformity.

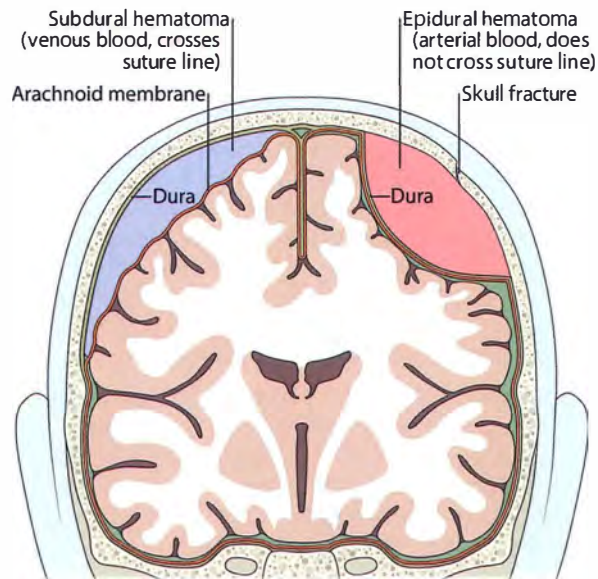


Figure 12-7: Subdural hematoma

Treatment for SDH is typically surgical—except for very small bleeds without any neurologic symptoms, which are observed closely.

Epidural Hematoma

Epidural hematomas, because of their **arterial** origin, evolve **more rapidly** than subdural hematomas. These are commonly caused by **temporal trauma** that damages the **middle meningeal artery**—in association with temporal bone fractures. Symptoms of increased ICP are usually rapidly progressive. However, a short period of lucidity can occur, followed by rapid obtundation.

As with SDH, you can diagnose epidural hematomas with NECT, but **MRI with FLAIR** is most sensitive.

Treatment consists of early evacuation of the hematoma via a craniotomy. If untreated, **herniation** occurs, with mortality ranging from 15–40%.

TRANSIENT GLOBAL AMNESIA (TGA) — STROKE AND TIA MIMIC

TGA is characterized by abrupt onset of global anterograde **amnesia**, with a variable impairment of retrograde memory not associated with any other major neurologic signs or symptoms. Except for amnesia during and around the event, patients **recover completely** in 2/3 of cases within 2–12 hours and in almost all cases within 24 hours. TGA is considered benign, and the condition recurs infrequently.

Patients are commonly between 50 and 80 years of age and suddenly develop an inability to make new memories. They act disoriented, asking multiple questions repeatedly (sometimes described as a “broken record”). The amnesia can even extend back to years, although more typically just days to weeks. Some patients have accompanying

nausea and dizziness. Consider TIA, which can present similarly.

Precipitating events are seen in many cases and include strenuous exercise, intense emotion, sexual intercourse, mild head trauma, pain, temperature extremes (e.g., swimming in cold water), cervical manipulation, coughing spells and other Valsalva-like activities, and medical procedures that require anesthesia (e.g., colonoscopy). The etiology is unknown, although migraine can be a predisposing factor.

NECT and brain MRI with DWI are usually **normal**. PET and SPECT studies have shown **hypoperfusion** and hypometabolism in the **hippocampi** and associated mesial temporal lobe structures during the attack, with resolution following the attack.

The attacks self-resolve. No treatment is necessary.

CNS: SPINAL CORD

MYELOPATHIES

PREVIEW | REVIEW

- Describe the findings in subacute combined degeneration due to B₁₂ deficiency.
- Which other mineral deficiency can present like the subacute combined degeneration due to vitamin B₁₂?
- What are the risk factors for an epidural abscess?
- What is the most common cause of epidural abscess?
- What causes Pott disease?
- Describe the clinical presentations of neurosyphilis.
- What is the clinical presentation of transverse myelitis?
- What is neuromyelitis optica? Which autoantibody is the culprit?
- What are the symptoms of cervical radiculopathy?
- What is lumbar spinal stenosis?
- What are the classic exacerbating and relieving body positions and movements of spinal stenosis?
- From the patient's history, which clues help you differentiate lumbar spinal stenosis from vascular claudication?
- What is the clinical presentation of syringomyelia?
- What is the hallmark clinical presentation of amyotrophic lateral sclerosis?
- Which conditions can cause upper and lower motor neuron signs in the same patient?

OVERVIEW

Myelopathies are diseases of the spinal cord. Typical manifestations are gait ataxia, spasticity, and hyperreflexia. Bowel and bladder incontinence arise as disease worsens. There are many subcategories.

METABOLIC MYELOPATHY — SUBACUTE COMBINED DEGENERATION OF SPINAL CORD

Subacute combined degeneration of the spinal cord due to B₁₂ deficiency is the prototype for metabolic myelopathy. Severe B₁₂ deficiency causes segmental loss of myelin, especially in the dorsal and lateral columns. Clinical presentation is gradual weakness with paresthesias and loss of proprioception with development of ataxia. Severe cases end in extensive bilateral lower extremity weakness, spasticity, and urinary incontinence +/- cognitive impairment. These cognitive changes include confusion, apathy, delusions, paranoia, and mental deterioration.

Tip: Think of B₁₂ deficiency in a patient with brisk knee jerks (due to pyramidal tract dysfunction) and absent ankle jerks (due to peripheral neuropathy).

Know that the neurologic changes can occur without any associated macrocytosis, megaloblastosis, or anemia! The CSF is typically normal and electromyography (EMG) shows slowing of sensory conduction.

Diagnose by measuring serum B₁₂, methylmalonic acid (MMA), and homocysteine levels. MMA and homocysteine are more sensitive tests that are included to make a diagnosis in patients who have low-normal or normal B₁₂ levels. In states of B₁₂ deficiency, both MMA and homocysteine are increased.

Treat the B₁₂ deficiency as early as possible with vitamin B₁₂ supplementation, usually by injections, which must continue indefinitely to prevent symptom recurrence.

Of note, copper deficiency can present with symptoms similar to myeloneuropathy due to B₁₂ deficiency; therefore, consider it in cases of GI absorption issues (i.e., gastric bypass) or excess zinc ingestion from oversupplementation or zinc-containing denture cream.

INFECTIOUS MYELOPATHIES

Acquired Immunodeficiency Syndrome (AIDS)

Advanced AIDS patients can get vacuolar myelopathy with vacuolation and deterioration of the dorsal and lateral spinal columns (seen on pathology, usually autopsy) that presents as ascending paresis with a sensory component (loss of vibration and proprioception) and urinary incontinence. MRI is normal, but CSF may have elevated protein and sensory evoked potentials are abnormal. Clinical presentation is very similar to subacute combined degeneration of the cord. It commonly accompanies HIV-associated dementia but occasionally occurs alone. Many other conditions can do this in a patient with virtually no immune system, but be sure to exclude a cord lesion with MRI.

Epidural Abscess

Spinal epidural abscess is a medical emergency that requires rapid diagnosis and treatment. The abscess can develop from bacteremic seeding from any source or from contiguous infection after spine surgery but also, rarely, from LP. Risk factors include immunodeficiency states (e.g., diabetes, HIV/AIDS), alcoholism, and any conditions or behaviors that cause transient bacteremia (e.g., injection drug use, boils). The abscess can start as a spinal osteomyelitis and progress to an abscess, causing cord compression. *Staphylococcus aureus* is the most common etiology of epidural abscess.

Remember: The main symptom of epidural abscess is back pain. Suspect epidural abscess in anyone with back pain and fever. For example, rule out epidural abscess in the postpartum patient who had an epidural during delivery—the cause is almost always some type of nosocomial *Staphylococcus* species.

Initial symptoms include a few days to 2 weeks of fever and backache with localized tenderness, radicular pain, and neurological deficits. Not all patients have all of the symptoms, and the diagnosis can be easily missed.

Abscess is best diagnosed with immediate contrasted MRI with FLAIR (contrasted CT is a less sensitive alternative). Perform myelography if the abscess is not clearly seen by MRI (or CT, if that is the only option).

Treatment: Immediate decompression with laminectomy and drainage is critical, particularly if there is any associated neurologic deficit. Continue treatment with appropriate antibiotics.

Tuberculosis

Pott disease is tuberculous osteomyelitis of the spine that sometimes causes cord compression. Usually, this form of TB is due to reactivation disease (rarely is it primary tuberculosis). Less than 40% of affected patients have constitutional symptoms (fever, night sweats, and weight loss). Most commonly they have back pain, but neurologic deficits and/or radicular symptoms are also possible.

Diagnosis is confirmed by biopsies for pathology and culture. A positive TB skin test or serum interferon-γ release assay (IGRA) supports the diagnosis. Treatment is with standard 4-drug TB therapy (see the Pulmonary Medicine section for details).

Syphilis

Neurosyphilis is a potential complication if syphilis is untreated and may present earlier in patients with HIV/AIDS. Both secondary and tertiary syphilis can affect the spinal cord. The secondary manifestation of meningovascular syphilis can present as stroke or as infarction of the spinal cord (rare). Tertiary syphilis presents as cognitive impairment, tabes dorsalis, and/or aortitis.

Remember cognitive impairment by the mnemonic PARESIS: personality, affect, reflexes, eyes (Argyll Robertson)

pupil), sensorium, intellect, speech. The Argyll Robertson pupil is constricted and reacts to accommodation but does not react to light.

Tabes dorsalis is syphilitic involvement of the posterior columns that causes deficits in proprioception, manifesting as ataxia and paresthesias. Tabes dorsalis is diagnosed with physical examination, along with the following:

- Screening tests for syphilis (RPR [rapid plasma reagin] or VDRL [venereal disease research laboratory])
- *Treponema pallidum*-specific testing (MHA-TP [microhemagglutination assay for *T. pallidum*])
- +/- LP and biopsies with routine path and cultures

Read more about diagnosis and treatment of syphilis (including neurosyphilis) in the [Infectious Disease](#) section.

INFLAMMATORY MYELOPATHY — TRANSVERSE MYELITIS

Transverse myelitis (TM) is a rare condition in which there is inflammation of both sides of 1 or 2 segments of the cord (usually thoracic). The exact cause is uncertain, but it appears to be an autoimmune reaction. Onset may follow a viral infection or (rarely) a vaccine, or be idiopathic, but it is also seen with multiple sclerosis (MS) and several other autoimmune disorders (systemic lupus erythematosus, mixed connective tissue disease, Sjögren's, sarcoidosis, scleroderma, and rheumatoid arthritis). A partial lesion, multiple spinal cord lesions, or associated lesions on an MRI of the brain suggests MS rather than an idiopathic transverse myelitis. Additionally, longitudinally extensive myelitis (over > 3 contiguous vertebral segments) is more suggestive of a recurrent process from defined etiologies, such as neuromyelitis optica (see below), neurosarcoidosis, a connective tissue disease (e.g., lupus, Sjögren's), or a dural arteriovenous fistula.

Clinical presentation is most often acute and progressive over a few days, with early paresthesias, bilateral leg weakness, and numbness with a sensory deficit below the level of the lesion. Sphincteric disturbances and backache are also common. Urinary incontinence, a sensory level over the trunk, or a Babinski sign differentiate it from a rapidly progressive polyneuropathy, such as Guillain-Barré syndrome.

MRI of the spinal cord with contrast shows the inflammation of the cord. CSF analysis shows increased protein, lymphocytosis, and normal glucose.

MRI of the brain is always done to exclude lesions consistent with MS.

Neuromyelitis optica (NMO; a.k.a. Devic disease): This variant of myelitis manifests primarily by attacking the optic nerves and/or longitudinally extensive segments of

the spinal cord. The presence of serum NMO-IgG antibodies, also known as **antiaquaporin** antibodies, is associated with increased risk of recurrent myelitis. NMO antibodies also have a sensitivity of 73% and specificity of 91% for the diagnosis of Devic disease.

TM Treatment: The 2011 AAN guidelines (since retired, with a new one in development) on transverse myelitis recommend **empiric steroids** and even plasmapheresis if there is no response to steroids, although the level of evidence for these is weak.

COMPRESSION-INDUCED MYELOPATHIES

Cervical Spondylosis with Myelopathy

Cervical spondylosis is age-related wear and tear on the cervical spine. It begins with changes in the intervertebral discs, which occur gradually and accumulate with age. Neck pain is common. If the disc herniates, it will compress a nerve root, causing a **radiculopathy** at that level. Note: Radiculopathy manifests by numbness, paresthesias, weakness, and hyporeflexia in the corresponding region that is supplied by the compressed nerve root. The area affected is referred to as dermatome (sensory) or myotome (muscle groups). Pain with rotation and extension of the neck (Spurling sign) is a specific but not sensitive finding for cervical radiculopathy.

When the spondylosis becomes more severe, it can result in compression of the spinal cord itself (**myelopathy**). Myelopathy results in spasticity, hyperreflexia, and gait abnormalities. Gait abnormalities may be attributed incorrectly to increasing age of the patient. A quick test is to check reflexes; in patients > 65 years of age, a **brisk ankle reflex** can be the sole clue to cervical myelopathy.

If a rheumatoid arthritis patient presents with a post-op focal neuro deficit, suspect C1–C2 spinal cord trauma induced by intubation. This is likely if the patient has chronic asymptomatic C1–C2 subluxation. Anesthesiologists are generally well aware of this susceptibility and may order C-spine flexion and extension views preoperatively to assess for any signs of cervical subluxation. Of course, other mechanisms can cause similar injury in these patients.

Thoracic Myelopathy

Thoracic sensory levels: T4/T5 disease is at nipple line and T10 disease is at umbilicus.

In thoracic myelopathies, think tumor, vertebral compression fracture, or transverse myelitis—not compression from spine osteoarthritis.

Lumbosacral Myelopathy

The cord ends at L1–L2. Lumbosacral disease affects the **cauda equina** and nerve **roots**, and may cause **L4, L5, or S1** radiculopathy with the following presentations.

Affected dermatomes:

- L4 = medial aspect of leg
- L5 = anterolateral aspect of leg and dorsum of foot, including great toe (L5 = large toe)
- S1 = lateral side of foot by the small toe and plantar aspect of foot

Affected myotomes:

- L5 = weakness of the **great toe extensor** and ankle dorsiflexion; patients have trouble standing on the heel and present with **foot drop**.
- S1 = weakness of ankle plantar flexion; patients have trouble standing on the toes; ankle reflex is absent.

Lumbar spinal stenosis is a congenital narrowing of the spinal canal, affecting the conus medullaris or cauda equina. Patients are more susceptible to myelopathy caused by impingement of the cauda equina secondary to disc disease, ligamentous degeneration, and arthritis.

Lumbar spinal stenosis can result in neurogenic claudication, characterized by a deep, progressive ache in the legs, sometimes causing lower extremity numbness, paresthesias, or weakness, which is precipitated by standing or walking for a few minutes. These symptoms are aggravated by upright posture, which extends the spine, and relieved by sitting or squatting (i.e., flexing the hips and spine).

Buzz phrases that help diagnose spinal stenosis include “gets better when **bending over**” or “improves when walking uphill.” These activities curve the vertebral bodies and open space in the canal.

Differential diagnosis for spinal stenosis includes vascular claudication, which also causes symptoms when walking or exercising leg muscles but not when standing upright (Table 12-5).

Table 12-5: Spinal Stenosis vs. Vascular Claudication

	Change in Symptoms		
	Walking	Standing	Sitting
Lumbar Spinal Stenosis	Worse (except when walking uphill)	Worse	Better
Vascular Claudication	Worse	Better	Better

A presumptive diagnosis of spinal stenosis is made clinically. Neuroimaging (usually MRI) before treatment is not necessary for patients < 50 years of age with no neurologic deficits. MRI is done if there are progressive symptoms, red flag symptoms (neurologic deficits), symptoms do not improve with 6 weeks of conservative management, or the patient is an intervention candidate (steroid injections or surgery). In patients > 50 years of age and in those with neurologic deficits, imaging is often done immediately to confirm the diagnosis before determining treatment.

Treatment is conservative—physical therapy and analgesics. Surgery is a last resort for patients who have debilitating pain not relieved with conservative measures. Surgery is indicated urgently, however, in patients with progressive neurologic deficits or incontinence.

MISCELLANEOUS MYELOPATHIES

Ischemic Myelopathy

Ischemic myelopathy is caused by decreased perfusion or infarction of the **anterior spinal artery** that supplies the anterior 2/3 of the spinal cord. The clinical presentation is bilateral leg weakness (often complete paraplegia) and leg sensory loss but with preservation of vibration and position sense (posterior columns). This can be seen after aortic trauma or dissection, aortic aneurysm repair, and revascularization procedures involving the iliofemoral vessels, but it can also occur spontaneously, typically in patients with severe generalized vascular disease. Diagnosis is with MRI, and treatment is often supportive, but there are some strategies available if they occur following vascular procedures.

Syringomyelia

Syringomyelia is a progressive myelopathy caused by **cavitation** of the **central spinal cord**, usually in the cervical region but sometimes extending into the thoracic region. It can be idiopathic, developmental, or acquired. About 2/3 of cases are associated with **Arnold-Chiari** (a.k.a. Chiari II) malformation—a congenital malformation in which there is a downward shift of the cerebellar tonsils and medulla through the foramen magnum into the cervical area of the spine, sometimes with syrinx (cyst) formation.

Syringomyelia causes a **painless weakness** and wasting of the hands and arms (brachial amyotrophy) and **segmental sensory loss** of dissociated type (i.e., loss of thermal and painful sensation with sparing of tactile, joint position, and vibratory sense). Symptoms of syringomyelia typically occur as a “suspended” or “**cape-like**” sensory deficit across the shoulders and proximal upper limbs.

The loss of pain and temperature, with initially preserved light touch and vibration sensation, indicates involvement of the crossing spinothalamic fibers in the central part of the cord. When the anterior horn cells are affected, with lateral expansion of the syrinx, weakness and atrophy of the upper limbs occur, starting in the hands and moving proximally to include the arms and then shoulder muscles. Occipital and nuchal headaches are also very common.

Diagnose syringomyelia with MRI.

Surgical decompression or shunt placement can be tried for ongoing pain or neurologic deterioration.

Anterior Horn Cell Disorders

Anterior horn cell problems cause **motor** deficits only. **Amyotrophic lateral sclerosis** (ALS; a.k.a. Lou Gehrig disease) is the most common cause of anterior horn cell disorder. The hallmark of ALS is marked, simultaneous **upper** and **lower** motor neuron signs. Men are affected more often than women.

A patient with ALS presents with some variation of:

- **hyperreflexia** and **spasticity** (upper motor neuron), along with
- **fasciculations**, asymmetric limb weakness, and atrophy (lower motor neuron).

Consider ALS in a patient with weakness or difficulty with fine motor skills as well as fasciculations and/or atrophy on exam. Additionally, consider it with progressive dysarthria or dysphagia, particularly when tongue fasciculations and atrophy are seen. Patients report muscle cramping. Shortness of breath becomes apparent as disease progresses with worsened shortness of breath while lying flat due to weakness of the diaphragm. Exaggerated laughing or crying (pseudobulbar affect) can be another clinical clue. Some cases may start with weakness of a limb progressing to other limbs first, whereas others may start with earlier swallowing, speech, or breathing dysfunction with progressive weakness ensuing (bulbar onset). Cognitive dysfunction is not a main feature, though an association with frontotemporal dementia may be seen.

ALS is relentlessly progressive, involving upper and lower extremities, respiratory, truncal, and bulbar musculature, and it is terminal usually within **3–5 years** after diagnosis. Management of these patients includes determining how to proceed with respiratory and nutritional support as the disease progresses. Riluzole is typically used but extends life by only about 3 months. Edaravone was approved for the treatment of ALS in 2017.

Polio used to be the most common cause of anterior horn cell disorder; now **postpolio syndrome** must also be considered. Postpolio syndrome is typified by **areflexia** and progressive weakness **without** upper motor neuron signs that can occur decades later in polio survivors. Spinal muscular atrophy is a set of hereditary disorders of the anterior horn lower motor neurons. Recent genetic therapy breakthroughs have been made for spinal muscular atrophy with recent FDA approval. A polio-like presentation today is more likely to be due to other viruses like West Nile virus or enterovirus.

Examples of conditions that cause upper motor neuron (UMN) and lower motor neuron (LMN) findings in the same patient include:

- ALS (motor)
- B₁₂ deficiency with subacute combined degeneration of the cord (motor + sensory)
- Cervical myelopathy (motor + sensory)
- Syringomyelia (LMN = arms, UMN = legs, motor + sensory)
- Friedreich ataxia (ataxia + motor + sensory)
- Syphilis (motor + sensory)

PERIPHERAL NERVOUS SYSTEM

RADICULOPATHIES

A radiculopathy is a peripheral nerve injury at the level of the **nerve root**, just as the nerve exits the spinal cord, whereas myelopathy refers to injury of the spinal cord itself. Problems caused by the radiculopathy occur along the nerve pathway. Radiculopathy presents with motor or sensory problems anywhere along the nerve path, such as weakness, loss of motor control, pain, and numbness. The diagnosis can be confirmed with EMG and MRI. MRI is a more sensitive test for disc herniation but is not specific for individual nerve root compression. EMG likely has a higher specificity due to the ability to localize nerve root levels of involvement.

L4–L5 and L5–S1 radiculopathies are the most common of the lumbar radiculopathies; see Table 12-6.

NEUROPATHIES

PREVIEW | REVIEW

- Where are the main points of compression for ulnar, median, and peroneal nerves?
- What frequently causes nocturnal awakening with hand pain? Which nerve?
- Mononeuritis multiplex is caused by which diseases?
- Which infection should you consider in a hiker who presents with new onset of foot drop?
- Name 5 disease processes that can cause facial palsy.

Table 12-6: Lumbar Radiculopathies

Disc Level	Root	Pain	Sensory Loss	Motor	Reflex
L3–L4	L4	To anterior thigh	Anterior-medial thigh	Quadriceps weakness	Decreased knee jerk
L4–L5	L5	To outer calf	Outer calf and great toe	Extensor hallucis	No loss
L5–S1	S1	To sole of foot	Outer calf, outer foot	Eversion of foot	Decreased ankle jerk

- What is the clinical presentation of Bell's palsy?
- Diabetes can cause which neuropathies?
- Which cerebrospinal fluid findings are characteristic of Guillain-Barré syndrome (GBS)?
- How does the treatment of chronic inflammatory demyelinating polyneuropathy differ from the treatment of GBS?
- Name the drug used to treat diabetes that also can induce B₁₂ deficiency and cause a severe peripheral neuropathy.

OVERVIEW

Neuropathies can be divided into several categories based on which nerves are affected.

If the process involves only 1 nerve, it is called **mononeuropathy**. Mononeuropathies are generally due to **entrapment** (as with carpal tunnel syndrome). Other causes include focal ischemia and trauma.

If ≥ 2 nerves are affected in a limited distribution, the term **mononeuritis multiplex** is used. Mononeuritis multiplex results from systemic disorders like **diabetes** or **vasculitis**.

The process may involve the plexuses—either the brachial or lumbosacral plexus. Involvement of multiple nerves within a plexus is referred to as **plexopathy**. The main symptoms are pain, weakness, and sensory loss in the distribution of the involved nerves. The most common causes are trauma, diabetes, and infections. MRI of the plexus may help to determine the etiology.

Neuropathies that symmetrically and diffusely involve the peripheral nerves are called **polyneuropathy** (or **peripheral neuropathies**). Typical axonal polyneuropathy involves **distal** segments more than proximal. There are many causes of peripheral neuropathy.

Inflammatory and **hereditary** neuropathies are the most frequently missed causes of polyneuropathy—consider inflammatory causes and include a careful family history in your evaluation of peripheral neuropathies!

The workup for any neuropathy includes glucose tolerance testing, free T₄ and TSH levels, vitamin B₁₂, creatinine, CBC, and serum and urine immunofixation.

Do an electromyography and nerve conduction study (EMG/NCS) regardless of whether the symptoms are mono- or polyneuropathy. EMG/NCS helps to identify any disease of muscle and nerve.

Do serum protein electrophoresis, immunoglobulin electrophoresis, and quantitative immunoglobulin assays if the patient is > 40 years of age, particularly if the EMG/NCS suggests a demyelinating neuropathy.

MONONEUROPATHIES

Focal / Compressive

Focal mononeuropathies are caused by localized peripheral nerve damage, usually from a compression injury (although ischemia can also cause damage, especially in autoimmune diseases associated with vasculitis). Single nerve involvement can be caused by leprosy, sarcoidosis, and herpes zoster.

The main sites of compression or entrapment are the **ulnar** nerve at the **elbow**, the **median** nerve at the **wrist**, the radial nerve at the spiral groove, and the **peroneal** nerve at the **knee** (discussed below). Because radiculopathies and mononeuritis multiplex can have presentations similar or identical to focal/compressive neuropathies, you must also consider them in the workup of patients presenting with focal neuropathic symptoms.

Radial neuropathy (acute wrist drop) is mostly from nerve **compression** but is occasionally seen as a result of **diabetic** neuropathy and can also occur with **lead** toxicity. It has been called “Saturday night palsy” in inebriated patients because it occurs after bouts of unconsciousness whereby the nerve becomes compressed in the radial groove of the humerus. It is also called “honeymoon palsy,” referring to a partner sleeping on the patient’s arm all night. Symptoms typically resolve slowly over several weeks or months—provided the patient does not continually re-injure the nerve! Physical therapy is the best treatment, using wrist splints.

Lower brachial plexus injury (from surgery/tumor/trauma) causes a claw-hand deformity, similar to that which may be seen with severe ulnar neuropathy.

Carpal tunnel syndrome (CTS) is median nerve entrapment at the wrist, commonly from repetitive stress, causing sensory loss, paresthesias, and weakness involving the first 3 or 4 digits of the hand, but patients can have pain anywhere in the arm or shoulder! Thumb muscle wasting may occur ([Figure 12-8](#)). Median nerve entrapment at the wrist almost invariably causes **nocturnal awakening** due to hand pain or paresthesias. Prevalence of hypothyroidism is 1–10% in patients with CTS. Do not forget about the association of CTS with acromegaly. (See more on acromegaly in the [Endocrinology](#) section.)

Initial treatment of CTS is neutral alignment with wrist **splints** and modifying behavior to avoid repetitive stress. If this is ineffective, steroid injection may help. The next step is surgical median nerve release.

Know: Pregnancy can cause an acute presentation of CTS, and symptoms typically improve after delivery. Splints are the best treatment for this patient group. For more on carpal tunnel during pregnancy, see the [Women’s and Men’s Health](#) section.

Ulnar neuropathy causes sensory loss and paresthesias in the little finger and ulnar aspect of the ring finger, as well as weakness of finger abductors and adductors in more severe cases. It is usually due to compression of the nerve at the elbow (cubital tunnel syndrome) but, **much less commonly**,



Figure 12-8: Thumb muscle wasting due to carpal tunnel syndrome

can also result from a lesion at the **wrist**. Rarely, trauma to the heel of the hand can result in distal ulnar injury (bicyclists can get a distal ulnar neuropathy at Guyon canal). Elbow pads and splints help. Surgery (anterior transposition) is also an option for refractory cases of cubital tunnel syndrome.

Meralgia paresthetica is due to compression or injury of the lateral femoral cutaneous nerve of the thigh, resulting in numbness to the lateral thigh. This compression is typically due to wearing a heavy belt (plumbers, police officers) or tight pants, but can also occur with hip trauma, surgery, or pregnancy. Obesity is a risk factor as well. Treatment is conservative and focuses on the underlying cause.

Sciatic nerve compression (sciatic neuropathy) is uncommon but can occur from surgical procedures of the hip, iatrogenic injections, trauma (e.g., gunshot wound to the upper leg), and prolonged compression (e.g., from loss of consciousness). This can cause weakness of both ankle and toe dorsiflexion (peroneal nerve) and plantar flexion (tibial nerve), as well as hamstring weakness. Numbness is below the knee. Ankle reflex is lost on the affected side.

When you hear the term sciatica, it generally refers not to compression of the sciatic nerve but to radicular irritation from the back; i.e., L5 or S1 radiculopathies. Sciatica might just be painful sensations shooting down the leg from lumbosacral root impingement and might have a normal neurologic exam.

Peroneal nerve compression typically occurs at the proximal head of the fibula, causing foot drop. Remember that L5 radiculopathy also causes foot drop.

To distinguish between peroneal nerve compression and L5 radiculopathy: Patients with peroneal nerve compression **cannot evert** the foot well but can still invert it, while L5 radiculopathy prevents or **hinders both** eversion and

inversion (Table 12-7). Also, it is useful to test proximal L5 innervated muscles, such as the hamstrings and thigh abductors, which is not affected with peroneal nerve compression.

Know: Charcot-Marie-Tooth (CMT) disease (discussed under [Charcot-Marie-Tooth Disease on page 12-47](#)) can cause symptoms similar to peroneal nerve compression, but it has a bilateral foot drop presentation with other features, such as distal atrophy and dysmorphic feet (high arches and hammer toes).

Mononeuritis Multiplex

Note that mononeuritis multiplex can present identically to the focal/compressive neuropathies under [Focal / Compressive](#). Rather than being caused by nerve compression, mononeuritis multiplex is caused by a **systemic disease**. Vasculitis and vascular occlusion of the vasa nervorum (vessels that supply the nerves) are the main causes.

Consider any of the following as a possible cause of mononeuropathy +/- multiplex:

- Rheumatoid arthritis
- DM
- Connective tissue diseases
- Vasculitis
- Polyarteritis nodosa
- Lyme disease (Think of this in a hiker with new-onset foot drop.)
- Neuralgic amyotrophy

Neuralgic amyotrophy (a.k.a. Parsonage-Turner syndrome, brachial plexus neuropathy, acute brachial radiculitis) is temporary inflammation of the brachial plexus that is commonly idiopathic. Initially, it causes extreme pain in the shoulder with radiation to the arm, neck, and back. Within hours to days after the onset of pain, the shoulder muscles and proximal arm musculature become weak and then later atrophic. Bilateral involvement can occur. Commonly affected nerves are the suprascapular, long thoracic (causing winging of the scapula), axillary, musculocutaneous, and anterior interosseous nerves. The plexus pattern can be patchy, affect multiple individual nerves, or even just one nerve. Diagnosis is clinical, supported by EMG/NCS. It improves in 1-3 years with conservative management.

Bell's and Other Facial Nerve Palsies

Bell's palsy is caused by dysfunction of the external 7th cranial nerve. It is regarded as idiopathic, but **herpes simplex** (or its associated immune response) is the cause of **most**

Table 12-7: L5 Radiculopathy vs. Peroneal Nerve Compression

	Foot Drop?	Able to Invert Foot?	Able to Evert Foot?
L5 Radiculopathy	Yes	No	No
Peroneal Nerve Injury	Yes	Yes	No

cases (definitively supported by finding evidence of the virus by PCR in the affected nerve roots).

Varicella zoster is also a cause and is diagnosed when vesicles involve the tympanic membrane and external auditory canal (Ramsay Hunt syndrome).

Important systemic diseases can also cause a facial palsy that presents identically:

- Lyme disease
- Acute HIV
- Neurosarcoidosis
- Guillain-Barré syndrome
- Diabetes mellitus

Some experts call these palsies Bell's, but others prefer to identify them as a systemic manifestation of underlying disease.

Other causes of facial palsy: schwannomas and parotid tumors.

Bell's palsy affects an entire half of the face, including the forehead. It causes ipsilateral facial muscle paralysis and occasionally results in no taste sensation on the anterior 2/3 of the tongue, loss of lacrimation, and hyperacusis. Pregeniculate lesions cause the loss of taste, salivation, and lacrimation, while more distal lesions spare these functions.

Note: For bilateral Bell's palsy, consider sarcoid, Lyme disease, HIV, or GBS.

To help differentiate Bell's palsy from other nerve damage, know that cortical lesions spare the muscles of the forehead and upper eyelid, whereas Bell's palsy affects them.

Diagnosis is clinical. Imaging of the head is reserved for patients who do not improve within 6 months or who continue to progress with facial weakness after 3 weeks.

Know that if the palsy is preceded by a period of facial twitching, the risk of tumor is higher. Perform urgent imaging of these patients.

Patients who begin to improve within 3 weeks commonly recover completely. If complete ipsilateral paralysis occurs, full recovery is less likely.

A week of prednisone shortens the course and improves function if started within 7 days of clinical onset. Studies assessing combined antiviral drugs (acyclovir or valacyclovir) + prednisone show conflicting results. Some experts give both; others do not unless obvious signs of herpes are present (i.e., vesicles). Lubricant eye drops and covering of the involved eye at night is important to prevent corneal ulceration. Eyelid surgery is reserved for patients with severe palsy, or when there is corneal anesthesia or xerophthalmia not amenable to eye lubricants.

Diabetic Mononeuropathies

Know: Diabetes can cause several cranial neuropathies and a lumbosacral plexopathy (diabetic amyotrophy). Neuropathies affecting cranial nerves 3, 4, and 6 present

with eye pain, drooping eyelids, and double vision; those affecting cranial nerve 7 present with Bell's palsy. Isolated median, radial, ulnar, and peroneal neuropathies are also more common in patients with diabetes.

Note that diabetic involvement of the 3rd cranial nerve typically presents with diplopia and weak eye movements without any changes in the pupil.

Remember: A diabetic 3rd cranial neuropathy spares the pupil. If a patient has a 3rd cranial neuropathy with pupillary dilation, think compression of the 3rd cranial nerve by an aneurysm of the posterior communicating artery. This warrants an urgent MRI and MRA!

Diabetic lumbosacral plexopathy (amyotrophy) presents with leg pain (82%) followed by proximal weakness of the leg. It initially tends to be unilateral (88%) but eventually involves both legs. Autonomic dysfunction occurs in 50% of patients; weight loss > 10 lbs occurs in about 80%. Sensory symptoms and signs can also occur. The condition develops over months and so does partial or complete recovery. No specific treatment exists, although steroids may help the pain.

POLYNEUROPATHIES

Demyelinating vs. Axonal Polyneuropathies

Axonal polyneuropathies are usually a sensorimotor combination, with sensory abnormalities appearing first (paresthesias progressing to numbness), and distal motor weakness (often mild) appearing later. The nerve conduction velocity is normal in these conditions.

Demyelinating polyneuropathies affect motor fibers significantly more than sensory fibers and present with weakness out of proportion to the typical metabolic axonal polyneuropathies. Nerve conduction studies are diagnostic, with slowing of conduction, with or without conduction block, in affected nerves. Of the patients with demyelinating neuropathy, approximately 10% have a serum paraprotein. Although occasionally associated with a solitary plasmacytoma, the paraprotein is usually benign.

Autoimmune, Inflammatory Polyneuropathies — Guillain-Barré Syndrome

Guillain-Barré syndrome (GBS) is the most common autoimmune, inflammatory polyneuropathy. GBS is a syndrome with demyelinating (most common) and axonal variants.

In the vast majority of cases, a mild gastrointestinal or respiratory infection precedes the polyneuropathy. GBS was reported after influenza vaccination in the late 1970s and 1990s and after the meningococcal conjugate vaccine in 2005. Causality has not been established for either vaccine, and the subject is highly controversial. There is no requirement with these vaccines to warn patients about possible GBS, but patients with a history of GBS are cautioned to avoid vaccination for the

1st year after their illness and indefinitely for a specific vaccine that was given within 6 weeks of the onset of a patient's GBS.

Classic **demyelinating** GBS (termed acute inflammatory demyelinating polyradiculoneuropathy [AIDP]; 90% of U.S. cases) presents as an **ascending paralysis** (with **distal** and **proximal weakness**), including weakness of respiratory muscles, with **areflexia**. Patients may initially have some mild sensory abnormalities and paresthesias, but GBS is primarily a motor illness with absent reflexes. Disturbances in autonomic function and urinary retention may also be seen. Back pain is often present due to inflammation of the nerve roots.

The Miller Fisher **axonal** variant (MFV; 5% of cases) is a type of GBS that includes only areflexia, ataxia, and ophthalmoplegia.

Two other **axonal** variants are even less commonly seen:

- 1) AMAN (acute motor axonal neuropathy), more associated with *Campylobacter* diarrhea
- 2) AMSAN (acute motor and sensory axonal neuropathy)

Paraparetic (partial paralysis), ataxic, Bickerstaff brainstem encephalitis, a cervical pharyngeal variant, and purely motor or purely sensory forms of the illness have also been observed.

In patients with any type of GBS, the CSF has a **normal** cell count and a **high protein** (albuminocytologic dissociation); suspect another diagnosis if the CSF has $> 10 \text{ WBC/mm}^3$ (i.e., HIV). EMG/NCS helps to characterize the variant (axonal or demyelinating).

Anti-GQ1b IgG is a unique serum protein measurable in over 80% of MFV cases of GBS, and it assists with diagnosis of this variant.

The acute axonal variants are typically associated with preceding *Campylobacter jejuni* infections and also with development of many antibodies against the gangliosides found in peripheral nerves (especially **anti-GQ1b**).

Close respiratory monitoring and care are important. Measurement of vital capacity (VC), maximal inspiratory pressure (MIP), and maximal expiratory pressure (MEP) are used for the bedside estimation of diaphragmatic strength and respiratory function. The trend of these measurements is a guide to the likelihood of respiratory failure. Use the 20–30–40 rule to determine need for ventilator support: VC $< 20 \text{ mL/kg}$, MIP less negative than $-30 \text{ cm H}_2\text{O}$, and MEP $< 40 \text{ cm H}_2\text{O}$.

Of note, significant neck flexion weakness (i.e., unable to raise head against gravity when lying flat) is another predictor of respiratory failure.

Plasmapheresis and IV immunoglobulin therapy (IVIG) are equally effective. Use one or the other if patient presents within 4 weeks of initial symptoms.

Steroids are **not** effective.

Complete recovery is the norm for about 80% of patients; however, 10% have a very prolonged course with or without significant residual weakness. ~ 5% of patients do not survive the illness.

Chronic Inflammatory Demyelinating Polyneuropathy

Chronic inflammatory demyelinating polyneuropathy (CIDP) begins **insidiously** and evolves **slowly**, either in a steadily progressive or stepwise manner, progressing or relapsing over a period of > 8 weeks. In about 15% of cases, CIDP begins like a mild or moderate variant of GBS, but it slowly worsens or has a chronic relapsing course.

Chronic symmetric sensorimotor loss, EMG findings of demyelination, and elevated CSF protein define the illness.

CIDP cases are usually not traceable to an inciting event, such as an infection. (Still, it is useful to think of CIDP as “Guillain-Barré that won't go away.”) Consider CIDP in the patient with a demyelinating polyneuropathy (by EMG/NCS) that extends beyond 8 weeks in duration.

Lumbar puncture and EMG results are **identical to GBS** (high protein, no pleocytosis, and demyelinating polyneuropathy). Exclude systemic disorders, specifically HIV, hepatitis viruses, Lyme, thyroid disease, diabetes, myeloma, sarcoidosis, and connective tissue disorders, such as lupus.

Unlike in Guillain-Barré syndrome, **glucocorticoids hasten** recovery and prevent relapse in CIDP. Plasmapheresis or IVIG are also standard treatments. (Pick 1 of the 3.) Several other immunomodulators are used chronically.

Charcot-Marie-Tooth Disease

Charcot-Marie-Tooth (CMT) disease is by far (90%) **the most commonly inherited** peripheral polyneuropathy. There are many “types” composed of > 50 separate gene associations under the general heading of CMT, all caused by mutations in myelin genes that are inherited variably (autosomal dominant [most common], autosomal recessive, or X-linked).

CMT diseases are demyelinating in the most common forms, but axonal or mixed in a sizable portion of the rest, and are differentiated based on genetic markers. All have **both motor and sensory** impairment and typically present within the first 2 decades of life. The neuropathy is symmetrical and progresses slowly. It is distal predominant with distal sensory loss and bilateral foot and, later, hand weakness. There tends to be dysmorphic feet (high arches and hammer toes) and a family history of neuropathy. Patients present insidiously, often with a long history of spraining ankles or having other minor symptoms before formal evaluation. Diagnosis is made with EMG to characterize the neuropathy subtype and genetic testing for confirmation. CMT1A (autosomal dominant, demyelinating form) is the most common and targeted genetic testing of *PMP22* and is ordered first for that; otherwise, gene panel testing has become the most cost effective and efficient way of trying to diagnose the genetic subtype. Treatment is supportive.

Diabetic Peripheral Neuropathy

Diabetes mellitus is the **most common** cause of polyneuropathy in general clinical practice. Diabetic peripheral neuropathy (DPN) is an axonal **neuropathy** that mainly causes **sensory** changes, including pain, paresthesias, and **numbness in a length-dependent, stocking glove fashion**.

Muscle weakness is generally mild. Some have distal loss of reflexes. In long-standing cases, trophic changes are noted. Some patients have predominant loss of joint position and vibration sensations.

Control of blood sugars is the most important therapy. Effective treatments for pain include the FDA-approved DPN drugs duloxetine (Cymbalta, Irenka) and pregabalin (Lyrica)—both are equally effective. Other drugs are used including tricyclic antidepressants, carbamazepine, gabapentin, lamotrigine, tramadol, and venlafaxine. Topical treatment with capsaicin cream and lidocaine also help. α -lipoic acid is a supplement that can be beneficial.

Be aware that **metformin** treatment of diabetes mellitus can occasionally result in malabsorption of vitamin B₁₂ with subsequent peripheral neuropathy resembling DPN. This is an easily prevented serious side effect of metformin.

Alcoholic Peripheral Neuropathy

Alcohol is directly toxic to both nerves and muscles and causes many kinds of neuropathies (i.e., peripheral, autonomic, compressive [e.g., passing out on arm]). The polyneuropathy is typically axonal but is made worse if demyelination is superimposed (caused by nutritional deficiencies).

Symptoms of alcoholic axonal neuropathy start with pain and numbness in the feet in a **stocking** distribution. Over time, patients lose reflexes, proprioception, and strength.

Patients slowly recover with multivitamin therapy and abstinence from alcohol.

Other Causes of Axonal Neuropathies

Know other somewhat common causes of axonal polyneuropathy, including:

- Toxins, such as heavy metals (e.g., lead, arsenic)
- Chemotherapy drugs (e.g., vincristine)
- Isoniazid
- B₆ (pyridoxine) overdose from nutritional supplements
- Organophosphates
- Systemic illnesses (myeloma, amyloidosis, porphyrias, thyroid disease, hepatitis viruses, amyloidosis, and HIV/AIDS)

Time of Onset

Time of onset helps to differentiate among the polyneuropathies:

- **Short** onset (days) is nearly always due to **inflammatory, immunologic, toxic, or vasculitic**

etiology. Think porphyria, GBS, and a few of the toxic polyneuropathies.

- **Long** onset (over several years) is seen with the hereditary disorders, such as CMT.
- **Subacute** onset (several weeks to 2 years) occurs in the majority of patients:
 - Toxicity (Lead and glue-sniffing cause mainly motor effects, while INH and vincristine cause sensorimotor effects.)
 - Nutritional deficiencies (especially B₁, B₆, and B₁₂)
 - Paraneoplastic syndromes (See [Lambert-Eaton Myasthenic Syndrome](#).)
 - Rheumatologic disorders
 - Diabetes
 - Of note, CIDP presents rather subacutely over weeks and then progresses or relapses over > 8 weeks.

NEUROMUSCULAR JUNCTION

DISEASES OF THE NEUROMUSCULAR JUNCTION

PREVIEW | REVIEW

- What are the clinical presentations of myasthenia gravis (MG)?
- How is MG diagnosed?
- Which other tests should be done in patients with MG?
- Which cancers cause Lambert-Eaton myasthenic syndrome (LEMS)?
- What happens to deep tendon reflexes in MG and LEMS?

MYASTHENIA GRAVIS (MG)

MG is an **autoimmune** disorder. Most patients have autoantibodies to:

- postsynaptic acetylcholine receptor (AChR; 85%) or
- muscle-specific tyrosine kinase (MuSK) receptor.

40% of those who test negative for acetylcholine receptor antibody (AChR-Ab) are MuSK antibody (MuSK-Ab) positive. A smaller group of MG patients has **neither** antibody (termed seronegative MG [SNMG]), though that proportion keeps getting smaller as newer commercial antibodies become available (most recently LRP4 antibody tests).

MG is associated with **thymomas** (~ 15% of patients) and **thymic hyperplasia** (~ 65%), although it is not understood exactly how the thymus is related to antibody formation.

There are 2 forms of MG:

- 1) **Generalized MG** presents as episodic weakness with repetitive movements (weakness—not tiredness, not soreness). Symptoms are worse at the end of the day.

Common presenting complaints include weakness while brushing hair, putting away dishes or climbing stairs, and diplopia after a long day. Weakening with repetitive muscle stimulation during the physical exam (muscle fatigability) suggests the diagnosis. Ptosis is common. In addition to weakness of extraocular muscles, muscles of facial expression, mastication, swallowing, and speech are affected in 80% of patients at some time in the illness. Muscle atrophy is rare, and tendon reflexes are normal.

- 2) **Ocular MG** presents as weakness localized to the eyes (lids and extraocular muscles).

Practice pearls: Demonstrating fatigable ptosis (i.e., worsening of ptosis on 30 seconds of sustained upgaze) is a good way to differentiate myasthenic ptosis from other forms of ptosis. Of course, the pupil size is normal, unlike in Horner syndrome (with **miosi**s, ptosis, anhidrosis). In addition, the pattern of extraocular muscle weakness often does not fit the distribution of a single oculomotor nerve, and may change from one examination to the next.

Diagnosis of MG is best confirmed by measuring **AChR-Abs** and **MuSK-Abs**. AChR-Abs are present in 85–90% of patients with generalized disease but only in ~ 60% of those with isolated ocular disease. Often, MuSK-Abs are present in patients who are negative for AChR-Abs (~ 50%). Antibody levels are not necessarily prognostic, but they do rise and fall with immunotherapy.

The classic edrophonium (Tensilon) test is **not** done much because results are not as reliable as antibody measurements.

The ice pack test can be used for patients with ptosis as part of their symptoms. Ice in a glove is applied to the closed eyelid for 2 minutes, which results in less ptosis. Sensitivity of this test is ~ 80%.

Electrodiagnostic studies, including repetitive nerve stimulation studies and single-fiber EMG, are useful in supporting the diagnosis.

Do thyroid function studies because **30%** of patients with MG have **chronic autoimmune thyroiditis** and image the chest with CT or MRI in all confirmed diagnoses to rule out thymoma. Look out for symptoms that suggest lupus, Sjogren syndrome, or rheumatoid arthritis because there is considerable overlap.

Treatments used for MG:

- Anticholinesterase agents (e.g., pyridostigmine [Mestinon])
- Immunomodulators in patients **uncontrolled** on pyridostigmine (e.g., steroids, cyclosporine, mycophenolate)
- IVIG or plasmapheresis (for myasthenic **crisis** only because duration of action is very short)
- Thymectomy (This has evidence-based support even without thymoma in patients with generalized MG < 60 years of age, but definitely perform in patients with **thymoma**.)

Myasthenic crisis is a rapid deterioration of myasthenia that can cause **respiratory failure** and severe weakness.

Infections or certain medications can precipitate crises. Blood gases are poor predictors of respiratory failure in MG. The functional respiratory capacity is a better indicator of impending respiratory failure; monitor it closely. Besides respiratory support, patients respond to plasmapheresis and IVIG.

Know the few drugs that can precipitate myasthenic crisis in patients with either known or undiagnosed MG:

- Aminoglycosides
- Fluoroquinolones
- β -blockers
- Procainamide
- α -interferon
- Magnesium sulfate
- Penicillamine
- Quinidine

LAMBERT-EATON MYASTHENIC SYNDROME

Lambert-Eaton myasthenic syndrome (LEMS) is a paraneoplastic syndrome. About 60% of cases are seen in patients with **small cell** lung cancer; other associated cancers include prostate, breast, stomach, rectum, and lymphomas. It is also seen rarely in **autoimmune** diseases. LEMS is itself an autoimmune disease in which antibodies are produced that are specific for **calcium channels** in presynaptic peripheral nerve terminals, causing decreased release of acetylcholine from the nerve terminals.

Know the following about symptoms:

- Typical symptoms are gradually progressive proximal muscle weakness, ptosis, erectile dysfunction, aching thighs, dry mouth (autonomic dysfunction), and hyporeflexia, especially in the lower extremities.
- It looks like MG, except it **rarely** involves the **ocular** muscles and **repetitive** exercise may actually **reverse** the weakness for the first few contractions. Also, deep tendon reflexes are depressed in LEMS as opposed to MG where they are preserved.

Diagnose Lambert-Eaton's by measuring voltage-gated calcium channel (**anti-VGCC**) **antibodies**. Anti-VGCC antibodies are not 100% specific; they are sometimes found in patients who do not have Lambert-Eaton's. Therefore, measure them only in patients who have a **high** pretest probability of true disease. EMG can help distinguish between Lambert-Eaton's and myasthenia—with decremental response (weakening) in myasthenia in general to 3-Hz stimulation but incremental response (strengthening) to rapid stimulation in Lambert-Eaton myasthenic syndrome (50 Hz).

Look for malignancy in anybody diagnosed with Lambert-Eaton's—especially small cell lung cancer.

Treatment includes addressing any underlying malignancy along with drugs that increase the amount of acetylcholine in the synapse for mild symptoms

(guanidine, 3,4-diaminopyridine, and pyridostigmine). For refractory or severe weakness, proceed to IVIG, plasmapheresis, azathioprine, cyclosporine, mycophenolate, rituximab, or prednisone.

MUSCLE

MYOPATHIES

PREVIEW | REVIEW

- Where is the muscle weakness that occurs with inclusion body myositis?
- Progressive limb girdle weakness in an adult patient who has a family history of the same is indicative of which diagnosis?

NOTE

Myopathy simply means muscle disease. Myopathies are typically classified under neuromuscular diseases (hence their discussion here). Symptoms can be muscle weakness, stiffness, cramps, and spasms.

INFLAMMATORY MYOPATHIES

Inflammatory myopathies are caused by chronic muscle inflammation, usually:

- Dermatomyositis
- Polymyositis
- Inclusion body myositis

Both dermatomyositis and polymyositis often cause:

- Elevated CPK
- Proximal muscle weakness

Both respond to corticosteroids.

Inclusion body myositis is a less common type of myositis in which patients present with:

- A slowly progressive, painless muscle weakness with involvement of proximal (initially) then distal muscles
- Hallmark signs are significant quadriceps and finger flexor weakness with some asymmetry.
- Elevated CPK
- Oculomotor muscle sparing

Inclusion body myositis does not respond well to corticosteroids. Muscle biopsy in inclusion body myositis shows vacuolar inclusions.

See more on dermatomyositis, polymyositis, and inclusion body myositis in the [Rheumatology](#) section.

ENDOCRINE MYOPATHIES

Proximal muscle weakness of varying degrees may be seen in patients with thyroid and parathyroid disease, acromegaly, severe vitamin D deficiency, and conditions of steroid excess.

Hypothyroid patients have generalized muscle weakness, myalgias, and slowness of contraction and relaxation; they can have increased CPK. Muscle cramping is prominent in hypoparathyroidism.

METABOLIC MYOPATHIES

Consider a metabolic cause of muscle dysfunction in patients with muscle fatigue, pain, cramping, and, in more severe cases, contractures and myoglobinuria. These symptoms are precipitated by exercise in patients with disorders of carbohydrate metabolism and by fasting in those with disorders of lipid metabolism. The major categories are:

- Disorders of **carbohydrate metabolism** (myophosphorylase and phosphofructokinase deficiency): Myophosphorylase deficiency (McArdle's) presents with difficulty with intense exercise (i.e., sprinting), prolonged cramping (known as contractures), and a "second-wind" phenomenon where moderate exercise capacity improves after about 10 minutes of exercising.
- Disorders of **lipid metabolism** (e.g., carnitine deficiency): Carnitine palmitoyltransferase 2 (CPT 2) deficiency is the hallmark aerobic defective metabolic myopathy, where prolonged exercise (e.g., long distance running), fasting, or illness can precipitate episodes of rhabdomyolysis.
- Disorders of **mitochondrial function**: Mitochondrial myopathies are distinguished by the presence of ragged red fibers on light microscopy of a muscle biopsy and a range of associated clinical features in addition to muscle disease, such as neuropathy, short stature, hearing loss, seizures, diabetes, and stroke.

MUSCULAR DYSTROPHIES

Duchenne muscular dystrophy is an X-linked disorder that causes progressive muscle weakness, starting at about 2 years of age, and progresses to death as a young adult due to cardiac or respiratory failure comorbidity. The weakness is more proximal than distal. Look for an elevated CPK.

Myotonic dystrophy consists of 2 types of inherited, adult-onset, neuromuscular disorders that have multisystem effects. Myotonic dystrophy Type 1 is caused by mutations in the *DMPK* gene, whereas Type 2 results from mutations in the *CNBP* gene. The genetic abnormalities result in weakened skeletal muscle, myotonia (prolonged contraction on muscle percussion), cardiac conduction defects, cataracts, hypogonadism, and insulin resistance. Patients characteristically have frontal balding and a "hatchet" face appearance as a result of jaw and temporal muscle wasting. Typically, patients complain of skeletal muscle weakness (limb girdle in Type 2 and more distal in Type 1) and have positive family history. Consider this disease in a patient who presents as an adult with symptoms of muscle dystrophy. Refer these patients to a neurologist who can make the diagnosis using genetic tests. Treatment is supportive only.

ACQUIRED IMMUNODEFICIENCY SYNDROME (AIDS)-RELATED MYOPATHY

AIDS-related myopathy is uncommon and typically thought to be due to **zidovudine**, but some investigators attribute it to the direct effects of the virus (controversial). Patients present with a generalized (proximal > distal) **weakness** and an **elevated CPK**. Treatment: **Stop the zidovudine**. Of note, muscle biopsy shows mitochondrial pathology with this medication.

MISCELLANEOUS DISORDERS

CNS TUMORS

BRAIN TUMORS

The most common tumors that metastasize to the brain include lung cancer, breast cancer, melanoma, and renal cancer. There are a wide variety of adult primary brain tumors. The most common malignant primary tumor is the highest-grade glioma, glioblastoma multiforme (more in the **Oncology** section), and the most common benign primary brain tumor is a meningioma. Neurofibromatosis Type 1 is autosomal dominant, sporadic, and associated with optic gliomas, soft tissue sarcomas, Lisch nodules, and café au lait macules. Neurofibromatosis Type 2 is autosomal dominant and associated with bilateral vestibular schwannomas, cataracts, and plaque-like or nodular skin lesions. Tuberous sclerosis is a genetic disorder that causes benign tumors with symptoms based on location (i.e., obstruction of periventricular aqueduct of Sylvius). Medulloblastomas occur in the cerebellum and are associated with familial adenomatous polyposis and nevoid basal cell carcinoma. von Hippel-Lindau syndrome is associated with the capillary-rich hemangioblastomas that appear as an enhancing nodule within a cyst anywhere in the CNS system.

Patients with brain tumors may present with a variety of focal neurologic deficits depending on the location of the tumor(s). Patients may also present with a first-time

seizure or symptoms of increased ICP, such as headache, nausea/vomiting, papilledema, or visual changes.

Order brain imaging for individuals with these symptoms.

Brain metastases can be treated surgically for a single lesion or with stereotactic radiosurgery for a limited number of small lesions. A high number of lesions require treatment with whole brain radiation. For malignant primary brain tumors, a combination of radiation, surgery, and chemotherapy may be undertaken. Long-term prognosis is generally poor. Alternatively, benign primary brain tumors can be monitored clinically. If the tumors are compressing structures in a symptomatic or dangerous way, they can be surgically removed, in which case surgery can be curative.

For acute management of edema related to tumor, corticosteroid therapy can be employed, such as dexamethasone, which does help decrease vasogenic edema. Corticosteroid therapy does not help treat cytotoxic edema, as is seen with stroke. Seizures related to malignant tumor are generally treated with an antiseizure medication that has minimal reaction with other medications or chemotherapy agents, such as levetiracetam.

See **Table 12-8** for further salient details about brain tumors.

SPINAL CORD TUMORS

Epidural metastases occurring at thoracolumbar regions are most commonly from breast cancer, multiple myeloma, lymphoma, prostate cancer, and lung cancer. Progressive back pain at the spinal level is usually the first symptom, followed by motor symptoms. Resulting spinal cord compromise is an acute neurological emergency, warranting a stat neurosurgery consultation for spinal decompression and/or radiation therapy to prevent loss of neurologic function. The most common primary spinal cord tumors are the glial tumors, ependymomas (can generally be resected) and astrocytomas (total resection success depends on tumor grade).

Table 12-8: Highlights for Selected CNS Tumors

Type	Description
Glioblastoma multiforme	Butterfly lesion across corpus callosum, poor prognosis, necrosis on pathology Treat with surgery, radiation, and chemotherapy (temozolomide as mainstay; bevacizumab for continued progression).
Oligodendroglioma	"Fried egg" cells on pathology
Meningioma	Generally benign, dural tail on imaging, psammoma bodies on pathology
Acoustic neuroma	Think neurofibromatosis Type 2 with bilateral acoustic neuroma.
Melanoma, renal cell carcinoma, choriocarcinoma, thyroid carcinoma	Metastatic lesions most likely to have hemorrhage
Primary CNS lymphoma	Treat with high dose methotrexate. AIDS-related primary CNS lymphoma is associated with Epstein-Barr virus.

CNS METASTASES

PREVIEW | REVIEW

- A patient with history of prostate cancer or new onset of urinary incontinence should make you consider which diagnosis?

CNS metastases commonly cause a slow onset of symptoms (headaches, focal neuro deficits, impaired cognition, seizures, and/or stroke symptoms), although they can be abrupt if there is hemorrhage into a tumor.

Know the following main mets to the brain (Table 12-9).

Parenchymal brain metastases occur most commonly with lung, renal, and breast cancer, as well as with melanoma and lymphoma.

Dural metastases occur with breast and prostate cancer.

Epidural metastases at the level of the spinal cord cause back pain, usually worse when lying down. New onset of bladder or bowel dysfunction (i.e., incontinence, urgency) is very important and alerts you to consider spinal epidural metastases, especially in the setting of new back pain. In a patient with a history of cancer—especially prostate, breast, and lung cancer—and with cord compression symptoms (i.e., cauda equina), metastases must be ruled out!

Meningeal malignancy is most frequently seen with lymphomas, carcinoma of the breast, and melanoma. It is less commonly seen in cancers of the lung and the gastrointestinal tract, childhood leukemia, and systemic lymphoma.

MRI with contrast is the best imaging study.

Treatment of CNS metastases depends on how many metastases are present, the cancer prognosis, and the functional status of the patient. An approachable, single metastasis in a functional patient is treated with surgery and radiation. Small lesions (< 3 cm) and/or surgically inaccessible lesions can be treated with stereotactic radiosurgery. Less functional patients with numerous lesions are usually treated with whole brain radiation and chemotherapy +/- corticosteroids.

METABOLIC AND TOXIC DISORDERS

PREVIEW | REVIEW

- How does the presentation of the typical Wernicke patient differ from that of the typical Korsakoff patient?
- What is Wernicke encephalopathy? How is it treated?
- What are the symptoms of lithium toxicity?
- What effect does a hyponatremic state have on lithium resorption by the kidney?

WERNICKE'S / KORSAKOFF'S

Wernicke encephalopathy and Korsakoff syndrome are considered different presentations of the same disease process. Wernicke's is acute in onset, milder, and has a better chance of recovery while Korsakoff's refers to the later onset, chronic, neuropsychiatric symptoms following Wernicke's that are often severe and rarely reversible. The cause of both syndromes is thiamine (B₁) deficiency.

Wernicke encephalopathy is most often associated with alcoholism, but it can be seen in cases of protein-energy malnutrition (i.e., extreme catabolic states, kwashiorkor, marasmus), malabsorption, and specific loss of thiamine during dialysis.

It is characterized by global confusion with inattention, apathy, disorientation, and memory loss that worsens over days to weeks. The major sites of brain involvement include the thalamus, hypothalamus, midbrain, floor of the 4th ventricle, and cerebellar vermis.

Abnormal eye movements are typical and include horizontal nystagmus and a disordered conjugate gaze that progresses to ophthalmoplegia (bilateral lateral rectus weakness, either in isolation or together with palsies of other extraocular muscles). The pupils may become sluggishly reactive to light. The person may have trouble standing or walking due to truncal ataxia.

Diagnosis is clinical. Recognize and treat the disease in the early stages or progressive loss of consciousness including stupor, coma, and death can rapidly follow within weeks.

Know the typical Wernicke's presentation: confused + staggering gait + trouble moving eyes.

Table 12-9: Main Mets to the Brain

	Breast	Lung	Prostate	Melanoma	Lymphoma	Renal
Parenchymal	+	+		+	+	+
Dural	+		+			
Epidural	+	+	+			
Meningeal	+			+	+	

Korsakoff syndrome is a chronic amnestic syndrome associated with alcoholism, malnutrition, and vitamin B₁ deficiency; it is often coincident with Wernicke's and may emerge as the symptoms of Wernicke's are treated. The amnesia that occurs with Korsakoff's can be **both** retrograde and anterograde. Attention and mentation appear normal. Patients often **confabulate** because of the memory problems.

The typical Korsakoff's presentation: an **underweight, poorly nourished**, but very attentive alcoholic who tells **fantastical stories** that could not possibly be true and then has no memory of the discussion. The stories are frequently happy-go-lucky fantasies, termed "gleeful confabulation."

Other neurologic manifestations of Wernicke's and Korsakoff's are peripheral neuropathy, retrobulbar optic neuropathy, impaired olfactory discrimination, and postural hypotension.

Treatment: Immediate treatment with thiamine resolves the problem of Wernicke's and prevents Korsakoff syndrome. Once Korsakoff's develops, thiamine has only partial effect; in fact, the majority of patients who emerge from Wernicke's have some irreversible symptoms of Korsakoff's.

Treatment for Wernicke's is thiamine, at a minimum dose of 500 mg (in saline) by infusion 3×/day for 2–3 days, followed by 250 mg thiamine IV or IM daily for another 5 days. Thereafter, continue oral thiamine supplementation, typically at a dose of 100 mg/day. Also, correct deficiency in other vitamins and minerals, especially niacin and Mg²⁺. Wernicke's usually improves within hours of thiamine replacement.

IV glucose can precipitate Wernicke's in alcoholics.

Remember: Give IV thiamine **before** IV glucose in any patient with a possible metabolic cause of coma.

LITHIUM TOXICITY

Lithium levels in the upper therapeutic range frequently cause tremor and asterixis. Above a level of 1.5–2 mEq/L (1.5–2 mmol/L), the patient develops confusion, delirium, dizziness, nystagmus, ataxia, stammering, diffuse myoclonus, nephrogenic diabetes insipidus, vertical nystagmus, and opsoclonus. Toxic lithium levels cause seizures and coma; treat with hemodialysis.

The symptoms of toxicity can resemble Creutzfeldt-Jakob disease.

Note: **Opsoclonus** is rapid, involuntary, multivectorial (horizontal and vertical), unpredictable, conjugate eye movements.

Remember: Hyponatremia causes **increased** lithium **resorption** from the kidney.

ANTICHOLINERGIC TOXICITY

Classically, symptoms are:

- Red as a beet (cutaneous vasodilation)
- Dry as a bone (anhidrosis)
- Mad as a hatter (hallucinations)
- Blind as a bat (mydriasis)
- Full as a flask (urinary retention)
- Hot as a hare (hyperthermia)

See the **General Internal Medicine** section for more detail on these and other toxicities and their treatments.

NARCOLEPSY

PREVIEW | REVIEW

- What 4 symptoms are associated with narcolepsy?

Narcolepsy is a rare disease caused by a selective loss of **hypocretin** in the hypothalamus, the etiology of which is unknown. More than 85% of Caucasian and Japanese patients with narcolepsy-cataplexy syndrome have a specific HLA haplotype that includes HLA-DR1501 (formerly called DR15 or DR2) and HLA-DQB1-0602 (formerly called DQ1 or DQ6).

Narcolepsy tetrad:

- 1) Daytime sleepiness
- 2) Cataplexy (60–75% of patients! With excitement, limbs become flaccid, often resulting in falls.)
- 3) Hypnagogic hallucinations (occurs as patient falls asleep)
- 4) Sleep paralysis (on waking)

Diagnosis is based on the clinical symptoms as well as polysomnogram with multiple sleep latency test (MSLT). MSLT is a key part of the diagnostic criteria.

Narcolepsy is treated with modafinil or armodafinil (nonamphetamine drugs), stimulants (such as methylphenidate or methamphetamine—many side effects and addictive potential), or sodium oxybate (especially in more severe cases with associated cataplexy). Scheduled daytime naps and avoidance of sleep deprivation is useful. Cataplexy can also be treated with tricyclics (e.g., imipramine, clomipramine, protriptyline) or the selective serotonin reuptake inhibitors (e.g., venlafaxine, fluoxetine).

VISUAL DISORDERS

PREVIEW | REVIEW

- What are causes of acute-onset unilateral blindness in older patients?
- What do flashes followed by decreased vision suggest?

ACUTE-ONSET UNILATERAL BLINDNESS

Know all of the following. See Table 12-10 for a summary.

In older patients, acute-onset of unilateral blindness is usually due to any of the following:

- Anterior ischemic optic neuropathy (AION), which may be:
 - Arteritic (especially giant cell arteritis; 5%)
 - Nonarteritic (thrombosis; 95%)
- Retinal vein occlusion (secondary to diabetic retinal vascular disease)
- Retinal artery occlusion (from thrombus or emboli from the carotid artery or heart)

In the younger patient, think optic neuritis, but sometimes it can be from migraine. Painful monocular visual loss in a young patient is concerning for optic neuritis. Migraine-induced blindness typically resolves rapidly, whereas blindness due to any of the other mentioned causes is prolonged or permanent.

Ischemic optic neuropathy, optic neuritis, and papilledema (e.g., from increased ICP) all can present with swollen discs with fundal splinter hemorrhages. Remember: Temporal (giant cell) arteritis also causes diplopia and jaw claudication.

Malingering as a cause of blindness (mono/bi) can be ruled out with evoked action potentials.

DIPLOPIA

Weak or paralyzed eye muscles cause ophthalmoplegia and manifest as diplopia. It can be a result of disease in the muscle itself, in the nerve that stimulates the muscle, or in the neuromuscular junction (myasthenia gravis).

A reminder of diseases that can present with diplopia (we have covered most of these separately):

- 3rd, 4th, and 6th cranial nerve palsies
- Myasthenia gravis
- Graves disease
- Wernicke encephalopathy
- Miller Fisher axonal variant of Guillain-Barré syndrome

- Botulism
- Tick paralysis
- Mitochondrial disease
- Oculopharyngeal muscular dystrophy
- Infections/Masses that affect the cavernous sinus
 - The cavernous sinus contains CN 3, 4, V1, V2, and 6.
 - Symptoms include proptosis, abducens palsy (CN 4), and sensory disturbance (V1 and V2 distribution).

If you see diplopia with pain:

- Think disease in the eyeball if pain is localized in the eye.
- Think myopathy or orbital processes if pain is present with movement of the eye. Influenza is a classic cause of orbital myopathy.

Optic neuritis may also cause pain on eye movement, but it does not cause diplopia!

VISUAL FIELD DEFECTS

Scotomas

Scotomas are alterations in an isolated area of the visual field with loss or dimness of vision. Do a complete ophthalmologic exam on any patient with any type of scotoma.

Acephalic migraine (migraine without headache) can cause fortification scotomas that constantly change in size and can be bilateral.

Moore lightning streaks occur in older patients upon entering a darkened area. They are caused by the vitreous pulling on the retina; they are benign.

Retinal detachment causes flashes followed by decreased vision (from blood) or increased floaters. This is an ophthalmological emergency.

Hemianopia and Quadrantanopia

Bitemporal hemianopia (Figure 12-9) is the term for blindness in the lateral (or temporal) half of both visual fields. It is a very specific finding caused by compression of the nasal retina nerve fibers in the optic chiasm

Table 12-10: Causes of Acute Transient Unilateral Blindness (Transient Monocular Vision Loss)

Age	Disease	Etiology	Clinical Course	Exam	Outcome
Older (> 50)	Anterior ischemic optic neuropathy	Giant cell arteritis; nonarteritic (thrombotic)	Nonprogressive	Optic disc infarction	From normal to complete blindness
	Central retinal vein occlusion	Vascular disease or venous thrombosis	Nonprogressive	Hemorrhagic retinopathy	Usually some visual impairment
	Central retinal artery occlusion	Embolic or thrombotic	Nonprogressive	Cherry red spot	Only ~ 25% maintain useful vision
Younger (< 40)	Optic neuritis	Multiple sclerosis	Progressive (hours to days)	Marcus Gunn pupil; optic disc pallor	90% recover completely
	Migraine	Neurovascular	Resolves rapidly	Normal	Normal vision

as they cross over each other to the contralateral side. The nasal portions of the retina receive visual input from the temporal visual fields.

The usual causes of bitemporal hemianopia are:

- Pituitary adenomas (the one we all remember)—most common (See the Endocrinology section.)
- Pituitary hyperplasia
- Craniopharyngioma
- Meningioma

Rare causes are aneurysm of the circle of Willis, sarcoidosis, and metastatic carcinoma.

Homonymous means the same part of the visual field is affected in each eye. Homonymous hemianopia is seen with:

- posterior cerebral artery (PCA) strokes affecting the medial occipital area,
- middle cerebral artery (MCA) strokes affecting all optic radiations between the optic chiasm and the occipital area, and
- internal capsule strokes also affecting all optic radiations.

Central sparing of the visual field (5° to 25°) means the stroke did not affect, or just partially affected, the posterior occipital lobe.

Quadrantanopia is when only a quadrant of the visual field is affected. Causes of quadrantanopia:

- an inferior homonymous quadrantanopia indicates a PCA stroke or lesion affecting optic radiations through the parietal lobe or
- a superior homonymous quadrantanopia indicates a PCA stroke or lesion affecting optic radiations through the medial temporal lobe.

NYSTAGMUS

PREVIEW | REVIEW

- Which brain lesion is suggested by upbeating jerk nystagmus? Downbeating?

Nystagmus is an involuntary oscillation of the eyes. The movements can be pendular (like a pendulum) or jerk. Jerk nystagmus has 2 components: slow and fast. The eyes drift (= slow component) and try to quickly recover (= fast component). The fast direction defines the direction of the nystagmus.

Nystagmus is sometimes (but not always) associated with vertigo.

Jerk nystagmus is most common in vestibular disorders but does not indicate whether the lesion is within the central nervous system or if it involves the cranial nerve itself. Upbeating jerk nystagmus usually indicates a lesion in the pons but can be seen in lesions of the medulla or cerebellum (i.e., infratentorial). Downbeating jerk nystagmus indicates a lesion at the cervicomedullary junction.

Gazing in particular directions precipitates the abnormal eye movements in certain types of nystagmus. For instance, drugs (e.g., antiseizure medications) can cause horizontal and vertical gaze-evoked nystagmus (occurring when the person looks right, left, or up)—in other words, it is present in all directions. Isolated vertical gaze-evoked nystagmus typically indicates disease in the posterior fossa.

DIZZINESS AND VERTIGO

PREVIEW | REVIEW

- Name the maneuvers frequently employed to treat benign paroxysmal positional vertigo.
- What are the clinical features of Ménière disease?
- In which area of the brain can a transient ischemic attack cause vertigo?

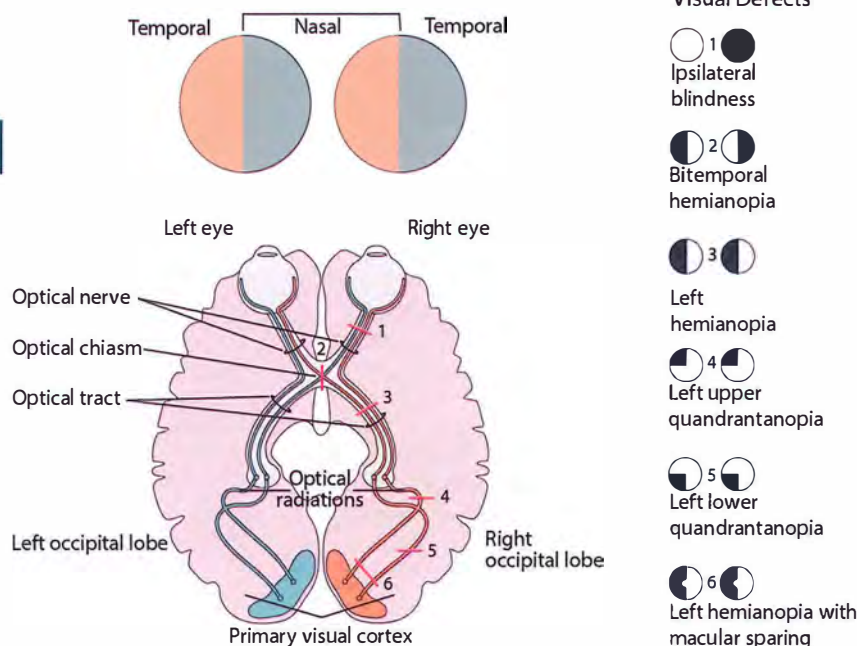


Figure 12-9: Visual field defects

SIGNS AND SYMPTOMS

When the term dizziness is used by a patient, it is necessary to differentiate among the following:

- Vertigo—a sense of spinning or swaying
- Lightheadedness—presyncope (“I feel like I’m going to pass out.”)
- Imbalance—unsteadiness
- Vague—not 1 of the 3 above. It may be hard for the affected person to describe.

When we discuss dizziness here, we are considering only vertigo.

CAUSES OF VERTIGO

Benign Paroxysmal Positional Vertigo (BPPV)

BPPV describes recurrent, brief episodes of vertigo caused by the motion of changing head position that generally lasts seconds at a time. It is thought to be due to loose otoconia (crystals that reside in the sacule and utricle) in the semicircular canal. When they escape this region, they can set up eddy currents in the endolymph, causing symptoms of vertigo. BPPV is also seen with head trauma, labyrinthitis, giant cell arteritis, migraine, hypertension, hyperlipidemia, stroke, and aging. The BPPV diagnosis is confirmed clinically with the **Dix-Hallpike** maneuver, in which the patient sits on the examination table with legs extended while you turn their head 30° to 45° toward one side and then help the patient quickly lie back so their head hangs over the end of the table. You then watch their eyes for the confirmatory involuntary eye movements (nystagmus). After they sit upright for a few minutes to recover from the vertigo, the procedure is repeated with their head turned in the opposite direction.

Most BPPV resolves spontaneously over a couple of weeks or can be treated successfully with various repositioning maneuvers that move the otoconia to a position of the inner ear that is less likely to induce vertigo. These are the **Epley** and **Semont** maneuvers and their variations. In some patients, episodes recur periodically from several days to many months—rarely for years.

Meclizine does not cure BPPV, but it is sometimes used to control nausea. Nonvertigo causes of dizziness are discussed in the [General Internal Medicine](#) section.

Vestibular Neuritis

Vestibular neuritis (e.g., vestibular neuronitis, acute peripheral vestibulopathy) causes a sudden onset of **non-positional** vertigo that is **self-limited** but may last weeks to months and occasionally can recur. This disorder occurs mainly in young to middle-aged adults, without preference for either gender.

Vestibular neuritis is caused by an inflammatory process affecting the vestibular portion of the 8th cranial nerve and

can be associated with viral infections. Pure vestibular neuritis does not affect hearing. If hearing is affected, it means it is no longer solely the nerve being affected but also the labyrinthine canals—and this is called vestibular **labyrinthitis**.

Usually the onset of vertigo is fairly abrupt, although some patients describe a prodromal period of several hours or days in which they felt off balance. Persistence of the symptoms for a day or more as a one-time event differentiates the disorder from Ménière disease, which is a paroxysmal disorder with vertigo that lasts for hours in discrete spells that also can be associated with aural fullness, hearing loss, and tinnitus. The head thrust test is a bedside assessment of visual fixation with the examiner rapidly turning the patient’s head. Inability to maintain fixation suggests vestibular neuritis versus a central lesion like a posterior circulation stroke.

Corticosteroids probably help recovery from vestibular neuritis. More studies are needed to confirm this effect. If steroids are not used, treatment is **symptomatic** only. During the acute stage, antihistamines (i.e., meclizine), antiemetics (i.e., promethazine), clonazepam, or scopolamine may be helpful in reducing the symptoms.

Aminoglycoside Toxicity

Aminoglycoside toxicity can cause sensorineural **hearing loss** and transient intermittent vertigo followed by more chronic disequilibrium, gait imbalance, and oscillopsia. Onset can be unpredictable and hearing loss can be permanent. There is currently no known therapy available to treat or reverse the ototoxic damage once it occurs.

Ménière Disease

Ménière disease is characterized by recurrent attacks of vertigo and intermittent tinnitus that begins between 20 and 40 years of age. The characteristic triad is episodic vertigo (often associated with nausea and vomiting) and **tinnitus**, with development of low-frequency **hearing loss** after recurrent episodes. Another commonly reported symptom is aural fullness. It frequently begins unilaterally but can become bilateral in 20–30% of patients.

An increase in the volume of endolymph and distention of the endolymphatic system (endolymphatic hydrops), partly related to salt intake, drive the disease process.

Diagnosis is **clinical**. Audiometry can help determine if hearing loss has occurred. If hearing loss is present at diagnosis, exclude neurosyphilis as a cause by checking a serum VDRL or RPR.

Antihistamines, antiemetics, and sedatives are used in acute episodes. Chronic treatment includes eradicating caffeine and reducing the intake of salt, alcohol, nicotine, and monosodium glutamate. Thiazide diuretics are used when spells continue after dietary modification. 95% of patients get their disease under control and function normally. For medically recalcitrant Ménière disease, endolymphatic sac surgery, surgical labyrinthectomy, and vestibular nerve sections remain therapeutic options.

Vertebrobasilar Transient Ischemic Attacks (TIAs) or Stroke

Vertebrobasilar TIAs may cause intermittent, recurrent vertigo. A posterior circulation TIA can be hard to diagnose because it may present with only vertigo and no other symptoms of **vertebrobasilar insufficiency**, but there typically are other clues, such as vision loss, diplopia, dysarthria, **ataxia**, and extremity motor or sensory dysfunction. Additionally, the patient usually has risk factors for stroke, though trauma in a younger patient can also cause vertebral artery dissection.

Workup of the posterior circulation requires special imaging. **Know:** Currently, the recommended testing for imaging of the posterior circulation is CT or **MR angiography**. CTA is preferred over MRA. **Know** that duplex Doppler ultrasound is not recommended for these vessels because of a lack of sensitivity, as it is assessing the anterior rather than the posterior circulation.

TINNITUS

Know these causes of tinnitus:

- Pulse synchronous tinnitus with idiopathic intracranial hypertension
- Intermittent tinnitus with Ménière's
- Aspirin overdose
- High noise levels
- Hearing loss

The tinnitus that occurs with hearing loss is thought to be a compensatory reaction to the hearing loss itself. Note that no tinnitus occurs with vestibular neuritis.

NEUROMA

PREVIEW | REVIEW

- How do you work up a patient with metatarsal pain?

Morton neuroma (a.k.a. Morton metatarsalgia) is a fairly common disease of the foot in which the patient has **metatarsal** pain. Palpation of the interspace and the metatarsal joint eliciting a clicking sound is called Mulder sign. Generally, Morton neuroma is diagnosed with MRI or ultrasound, which shows a small intermetatarsal ovoid mass. Differential diagnosis includes a metatarsal stress fracture. Treatment is with shoe inserts, local corticosteroid injections, and, at last resort, surgical excision.

COMPLEX REGIONAL PAIN SYNDROME (CRPS)

CRPS is extreme tenderness, pain, swelling, dysesthesias, atrophy of the dermal components of the affected area, and vasomotor instability in an extremity after a traumatic injury.

Prevention is the best treatment. The best studied preventive treatment is giving **vitamin C**, which significantly reduces the chance of developing CRPS. The higher the dose (1,500 mg/day), the better the results.

Early mobilization is thought to be preventive, but there are no good studies proving this.

Management of CRPS is usually with a team approach, starting as early as possible and using a combination of physical therapy, occupational therapy, and medications (e.g., NSAIDs, topical lidocaine, gabapentin, bisphosphonates, amitriptyline). Limited data suggests patients with early CRPS may benefit from corticosteroids, but there is no evidence of benefit in chronic patients. One combination of therapy has not been proven to be better than another.

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Cardiology

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PHYSICAL EXAM

PREVIEW | REVIEW

- True or false? Pulsus paradoxus can be seen in cardiac tamponade.
- What is pulsus bisferiens? What does it indicate?
- What does pulsus alternans indicate?
- True or false? Sustained handgrip increases the murmur of mitral valve prolapse but decreases the murmur of hypertrophic cardiomyopathy.
- When is a persistently split 2nd heart sound (S₂) heard?
- What causes a paradoxically split S₂?
- In which patient population is a 3rd heart sound usually pathologic?
- When are large v waves seen?
- When is rapid x and y descent seen?
- When are large a waves seen?
- When are cannon a waves seen?
- When does a slow y descent occur?
- When is the y descent absent with neck veins distended?
- When are tall, left-sided v waves seen?
- When are large, left-sided a waves seen?

PULSES

Pulsus **paradoxus** is an exaggeration of the normal decrease in systolic blood pressure with inspiration. It can be detected clinically using a manual (not automatic) blood pressure cuff. While deflating the cuff very slowly, note the systolic blood pressure where the 1st Korotkoff sound is heard only during expiration. Slowly deflate the cuff and note the systolic pressure at which the Korotkoff sounds continue through both inspiration and exhalation. The difference between these 2 pressures quantifies the pulsus paradoxus. A difference of ≥ 10 mmHg is considered abnormal. Pulsus paradoxus is seen with:

- cardiac tamponade (especially),
- constrictive pericarditis,
- asthma, and
- tension pneumothorax.

Note: Korotkoff sounds are those heard during manual blood pressure measurement with a sphygmomanometer.

The paradox is that, when severe, the pulse palpated on examination is of variable strength, while precordial pulse is regular.

Pulsus **bisferiens** (2 systolic peaks of the aortic pulse per cardiac cycle) is seen with aortic regurgitation (with or without stenosis!) and hypertrophic cardiomyopathy (HCM; see [Hypertrophic Cardiomyopathy \(HCM\) on page 13-72](#)).

Pulsus **alternans** (varying pulse pressure with a regular pulse rate) is seen with severe left ventricular systolic dysfunction.

Pulsus **parvus et tardus** (parvus—low amplitude, tardus—slow upswing) = aortic stenosis.

Brachiofemoral delay, the femoral pulse occurring after the brachial pulse, is present in coarctation of the aorta.

Pulse **asymmetry** occurs in aortic dissection: strong upper extremity pulses but diminished or absent lower extremity pulses. The asymmetry can also occur between the left and right upper extremities.

Peripheral arterial disease (PAD; previously called peripheral vascular disease [PVD]) can cause **decreased or absent** peripheral pulses. A **bruit** may also be heard over the proximal arteries (such as the femoral artery).

MURMURS AND HEART SOUNDS

Know heart sounds and murmurs! Know the differentiating maneuvers in [Table 13-1 on page 13-2](#) and the heart sounds described in [Table 13-8 on page 13-50](#) and [page 13-51](#) and under [Valvular Heart Disease on page 13-48](#). Learn these topics so you can determine how an abnormal finding (e.g., a particular heart sound) correlates with certain findings on electrocardiogram (ECG) and chest x-ray (CXR). MedStudy Heart Sounds (available at medstudy.com/products/heart-sounds-1) provides additional practice in recognizing various heart sounds and their causes.

Murmurs

All valve murmurs increase in intensity when blood flow increases across the valve. **Standing** and the strain phase of **Valsalva** decrease right and left cardiac filling and cause the sound of most murmurs to **decrease**, but these actions **increase** the intensity of the murmurs of mitral valve prolapse (MVP) and HCM. **Squatting** and **lying down** (or passive straight-leg raises if already supine) increase cardiac volume. This increased volume and afterload **increases** intensity of all murmurs except, again, MVP and HCM (see [Mitral Valve Prolapse \(MVP\) on page 13-54](#) and [Hypertrophic Cardiomyopathy \(HCM\) on page 13-72](#)).

Sustained handgrip (20–30 seconds) boosts systemic vascular resistance and left ventricular volume and, therefore, **decreases** the intensity of murmurs of HCM and aortic stenosis (AS). It **delays** the murmur of MVP by increasing left ventricular volume. Handgrip is most useful to differentiate between AS (murmur intensity decreases) and mitral regurgitation (MR; murmur intensity increases).

Keep in mind that the murmur of HCM worsens with any drop in left ventricular volume. So, any maneuver that increases ventricular volume decreases the murmur of HCM.

Right-sided murmurs and heart sounds are louder during **inspiration** and any maneuvers that increase venous return, such as passive leg raises and abdominal compression. Left-sided murmurs and heart sounds are louder during **expiration**. The only exception to this rule is

a right-sided ejection click due to pulmonic stenosis; this disappears with inspiration. (On a CXR, pulmonic stenosis can appear as an enlarged pulmonary artery.)

Table 13-1 describes various maneuvers that are used to diagnose murmurs.

Refer to Table 13-8 on page 13-50 and page 13-51 for more on murmurs and see Figure 13-1 for murmur illustrations.

Heart Sounds

S_1 is caused by the closing of the mitral and tricuspid valves. S_1 intensity is **decreased** when there is a prolonged PR interval, MR, acute aortic regurgitation (increased left ventricular [LV] pressures cause early valve closure), or a severely calcified mitral valve.

S_1 intensity is **increased** (i.e., the mitral valve slams shut) by a short PR interval, mitral stenosis, or hyperdynamic ventricular function.

S_2 is caused by the closing of the aortic (A_2) and pulmonic (P_2) valves at the end of systole. P_2 usually occurs just after A_2 . This **physiologic split** is **increased** with **inspiration** because the increased volume of blood in the right ventricle (RV) prolongs RV systole and delays closure of the pulmonic valve. It generally disappears on expiration.

A **persistently** (or **widely**) split S_2 varies with respiration but does not disappear on expiration. A widely split S_2 can be due to pulmonic stenosis, acute pulmonary embolism (PE), ectopic beats originating in the **left** ventricle, pulmonary hypertension, or right bundle-branch block (RBBB)—all of which cause **delayed** or **prolonged contraction** of the **right ventricle**. A widely split S_2 can also be caused by early closure of the aortic valve, as in MR. **Pulmonic stenosis** is especially likely if the patient has an ejection click that **disappears** with inspiration.

A **fixed** split S_2 does not vary with respiration. You hear a fixed split S_2 with atrial septal defect. The patient presents

Table 13-1: Maneuvers to Differentiate Murmurs

Maneuver	Result
Passive straight-leg raise (to 45°; listen after 15 seconds)	Increases venous return
Valsalva (hold for 20 seconds; listen just before end)	Decreases venous return
Standing (squat for > 30 seconds then quickly stand; listen during first 15 seconds after standing)	Decreases venous return
Transient arterial occlusion (BP cuff on both arms, inflated > 20 mmHg above systolic pressure)	Increases systemic vascular resistance
Handgrip (isometric; listen at end of 1-minute max grip)	Increases systemic vascular resistance
Squatting	Increases venous return and increases systemic vascular resistance, but preload effect is stronger than afterload effect
Maneuvers for diagnosing systolic murmurs	
To Diagnose HCM	Result
Standing (from squat)	Increased murmur intensity
Valsalva (if cannot do squat-to-stand)	Increased murmur intensity
Passive straight-leg raise	Decreased murmur intensity
Handgrip	Decreased murmur intensity
To Diagnose MVP	Result
Standing and Valsalva	Click-murmur moves earlier
Transient arterial occlusion	Click-murmur moves later
Handgrip	Click-murmur moves later
To Diagnose VSD	Result
Standing and Valsalva	Decreased murmur intensity
Transient arterial occlusion	Increased murmur intensity
Handgrip	Increased murmur intensity
To Diagnose AS	Result
Transient arterial occlusion	Decreased murmur intensity
Handgrip	Decreased murmur intensity

AS = aortic stenosis; HCM = hypertrophic cardiomyopathy; MVP = mitral valve prolapse; VSD = ventricular septal defect

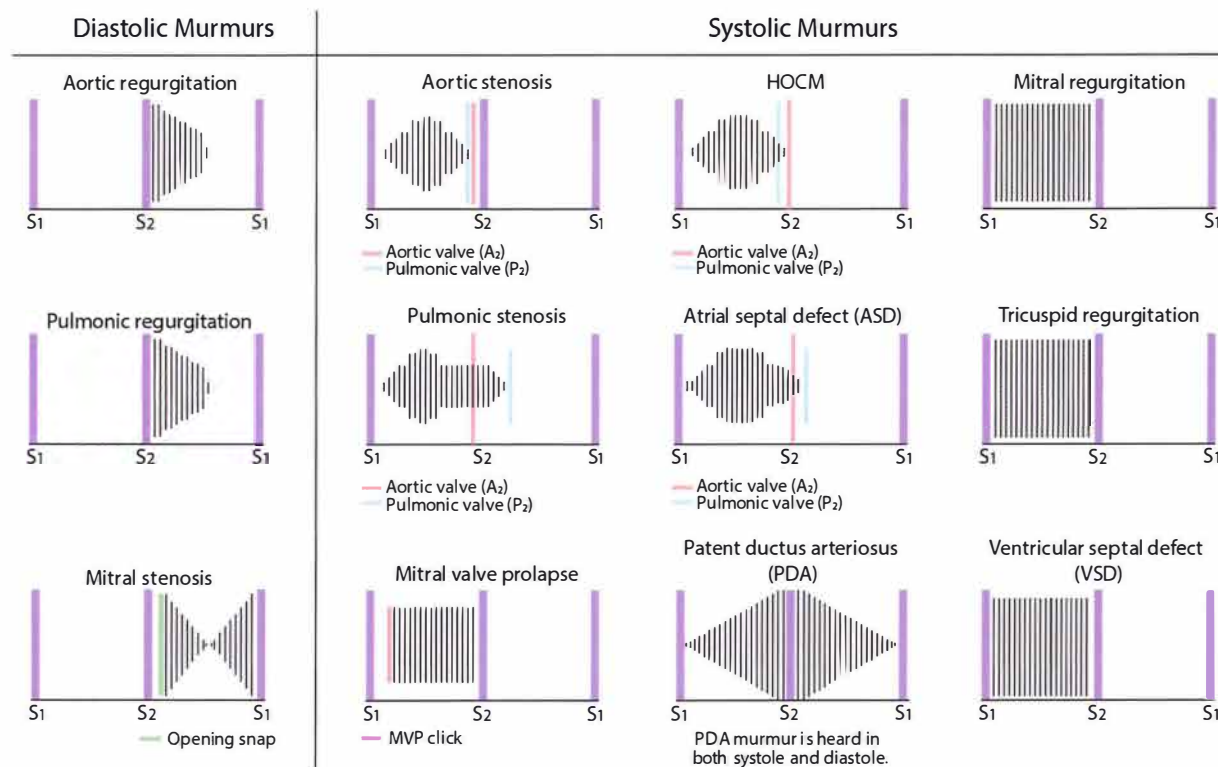


Figure 13-1: Diastolic and systolic murmurs

with a fixed split S_2 , a systolic ejection murmur (SEM), and pulmonary vascular congestion on the CXR. You can also hear a fixed split S_2 with RV failure when the stroke volume is unable to increase with inspiration.

A delay of aortic closure (A_2) causes a **paradoxically split** S_2 , with P_2 occurring before A_2 . In this case, you hear increased splitting with expiration instead of inspiration. This is commonly caused by left bundle-branch block (LBBB), advanced HCM, AS, patent ductus arteriosus (PDA), or ectopic or escape beats originating in the right ventricle.

Quick review of split heart sounds:

- **Physiologically split** S_2 is split on inspiration but not on expiration.
- **Persistently/widely split** S_2 (widely split on inspiration, decreases but remains split on expiration) occurs with pulmonic stenosis, acute PE, RBBB, and LV ectopic beats.
- **Fixed split** S_2 (A_2 - P_2 interval remains the same throughout breathing cycle) from atrial septal defect (ASD)
- **Paradoxically split** S_2 (P_2 before A_2 , splitting with expiration instead of inspiration) is caused by severe HCM, LBBB, RV ectopic or escape beats, AS, and PDA.

S_3 , when present, follows immediately after S_2 and indicates the end of rapid ventricular filling (sounds like “lub-dub-huh” or “Ken-tuc-ky”). This is early diastole, when the first 70% of ventricular filling occurs as the ventricle relaxes. The sound is thought to be due to the

tensing of the chordae tendineae. An S_3 is a normal finding in children and in persons with high cardiac output (CO), such as pregnant women. In patients > 40 years of age, it is usually pathologic. It can be caused by any condition that increases early LV filling rate or volume, such as acute ventricular decompensation or severe aortic or mitral regurgitation. S_3 in a patient with known LV dysfunction is a **poor** prognostic indicator. **Pericardial knock** is an early, sharp S_3 heard in constrictive pericarditis. It is caused by the restriction of ventricular filling to early diastole.

Both S_3 and S_4 are best heard in the left lateral decubitus position using the bell of the stethoscope.

S_4 , when present, is heard just before S_1 at the end of diastole (sounds like “huh-lub-dub” or “Ten-nes-see”). The S_4 sound is caused by ventricular filling during atrial contraction, and you hear it in patients with decreased ventricular compliance. You may hear an S_4 in ischemic heart disease, AS, HCM, and hypertensive heart disease with concentric hypertrophy. You do **not** hear an S_4 in patients with atrial fibrillation (because the sound requires atrial contraction) or mitral stenosis (where there is obstruction of ventricular inflow).

JUGULAR VENOUS WAVEFORMS

Jugular venous pulse and jugular venous waveforms are best visualized on the right side of the neck (more direct path to the heart than the left). The jugular venous pulse is used to assess the right side of the heart (Table 13-2 on page 13-4 and Figure 13-2 on page 13-4). Know this!

Know the following about jugular waveforms:

- **Large v waves** are seen with ASD, tricuspid regurgitation, and heart failure. This can be right heart failure or combined left and right heart failure.
- **Rapid x and y descents** are seen with constrictive pericarditis and restrictive cardiomyopathy.
- **Large a waves** are seen in severe tricuspid stenosis (TS), right heart failure, severe pulmonic stenosis, and severe noncompliant right ventricular hypertrophy (RVH).
- **Cannon a waves** occur in complete heart block, ventricular tachycardia, asynchronous ventricular pacing, and all conditions with **atrioventricular (AV)**

Table 13-2: Jugular Venous Waveforms

Condition	Neck Vein Appearance	Other Diagnostic Features
Pulmonary hypertension	Elevated a and v waves	Accentuated P ₂ , early systolic click, midsystolic ejection murmur
Tricuspid regurgitation (TR)	Large v waves	TR murmur (see Table 13-8 on page 13-50), pulsatile liver
Constrictive pericarditis	Rapid x and y descents	Kussmaul sign (paradoxical increase in jugular venous pressure during inspiration), pericardial knock (an early, sharp S ₃)
Tamponade	Distended neck veins, rapid x descent, blunted y descent	Pulsus paradoxus, hypotension
Tricuspid stenosis (TS)	Large a waves, slow y descent	TS murmur (see Table 13-8 on page 13-50)
Restrictive cardiomyopathy	Rapid x and y descents	Low-voltage ECG; diagnose with echocardiography, myocardial biopsy
Tension pneumothorax	Distended neck veins	Dyspnea, pulsus paradoxus, unilateral decreased or absent breath sounds, deviated trachea; diagnose with CXR
Superior vena cava syndrome	Unilateral distended neck veins	Facial edema and cyanosis, diagnosis of cancer
Atrioventricular dissociation	Irregular cannon a waves	Diagnose with ECG
Atrial fibrillation	Absent a waves	Diagnose with ECG
RV infarction	Elevated a and v waves	Acute inferior myocardial infarction, Kussmaul sign
ASD	Large v waves and rapid y descent	Fixed split S ₂ ; diagnose with echocardiography

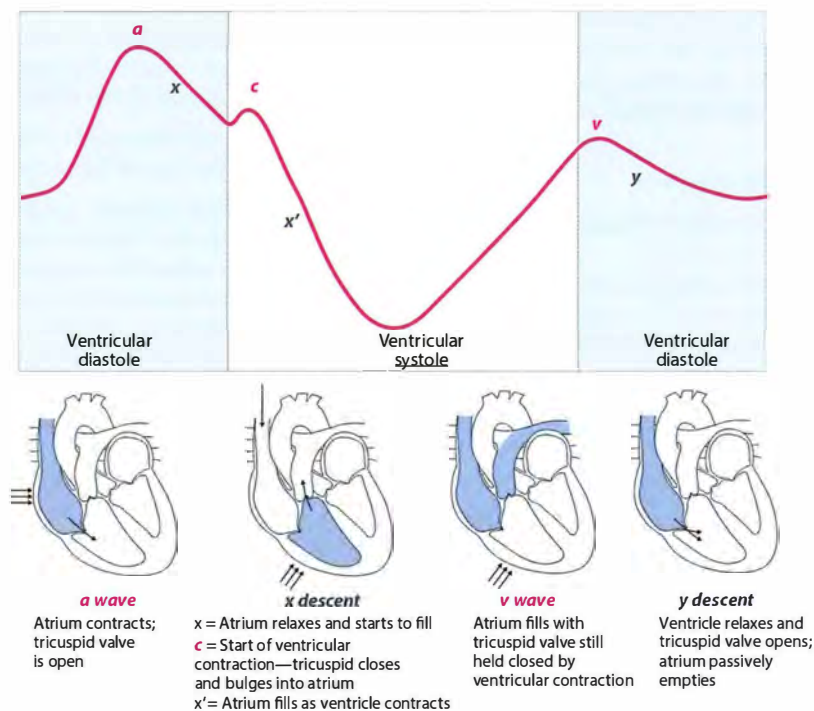


Figure 13-2: Jugular venous pulse

dissociation (times when the atrium is contracting against a closed tricuspid valve).

- **Slow y descent** is from delayed atrial emptying, as in TS.
- **A rapid x descent and loss of the y descent** with distended neck veins are seen with pericardial tamponade, tension pneumothorax, and superior vena cava syndrome.

The left side of the heart also has “venous” waveforms that are actually left atrial pressures, which are measured during pulmonary artery catheter (Swan-Ganz) monitoring. These pulsations, seen on the pulmonary artery tracing, are called **left-sided v** and **a** waves:

- With severe mitral regurgitation, there are tall, **left-sided v waves** from the regurgitation during systole.
- **Large, left-sided a waves** are seen with mitral stenosis.

Also see [Table 13-8 on page 13-50](#) and [page 13-51](#) for a review of the valve defects.

CHEST X-RAYS (CXR_s)

PREVIEW | REVIEW

- On a lateral view chest x-ray (CXR), extension of the heart border posteriorly and inferiorly indicates enlargement of which ventricle?
- On a lateral view CXR, extension of the cardiac shadow of the lower part of the anterior clear space behind the sternum indicates enlargement of which ventricle?

Know all the following CXR findings!

The CXR can tell you about overall heart size and (sometimes) heart chamber sizes.

On the **posteroanterior** view ([Figure 13-3](#)), the left ventricle (LV) causes the bulge in the left-lower side of the cardiac silhouette. The right atrium (RA) causes the outline on the right. The cardiac “waistline”—between the aortic knob and the LV—is formed by the main pulmonary artery and the left atrial (LA) appendage.

You can also estimate the cardiothoracic ratio from the posteroanterior view = the width of the cardiac silhouette divided by the chest diameter (measured from the inside rib margin at the widest point above the costophrenic angles). A cardiothoracic ratio > 0.5 indicates either cardiomegaly or a pericardial effusion. This ratio is valid only for an upright, nonrotated film on full inspiration, with a well-visualized cardiac outline, and when there is no abdominal compression on the diaphragm (e.g., ascites, pregnancy).

On the **lateral** view ([Figure 13-4](#)), if the cardiac shadow extends posteriorly and lower—closer to the diaphragm—this indicates increased LV mass. When the lower part of the anterior clear space behind the

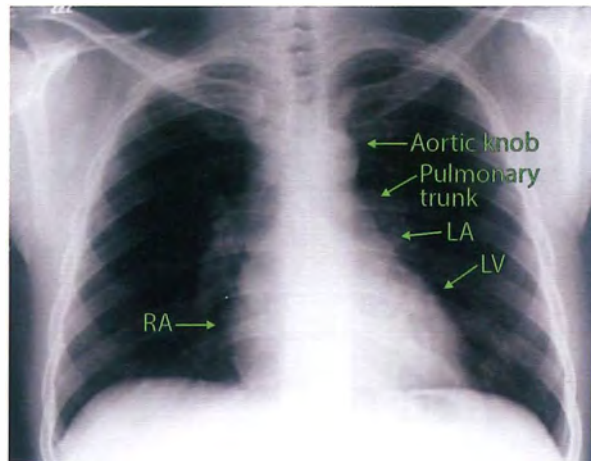


Figure 13-3: Normal posteroanterior chest x-ray

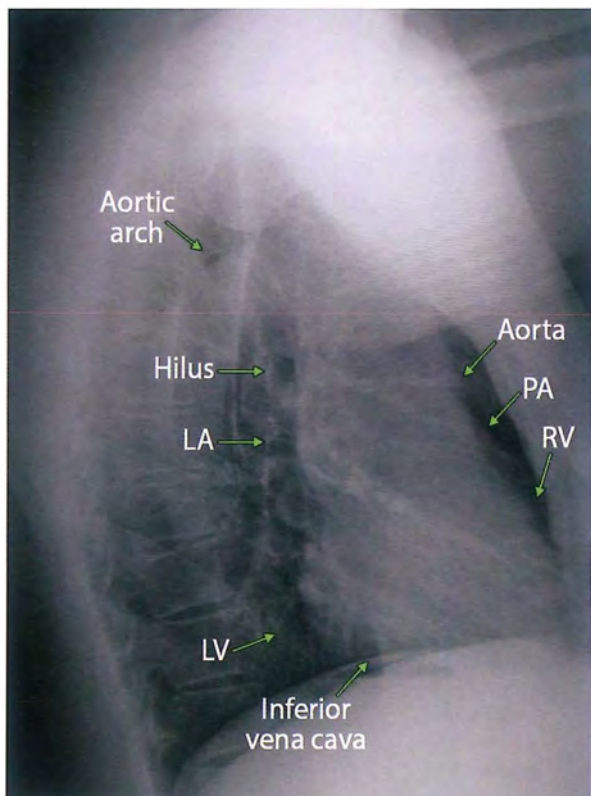


Figure 13-4: Normal lateral chest x-ray

Source: James Heilman, MD

sternum is filled in, this indicates increased right ventricular (RV) mass.

With **coarctation** of the aorta (COA), the aortic arch is abnormal. Look for the “3” sign ([Figure 13-5 on page 13-6](#)), which is created by a prominent left subclavian artery, the coarctation, and poststenotic dilation of the descending aorta. The barium swallow can show a “reversed 3” due to the impressions of the arterial structures on the esophagus. CXR in adults can also show intercostal rib notching ([Figure 13-6 on page 13-6](#)) due to collateral flow through tortuous intercostal arteries.



Figure 13-5: "3" sign in COA



Figure 13-6: Intercostal rib notching in COA

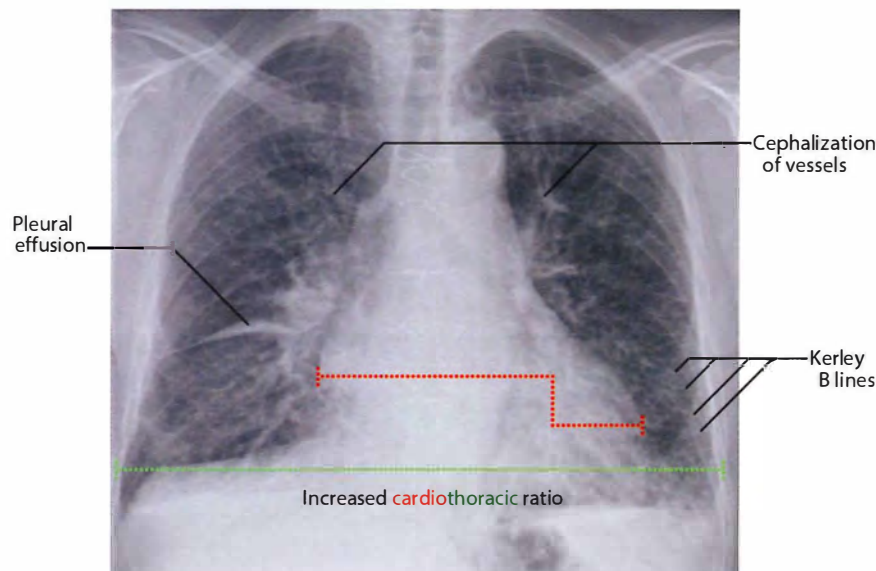


Figure 13-7: Heart failure chest x-ray with edema and Kerley B lines

Heart failure (HF; Figure 13-7) is indicated by cardiomegaly, pulmonary vascular redistribution (with visibly thickened upper lobe pulmonary veins, also called cephalization of vessels), Kerley B (interlobular septal) lines, and pleural effusions (usually right > left), all indicating pulmonary edema.

An **anomalous pulmonary vein** that drains into the inferior vena cava can create a scimitar sign on CXR. This is a curvilinear opacity in the right lower lung field due to associated lung hypoplasia.

Aortic abnormalities seen on CXR include tortuosity, ectasia, and calcification. An aortic aneurysm is sometimes visible on the lateral film. An aortic dissection can show up as mediastinal widening on the postero-anterior projection (Figure 13-8), but remember that the absence of mediastinal widening does **not** rule out dissection.

Pericardial effusion is suggested by a **water bottle** or a water balloon shape to the heart, sometimes with significant enlargement of the cardiac silhouette (Figure 13-9).

Shunt vascularity (enlarged, sharply defined pulmonary vasculature) can be visible with ventricular septal defect (VSD), ASD, or other left-to-right shunts.

Areas of calcification on CXR:

- **Aortic:** Think **dissection** if you see a separation between calcification and the aortic border, especially if the mediastinum appears wide.
- **Myocardial:** typically from an apical aneurysm or calcified thrombus
- **Valvular:** commonly the aortic valve
- **Annular (ring-shaped):** Mitral annular calcification; if it is a perfect ring, then a prosthetic valve is likely (especially if surgical clips are also present).

- Pericardial (Figure 13-10): Think constrictive pericarditis; or think tuberculosis if the clinical history suggests exposure.

Know that a single lead in the apex of the RV indicates the presence of an electronic ventricular pacemaker or implanted defibrillator—defibrillator leads are larger and wider than pacemaker leads. 2 leads indicate an atrioventricular sequential (dual-chamber) pacemaker, and 3 leads indicate a biventricular pacemaker.

See [The 12-Lead ECG on page 13-85](#).



Figure 13-8: Aortic dissection with widened mediastinum and large aortic knob



Figure 13-9: Water bottle heart
Source: David Ferry, MD



Figure 13-10: Pericardial calcification
Source: David Ferry, MD

PROCEDURES AND LABS

ECHOCARDIOGRAPHY

PREVIEW | REVIEW

- Name the anatomic structures and conditions that are evaluated with a transesophageal echocardiogram.

Echocardiography (cardiac echo) is an ultrasound modality used to image the heart. It utilizes M-mode, 2D, and 3D structural imaging, and Doppler to assess blood flow rate and direction.

Echo is good for assessing:

- Left ventricular systolic or diastolic dysfunction
- Right ventricular systolic dysfunction
- Valvular heart disease
- Congenital heart disease
- Myocardial infarction (MI; including post-MI complications)
- Cardiomyopathy (both decrease in ejection fraction and hypertrophy of myocardium)
- Pericardial disease
- Cardiac masses (tumor, thrombus, and vegetation)
- Diseases of the aorta and pulmonary artery
- Estimation of pulmonary pressure
- Cardiac sources of emboli

Transesophageal echocardiography (TEE) is an echo performed with an esophageal probe (and is thus an invasive test). It offers **higher-resolution** images

than **transthoracic** imaging and is especially useful for evaluating:

- Valvular structure and function, especially the mitral valve
- Left atrium (including left atrial appendage thrombi)
- Cardiac masses
- Intracardiac shunts
- Endocarditis
- Aortic dissection

A **bubble study** (performed by injecting hand-agitated saline into the venous system) is used to evaluate intracardiac shunts.

In technically challenging studies, a contrast agent may be intravenously administered to improve imaging of the chambers.

Doppler echo measures the **velocity** and **direction** of the blood flow. Doppler echo determines mean gradients, peak velocities, and valve area. Doppler is useful in determining the severity of valvular stenosis or regurgitation, as well as in evaluating left ventricular diastolic function, left ventricular outflow tract gradients, and intracardiac shunts.

Doppler is also used to estimate pulmonary artery pressure.

CARDIAC STRESS TESTS

PREVIEW | REVIEW

- What are absolute indications for terminating an exercise tolerance test (ETT)?
- When are stress imaging studies done instead of an ETT?
- Which form of stress testing is used in patients with left bundle-branch block? With paced ventricular rhythm?
- When are exercise stress echo and myocardial perfusion imaging indicated instead of ETT?

Cardiac stress testing is used to assess patients with coronary artery disease (CAD). Stress testing relies on the **increased demand** for myocardial **oxygen** with exercise or pharmacologic agents. Stress tests have an integral role in both the detection of CAD (**diagnostic** tool) and in stratification of risk (**prognostic** tool). To appropriately utilize stress tests, you must take into account the pretest probability of CAD. (A positive test in a low-risk patient has a higher likelihood to be a false positive, and a negative test in a high-risk patient has a higher likelihood to be a false negative.) Diagnostic testing is **most valuable** when pretest probability for CAD is **intermediate**. Cardiac stress testing is not recommended in most asymptomatic patients, especially those with low 10-year atherosclerotic cardiovascular disease (ASCVD) risk. Patients with obesity should be given lifestyle counseling for weight loss.

There are 2 general types of cardiac stress tests:

- 1) Exercise tolerance test (ETT; basic treadmill or stationary bicycle testing without imaging)
- 2) Stress imaging test—**stress** is induced with:
 - ETT or
 - pharmacologic stress (either dobutamine or a vasodilator, such as adenosine).

Then, **imaging** is done with:

- Echocardiography (a.k.a. stress echo)
- Myocardial perfusion imaging (MPI; a.k.a. nuclear stress test)
- Cardiac magnetic resonance (CMR) imaging

Exercise Tolerance Test (ETT)

ETT, using either a treadmill or stationary bicycle, is the standard **diagnostic** test for **ischemia** and **functional capacity** and for determining **prognosis** (including post-MI).

Despite an overall low sensitivity and specificity (men: sensitivity = 68%, specificity = 77%; women: sensitivity = 61%, specificity = 70%), ETT has a number of advantages, including the ability to test functional capacity, safety, widespread availability, and relatively low cost. Due to the low predictive value, it is most commonly performed in conjunction with nuclear or echocardiographic imaging.

The patient typically exercises on a treadmill using standard exercise protocols, such as the Bruce protocol. The level of maximal exercise achieved on the ETT is measured in metabolic equivalents (**METs**).

ETT without imaging is **not** recommended in 2 groups:

- 1) Patients unable to exercise sufficiently (**must achieve 85%** of age-predicted maximum heart rate)
- 2) Patients with **baseline ECG abnormalities** that can interfere with interpretation of the stress test (e.g., left ventricular hypertrophy [LVH], LBBB, Wolff-Parkinson-White [WPW] syndrome, ventricular pacing, resting ST depression, digoxin use)

Know the following information related to ETTs.

The definition of a **positive ETT** is flat or downsloping ST-segment depression > 1 mm at 80 ms after the J-point in **3** consecutive beats.

Unlike ST elevation, ST depression does **not** correlate with the anatomic location of myocardial ischemia. Isolated ST depression in inferior leads is far less specific than ST depression in lateral leads (V4-V6).

ST elevation during an ETT in 3 contiguous leads without Q waves of prior MI is unusual and suggests marked ischemia (but can also be seen with coronary artery spasm).

Terminate the **ETT immediately** if you see:

- ST elevation > 1 mm in leads without Q waves from prior MI (excluding aVR, aVL, and V1)
- Decrease in systolic blood pressure (BP) > **10** mmHg with other evidence of ischemia or hypoperfusion

- Moderate or severe angina
- Central nervous system symptoms (e.g., ataxia, dizziness, near syncope)
- Signs of poor perfusion (e.g., cyanosis/pallor)
- Sustained 2nd or 3rd degree atrioventricular block
- Technical difficulties in monitoring ECG/BP
- Patient requests to stop
- Serious arrhythmia (e.g., sustained ventricular tachycardia)

Achieving target heart rate alone is not a reason to discontinue the ETT; encourage the individual to go as long as tolerated until required to stop for some reason (e.g., dyspnea, fatigue, exhaustion).

Excellent exercise tolerance (> 10 METs) correlates with a good prognosis independent of the degree of CAD.

Absolute contraindications to ETT:

- Acute MI within 2 days
- Unstable angina not previously stabilized by medical therapy
- Uncontrolled arrhythmias causing symptoms or hemodynamic compromise
- Symptomatic severe aortic stenosis
- Decompensated symptomatic HF
- Acute pulmonary embolus or infarction
- Acute myocarditis or pericarditis
- Acute aortic dissection

Stress Imaging Tests

Stress **imaging** studies include **stress echo**, **MPI**, and **CMR** (discussed under **Cardiac MRI (a.k.a. Cardiac Magnetic Resonance [CMR])** on page 13-10). The choice of which to use is often based on operator experience at the facility.

Stress imaging studies are used as the initial diagnostic method when there are ECG changes at rest that can interfere with interpretation of the ECG during exercise. They are also preferred in patients with prior revascularization or infarction.

Stress imaging studies have greater sensitivity and specificity than the standard ETT. They are used when measurement of **ejection fraction** or **myocardial viability** is desired in addition to identifying CAD.

Stressing the Heart for Imaging Studies

The stress portion of imaging study tests can be performed with **exercise** or **pharmacologic** agents.

Exercise imaging studies are done with a standard ETT and require the same ability to meet 85% of age-predicted maximum heart rate. **Exercise stress** is preferred over pharmacologic stress because it provides additional functional and prognostic information. Exercise is **not** recommended in patients with **pacemakers** or **LBBB** because it can cause false-positive left ventricular antero-septal perfusion defects. These patients require stress imaging with **pharmacologic** agents. Also, patients

with severe claudication, peripheral arterial disease, or other conditions that limit their ability to achieve 85% of age-predicted maximum heart rate with exercise should undergo stress testing with pharmacologic agents.

Pharmacologic agents used for stress imaging studies include dobutamine and vasodilators. **Dobutamine** is both inotropic + chronotropic and causes the heart to respond as it would to exercise. As with exercise, a target heart rate must be achieved with dobutamine. Also, as with exercise, dobutamine is usually **not** used in patients with **pacemakers**. Dobutamine is used for patients who are unable to exercise and have a contraindication to vasodilators (e.g., **bronchospasm**, **severe carotid artery stenosis**).

Vasodilators: **Adenosine**, **dipyridamole**, and **regadenoson** are the main coronary vasodilators used in pharmacologic **MPI** stress tests. Vasodilators do not stress the heart by increasing heart rate as with exercise or dobutamine. These agents increase blood flow in normal coronary vessels while doing little to change the flow in stenotic vessels. The dilated normal vessels steal flow from the stenotic vessels, causing perfusion defects in the region of the left ventricle supplied by the stenotic vessel (and ST segment changes in ECGs). Use vasodilators cautiously in patients with a history of **bronchospasm**.

Regadenoson is a selective adenosine A2A receptor activator that causes less bronchospasm and allows for a faster stress test. Even so, **dobutamine** remains the pharmacologic agent of choice for patients with a history of **bronchospasm**.

Stress Echo and Stress Myocardial Perfusion Imaging (MPI) Indications

Unlike ETT, exercise stress echo or stress MPI can be used in patients with:

- resting ECG ST changes (e.g., LVH, resting ST depression),
- left bundle-branch block,
- a paced rhythm,
- WPW syndrome, or
- on digoxin therapy.

Note that it is a common misconception that these patients require pharmacologic stress, but this is definitely not true! If they can exercise, these patients can get a stress echo **with exercise** or MPI **with exercise** (i.e., these patients need the **imaging**, not the pharmacologic stress).

Stress Echo

Stress echo is a widely used test for myocardial ischemia; it detects stress-induced wall motion abnormalities. Stress echo is less sensitive but more specific than MPI for the detection of CAD.

Use **exercise** or **dobutamine** to achieve target heart rate. Abnormal wall motion or failure of the wall to thicken (contract) appropriately suggests ischemia of that region of the myocardium. Stress echo is less expensive than MPI and does not involve radiation exposure.

Criteria for abnormal stress echo are new regional wall motion abnormalities, left ventricular cavity dilation, and decline in global left ventricular systolic function with stress (suggests multivessel disease).

Vasodilators are **not** used for stress echo.

MPI

MPI uses radioisotopes with single-photon emission computed tomography (SPECT). These tracers distribute in heart tissue in proportion to blood flow; this distribution is recorded by a γ camera. Perfusion is compared visually between the resting and stressed states. With ischemia, myocardial perfusion is normal at rest but decreased during stress (**reversible** defect). With myocardial infarction, perfusion is reduced both at rest and during stress (**fixed** defect). Other MPI findings suggestive of multivessel disease include left ventricular (LV) transient ischemic dilation, reduced poststress LV ejection fraction, and increased lung or right ventricular uptake.

Exercise or dobutamine require a target heart rate to be achieved. With vasodilators, such as adenosine, dipyridamole, or regadenoson, it is not necessary to achieve a target heart rate. Other imaging modalities that can be used for MPI (as an alternative to SPECT) include cardiac positron emission tomography (PET) and cardiac magnetic resonance imaging (cardiac MRI; a.k.a. cardiac magnetic resonance [CMR]), both of which can also assess for myocardial ischemia and viability.

MPI is more expensive than stress echo, and it involves radiation exposure.

Picking the Correct Cardiac Stress Test

In review:

- Exercise is the preferred modality for inducing cardiac stress.
- When the ECG is nondiagnostic, a patient is unable to exercise sufficiently, or for enhanced diagnostic value, use echocardiographic or nuclear imaging.
- Vasodilators can be used in lieu of exercise for MPI only, while dobutamine can be used for stress echocardiography or MPI.
- Dobutamine is contraindicated in severe hypertension or ventricular tachycardia.
- Do not use dobutamine in paced ventricular rhythms due to distortion of normal ventricular contraction.
- Many vasodilators are contraindicated in bronchospasm or severe carotid artery disease.

CARDIOPULMONARY EXERCISE TESTING (CPET)

PREVIEW | REVIEW

- Which patients may benefit from cardiopulmonary exercise testing?

CPET is a special exercise test that measures ventilation and concentrations of oxygen and carbon dioxide during progressive exercise (stationary bicycle/treadmill) and is the gold standard aerobic exercise test. CPET provides the most accurate and reproducible measurement of cardiorespiratory fitness, severity of impairment, and response to intervention. CPET is used to evaluate patients with systolic HF, especially those undergoing a pretransplant assessment, and patients with unexplained exertional dyspnea.

CARDIAC CATHETERIZATION AND OTHER CARDIAC IMAGING TESTS

Contrast Cardiac Catheterization

Coronary angiography (a.k.a. left heart catheterization or simply “cath”) is the **gold standard** for the diagnosis of CAD.

Not only can contrast left-heart catheterization assess coronary anatomy, but with contrast **ventriculography** it can also assess ejection fraction, wall motion abnormalities, ventricular dilatation, degree of mitral regurgitation, and the presence of a ventricular aneurysm. However, cardiac catheterization is an invasive procedure with ~ 1% risk of serious complications (i.e., death, MI, stroke, arrhythmia, renal failure, bleeding).

Left-heart catheterization requires arterial access, radiation, and contrast exposure.

Cardiac Computed Tomography (CT)

Cardiac CT is a noninvasive modality for imaging the heart. Cardiac CT includes:

- Coronary computed tomographic angiography (CCTA)
- Coronary artery calcium (CAC) scoring

CCTA requires **IV contrast** (check creatinine!); also, the heart rate must be **< 60 bpm** and regular, and patients must be able to **hold their breath**.

CCTA is a reasonable diagnostic test for symptomatic patients who are at intermediate risk for CAD or have congenital abnormalities. The negative predictive value of CCTA is very high; that is, a negative CCTA is very helpful in excluding significant CAD. Usefulness is reduced in patients with pronounced coronary calcification.

CAC scanning detects atherosclerosis and, unlike CCTA, does not require IV contrast. CAC is used for risk stratification in asymptomatic, intermediate-risk patients. A CAC score of zero is considered low cardiovascular risk, and > 400 indicates an elevated (~ 3-fold) 10-year risk for a cardiovascular event.

Cardiac MRI (a.k.a. Cardiac Magnetic Resonance [CMR])

Static and dynamic cardiac MRI (CMR) allows high-resolution imaging of ventricular function, valvular motion, and myocardial perfusion.

CMR is useful to assess cardiac structure and function, valvular heart disease, coronary takeoff, the great vessels, pericardial disease, cardiac masses, myocarditis, and infiltrative diseases. CMR also can be used to assess for myocardial ischemia and post-MI tissue **viability**.

Cardiac MRI involves the use of gadolinium; therefore, avoid use it in patients with advanced renal failure due to the risk of nephrogenic systemic fibrosis.

PULMONARY ARTERY CATHETERIZATION (PAC)

PREVIEW | REVIEW

- When is pulmonary capillary wedge pressure (PCWP) increased?
- At which PCWP do you expect to see frank pulmonary edema?
- In which conditions is diastolic pressure equal in all 4 chambers?

PAC can be used to assess right and left heart filling pressures, cardiac output (CO), right ventricular (RV) and pulmonary artery pressures, and systemic and pulmonary vascular resistance. This is useful to determine a patient's volume status, causes of shock, and existence of pericardial disease. Clinically, it is no longer used as often as in the past, due to a lack of evidence of a beneficial effect on outcomes, and risk associated with placement (pneumothorax, damage to vascular bed, infection risk, and cardiac injury).

The pulmonary capillary wedge pressure (PCWP) is the dampened LA pressure that reflects left ventricular end-diastolic pressure (LVEDP) in most cases. This reflects LVED volume.

Normal pulmonary artery catheterization pressures:

- RA: < 8 mmHg (Jugular venous distention [JVD] in the upright position indicates RA pressure > 5 mmHg.)
- RV: 15–30/1–7 mmHg
- PAP: 15–25/8–15 mmHg
- PCWP: 4–12 mmHg

Abnormalities in the PCWP are common:

- PCWP increases with LV systolic and diastolic failure, mitral stenosis, aortic and mitral insufficiency, tamponade, and constrictive pericarditis. Consider LV failure if the PCWP is > 15–18 mmHg.
- PCWP 15–25 mmHg is associated with dyspnea on exertion.
- PCWP 25–35 mmHg is associated with dyspnea at rest, orthopnea, and interstitial edema.
- PCWP > 35 mmHg (acutely) causes frank pulmonary edema.

Note: Conditions that decrease ventricular compliance, like LVH and right ventricular hypertrophy (RVH), also increase RA pressure and PCWP.

A few PAC scenarios are shown in [Table 13-3](#). Notice that the pulmonary artery diastolic pressure is typically very close to PCWP (usual difference < 5 mmHg) in all scenarios except pulmonary hypertension (HTN; item 6)!

See [Pericardial Diseases](#) on page 13-79 for the tests that differentiate between tamponade and constrictive pericarditis. Also know that septic shock is mainly due to a low systemic vascular resistance. These patients have low BP, systemic vascular resistance, and PCWP—and a high CO.

CARDIAC BIOPSY

PREVIEW | REVIEW

- Name one indication for endomyocardial biopsy.

Consider endomyocardial biopsy in the following situations:

- To diagnose or monitor for rejection after cardiac transplantation
- To determine the etiology of **cardiomyopathy** or **myocarditis** when the diagnosis is uncertain and would change management
- In rapidly progressive HF or worsening ventricular dysfunction that persists despite appropriate medical therapy
- In suspected myocarditis (e.g., giant cell myocarditis) or a myocardial infiltrative process (e.g., amyloidosis)

Table 13-3: Pulmonary Artery Catheterization Scenarios

Condition	RA Press (mmHg)	Pulmonary Artery Press (mmHg)	PCWP (mmHg)	BP (mmHg)	Comments
Normal	< 8	(13–28)/(3–13)	4–12	110/70	
Tamponade or constrictive pericarditis	18	32/18	19	70/50	Diastolic pressure equal in all 4 chambers!
RV failure due to RV infarct	15	21/11	10	70/50	RV unable to fill the L heart: high RA pressure and low PCWP and CO
Biventricular failure	18	30/20	20	70/50	Low CO in setting of high RA and PCWP; cardiogenic shock is common!
Mitral stenosis	18	90/32	30	110/70	
Pulmonary HTN	18	90/32	10	110/70	

HYPERTENSION (HTN)

PREVIEW | REVIEW

- In which patients should you suspect secondary hypertension?
- True or false? A systolic abdominal bruit without a diastolic bruit suggests renal vascular hypertension.
- What disorder should you think of if a patient presents with hypertension, hypokalemia, and low renin?
- What is hypertensive emergency?

The 2017 American College of Cardiology/American Heart Association (ACC/AHA) Guidelines for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults define HTN as systolic blood pressure (SBP) ≥ 130 mmHg or diastolic blood pressure (DBP) ≥ 80 mmHg. This is **lower** than the $\geq 140/90$ definition from previous guidelines.

Here's what you need to know about the 2017 HTN guidelines:

- Everyone with HTN ($\geq 130/80$) should be treated with lifestyle interventions: stop smoking, lose weight, moderate alcohol, exercise, eat a low-sodium healthy diet.
- Low-risk patients (10-year ASCVD [atherosclerotic cardiovascular disease] risk $< 10\%$): Use medications for SBP ≥ 140 mmHg or DBP ≥ 90 mmHg.
- Everyone else: Use medications for SBP ≥ 130 mmHg or DBP ≥ 80 mmHg.

"Everyone else" includes patients with clinical ASCVD (secondary prevention), patients with a 10-year ASCVD risk $> 10\%$, and patients with comorbidities, including diabetes mellitus (DM), chronic kidney disease; including kidney transplantation), heart failure, prior stroke, and peripheral arterial disease.

Suspect **secondary** causes of HTN in patients who develop HTN at < 30 years of age, who have drug-resistant HTN (poorly controlled blood pressure while on ≥ 3 drugs including a diuretic, or blood pressure that is controlled with ≥ 4 drugs), or who develop uncontrolled HTN that was previously well controlled.

Systolic abdominal bruits (without a diastolic bruit) suggest **renovascular HTN**. Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) are very effective in bringing down the blood pressure in renovascular HTN but can cause a decline in renal function, especially with bilateral renal artery stenosis (RAS). Large, randomized, controlled trials have shown no benefit of revascularization (angioplasty or stenting) over pharmacologic therapy in atherosclerotic RAS. For this reason, medical therapy is recommended first; consider revascularization if medical therapy fails. If you're

considering revascularization, start with noninvasive tests—duplex ultrasonography, CTA (in individuals with normal renal function), and magnetic resonance angiography (MRA). The diagnosis is confirmed by angiography. When clinical suspicion is high and results of noninvasive tests are inconclusive, catheter angiography with intent to revascularize is reasonable.

Think of **primary aldosteronism** in a hypertensive patient with **hypokalemia**, volume expansion, and **low renin**.

Think of **pheochromocytoma** in a patient with recurrent and intermittent episodes of severe HTN accompanied by palpitations, headaches, and severe apprehension.

Hypertensive emergency is severe hypertension (SBP ≥ 180 or DBP ≥ 120) associated with new or worsening end organ damage.

Much more on HTN is in the [Nephrology](#) section.

CARDIAC MEDICATIONS

PREVIEW | REVIEW

- True or false? Digoxin prolongs survival.
- Which medications have been shown to prolong survival both after myocardial infarction and for patients with heart failure?
- With which medication should a nitrate be paired to improve survival in heart failure patients?

Refer to [Table 13-4](#) for an overview and comparison of commonly used cardiac medications. Pay particular attention to those that prolong survival! Note the following about cardiac medications:

- A **negative inotrope** decreases cardiac contractility.
- A **negative chronotrope** slows heart rate.
- A **negative dromotrope** slows conduction through the atrioventricular node.

ANGINA

OVERVIEW

PREVIEW | REVIEW

- What is the most common cause of acute coronary syndrome?
- What is the cause of Prinzmetal angina?
- What does transient ST-segment elevation suggest on an exercise ECG stress test?
- What are causes of resting ST-segment elevation?
- Explain the similarities and differences between hibernating myocardium, reperfusion injury, and stunned myocardium.

Table 13-4: Common Cardiac Medications

Medication	Negative Inotrope	Negative Chronotrope	Negative Dromotrope	Vasodilator	Antianginal	Prolong Survival Post-MI	Prolong Survival in HF	Indications
Digoxin		+	+					Systolic HF, arrhythmias
Metoprolol and bisoprolol	+++	+++	+++		Yes	Yes	Yes	HTN, angina, HF, arrhythmias
Carvedilol	++	+++	+++	Yes	Yes	Yes	Yes	HTN, angina, HF, arrhythmias
Nifedipine	++			Yes	Yes			HTN, angina
Amlodipine	+			Yes	Yes		Yes (in DCM)	HTN, angina, DCM
Diltiazem	++	++	++	Yes	Yes			HTN, angina, arrhythmias
Verapamil	+++	+++	+++	Yes	Yes			HTN, angina, arrhythmias
Nitrates				Yes	Yes		Yes (with hydralazine)	Angina, HF
ACEIs				Yes		Yes	Yes	HTN, HF
ARBs				Yes		Yes	Yes	HTN, HF
Hydralazine				Yes			Yes (with nitrates)	HTN, HF
Spironolactone							Yes	HTN, HF
Eplerenone						Yes (with HF)	Yes (post-MI)	HF (post-MI)

ACEIs = angiotensin-converting enzyme inhibitors; ARBs = angiotensin receptor blockers; DCM = dilated cardiomyopathy; HF = heart failure; HTN = hypertension; MI = myocardial infarction

Angina is chest pain or discomfort caused by myocardial ischemia. It is typically classified as either **stable** or **unstable**:

- **Stable angina:** Chest discomfort occurs predictably and reproducibly—usually with exertion—and remits with rest.
- **Unstable angina:** Angina occurs at rest, with new onset, or with increased frequency.

Obstructive atherosclerotic coronary artery lesions (supply problem) are the most common cause of stable angina (Figure 13-11). Plaque rupture or erosion with superimposed thrombus is the most common trigger for **acute** coronary syndrome (ACS).

Myocardial ischemia occurs when myocardial oxygen demand exceeds supply. There are many causes of **increased demand** (e.g., tachycardia, fever, thyrotoxicosis) and many other causes of **decreased supply** (e.g., hypotension, coronary vasospasm, anemia, hypoxia). Coronary blood flow can be impaired in severe aortic valve disease with left ventricular hypertrophy (LVH), hypertension (HTN), idiopathic dilated cardiomyopathy (DCM), and hypertrophic cardiomyopathy, even in the absence of epicardial coronary artery disease (CAD).

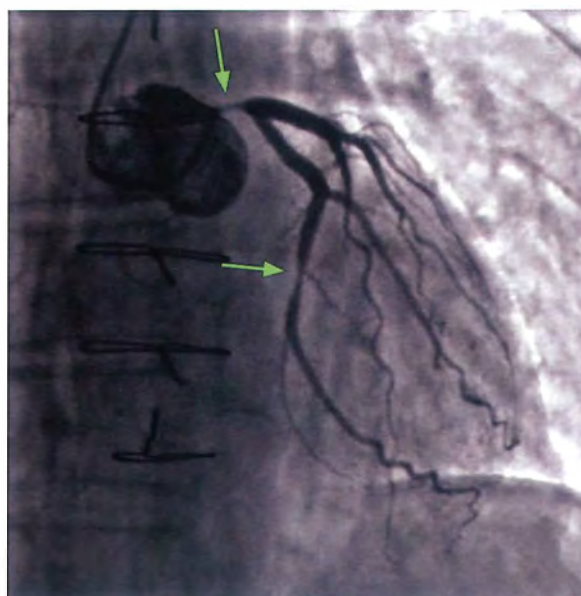


Figure 13-11: Angiogram showing narrowing in coronary artery

Note: Only ~ 20% of patients have classic angina at the moment of ischemic ST changes. Silent myocardial ischemia is painless but just as harmful as angina-associated ischemia. Silent ischemia is seen frequently in **diabetic** patients as well as those with prior ischemic events or prior bypass surgery. Silent ischemia, myocardial infarctions, and thrombotic strokes tend to occur in a circadian rhythm, with the highest incidence in the early morning hours.

Distinguishing between stable and unstable angina is key in determining management and diagnostic strategies. Unstable angina is an ACS, along with non-ST-elevation myocardial infarction and ST-elevation myocardial infarction. Long-term risk (death and myocardial infarction [MI]) in patients with ACS is much higher than in patients with stable angina; therefore, patients with ACS warrant emergent medical attention, inpatient management, and, much more commonly, revascularization. (See [Acute Coronary Syndromes \(ACSs\) on page 13-17](#).) Stable angina, on the other hand, is generally evaluated in the outpatient setting and symptoms are often managed medically.

The **most important** and accessible prognostic factor in patients with CAD is the **degree of LV dysfunction**. If severe, it often reflects multivessel or left main/left main-equivalent disease.

The exercise tolerance test (ETT) is an excellent, objective way to determine the **severity** of angina and to determine prognosis. Patients who are able to complete 12 minutes of the Bruce protocol have a nearly 100% 5-year survival, while those who can complete < 3 minutes have only a 50% 5-year survival! Note that coronary **angiography** is **not required** for this determination.

Coronary spasms cause **vasospastic angina** (a.k.a. **Prinzmetal angina**). During stress testing, this can show up as transient ST-segment **elevation**.

Microvascular angina occurs when patients with normal coronary arteries (per cardiac catheterization) have angina and ST depression with cardiac stress testing. This is caused by microvascular and endothelial dysfunction in the cardiac tissue. It is a diagnosis of exclusion.

What causes **resting** ST-segment elevation? Acute MI, coronary artery spasm, pericarditis, left ventricular (LV) aneurysm, LBBB, ventricular pacing, LVH, and benign early repolarization.

Hibernating myocardium is chronically underperfused myocardium. There is no irreversible myocyte injury. When perfusion is restored, contractility may return to normal. Hibernating myocardium can also occur within an infarcted region, so the degree of viability may determine the extent of myocyte recovery when reperfused.

Reperfusion injury occurs when a severely ischemic myocardium is reperfused after ~ 1 hour, causing further irreversible microvascular damage and damage to the myocardial cells.

Stunned myocardium is transient LV dysfunction following acute ischemia. From the time perfusion is restored, it can take 7-10 days for the ventricular function to return to normal.

Treatment of all angina: Modify risk factors and correct aggravating factors such as anemia, HTN, smoking, drug abuse, and noncompliance. (Good luck!)

ANTIANGINAL DRUGS

PREVIEW | REVIEW

- What are the main drugs used to treat angina?
- Which patients might benefit from ranolazine?
- Which antianginal drugs decrease myocardial oxygen demand?
- Which antianginal drugs decrease afterload?
- Which antianginal drugs decrease preload?
- Which antianginal drug do you avoid in patients with right ventricle infarct? Why?

β-blockers and **nitrates** are the staples of medical treatment of angina. β-blockers decrease myocardial O₂ demand by decreasing HR, BP, and contractility. Nitrates decrease myocardial O₂ demand by reducing preload (and, to a lesser extent, afterload), and by dilating coronary vessels. β-blockers complement nitrates well because they decrease the reflex tachycardia caused by nitrates. **Calcium channel blockers** can also help treat angina. Nifedipine and amlodipine decrease angina by both coronary artery vasodilation and peripheral vasodilation (decreasing workload). The main antianginal effect of diltiazem and verapamil is due to their negative chronotropic effect.

Aspirin lowers risk of mortality and MI in unstable (and probably stable) angina. Use clopidogrel in patients who cannot tolerate or are allergic to aspirin. Remember to **not** use aspirin in patients with purely vasospastic angina.

Ranolazine can help patients with chronic angina despite maximal standard therapy, or as a substitute for β-blockers. It is thought to work by inhibiting the late Na⁺ current in cardiac myocytes, thereby reducing Na⁺ and Ca²⁺ overload that follows ischemia. This improves myocardial relaxation and reduces left ventricular diastolic stiffness, which in turn enhances myocardial contractility and perfusion.

More on antianginal drugs:

- Nitrates, β-blockers, and calcium channel blockers **all** decrease myocardial O₂ demand, and **all** decrease afterload.
- Nitrates decrease preload more than afterload and also dilate coronary vessels. Acute preload reduction is why nitrates can cause severe **decompensation** in patients with an acute **right** ventricular MI. (Remember, do not give nitrates during acute right ventricular infarct; see [Right Ventricular Infarction \(RVI\) Complications on page 13-30](#).)
- Nitrates cause sympathetic reflex tachycardia.
- Nitrates are metabolized by the **liver**. Tolerance (tachyphylaxis) develops rapidly but can be avoided

by having a 6-hour nitrate-free window 1×/day (e.g., between midnight and 6 a.m.).

- Avoid nonselective β -blockers, such as propranolol, which have been shown to actually prolong the duration of vasospasm in patients with vasospastic angina.
- Calcium channel blockers: The combined vasodilatory and antihypertensive effects make them ideal for patients with angina/ischemia and HTN. See Table 13-4 on page 13-13. Use verapamil and diltiazem cautiously, if at all, in patients with systolic heart failure (HF) due to the negative inotropic effects. Short-acting nifedipine is contraindicated due to steep drops in BP and reflex tachycardia, which can cause myocardial ischemia/infarction.

EVALUATION OF CHRONIC STABLE ANGINA (STABLE ISCHEMIC HEART DISEASE)

PREVIEW | REVIEW

- Why should you determine the probability of coronary artery disease in a person with intermittent chest pain?
- What is the most important test for risk stratification in patients with stable ischemic heart disease?
- For which patients with chronic stable angina do you do an echocardiogram? Why?
- A patient undergoing a workup for chronic stable angina is determined to be at high risk for death. What is the next step?

The following is drawn from the 2014 ACC/AHA/AATS/PCNA/SCAI/STS Stable Ischemic Heart Disease guidelines. First and foremost: Involve and inform your patients. Diagnostic and therapeutic choices should be made through a process of shared decision-making involving the patient and physician, with the physician explaining the risks, benefits, and costs to the patient.

Evaluation of a patient with chest pain is a 3-step process:

- 1) Determine the probability of CAD.
- 2) Noninvasive testing for diagnosis and risk stratification
- 3) Additional workup based on estimated risk

History and Physical Exam — Determine Probability of Coronary Artery Disease (CAD)

First, determine the probability of CAD by assessing the following factors:

- Type of chest pain (i.e., typical angina, atypical angina, noncardiac chest pain)
- Age
- Gender
- Risk factors (particularly DM, smoking, and HTN)
- ECG (Q waves and ST abnormalities)

This step is very important because it determines **pretest probability** for the rest of the tests, which determines the positive and negative predictive values of these tests.

Typical vs. atypical vs. noncardiac chest pain: This is determined by assessing quality, location, and duration of the chest pain. Typical angina is provoked by exertion or stress and relieved by rest or nitroglycerin. Atypical chest pain can occur at rest. Noncardiac chest pain can be sharp, stabbing pain associated with eating or muscle tenderness. There is overlap between these presentations.

Cardiovascular risk factors include DM, HTN, smoking, hyperlipidemia, chronic kidney disease, family history of CAD, and postmenopausal status (in women). Elicit any history of substance abuse: Cocaine accelerates atherosclerosis, enhances platelet aggregation, causes vasospasm, and increases myocardial oxygen demand.

Conditions that can precipitate angina in the presence of CAD (or, when severe, in the absence of CAD) include:

- Increasing cardiac demand: hyperthyroidism, cocaine use, severe uncontrolled HTN, significant valvular disease (e.g., aortic stenosis), and hypertrophic cardiomyopathy
- Decreasing myocardial oxygen supply: anemia, hypoxemia, and increased blood viscosity

From the above, determine if the patient has **high, intermediate, or low** probability of CAD. Low probability needs no further testing. Pretest probability helps determine the next step. Those with intermediate or high probability of CAD should undergo risk stratification with further testing.

Noninvasive Tests for Chronic Stable Angina — Diagnosis and Risk Stratification

ECG: Check first for ST-T wave changes that suggest ischemia, such as T-wave inversions, ST-segment depression, and ST-segment elevation. Also look for signs of prior infarction in the form of Q waves or persistent ST changes. An ECG finding of LVH can alert you to the presence of HTN, which is a strong risk factor for CAD. There are other findings (e.g., RBBB, LBBB, atrial fibrillation, bifascicular block) that can be caused by underlying ischemia, although they are **not** specific indicators of CAD.

CXR is recommended if there are signs of HF, valvular disorders, or pericardial disease.

Stress testing is the **most important test** in risk stratification. Remember: Exercise testing is preferred for all patients with stable angina who can exercise. This is because exercise capacity is one of the best indicators of long-term risk. In addition, exercise can provide a higher physiological stress than pharmacological testing can achieve.

Assess LV systolic function (generally with **echo**) in patients with prior MI, pathological Q waves, symptoms or signs of HF, arrhythmias, or heart murmur—it will help guide treatment.

If the test results will not change management (e.g., severe comorbidities that preclude revascularization, patient does not want revascularization), further testing is not warranted.

Determination of Further Workup in Chronic Stable Angina

Based on clinical characteristics and stress test results, determine the probability of death or MI and stratify the patient into a **high-risk** (> 3% per year), **intermediate-risk** (1–3% per year), or **low-risk** (< 1% per year) group. Refer **high-risk patients for coronary angiogram**. Patients with low or intermediate risk should be treated with medical therapy to improve symptoms and function, and further workup can be deferred if symptoms can be controlled with medical therapy.

The Duke treadmill score uses 3 parameters from the ETT to predict cardiovascular risk: exercise time, magnitude of maximum ST-segment deviation, and occurrence of angina.

TREATMENT OF CHRONIC STABLE ANGINA

PREVIEW | REVIEW

- What is the goal for blood pressure management in a patient with stable ischemic heart disease?

Treatment goals for chronic stable angina include reducing the risk of premature cardiovascular death; preventing complications, including MI and HF; eliminating (or nearly eliminating) symptoms; and improving functional capacity and quality of life.

Medical therapy to **prevent MI and death**:

- Antiplatelet therapy: aspirin (clopidogrel if aspirin is contraindicated)
- High dose of a high-efficacy statin (e.g., atorvastatin)
- β -blockers (if left ventricular ejection fraction [LVEF] < 40% or prior MI)
- ACEIs (if LVEF < 40%, DM, HTN, or chronic kidney disease [CKD])

Medical therapy for **relief of symptoms**:

- β -blockers as initial therapy (Use cardioselective agents [e.g., metoprolol] for patients with lung disease.)
- Calcium channel blockers or long-acting nitrates when β -blockers cannot be used, or in combination with β -blockers when β -blockers are not sufficient
- Ranolazine in combination with maximally tolerated β -blockers

High-risk patients and patients with low or intermediate risk who remain significantly symptomatic despite maximal medical therapy should be referred for coronary angiogram.

Compilation of all recommendations:

- **Smoking** cessation (i.e., ask, advise, assess, assist, arrange, avoid); avoid exposure to environmental tobacco smoke.
- Diet: Limit saturated fats to < 7% of total calories, eliminate trans fats, and limit cholesterol intake to < 200 mg/day.
- Physical activity: **30–60 minutes/day** of moderate-intensity aerobic activity for 5–7 days/week
- Weight loss (if body mass index [BMI] > 25 kg/m²)
- Blood pressure management (goal < 130/80 mmHg per 2017 ACC guidelines): ACEI/ARB first; add thiazide diuretics or calcium channel blockers if needed.
- Influenza vaccine annually
- **Statin** in all patients (if no contraindications/adverse effects)
- Antiplatelet therapy: **aspirin** 75–162 mg/day indefinitely; clopidogrel when aspirin is contraindicated
- **β -blockers**: started and continued for 3 years in all patients with normal LV function. Continue indefinitely if LVEF < 40%. Use carvedilol, metoprolol succinate, or bisoprolol in all patients with LVEF < 40%, unless contraindicated.
- **ACEIs** in all patients who also have HTN, DM, LVEF < 40%, or CKD, unless contraindicated (Use ARB if ACEI intolerant.)

CARDIOVASCULAR DISEASE (CVD) PREVENTION IN WOMEN

PREVIEW | REVIEW

- Would you recommend aspirin in a healthy woman < 65 years of age for primary prevention of MI?

A 2011 update of the AHA guidelines for CVD prevention in **women** warns that the following should **not** be used for **primary or secondary** prevention of CVD:

- Hormone therapy
- Antioxidants (e.g., vitamins C and E, β -carotene)
- Folic acid or vitamin B₆
- Garlic, coenzyme Q₁₀, selenium, or chromium

Likewise, do **not** use aspirin in healthy women < 65 years of age for **primary prevention** of MI. (Aspirin is okay for those $\geq$ 65 years of age.)

Other points to remember regarding heart disease in women include:

- Chest pain is the most common angina symptom in both men and women and is described similarly in both.
- Treadmill exercise stress testing has a higher false positive rate in women than in men.
- Women have a lower rate of sudden cardiac death than men at all ages and risk levels.
- Coronary artery disease is more likely to present with chest pain in men than women.

ACUTE CORONARY SYNDROMES (ACSs)

IMPORTANT DEFINITIONS

PREVIEW | REVIEW

- What is the difference between angina and myocardial infarction (MI)?

Blood supply to the heart is provided via its coronary arteries. Adequate tissue perfusion requires a balance between oxygen **supply** and **demand**. The oxygen demand of an exercising heart at 140 bpm is higher than that of a resting heart at 65 bpm. When there is an increase in oxygen demand, the heart requires a corresponding increase in blood and oxygen supply, or ischemia develops. **Ischemia** (decreased blood and oxygen supply) of the myocardial tissue results in **angina** (chest pain). Because myocardial depolarization and repolarization are energy-dependent actions, a decreased oxygen supply results in electrocardiographic changes such as ST-segment depression and T-wave inversion. If ischemia is prolonged (> 20 minutes), the affected myocardial tissue **necrotizes**, causing **myocardial infarction (MI)**. Necrotic myocardial cells release their structural proteins, creatine kinase and troponin, into the blood stream.

Both angina and MI can manifest as chest pain. Angina is chest pain caused by myocardial tissue **ischemia**, which is **reversible**, while MI means there is myocardial tissue **necrosis**, which is **irreversible**.

In this topic, we discuss 2 common mechanisms that cause angina: coronary stenosis and intracoronary thrombus. **Know this well!**

Stable coronary artery disease (CAD) can allow enough perfusion during rest, but not during exercise when oxygen demand is higher. A sudden increase in oxygen demand in the setting of fixed oxygen supply—when coronary stenosis limits blood flow—results in exertional angina, or **stable angina**. As the severity of CAD progresses and the stenosis in the coronary artery becomes more severe, ischemia and corresponding angina can develop with lower levels of exertion.

Stable angina indicates a gradual and progressive pathology. This is the concept behind performing exercise stress testing to detect significant CAD: If ischemia develops during exercise, physical symptoms (e.g., angina) and electrical changes (e.g., changes in ST segments and T waves) occur that indicate significant coronary stenosis.

On the other hand, a **sudden** decrease in blood flow (and oxygen supply) can cause acute ischemia, even at rest. This can be caused by rupture of a previously stable plaque in a patient with CAD and formation of a thrombus. This can also be caused by an embolized thrombus, which can obstruct coronary blood flow even in normal coronary arteries without significant stenosis. This is called **unstable angina**—oxygen supply suddenly decreases, despite no change in oxygen demand.

If angina (ischemia) continues without treatment (> 20 minutes), the affected myocardial tissue starts to necrotize, and MI develops. Recognize unstable angina early—untreated, it can lead to MI (tissue necrosis). In contrast, patients with stable angina are not at immediate risk for MI, because angina forces patients to rest, reducing their oxygen demand and resolving the ischemia. The management and prognosis of stable and unstable angina are completely different.

CHEST PAIN

PREVIEW | REVIEW

- What are the 4 diagnoses that should never be missed in patients with chest pain?

Differential diagnosis of chest pain is broad, but as a rule of thumb, anything in the chest can cause chest pain. Consider all the structures within the chest and correlate them with the history and findings from physical examination. These include:

- Heart (e.g., acute coronary syndromes [ACSs], heart failure)
- Lungs (e.g., pulmonary embolism [PE])
- Aorta (e.g., aortic dissection)
- Esophagus (e.g., esophageal perforation and rupture)
- Pericardium (e.g., pericarditis)
- Pleura (e.g., pleurisy)
- Mediastinum (e.g., mediastinitis)
- Bones (e.g., periostitis, primary bone malignancy, metastases to bones from a different primary malignancy, costochondritis)
- Skin (e.g., shingles)

The main 4 diagnoses that should never be missed are 1) ACS, 2) aortic dissection, 3) PE, and 4) esophageal perforation and rupture.

These diagnoses are life-threatening. You should always **actively exclude** each one of these in **all** patients presenting with chest pain and tailor the workup to each individual case. Sometimes patients have 2 of these at the same time, so always actively rule out each diagnosis.

NOTES

PREVIEW | REVIEW

- Which groups of patients are most likely to present with myocardial infarction without chest pain?

15% of acute myocardial infarctions (MIs) are asymptomatic.

MI **without** chest pain or with **atypical** chest pain is more common in:

- Elderly patients (about 2/3 of silent MI patients are > 75 years of age)
- Diabetics

- Women
- Patients with known obstructive coronary artery disease

Arrhythmias, such as ventricular tachycardia (VT) and ventricular fibrillation (VF), can occur in the first 48 hours after MI. Post-MI arrhythmias are due to acute ischemia (or are reperfusion related) and do **not** require long-term antiarrhythmic therapy or implantable cardioverter-defibrillator. Treatment instead involves immediate restoration of coronary blood flow, using percutaneous coronary intervention or thrombolytics.

Inferior MIs (usually right coronary artery) result in more **benign** arrhythmias and conduction abnormalities, such as sinus bradycardia, 2nd degree heart block Mobitz 1, and **intranodal** complete heart block (very often resolves in 48 hours without a need for temporary or permanent pacemaker). Inferior MIs have a **better outcome**. However, **acute mitral regurgitation** due to papillary muscle dysfunction or rupture is seen more commonly with inferior MIs.

Anterior MIs (left anterior descending coronary artery) can cause more **serious** arrhythmias and conduction abnormalities, such as 2nd degree heart block Mobitz 2, bundle-branch block, and **infranodal** complete heart block. Infranodal heart block includes intra-Hisian and infra-Hisian blocks, which require temporary pacing and sometimes permanent pacing if arrhythmias do not resolve in 2 weeks. Anterior MIs have a **poorer outcome**. Additionally, the amount of infarcted myocardium is typically **larger** with anterior MIs. See [Complications of Myocardial Infarction \(MI\) on page 13-29](#).

Ventricular septal rupture (VSR) can occur with either anterior or inferior MI. VSR due to inferior MI has a better outcome than VSR due to anterior MI.

MARKERS FOR ACUTE MYOCARDIAL INFARCTION (MI)

PREVIEW | REVIEW

- How are troponin I and T used?
- How long do troponin I and T stay elevated after an MI?

Troponins (Tns) and creatine kinase myocardial bands (CKMBs) are serum markers of myocardial necrosis. Troponins are more sensitive and specific, so CKMBs are no longer routinely used for the diagnosis of acute MI. Troponin levels begin to rise 3–6 hours after onset of MI, peak at 24 hours, and remain elevated for up to 2 weeks. CKMBs peak within 24 hours and return to normal in 2–3 days. Patients presenting with a new episode of chest pain within 2 weeks of a previous MI will have elevated troponin, which makes it difficult to diagnose recurrent MI. In this case, CKMBs are useful for diagnosing a new acute MI because they normalize within 2–3 days of the previous MI.

Know **all** of the following!

Troponins are highly specific for myocardial injury. Assays to detect components of cardiac muscle—troponin I and troponin T (**cTnI** and **cTnT**)—are the gold standard for the detection of myocardial necrosis. cTnI and cTnT levels are predictive of both acute MI and cardiac death. The 2 troponin assays are equally useful, and local preferences dictate which one is used.

Troponins (Tns) first become elevated 3–6 hours following an MI and peak at about 24 hours after the event ([Figure 13-12](#)). They can remain elevated for 10–14 days after an MI. Because they stay elevated so long, troponins are useful even when patients present > 24–48 hours after onset of symptoms.

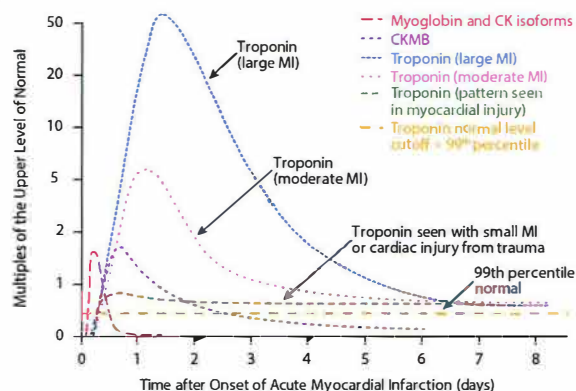


Figure 13-12: Activity of markers for acute myocardial infarction

cTnI or cTnT should be measured at presentation and 3–6 hours after symptom onset in all patients with suspected ACS until:

- they are elevated, confirming (i.e., ruling in) an MI or
- 3 sets of troponin are negative, ruling out MI.

Be aware that troponin level can also be elevated in chronic kidney disease, myopericarditis, heart failure (HF), sepsis, PE, cardiotoxic drugs (such as chemotherapy), and cardiac trauma. Other causes of myocardial tissue necrosis can also elevate the Tn. For example, trauma to the heart (from a punch or stab) results in Tn elevation from myocardial tissue damage, but this does not mean MI or ACS. For this reason, always look for the characteristic rise/fall of Tn levels, which is more specific for acute MI.

Remember: Tns are **sensitive** but **not highly specific** for the diagnosis of acute MI. In other words, they are **good for excluding** acute MI when they are negative, but not as good for confirming it when they are positive. In general, the larger the infarct, the higher the Tn level.

Keep in mind that the overall **trend** is **important** and gives added information beyond a single elevated value (trending enzymes). An individual whose enzymes continue to rise is in a very different situation than someone whose enzymes peaked earlier in the day, even in the absence of symptoms! In the first patient, where the Tn has not yet peaked, you should consider

ongoing ischemia or infarction, whereas the second patient has already completed the infarct. This can help determine the type and timing of further testing.

There are different ways to categorize MI; they may be categorized in the following ways:

- By mechanism: Type 1 MI (ACS), Type 2 MI (supply-demand mismatch)
- By anatomic location: e.g., anterior MI, inferior MI
- By ECG findings: **ST-elevation** MI (STEMI), **non-ST-elevation** MI (NSTEMI)

The ECG categorization indicates mortality risk—STEMI has a much higher in-hospital mortality than NSTEMI. Such differences dictate the management; therefore, ECG remains an important diagnostic tool.

CLASSIFICATION OF ACSs

PREVIEW | REVIEW

- What are the 2 major categories of acute coronary syndromes?

Know this well!

ACSs are caused by atherosclerotic plaque disruption (rupture, fissuring, or erosion) resulting in the development of an intracoronary thrombus. This results in acute ischemia (unstable angina), then myocardial infarction. There are 2 categories of ACSs:

- 1) Non-ST-elevation acute coronary syndromes
- 2) ST-elevation acute coronary syndrome

Non-ST-elevation acute coronary syndromes (NSTEMI, ACSs) are unstable angina and non-ST-elevation MI (NSTEMI).

ST-elevation acute coronary syndrome is **ST-elevation** MI (STEMI).

Note: ACS does not automatically mean MI (remember ACSs include unstable angina, which is not an MI). On the other hand, MI does not automatically mean ACS either. ACS is due to an atherothrombotic event (development of an intracoronary thrombus because of atherosclerotic plaque disruption). However, coronary spasm and embolization of a thrombus into a coronary artery can result in unstable angina and MI. These should not be considered ACSs because of the lack of atherosclerotic plaque disruption as a trigger. Mortality is higher in ACSs. Per the Fourth Universal Definition of MI released in 2018, MI has 5 different types. The main ones to remember are Type 1 MI (which includes STEMI and NSTEMI in ACS) and Type 2 MI (which is a supply-demand mismatch).

Common clinical scenarios include:

- Presence of ST elevation or new (or presumably new) left bundle-branch block (LBBB) is enough to establish the diagnosis of **STEMI**, without the need

to confirm with positive cardiac biomarkers—troponin takes 3–6 hours to peak, so it can be negative in early presentations of MI. See [ST Segment](#) on page 13-93 and [Left Bundle-Branch Block \(LBBB\)](#) on page 13-99.

- If there is new ST depression and/or T-wave inversion, there are 2 possible diagnoses:
 - Unstable angina if cardiac biomarkers are **negative**
 - NSTEMI if cardiac biomarkers are **positive**
- If cardiac biomarkers are **positive** without ST elevation, this is also termed NSTEMI.

STEMI can be localized to identify which myocardial wall it involves, while NSTEMI is not localized. Therefore, you can say anterior STEMI, but cannot say anterior NSTEMI. Therefore, if you read “anterior myocardial infarction” or “anterior MI,” know that it means anterior STEMI. On the other hand, if the term “MI” is used without further specifications, this can mean either STEMI or NSTEMI.

Note: MI was previously divided into Q-wave MI and non-Q-wave MI. However, this terminology is not commonly used any more.

Distinction between STEMI and NSTEMI is vital in clinical practice. It dictates management and provides insight into prognosis. Patients with NSTEMI have a smaller infarct size and lower risk of early mortality than those with STEMI. **However**, they have a **higher** risk of recurrent angina and **reinfarction**, and higher 1-year mortality! This is because comorbidities (e.g., diabetes mellitus, hypertension, chronic kidney disease) and diffuse coronary disease are more common in NSTEMI patients.

Again, although patients with NSTEMI have a lower early mortality, they have a higher 1-year mortality than patients with STEMI. Remember that patients with **NSTEMI** are more likely than those with STEMI to have had a **prior MI or angina**! In summary, STEMI kills patients soon (high **early** mortality), but NSTEMI signifies how sick patients are (high **late** mortality).

Differential diagnosis of chest pain includes stable angina, ACSs (unstable angina, NSTEMI, and STEMI), PE, aortic dissection, HF, pericarditis, esophageal or biliary tract problems, pneumothorax, pleuritic pain related to pneumonia, musculoskeletal inflammation, and psychogenic causes.

DIAGNOSIS AND MANAGEMENT OF ACSs

PREVIEW | REVIEW

- What are the prehospital guidelines for chest pain?
- What are the major things you should do in early risk stratification of a patient who presents to the emergency department with symptoms suggestive of an acute coronary syndrome?

Prehospital Management

Per the 2019 AHA guidelines for emergency cardiovascular care of acute coronary syndromes:

- Call **emergency services** for transport to hospital by **ambulance** (rather than friends/relatives).
- Give nonenteric-coated **aspirin (ASA)**; 162–325 mg) as chew and swallow $\times 1$.
- Perform **ECG**. If nondiagnostic or normal, repeat every 10 minutes (leave electrodes in same location to avoid changes in lead position causing slight variation in voltage).
- If STEMI on ECG, notify the receiving hospital (to prepare for fibrinolysis or percutaneous coronary intervention).
- **Nitroglycerin** (tablets or spray)—administer up to three doses at 3- to 5-minute intervals. Note nitroglycerin is **contraindicated** in the following situations, due to risk of severe hypotension:
 - Systolic BP < 90 mmHg, or 30 mmHg below baseline
 - Right ventricular (RV) infarction
 - The patient has taken a **phosphodiesterase-5 inhibitor** (e.g., sildenafil, vardenafil) within 24 hours (48 hours for tadalafil)
- Consider morphine in patients with STEMI and chest pain unresponsive to nitrates.
- Be prepared to recognize and manage ventricular arrhythmias.

Evaluation of Possible ACS

Early evaluation: For patients who present to the emergency department with symptoms suggestive of ACS, immediately (**within 10 minutes**) get an ECG, draw blood for cardiac markers, give ASA if not contraindicated, and conduct a **directed** history and physical examination.

High-risk features:

- Ongoing chest pain for > 20 minutes
- New ST changes (any one of the following):
 - ST depression ≥ 0.5 mm
 - ST elevation ≥ 2 mm in V1, V2, V3
 - ST elevation ≥ 1 mm in leads other than V1, V2, V3
- Elevated cardiac enzymes (cTnI or cTnT)
- Signs of heart failure
- Hypotension

What happens next depends on the **ECG**:

- If the ECG is abnormal, assign the patient to the **definite ACS** group in the ACC/AHA protocol outlined below.
- If the ECG is normal or nondiagnostic, repeat the ECG q 10 minutes or continuously monitor the patient.

Note: An acute MI involving the left circumflex coronary artery can present as a nondiagnostic (or normal)

12-lead ECG because the leads do not cover its supplied lateral wall (which is a posterior structure in the chest). If the clinical presentation is very concerning, consider obtaining V7–V9 leads (posterior chest wall leads).

Based on this early assessment, assign patients to 1 of the following 3 groups in the ACC/AHA protocol:

- 1) **Noncardiac** chest pain or chronic stable angina—treat accordingly. See **Treatment of Chronic Stable Angina** on page 13-16.
- 2) **Possible ACS** with nondiagnostic ECG and normal initial serum markers (**Figure 13-13**)—observe for ≥ 12 hours following symptom onset. If there is no recurrence of symptoms, a 2nd Tn is negative, and repeat ECG is unchanged, perform further risk stratification with an appropriate stress test. Patients who have a negative or low-risk stress test can be discharged to home and followed as outpatients (see the green box in **Figure 13-13**). If observed patients have recurrent symptoms, subsequent positive Tn, ECG changes, or a positive stress test, admit and manage according to the acute ischemia pathway (**Figure 13-14**).
- 3) **Definite ACS**—immediately determine whether there is ST elevation or new LBBB (**Figure 13-15**):
 - Admit and treat patients **without** ST elevation or new LBBB according to the acute ischemia protocol (**Figure 13-14**).
 - Consider patients **with** ST elevation or new LBBB for emergent reperfusion therapy.

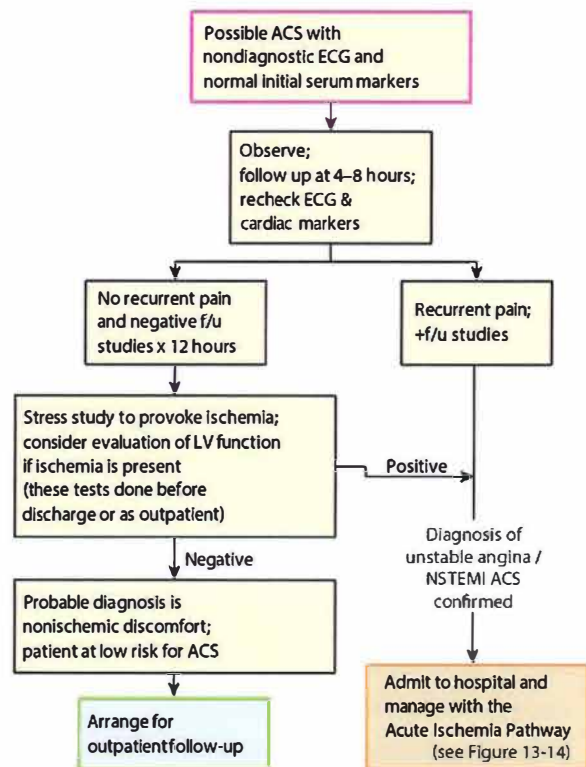


Figure 13-13: Diagnostic pathway for **possible ACS**

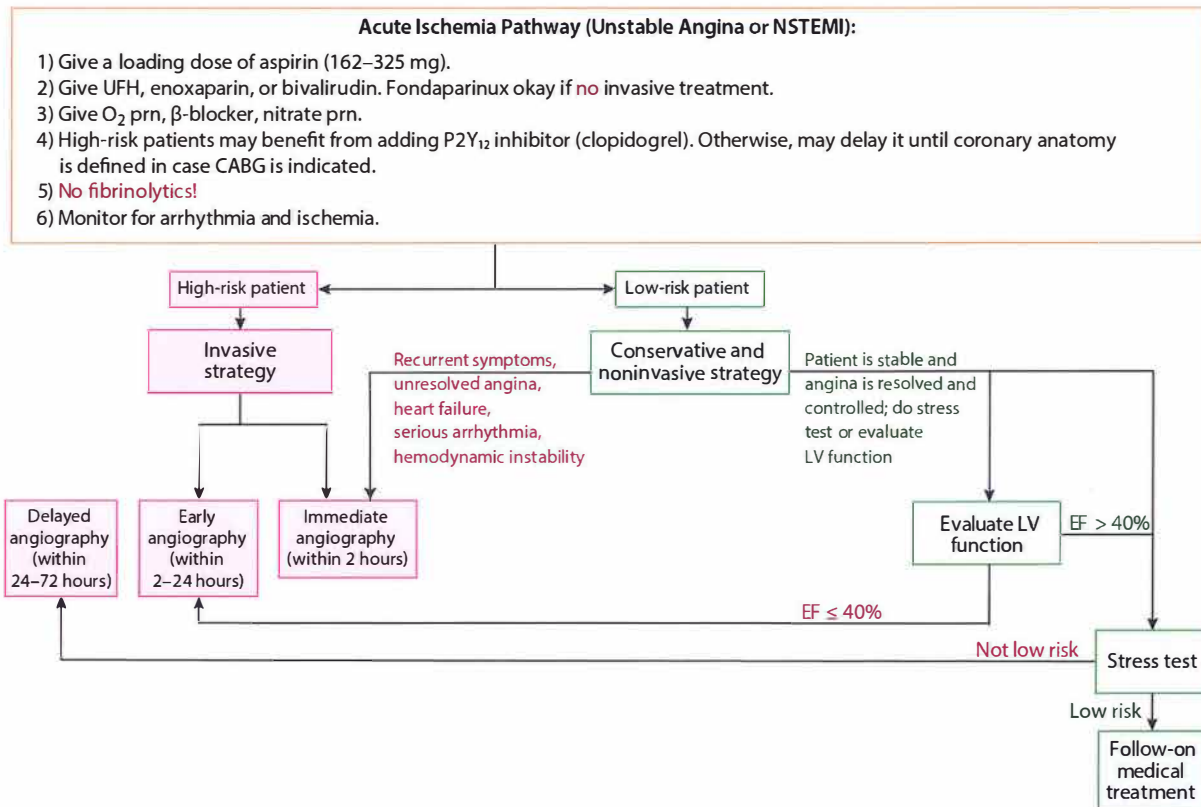


Figure 13-14: Acute ischemia treatment pathway — unstable angina or NSTEMI

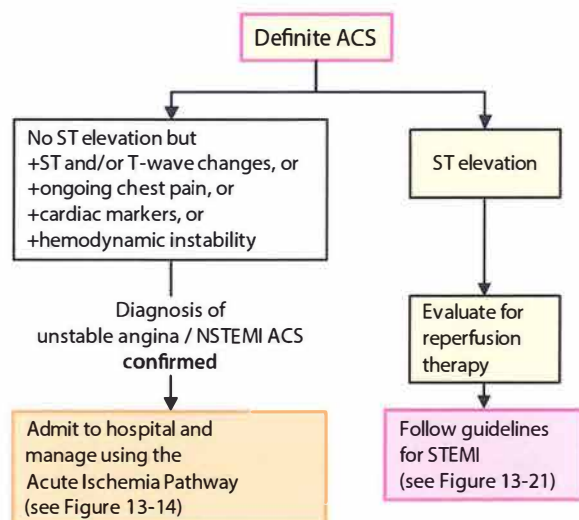


Figure 13-15: Initial treatment pathway for definite ACS

Note: LBBB distorts repolarization and interferes with ECG analysis and detection of ST elevation if present (ST elevation can be hidden within the LBBB). In a patient with a presentation concerning for ACS, **new** LBBB should be managed as STEMI. If there is no prior ECG to compare with, then **presume** the LBBB is new, and manage as STEMI. See Figure 13-16 on page 13-22 and Figure 13-17 on page 13-22.

Anterior wall STEMI due to proximal left anterior descending (LAD) coronary artery occlusion can present with a new LBBB that hides ST elevation. This happens when proximal LAD occlusion blocks flow to both the anterior wall and the main septal branches that perfuse the left bundle.

Note: Confirming or presuming a new LBBB in a patient without a suspected ACS (for example, during routine outpatient follow-up), does not mean STEMI. The patient must have other features of ACS or a positive troponin for STEMI diagnosis in this setting.

In **posterior** wall STEMI (Figure 13-18 on page 13-22), you see ST **depression** (rather than elevation) in V1 and V2 and tall **R** (rather than Q) waves in V1 and V2. This makes sense, because the posterior left ventricular (LV) wall is away from the anterior chest wall where the V1 and V2 leads are placed (Figure 13-19 on page 13-22). Those anteriorly placed leads show mirror images of the ST elevation and Q waves in the posterior LV wall. Placing posterior leads (V7, V8, and V9) can show the true ST elevation and Q waves because they overlie the posterior LV wall. Posterior STEMI very rarely occurs alone, and usually presents with inferior STEMI (called infero-posterior STEMI; Figure 13-20 on page 13-23). If you flip the ECG upside down and look at it from behind, you see ST elevation and Q waves in V1 and V2.

We will discuss each of these scenarios shortly, but first let's talk about general measures considered for **all** patients with ACS.

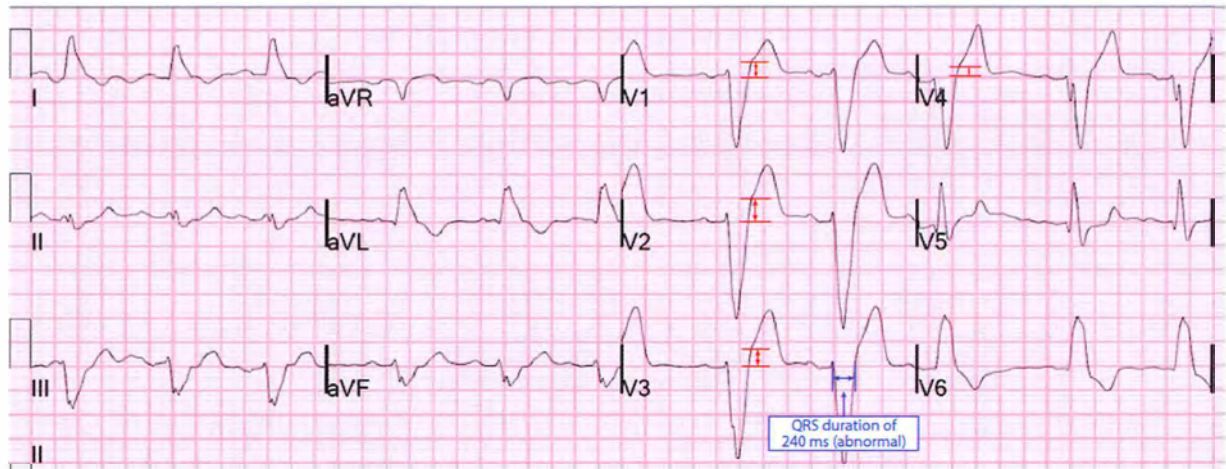


Figure 13-16: ECG — LBBB after cardiac arrest. Note the wide QRS duration and the accompanying ST elevation (blue, QRS duration; red, ST elevation).

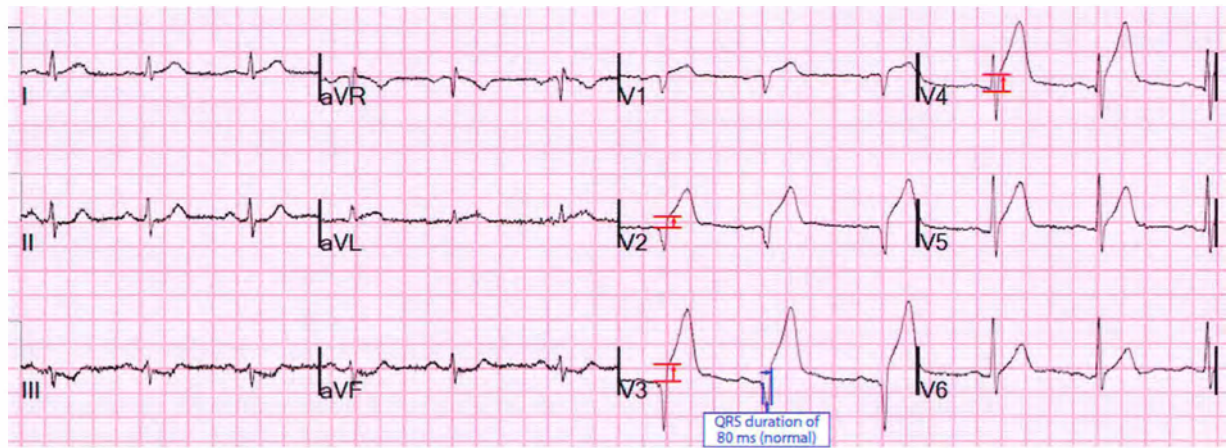


Figure 13-17: ECG — Anterior STEMI without LBBB. Note the normal QRS duration but ST elevation (blue, QRS duration; red, ST elevation).

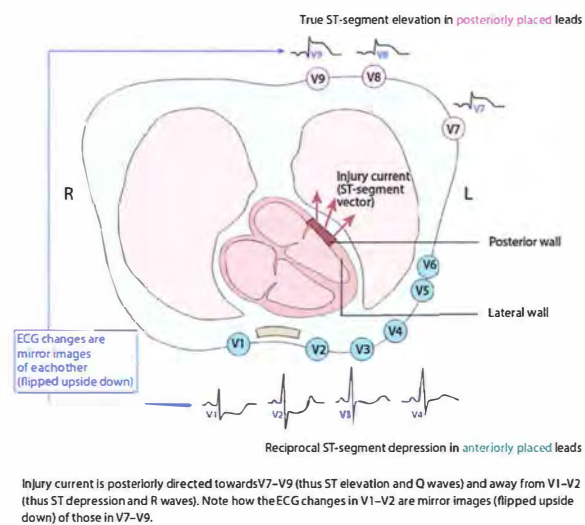


Figure 13-18: ECG lead placement and traces for posterior myocardial infarction

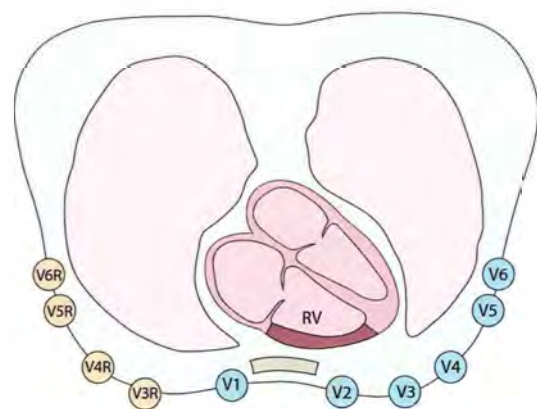


Figure 13-19: ECG lead placement for right ventricular infarction (RV1). If there is suspicion of RV1, additional leads are placed as shown, with leads on the right side of the chest (V3R-V6R) set as mirror images to the placement of those on the left side of the chest.

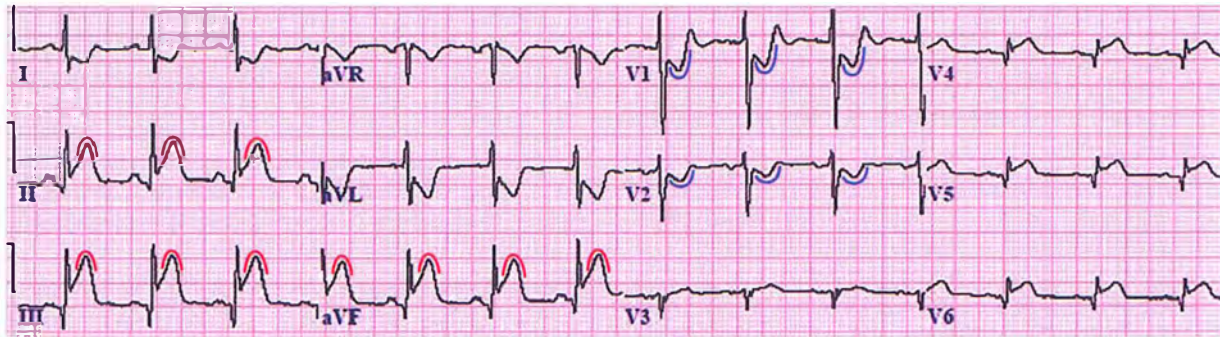


Figure 13-20: ECG — Inferoposterior STEMI. Note the ST-segment elevation (red curves) in the inferior leads and accompanying reciprocal ST-segment depression (blue curves) in V1 and V2.

ACSs — EARLY MEDICAL THERAPY

PREVIEW | REVIEW

- Which antiischemic measures are done initially for all patients with acute coronary syndromes (ACSs)?
- Which patients should receive a platelet glycoprotein IIb/IIIa inhibitor?
- Of those with ACS, which group gets considered for fibrinolytic therapy and which group definitely does not?

Management goals in ACSs (STEMI, NSTEMI, and unstable angina) include:

- Alleviating symptoms (with antiischemic therapy and morphine)
- Managing the intracoronary thrombus with antiplatelet (using single or dual drugs) and anticoagulation therapies
- Restoring flow in the affected coronary artery with percutaneous coronary intervention (PCI) or thrombolytic therapy if appropriate
- Monitoring and prompt treatment of life-threatening arrhythmias (e.g., VT, VF), HF (pulmonary edema), or mechanical complications of MI (e.g., ventricular septal rupture, free wall rupture)
- Optimization of medical therapy to prevent future recurrence of ACS

ECG, Nitroglycerin (NTG), Morphine, β -Blockers, Angiotensin-Converting Enzyme Inhibitors (ACEIs), and Atropine

General antiischemic measures for all patients with an ACS include:

- Continuous ECG monitoring
- ASA
- Sublingual NTG $\times$ 3 prn for angina and IV NTG for persistent angina or hypertension
- **Morphine** if pain is not relieved by NTG. Never give nonsteroidal antiinflammatory drugs

(NSAIDs) except ASA; they increase risk of adverse cardiovascular events!

- Oral **β -blocker** and an angiotensin-converting enzyme inhibitor **ACEI** if the patient is hypertensive or has LV dysfunction (ejection fraction [EF] $\leq$ 40%); but avoid β -blocker if HF is not stabilized.

Administer supplemental **oxygen** to patients with ACS with an arterial saturation (S_aO_2) $<$ 90%, or respiratory distress, or other high-risk features for hypoxemia. (Pulse oximetry is useful for continuous measurement of S_aO_2 .)

β -blockers reduce myocardial O_2 consumption. By blocking excessive sympathetic activity, they reduce cardiac workload and decrease the likelihood of arrhythmias. Oral use is preferred. **Do not** give β -blockers if the patient is hypotensive (SBP $<$ 90 mmHg), has an advanced atrioventricular (AV) block (Mobitz 2 second-degree AV block or third-degree AV block), or has signs of decompensated HF or cardiogenic shock (pulmonary edema). See **β -Blockers** on page 13-77.

Nondihydropyridine calcium channel blockers (e.g., **verapamil**, **diltiazem**) can be given if β -blockers are contraindicated and the patient continues to have ischemia and hypertension but **not** if the patient has **LV** dysfunction (because these drugs have negative inotropic effects).

Use **atropine** to treat acute sinus bradycardia with signs of low cardiac output while preparing for temporary pacing. Sinus bradycardia is usually seen with inferior MI. It is usually transient, and atropine alone may be sufficient.

Antithrombotic Therapy in ACSs

Antithrombotic therapy is a mainstay of treatment of ACS. It includes intense **parenteral anticoagulation** and **antiplatelet** medications. This makes sense because an ACS involves the development of an intracoronary thrombus. All patients presenting with an ACS should receive IV anticoagulation plus antiplatelet therapy (ASA [162–325 mg] $\pm$ a $P2Y_{12}$ receptor inhibitor).

Parenteral Anticoagulants

Options for parenteral anticoagulants include unfractionated heparin (UFH), enoxaparin, fondaparinux, and bivalirudin. Most patients with ACS should get one of these agents:

- UFH is preferred in many cases because of its short half-life. It is easy to manage and dose, even in the cath lab, and can be stopped if coronary artery bypass graft (CABG) surgery is needed.
- Enoxaparin is not used frequently. Remember to reduce the dose in patients with renal impairment (eGFR < 30 mL/minute).
- Consider fondaparinux in patients with increased risk of bleeding, especially if **only** medical therapies (anticoagulation and antiplatelet therapies) are planned—this approach is also referred to as conservative or noninvasive strategy. Fondaparinux is **not** used if **percutaneous coronary intervention** is planned (this approach is referred to as invasive strategy) because it increases the risk of catheter thrombosis and coronary complications.
- Bivalirudin is an alternative to UFH in patients who will undergo PCI within 4 hours, particularly in patients at high risk of bleeding.

Vitamin K antagonists (e.g., warfarin) and direct oral anticoagulants (dabigatran, rivaroxaban, apixaban, and edoxaban) are **not** recommended in ACS.

Antiplatelet Therapy

Aspirin

Immediately administer nonenteric-coated aspirin (a.k.a. acetylsalicylic acid; ASA) at a loading dose of 162–325 mg to **all** patients with ACS. According to the 2016 ACC/AHA Guidelines Focused Update on Duration of Dual Antiplatelet Therapy (DAPT Guidelines) in Patients with Coronary Artery Disease, ASA should be continued at a maintenance dose of 75–100 mg daily (indefinitely) unless there are contraindications. **Do not interrupt** ASA within the first 12 months after ACS.

Platelet P2Y₁₂ Receptor Inhibitors

The thienopyridines **clopidogrel** and **prasugrel** have an **additive** effect with aspirin. These drugs irreversibly block the adenosine diphosphate receptor, P2Y₁₂, on platelets. Ticlopidine is a thienopyridine that is no longer routinely used due to its side effect profile (agranulocytosis).

The safety of combining proton pump inhibitors and thienopyridines is controversial. Although a 2010 American College of Cardiology and American Heart Association (ACC/AHA) expert consensus statement reported no clear-cut evidence of harm, there is a concern for increased risk of cardiovascular events in patients taking omeprazole with clopidogrel.

Clopidogrel requires the liver enzyme CYP2C19 to become active. Overall, 16–50% of patients may be clopidogrel resistant, either due to impaired absorption, drug interactions, or **poor CYP enzyme activity**. In 2010, clopidogrel received an FDA (Food and Drug Administration) **black box warning** about poor metabolizers and the availability of genetic testing, but routine genetic testing is not recommended because studies do not show better outcomes with testing.

Prasugrel has a faster onset of action and is effective in **clopidogrel-resistant** patients. It has significantly more antiplatelet activity and therefore results in a lower rate of cardiovascular events—but also higher rates of significant bleeding. Prasugrel is contraindicated in the elderly, those who weigh < 132 lb (60 kg), and patients with history of previous stroke or transient ischemic attack (TIA). Because of high bleeding risk, this drug is never to be initiated outside the cath lab, even in ACS patients.

Clopidogrel and prasugrel can be used interchangeably for all patients with ACS **unless** CABG is imminent (operative bleeding complications).

The **nonthienopyridines** (e.g., ticagrelor, cangrelor) are reversible antagonists of the platelet P2Y₁₂ receptors. Cangrelor is an intravenous P2Y₁₂ receptor inhibitor; its use and indications are beyond the scope of the generalist. Here, we exclusively discuss the oral medication, ticagrelor.

Ticagrelor has a rapid onset of action. Like prasugrel, it is more effective than clopidogrel, but without the increased bleeding risk. It can be used as an alternative to clopidogrel or prasugrel. Know that the aspirin maintenance dose in combination with ticagrelor must never exceed 100 mg daily, as higher doses render ticagrelor less effective.

Note: According to the 2016 ACC/AHA Guidelines Focused Update on Duration of Dual Antiplatelet Therapy (DAPT Guidelines) in Patients with Coronary Artery Disease, clopidogrel or ticagrelor should be continued for at least 1 year following MI.

Duration of DAPT is determined by the indication. For **ACS**, continue DAPT for ≥ 12 months without interruptions, regardless of whether the patient received a drug-eluting stent (DES), bare-metal stent (BMS), or no stent. Interruption of DAPT increases risk of recurrent ACS. In contrast, if stents are used in **stable coronary artery disease**, then duration of DAPT is determined by the type of stent—6 months with DES and 1 month with BMS. Earlier interruption of DAPT in these cases causes stent thrombosis that presents as an acute MI and has high mortality.

Sometimes, patients need to undergo unplanned surgery after ACS. In these cases, **do not stop** clopidogrel, prasugrel, or ticagrelor until at least **6 months** after ACS diagnosis. All elective surgeries and procedures (such as knee replacements or screening colonoscopies) should be delayed until DAPT is completed (i.e., after 12 months).

All P2Y₁₂ receptor inhibitors should be loaded to ensure achievement of adequate serum level and early activity. Loading doses of these agents are as follows:

- Clopidogrel—loading doses vary depending on clinical setting, but maintenance dose is always 75 mg daily:
 - STEMI undergoing emergent PCI: Load with 600 mg.
 - STEMI undergoing fibrinolytic therapy: If ≤ 75 years of age, load with 300 mg; if > 75 years of age, do not load.
 - NSTEMI undergoing nonemergent PCI or being treated medically: Load with 300 mg.
- Prasugrel—loading dose is 60 mg and maintenance dose is 10 mg daily.
- Ticagrelor—loading dose is 180 mg and maintenance dose is 90 mg bid.

Note: To get the serum concentration to an effective level, all antiplatelet drugs need a loading dose if the patient is not taking them routinely or is not compliant with regular dosing. Thereafter, a maintenance dose sustains that therapeutic level. So, give a loading dose when needed and then begin a maintenance dose. If you do not properly load when needed, it will take a few days for the serum level to reach an effective dose; meanwhile, the patient will continue to infarct!

Glycoprotein IIb / IIIa Inhibitors

Glycoprotein (GP) IIb/IIIa inhibitors are very potent antiplatelet drugs because they act on the final common pathway of platelet aggregation—where fibrin binds platelets together by connecting to the GP IIb/IIIa receptor. The most studied drug is **abciximab**. Others are **eptifibatide**, **tirofiban**, and **lamifiban**. Only the IV forms are effective. GP IIb/IIIa inhibitors are rarely used in ACS because of their high bleeding risk. They are reserved for special cases, such as large thrombus burden in the coronary artery or saphenous venous bypass graft.

Fibrinolytic (a.k.a. Thrombolytic) Therapy in ACSs

Do **not** give fibrinolytic therapy to patients with NSTEMI-ACSs because it **increases** mortality. Do give fibrinolytic therapy to STEMI patients (ST elevation or new LBBB) if immediate PCI is **not** available and if there are no contraindications (discussed under [Fibrinolytic Therapy in STEMI on page 13-28](#)). Fibrinolytic therapy should be administered within 30 minutes of presentation to the emergency department or initial contact with the emergency medical service personnel. This is referred to as door-to-needle time, where “door” represents when the patient enters the emergency department or first encounters emergency personnel, and “needle” represents when the patient receives the intravenous injection of fibrinolytic drug.

ACSs — MANAGEMENT OF NON-ST-ELEVATION ACUTE CORONARY SYNDROMES (NSTEMI-ACSs) — THE ACUTE ISCHEMIA PATHWAY

PREVIEW | REVIEW

- Which non-ST-elevation acute coronary syndromes patients should be considered for an **immediate** invasive strategy (within 2 hours)?

Invasive vs. Ischemia-Guided Therapy

The 2014 AHA/ACC NSTEMI-ACS treatment guidelines have 2 areas of focus ([Figure 13-14 on page 13-21](#)):

- 1) Antithrombotic (i.e., antiplatelet and anticoagulation) therapy with multiple agents
- 2) Aggressive use of early percutaneous coronary intervention (PCI; cardiac catheterization to determine the culprit vessel and treatment, usually with a stent) in those with moderate-to-high risk

Okay, you have determined the patient is having an ACS and have initiated treatment according to the general measures under [Diagnosis and Management of ACSs on page 13-19](#). You've drawn labs and done the ECG, which reveals **no** acute ST elevation. The labs come back, and you determine that the patient has NSTEMI (cTn abnormal) or unstable angina (cTn normal).

You have 2 options:

- 1) Invasive therapy (coronary angiography), which can be immediate (within 2 hours), early (within 2–24 hours), or delayed (within 24–72 hours)
- 2) Ischemia-guided therapy (medical or conservative therapy)

If you have determined the patient is having STEMI, pursue immediate invasive therapy (see [ACSs – Management of ST-Elevation Myocardial Infarction \(STEMI\) on page 13-26](#)).

Invasive Therapy in NSTEMI-ACSs

Indications for **immediate** invasive therapy (coronary angiography within 2 hours) for NSTEMI-ACSs:

- Signs or symptoms of HF
- Hemodynamic instability
- Recurrent or refractory angina that is not responding to medical therapy
- Life-threatening arrhythmias (i.e., VT, VF)

Indications for **early** invasive therapy for NSTEMI-ACSs (**within 2–24 hours**):

- Global Registry of Acute Coronary Events (GRACE) score > 140 (which signifies increased early mortality) without indications for immediate invasive therapy
- New ST depression
- Positive troponin

Indications for **delayed** invasive therapy for NSTEMI-ACSs (within 24–72 hours):

- Absence of the indications listed for immediate and early invasive therapy
- Diabetes
- Chronic kidney disease (glomerular filtration rate < 60 mL/minute/1.73m²)
- EF ≤ 40%
- PCI within the previous 6 months
- Early postinfarction angina
- Prior CABG
- GRACE risk score 109–140 or **TIMI** (thrombolysis in myocardial infarction) score ≥ 2

GRACE and TIMI scores are calculated using online calculators or smart device apps. They use clinical features including age, systolic blood pressure, heart rate, presence of ST changes, cardiac arrest at presentation, serum creatinine, elevated serum cardiac biomarkers, CAD risk factors, prior documented CAD, and recent anginal episodes.

Both NSTEMI-ACS and STEMI patients selected for invasive therapy get parenteral anticoagulation and dual antiplatelet therapy (see [Parenteral Anticoagulants on page 13-24](#) and [Antiplatelet Therapy on page 13-24](#)).

Remember: NSTEMI-ACS patients do not receive fibrinolytic therapy, as fibrinolytics actually increase mortality in the absence of ST elevation. Fibrinolytic therapy is given in STEMI **only** (and only if PCI is not immediately available).

Ischemia-Guided Therapy in NSTEMI-ACSs

Patients with NSTEMI-ACSs who are at **low risk** for immediate and 1-year mortality and can be followed **without** invasive evaluation (coronary angiography). This applies to those who:

- respond to intense medical therapy,
- have none of the indications for invasive therapy as listed in [Invasive Therapy in NSTEMI-ACSs on page 13-25](#) (especially, a lack of elevated troponin), and
- do well on post-ACS stress testing.

Ischemia-guided therapy for NSTEMI-ACSs patients:

- Parenteral anticoagulant:
 - UFH, enoxaparin, or fondaparinux for 48 hours. Fondaparinux is especially useful if there is risk of bleeding.
- Antiplatelet therapy:
 - Aspirin plus either clopidogrel or ticagrelor. Always give **dual** antiplatelet therapy.
 - Prasugrel or GP IIb/IIIa inhibitors are **not** given for conservative therapy.

This is basically the same anticoagulant/antiplatelet treatment as for those getting unstable angina/NSTEMI invasive therapy, except that fondaparinux is considered a reasonable option and GP IIb/IIIa inhibitors and prasugrel are not used.

Long-Term Antiplatelet Therapy after NSTEMI-ACSs

Based on the 2016 ACC/AHA DAPT Guidelines, the duration of DAPT should be the following.

With bare-metal stent:

- ASA 81 mg (range is 75–100 mg) daily for life
- Clopidogrel 75 mg daily, ticagrelor 10 mg daily, or prasugrel 90 mg bid for ≥ 1 year

With a drug-eluting stent:

- ASA 81 mg (range is 75–100 mg) daily for life
- Clopidogrel 75 mg daily, ticagrelor 10 mg daily, or prasugrel 90 mg bid for ≥ 1 year

With no stent (medical therapy alone):

- ASA 81 mg (range is 75–100 mg) daily for life
- Clopidogrel 75 mg daily or ticagrelor 10 mg daily for ≥ 1 year

Note: Duration of DAPT is determined by the indication. In ACS, continue DAPT for at least 1 year without interruptions, regardless of whether patients received a stent (DES or BMS) or not. Interrupting DAPT increases risk of recurrence of ACS—even if just 1 dose is missed.

The minimum duration of DAPT after NSTEMI-ACS is 1 year. If there is not a high risk of bleeding, then duration of DAPT can be extended beyond 1 year.

ACSs — MANAGEMENT OF ST-ELEVATION MYOCARDIAL INFARCTION (STEMI)

PREVIEW | REVIEW

- Which reperfusion therapies are appropriate in patients with ST-elevation MI (STEMI)? Who gets what?
- What are the absolute and relative contraindications to fibrinolytic therapy?
- How does management of right ventricle infarction differ from left ventricle infarction?
- Which patients with tachyarrhythmias after MI undergo direct-current cardioversion?
- What are the medical options for hemodynamically stable MI patients with ventricular tachycardia?
- In what time frame after MI do the major mechanical complications tend to occur? How do they present? What is the best test to diagnose such a complication?
- When should a patient with STEMI be referred for an implantable cardioverter-defibrillator?

In this discussion, refer to [Figure 13-21](#).

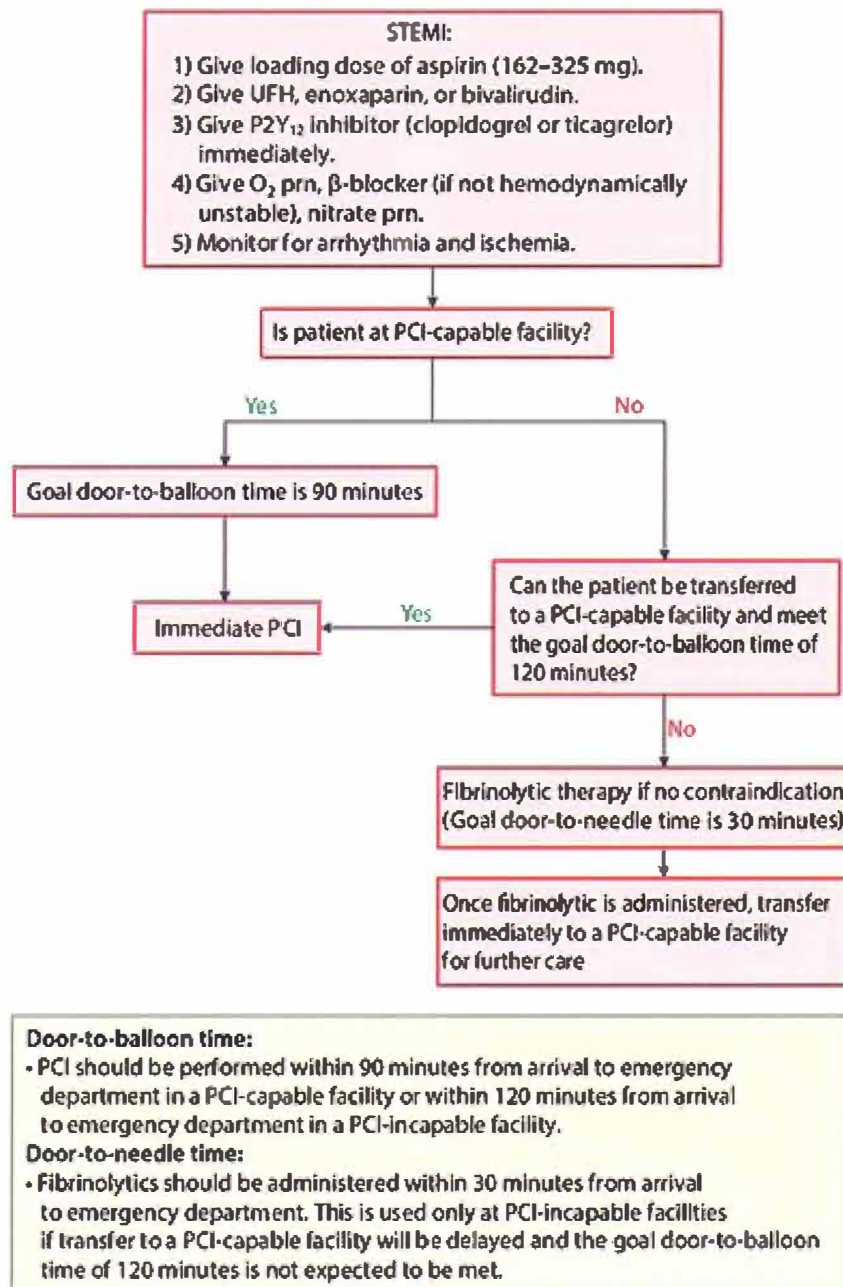


Figure 13-21: Acute MI treatment pathway with STEMI

The following are additions to the general measures for all ACS patients discussed under [Diagnosis and Management of ACSs](#) on page 13-19.

Remember, all STEMI patients get the following medical therapy:

- Parenteral anticoagulant—UFH, bivalirudin, or enoxaparin. Give UFH or bivalirudin if going to cath lab.
- Dual antiplatelet therapy (DAPT)—ASA 162–325 mg **plus** clopidogrel 600 mg or ticagrelor 180 mg (in emergency department)

Immediate Reperfusion Therapies

Consider emergent reperfusion (primary PCI **or** fibrinolytic therapy) in **all** patients who present with a STEMI within 12 hours of the onset of symptoms.

Primary Percutaneous Coronary Intervention (PCI)

Primary PCI is an **emergent** reperfusion procedure. The occluded coronary artery is opened with a balloon; then, usually, a bare-metal or drug-eluting stent is placed.

Primary PCI is superior to fibrinolytic therapy in patients with STEMI. Outcomes are better than fibrinolytic therapy as long as an experienced practitioner performs the procedure **within 12 hours** of the onset of symptoms—and within **90 minutes** of the arrival of the patient in the emergency department. **Door-to-balloon time** is a commonly measured metric for quality of care in STEMI, where “door” represents the time when the patient enters the emergency department or first encounters emergency personnel, and “balloon” represents the time when the balloon is inflated within the vessel to restore blood flow.

Transfer patients with STEMI who initially present to a facility without PCI capabilities to a PCI-capable facility—if a door-to-balloon time of no more than 120 minutes can be achieved. This time starts the minute the patient walks into the PCI-incapable facility, includes the transfer time to the secondary (PCI-capable) facility, and stops once the balloon is inflated within the affected coronary artery.

In summary, PCI is always preferred over fibrinolytic therapy for STEMI, if door-to-balloon time goals can be met. If a patient with STEMI presents to the emergency department of a PCI-capable facility or is assessed by emergency personnel and can be transferred immediately to a nearby PCI-capable facility, then goal door-to-balloon time is **90 minutes**. If the patient with STEMI presents to a PCI-incapable facility and can be transferred to a PCI-capable facility, then goal door-to-balloon time is **120 minutes** (the extra 30 minutes is for interfacility transfer). If these goals cannot be met, consider fibrinolytic therapy (see [Fibrinolytic Therapy in STEMI](#)).

Primary PCI is particularly beneficial in patients with the highest risk for mortality (e.g., cardiogenic shock) or bleeding (e.g., elderly, trauma, low body weight). Remember that bleeding, including intracranial hemorrhage, is a potential complication of fibrinolytic therapy.

In the patient who presents with completed STEMI (beyond 12 hours after the onset of symptoms and all involved myocardial tissue has infarcted already), immediate coronary angiography is indicated if:

- The patient continues to have chest pain (which suggests viable myocardial tissue at risk) or is in heart failure.
- Left ventricular ejection fraction (LVEF) is moderately to severely reduced.
- Ventricular tachycardia or ventricular fibrillation is present.
- Post-MI stress test shows significant ischemia.

If none of these factors is present, coronary angiography does not need to be performed immediately but should still be performed within 24 hours.

Fibrinolytic Therapy in STEMI

Unfortunately, it is not always possible to meet the goal door-to-balloon time of 90 or 120 minutes from

presentation (as discussed in [Primary Percutaneous Coronary Intervention \(PCI\)](#) on page 13-27). A PCI-capable facility may be too far away, or weather can cause delays or make transfers unsafe. When primary PCI cannot be accomplished in a timely fashion, immediately administer fibrinolytic (i.e., thrombolytic) therapy (a goal door-to-needle time of 30 minutes) unless contraindicated.

The sooner the patient receives fibrinolytic therapy, the greater the mortality benefit. The most benefit occurs when a patient is treated within the first hour, but there is some benefit from treatment within the first 4 hours. Over time, the intracoronary thrombus organizes, and it becomes less likely that fibrinolytics will successfully resolve it. In STEMI with late presentation, do not use fibrinolytics—it exposes patients to significant bleeding risk with questionable benefit.

Fibrinolytic therapy results in successful reperfusion in 50% of cases (compared to > 90% success in those treated with PCI). Successful reperfusion with fibrinolytics can be assumed if chest pain resolves or ST elevation decreases by 50% within 60–90 minutes.

Note: Fibrinolytics are used at facilities that do not have the capabilities for emergent PCI. Following administration of fibrinolytic therapy, **all** STEMI patients should be transferred **immediately** (without delays) to a PCI-capable facility to receive further care. All patients who received fibrinolytic therapy should undergo coronary angiography within 24 hours. If the patient continues to have chest pain (suggesting unsuccessful fibrinolytic therapy) or has signs of hemodynamic or electrical instability (e.g., hypotension, cardiogenic shock, VT, VF), coronary angiography should be performed immediately to assess coronary flow and perform PCI if indicated.

Regardless of success of fibrinolytic therapy, patients should **always** undergo coronary angiography after STEMI. The only difference is the **timing** of the procedure. If fibrinolytic therapy is unsuccessful or the patient has recurrent symptoms, then perform coronary angiography immediately. If fibrinolytic therapy is successful, perform coronary angiography within 24 hours.

Fibrinolytic agents include the recombinant, tissue-type plasminogen activators (e.g., alteplase [tPA], tenecteplase [TNKase]), anistreplase, streptokinase, and urokinase.

Remember: Always give anticoagulation and DAPT in patients with STEMI, even those getting fibrinolytic therapy.

Contraindications to fibrinolytic therapy can be either absolute or relative.

Absolute contraindications:

- Previous hemorrhagic stroke at any time; other cerebrovascular events within 1 year
- Intracranial neoplasm

- Active internal bleeding
- Suspected aortic dissection

Relative contraindications:

- Persistent BP > 180/110 mmHg
- Remote nonhemorrhagic cerebrovascular accident (> 1 year)
- Current use of anticoagulants with INR (international normalized ratio) > 2–3; bleeding diathesis
- Recent (within 2–4 weeks) major trauma or surgical procedure
- Noncompressible vascular puncture
- Previous exposure to streptokinase/anistreplase
- Pregnancy
- Active peptic ulcer

Of the patients with STEMI initially evaluated for fibrinolytic therapy, almost 2/3 do **not** receive fibrinolytic therapy for one the contraindications listed above. The risk of intracranial hemorrhage (which is usually fatal) increases with age, to as much as 1% in patients > 75 years of age, but age by itself is not a contraindication.

Primary PCI is the standard of care in STEMI because of its higher success rate and lower bleeding risk than fibrinolytic therapy.

Note: The larger the infarct, the greater the benefit of reperfusion therapies (PCI or fibrinolytics). For example, the salvageable myocardial tissue is much larger in an anterior MI than in isolated posterior MI; thus, reperfusion therapy will benefit the former more. The same applies to patients with new LBBB, who may have anterior wall MI.

Recall that fibrinolytics are indicated in STEMI only. They should never be given in NSTEMI.

Cocaine and Methamphetamine Users with ST Elevation

Give nitroglycerin, calcium channel blockers, and benzodiazepines. Avoid β -blockers. If ST segments are elevated and there is no immediate improvement with treatment, proceed with coronary angiography (or fibrinolytics if cath lab is not available). If chest pain resolves with treatment, troponin is not elevated, and there are no ST-segment abnormalities, the patient does **not** need coronary angiography or a stress test.

Additional Recommendations from the 2013 ACC / AHA STEMI Guidelines

For patients with STEMI:

- Stop all NSAIDs (except ASA), including COX-2 inhibitors!
- Start an oral β -blocker within 24 hours for patients who do **not** have any of the following contraindications: signs of HF or low-output state; increased risk

for cardiogenic shock; PR interval > 0.24 seconds; 2nd degree Mobitz 2 or 3rd degree heart block; active asthma or reactive airway disease.

- Do **not** give fibrinolytic therapy if immediate PCI is anticipated. In addition, there is no role for partial- or low-dose fibrinolytic therapy before PCI (also referred to as facilitated PCI).
- Give loading doses of nonenteric coated aspirin, 162–325 mg, plus clopidogrel 600 mg or ticagrelor 180 mg.
- Start anticoagulation therapy.
- Start a high-dose statin.
- Give angiotensin-converting enzyme inhibitors (ACEIs) within 24 hours to all with anterior STEMI, HF, or EF $\leq$ 40% (unless contraindicated). Use an angiotensin receptor blocker if ACEI intolerant.
- Give an aldosterone antagonist (e.g., spironolactone, eplerenone) to those with no contraindications who are already receiving an ACEI and β -blocker, have an EF $\leq$ 40%, and have either symptomatic HF or diabetes mellitus.
- Administer IV nitroglycerin in the first 24 hours for ongoing chest pain or hypertension.
- In patients with diabetes, keep blood sugars < 180 mg/dL using insulin-based regimens while avoiding hypoglycemia.
- Vaccinate for influenza yearly.
- Patients resuscitated after out-of-hospital cardiac arrest due to ventricular fibrillation or ventricular tachycardia should undergo immediate coronary angiography and PCI because acute coronary syndrome can be the cause.

Complications of Myocardial Infarction (MI)

Left Ventricular Dysfunction and Cardiogenic Shock

Left ventricular dysfunction after MI has a poor prognosis. Cardiogenic shock after MI is less common now than it was in the past, prior to the routine use of PCI and its high success rate. However, when cardiogenic shock after MI does occur, in-hospital mortality remains high—around 50%. This high mortality has not changed over the past decades, even with the widespread use of mechanical support, such as intraaortic balloon pumps and left ventricular assist devices. Mortality is highest with delayed treatment of cardiogenic shock; early treatment (before end-organ dysfunction starts) can improve outcomes.

Cardiogenic shock is characterized by **low cardiac output (CO)**, **high pulmonary capillary wedge pressure (PCWP)**, and **high right atrial (RA) pressure**. If the patient is not hypotensive, treat with preload reducers (e.g., diuretics) and afterload reducers (e.g., vasodilators, such as nitroglycerin and nitroprusside). If the patient is hypotensive (hemodynamically unstable), do not use afterload reducers—these will lower the blood pressure further. Instead, give inotropes (e.g., dobutamine, milrinone). Mechanical circulatory support devices such as intraaortic balloon pumps and left

ventricular assist devices (e.g., Impella, TandemHeart) should also be considered and used early when indicated, especially if the patient is hemodynamically unstable and cannot tolerate medical therapies.

Right Ventricular Infarction (RVI) Complications

RVI frequently accompanies an **inferior** MI and is almost always due to occlusion of the proximal **right coronary artery** (because it gives all branches to the RV). Inferior MI complicated by RVI has a significantly worse prognosis than inferior MI alone.

ST elevation in right-sided chest leads (i.e., V3R–V6R) indicates infarction of the RV. Normally, precordial leads (V1–V6) predominantly overlie the thick-muscled left ventricle (**thick muscles generate more voltage**), and thus these leads mostly record LV electrical activity. The electrical activity of the thin-walled right ventricle (**thin muscles generate less voltage**) is buried within the LV electrical activity. Because right-sided leads are placed away from the LV and close to the RV, they record electrical activity (and ST changes) of the right ventricle without interference from the left ventricle. If you suspect RVI in inferior STEMI, place right-sided leads and look for ST elevation in those leads. See [Figure 13-19 on page 13-22](#). With standard chest leads, notice that V1 is positioned on the right side of the chest wall (closer to the RV), and therefore acts like a right-sided lead. Look at V1 to determine whether there is ST elevation concerning for RVI.

Evaluate for RVI, which typically presents with the clinical triad of **hypotension**, **clear lung fields**, and **elevated jugular venous pressure**, in all cases of inferior MI. Kussmaul sign (paradoxical increase in jugular venous distention during inspiration) is frequently present.

If you perform right-heart catheterization, an **elevated RA pressure** of ≥ 10 mmHg with low PCWP and low cardiac output (CO) are quite specific for RVI.

Management of RVI is in some ways diametrically opposed to that of LV infarction. Do not give nitroglycerin and nitrates, because these result in venous dilation, decreased preload to the RV, and a corresponding decrease in RV CO. This leads to decreased filling of LV and hypotension. Instead, treat with IV fluid (to ensure adequate RV preload) until the blood pressure returns to normal. This sounds like stressing an already stressed RV—and it is—but there is a net-positive effect when BP and, hence, coronary artery blood flow, return to normal and heart rate slows. If hypotension continues despite adequate IV fluids, inotropic support, typically with dobutamine, may be necessary. The RV usually recovers within 2 weeks after MI. Know that the patients with RV dysfunction after MI have better outcomes than those with LV dysfunction after MI.

Arrhythmias and Conduction Abnormalities

A variety of tachyarrhythmias can occur with MI and cardiac ischemia. Rule of thumb for treatment: Any hemodynamically unstable tachyarrhythmia should be cardioverted immediately.

Atrial fibrillation (A-fib) with hemodynamic instability requires emergent treatment with direct-current (DC) **synchronized** cardioversion. In patients without hemodynamic instability, control the ventricular rate with β -blockers, diltiazem, or digoxin. Restoring sinus rhythm is the goal if the A-fib is new, but it should be delayed in hemodynamically stable patients until left atrial thrombus is ruled out with transesophageal echocardiography. Otherwise, cardioversion can result in stroke from cardioembolization.

Treat ventricular fibrillation (VF) and pulseless ventricular tachycardia (VT) with defibrillation—DC **unsynchronized** cardioversion. For sustained VT with a pulse with **hemodynamic instability**, treat with DC **synchronized** cardioversion.

For sustained VT **without hemodynamic instability**:

- **Amiodarone** is the drug of choice. It is given IV, either as a continuous infusion or as boluses every 10–15 minutes. Lidocaine can be used as well.
- Check for and correct any **hypokalemia** or **hypomagnesemia**.
- Routine **prophylactic** use of lidocaine to prevent VT is no longer recommended.

Patients who develop VT or VF **< 48 hours** after MI do not need an electrophysiologic study or implantable cardioverter-defibrillator (ICD) placement. Treat VT/VF by addressing the underlying cause (ischemia)—identify the culprit coronary lesion and treat it with PCI.

For patients who develop VT or VF **≥ 48 hours** after MI, or who have no treatable culprit coronary lesion, short-term and long-term mortality rates are high. Consider an electrophysiologic study and place an ICD if indicated.

Patients with **isolated**, premature ventricular contractions or runs of nonsustained (**< 30 seconds**) VT **do not** routinely need antiarrhythmic therapy. β -blockers are effective for ventricular ectopic activity and arrhythmia prevention.

Bradycardia and **AV block** are more common with **inferior** MIs than anterior MIs because inferior MIs cause increased vagal tone and AV nodal ischemia. Remember: Prognosis is related to the size of the infarct, not the presence of AV block itself. The block in inferior MI is often transient and does **not** require a permanent pacemaker.

AV block accompanying an **anterior** MI implies destruction of a large amount of myocardium in the interventricular septum. This has a **high mortality**, and frequently requires **permanent pacing** if the patient survives.

Indications for temporary transvenous pacing at the time of an MI include:

- Symptomatic bradyarrhythmias unresponsive to medical treatment
- Asystole or sinus arrest resulting in hemodynamic instability
- Complete (3rd degree) AV block or Mobitz Type 2 2nd degree AV block in the setting of anterior MI

Note: Complete (3rd degree) AV block can manifest as irregular cannon a waves on jugular venous waveform examination. With complete AV block, there is no communication between atrial and ventricular activity—each is depolarizing and contracting independently. When the atria happen to contract simultaneously with the ventricles, they squeeze blood against closed AV valves (mitral and tricuspid valves). So, blood from the right atrium ejects back into the inferior vena cava, the superior vena cava, and the internal jugular vein.

Complete AV block can result in lightheadedness even if blood pressure is stable. This is believed to be due to back ejection of blood into the cerebral veins (via the internal jugular vein) and congestion of those veins.

Mechanical Complications after MI

Major mechanical complications after MI include papillary muscle rupture, ventricular septal rupture, and free wall rupture. Fortunately, these catastrophic complications are now rare in developed nations due to widespread access to early PCI (early restoration of coronary flow means less infarcted myocardial tissue). However, they still may occur, especially in patients who present late after development of symptoms (with very large infarcts) or receive fibrinolytic therapy (which does not have a high success rate). It makes sense: Macrophages start cleaning up debris from the necrotic myocardial tissue, the affected tissue is weak and without a scar (which takes weeks to develop and strengthen), and the muscle may break down. Mortality is very high with any of the following mechanical complications; therefore, you must anticipate them and be able to recognize them, as each constitutes a surgical emergency. Typically, mechanical complications occur 3–7 days after MI:

- **Papillary muscle rupture** usually occurs after an inferior MI. The patient rapidly develops shock and acute pulmonary edema from severe acute mitral regurgitation. You may or may not hear the classic murmur—holosystolic, but sometimes early or midsystolic, at the apex, sometimes radiating to the back, sternal border, or axilla. The intensity of this murmur does not correlate with the severity of mitral regurgitation. Treatment is emergent cardiothoracic surgery.
- **Ventricular septal rupture (VSR)** usually occurs after inferior or anterior MI. Incidence is about 0.3% of

MIs (before the reperfusion therapy era, incidence was 1–3%). Again, the patient rapidly develops shock. A holosystolic murmur is heard, loudest at the left sternal border and is associated with a thrill. The murmur is very loud because the blood jet is going from a high-pressure chamber (LV) into a low-pressure chamber (RV). Treatment is emergent cardiothoracic surgery.

- **Free wall rupture** of the LV occurs after a large anterior MI, most frequently in elderly hypertensive women. Sudden syncope is typical. The neck veins are grossly engorged from tamponade. The classic triad of tamponade is pulsus paradoxus, tachycardia, and hypotension. There is dyspnea due to decreased cardiac output and decreased oxygen delivery, but lungs are clear. Hemodynamic collapse occurs quickly. There have been a few heroic saves with emergent surgery, but rapid death is the usual outcome.

Perform echocardiography in any hemodynamically unstable MI patient—it is the diagnostic modality of choice for all of these conditions. In addition to urgent cardiothoracic surgery, patients with these mechanical complications require intensive supportive care. Arterial pressure monitoring with an indwelling arterial line is appropriate. Mechanical support with intraaortic balloon pump or left ventricular assist device (e.g., Impella, TandemHeart) is indicated as a bridge to emergent revascularization and/or surgery in patients in cardiogenic shock after STEMI who do not quickly stabilize with pharmacological therapy or who have a mechanical complication.

Note: Differentiate VSR from ventricular septal defect (VSD). VSR occurs acutely as a complication from STEMI—a hole suddenly develops in a previously normal septum. The left ventricle (LV) and right ventricle (RV) are not used to exchanging blood directly. So, exposing the RV (and its low-pressure pulmonary circulation) to high systemic pressure from the LV causes hemodynamics to deteriorate acutely. This life-threatening complication requires emergent surgical repair. In contrast, VSD (see Ventricular Septal Defect (VSD) on page 13-83) is a congenital anomaly that rarely requires emergent correction.

Implantable Cardioverter-Defibrillators (ICDs) after STEMI

Patients with STEMI can present with cardiac arrest due to VF or VT. These arrhythmias are life-threatening, but if the culprit coronary lesion is treated, they should not recur after 48 hours. Therefore, ICD therapy is not indicated in these patients if the arrhythmias occurred within 48 hours after STEMI and patients underwent revascularization. However, ICD therapy is indicated before discharge in patients who develop sustained VT or VF > 48 hours after STEMI, provided the arrhythmia is not due to transient or reversible ischemia,

reinfarction, or metabolic abnormalities (i.e., there is no identifiable cause that can be reversed or corrected).

In addition, ICDs prolong survival in post-STEMI patients with either:

- 1) $LVEF \leq 35\%$ and New York Heart Association (NYHA) Class II or III heart failure
- 2) $LVEF \leq 30\%$ regardless of their NYHA class

Do **not** use left ventricular ejection fraction (LVEF) assessment **at discharge** as an indication for ICD placement because LVEF can improve later, after the stunned myocardium recovers from revascularization. (Think of the heart as feeling woozy for a number of weeks as it recovers from the MI.) Instead, LVEF should be assessed after 40 days (~ 6 weeks). After 40 days, if LVEF and NYHA class continue to meet the criteria above, placement of ICD is indicated. ICD placement sooner than 40 days after STEMI does not improve overall mortality in these patients.

Note: The recommendations cited here are for ICD therapy after STEMI complicated by decreased LVEF (heart failure). However, the recommendations for ICD therapy in patients with HF without STEMI are different and are discussed elsewhere (refer to Heart Failure [Other Therapy on page 13-78](#)).

CORONARY ARTERY DISEASE (CAD)

NOTE

The **risk factors** for CAD, recommendations for **screening and treatment** of hyperlipidemia, and **revascularization options** are outlined here. We will discuss revascularization options first and then the risk factors.

REVASCULARIZATION

PREVIEW | REVIEW

- Which patient groups get similar benefit from both percutaneous coronary intervention and coronary artery bypass graft (CABG)?
- In 3-vessel disease, what is the benefit of CABG—survival, symptoms, or both?
- Which patient groups definitely should get CABG?
- Why is dual antiplatelet therapy so important after stent placement?

The revascularization options for coronary artery disease are:

- Coronary artery bypass graft
- Percutaneous coronary intervention with a stent (drug-eluting or bare-metal) or angioplasty (ballooning without a stent)

Coronary Artery Bypass Graft (CABG) vs. Percutaneous Coronary Intervention (PCI) in Stable CAD

The following recommendations are based on the 2017 ACC/AHA Appropriate Use Criteria for Coronary Revascularization in Patients With Stable Ischemic Heart Disease. Pay attention to the language used in the guidelines, which depend on the strength of evidence behind them: “Recommended” constitutes a strong indication, and “reasonable” signifies a weaker indication.

For patients with **stable CAD**, perform revascularization (PCI or CABG) when there are unacceptable angina symptoms despite maximal medical therapy, when there is a survival benefit based on the anatomy of coronary disease (location, severity, and number of diseased vessels), or when there is presence of left ventricular (LV) dysfunction:

- CABG is **recommended** (strong indication) to improve survival for all patients with:
 - Significant **left main CAD** (> 50% diameter stenosis)
 - Significant stenoses (> 70% diameter) in **3 major coronary arteries** or significant stenosis (> 70%) in the proximal left anterior descending (LAD) coronary artery **plus 1** other major coronary artery (e.g., circumflex)
 - **Diabetes mellitus** and **multivessel CAD** (3-vessel CAD or complex 2-vessel CAD involving the proximal LAD)
- CABG is **reasonable** (weaker indication) to improve survival in patients with:
 - Significant (> 70% diameter) stenoses in **2 major coronary arteries** with severe or extensive myocardial **ischemia** or target vessels supplying a large area of viable myocardium. Indicators of severe/extensive ischemia include high-risk criteria on stress testing, abnormal intracoronary hemodynamic evaluation, or > 20% perfusion defect by myocardial perfusion stress imaging.
 - Significant (> 70% diameter) stenosis in **proximal LAD alone**
 - **Systolic dysfunction** is present (left ventricular ejection fraction [LVEF] < 50%) regardless of location and number of diseased vessels
- PCI or CABG is **recommended** (strong indication) to improve survival for survivors of sudden cardiac arrest with presumed ischemia-mediated ventricular tachycardia caused by significant (> 70% diameter) stenosis in a major coronary artery.
- PCI or CABG to improve symptoms is **reasonable** (weaker indication) in patients with ≥ 1 significant (> 70% diameter) coronary artery stenoses amenable to revascularization and unacceptable angina despite optimal medical therapy or due to patient preference.

- PCI is **reasonable** (weaker indication) as an alternative to CABG in select stable patients with significant (> 50% diameter stenosis) unprotected left main CAD with anatomy compatible with a low risk of PCI complications and clinical characteristics predicting a significantly increased surgical morbidity/mortality.

CABG vs. PCI for stable CAD—know these summary points very well and understand the concepts behind them:

- Outcomes with CABG are **better** than with PCI in patients with stable CAD. If main arteries (such as the **left main or proximal LAD**) are involved, CABG is better than PCI in terms of survival. The CABG scenario that yields the best survival benefit is when the **LIMA** (left internal mammary artery) is used as a graft to bypass the proximal LAD because it is a very durable graft.
- Patients with **diabetes mellitus (DM)** or **LV dysfunction (LVEF < 50%)** benefit more from CABG than from PCI.
- PCI can be an alternative to CABG if the complexity of the procedure is reasonable, but there is **no** evidence that demonstrates a survival benefit equal to CABG.
- Note that these recommendations are for **stable CAD**. In **ACS** patients needing prompt revascularization, PCI is better because it immediately opens the occluded vessel.

So, CABG improves symptoms and survival in:

- Left main CAD or left main-equivalent disease (2-vessel disease with 1 vessel being proximal LAD)
- 3-vessel CAD
- Multivessel CAD or proximal LAD disease with LV dysfunction and viable myocardium
- Multivessel CAD with DM or LV dysfunction (LVEF < 50%)

Stents

Stents are the mainstay of PCI. These are placed in the area of blockage within the coronary artery, and then expanded using a balloon, thereby opening the lumen to normal size. We used to treat blocks with balloon angioplasty **alone** (inflating a coronary balloon in the stenotic area), but the outcome was not durable because **restenosis** occurred in 50% of cases. Patients with restenosis had recurrent angina and needed repeat angioplasty.

The advent of the **bare-metal stent (BMS)** revolutionized vascular angioplasty because its metallic scaffold prevents recoil and restenosis (decreased to 20–30% of cases). However, the prothrombotic metal in the coronary vessel can cause **stent thrombosis**, which occludes coronary flow (like in acute coronary syndromes) with **high mortality**. Dual antiplatelet therapy (DAPT; aspirin

plus P2Y₁₂ receptor inhibitor) decreases the risk of stent thrombosis.

The drug-eluting stent (DES) evolved from bare-metal stents and further improved the restenosis rate (decreased to 10–15% of cases). The lower **DES** restenosis rate is a result of a layer of **immunosuppressive drug** (e.g., paclitaxel, sirolimus) that covers the metallic scaffold. The drug elutes slowly over time and suppresses the proliferation of smooth muscles in the vascular wall that causes restenosis. However, the immunosuppressive drug also **delays healing** (and endothelialization) of the treated vessel. Because the vascular endothelium is crucial in preventing thrombosis of the vessel, suppressing endothelialization results in a high risk of stent thrombosis.

The **duration of DAPT** depends on the **primary indication** of the procedure (ACS vs. stable CAD) and the **bleeding risk** of the patient:

- In **acute coronary syndromes (ACSs)**, the duration of DAPT should always be **at least 12 months regardless** of the treatment strategy (medical therapy alone, balloon angioplasty, or stenting with BMS or DES). This is because DAPT in ACS is used to prevent recurrent cardiac events, not just stent thrombosis.
- In **stable CAD**, the duration of DAPT can be shorter because the systemic proinflammatory state seen in ACS is not present, and once vascular healing occurs, DAPT is not needed. DAPT duration depends on the type of procedure being performed (balloon angioplasty alone vs. stenting) or the type of device used (BMS vs. DES):
 - DAPT after **balloon angioplasty alone** (without stenting) is only **2 weeks**; endothelial healing occurs quickly (like a skin cut), and there are no foreign bodies left behind in the coronary artery to cause thrombosis.
 - DAPT after a **bare metal stent** is **4 weeks** without interruptions, until healing of the intima and endothelialization of the vascular lumen is complete.
 - DAPT after a **drug-eluting stent** is **6–12 months** without interruptions. The longer duration is because the eluted immunosuppressive drugs inhibit healing of intima and complete endothelialization of the vascular lumen and expose the patient to risk of stent thrombosis.
- DAPT duration is also determined by the bleeding risk of the patient. Patients with a high risk of bleeding, like those on anticoagulation with **warfarin** for atrial fibrillation, may not tolerate a long duration of DAPT. Both the primary indication and the patient bleeding risk should be considered in a benefit-risk balance: Though DAPT can reduce risk of myocardial infarction (and death), patients can also die from major bleeding.

RISK FACTORS FOR CAD

PREVIEW | REVIEW

- What are the primary risk factors for coronary artery disease?

The **primary** risk factors for CAD:

- Older age
- Male gender
- Family history of **early** CAD (i.e., diagnosis of CAD in female relatives < 65 years of age or male relatives at < 55 years of age)
- Smoking
- Hypertension
- Diabetes mellitus (DM)
- Elevated low-density lipoprotein (LDL) cholesterol
- Low high-density lipoprotein (HDL) cholesterol
- Chronic kidney disease (CKD)
- Obesity

Aerobic exercise and elevated HDL are **protective** against CAD.

Smoking is an independent risk factor for CAD and multiplies the risk of other CAD risk factors. It is the single most important modifiable risk factor for CAD. Smoking cessation should be addressed at every visit for patients with atherosclerosis and those at high risk for atherosclerosis. Smoking causes a proinflammatory state that can lead to coronary plaque disruption and, consequently, ACS. Benefits of smoking cessation are seen within weeks, and those who abstain for 10 years return their risk for CAD to that of nonsmokers. Smokers who quit tobacco use between 25 and 34 years of age add 10 years to their life expectancy. Those who quit smoking between 45 and 54 years of age gain 6 years of life expectancy. Women appear to be more vulnerable to smoking, as the hazard ratio for heart disease in women who smoke is 1.25× that of men who smoke.

DM is an important independent risk factor for CAD. In fact, DM is regarded as equivalent to having an established diagnosis of CAD when performing a risk assessment for atherosclerotic cardiovascular disease (ASCVD). All patients with DM should be regarded as high risk, meriting high-intensity statin therapy. Diabetes increases the risk of CAD 2.5-fold in both men and women. Over 25% of Americans > 65 years of age have DM.

Hypertension is another independent risk factor for CAD. The 2017 ACC/AHA guidelines define hypertension as blood pressure $\geq 130/80$ mmHg and set the treatment goal to < 130/80 mmHg in all patients, regardless of their comorbidities (HF, DM, or CKD). Counsel patients to reduce sodium intake, get regular aerobic exercise, and lose weight when appropriate; medically manage hypertension with antihypertensive drugs.

HYPERLIPIDEMIA SCREENING

PREVIEW | REVIEW

- Which lab tests should general lipid screening include?
- In which situations are low-density lipoprotein receptors down-regulated? Up-regulated?
- Which familial dyslipidemia is the most common? Which lipoproteins are elevated?
- Which lipid test result suggests the need to work up familial hypoalphalipoproteinemia?

Evaluation of Hyperlipidemia

High cholesterol usually indicates elevated low-density lipoprotein (LDL). High triglycerides mean elevated chylomicrons, elevated very-low-density lipoprotein, and/or elevated intermediate-density lipoprotein. High LDL, high triglycerides, and low high-density lipoprotein (HDL) are predictors of coronary artery disease. Therefore, general cholesterol screening uses the fasting lipid panel that includes **total cholesterol**, **LDL**, **HDL**, and **triglycerides**. LDL is the single most important test because lipid-lowering therapy recommendations are based mostly on LDL level. LDL can be **measured** (expensive), but it is usually **calculated** (cheaper) using the formula: $LDL = \text{total cholesterol} - HDL - (\text{triglycerides} / 5)$. If a lipid panel is obtained in a nonfasting state, especially after eating a fatty meal, triglycerides levels will be elevated, and calculated LDL will be an underestimation of the true level (see **Low-Density Lipoprotein (LDL)**).

Review of Lipoproteins

Lipoprotein review: Follow along in **Figure 13-22** as we review the individual lipoproteins.

Lipoproteins have a hydrophobic core (triglycerides and/or cholesterol), surrounded by a hydrophilic phospholipid outer layer that facilitates transport through the serum. Apolipoproteins (a.k.a. apos) bind and transport lipids in the bloodstream.

Chylomicrons

Chylomicrons (with apos B48, CII, and E) are large globules that mostly consist of triglycerides but also contain some cholesterol. Chylomicrons are formed in the intestinal epithelium from dietary fats. Decreased clearance of chylomicrons results in hypertriglyceridemia. The **apo B48** on their surface is **unique to chylomicrons**. Chylomicrons enter the circulation by way of the intestinal lymphatics. In the circulation, chylomicrons attach to receptors on muscle and fat cells, where the CII apolipoproteins on the surface of the chylomicrons activate **lipoprotein lipase (LPL)**.

The activated LPL removes the triglycerides from the inside of the chylomicrons by breaking down the triglycerides into free fatty acids, which are either utilized or

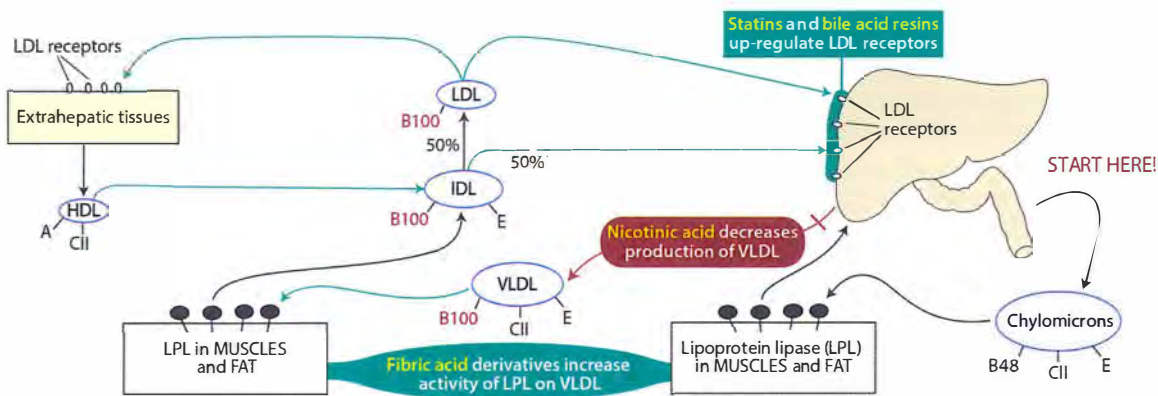


Figure 13-22: Lipoprotein pathways and how they are affected by drugs

stored. The shrunken remnant, now high in cholesterol relative to triglycerides, is called (appropriately enough) a chylomicron remnant. It is taken up by the liver via receptors specific for apo E. The liver degrades the remnants, and the cholesterol goes either into bile or on to further synthesis reactions.

The apo B48 is a **chylomicron marker**; apo CII activates the LPL to suck out the triglycerides; and apo E is a marker recognized by the **liver**. Deficiency of either apo CII or LPL causes **familial hyperchylomicronemia** and markedly elevated triglycerides, which can cause acute pancreatitis and eruptive xanthomas.

Another cause of hypertriglyceridemia is oral estrogen, which is sometimes used as hormone replacement therapy. Oral estrogen increases triglycerides by increasing hepatic VLDL secretion and decreasing hepatic triglyceride lipase as a first-pass effect through the liver. Switching to transdermal estrogen avoids the first-pass and resolves the issue.

Very-Low-Density Lipoprotein (VLDL)

VLDL (with apos B100, CII, and E) is synthesized by the liver to supply energy to the body. VLDL and all subsequent lipoproteins except HDL (high-density lipoprotein) have apo B100. VLDL is similar to chylomicrons, except that it is smaller and contains less triglyceride and more cholesterol. VLDL function is analogous to chylomicrons in that VLDL transports triglycerides to the capillaries of the muscle and fat and is metabolized by the peripheral LPL (lipoprotein lipase; activated by CII).

Intermediate-Density Lipoprotein (IDL)

Following its secretion from the liver and catalyzation by LPL (lipoprotein lipase), VLDL (very-low-density lipoprotein) forms a remnant—**IDL**—that still has triglycerides and some cholesterol. 50% of IDL particles are identified and consumed by the liver via the LDL (low-density lipoprotein) receptor, which recognizes apo E and apo B100. The other 50% remain in the plasma, where they lose the rest of the triglycerides and all of the apolipoproteins, except **B100**, and thereby are converted to low-density lipoprotein. Apo E deficiency causes high IDL.

Low-Density Lipoprotein (LDL)

LDL is formed from IDL (intermediate-density lipoprotein). LDL consists of only cholesterol and apo B100. It provides cholesterol for the synthesis of hormones, cell membranes, and bile acids. The **only** apolipoprotein on LDL you need to remember is apo B100!

LDL is either taken up by the LDL receptor (2/3) or scavenged (1/3) by monocytes or smooth muscle cells. The LDL receptor is present on **all** cells, but it is much denser in the liver. This receptor binds lipoproteins with apos E and B100. Affinity is greater for those with both apo E and apo B100, which is why there is no accumulation of **IDL** in a healthy person.

LDL receptors are **down-regulated** or decreased:

- When dietary cholesterol or saturated fats are high
- With age (increasing cholesterol with age)
- In patients with familial hypercholesterolemia (heterozygotes = 50% of LDL receptor activity; homozygotes = no receptor activity)

LDL receptors are **up-regulated** or increased by:

- Low dietary cholesterol or saturated fats
- Estrogen
- Thyroxine
- Statins (3-hydroxy-3-methyl glutaryl coenzyme A [HMG-CoA] reductase inhibitors)
- Decreased bile acid uptake from the intestines (as with bile acid resins)

Lipoprotein(a) [Lp(a)] contains apolipoprotein(a) [apo(a)], which is covalently bound by a disulfide bond to the **apo B100** of LDL. High Lp(a) is an **independent** risk factor for coronary heart disease and stroke. The exact mechanism is unknown; however, because of the high homology of apo(a) and plasminogen, it has been hypothesized that Lp(a) is **prothrombotic**. Lp(a) levels are **genetically determined** and are 2× higher in African Americans than in Caucasians, although they may not cause increased risk in African Americans. Treatments for high Lp(a) include nicotinic acid, mipomersen, and proprotein convertase subtilisin/kexin Type 9 (PCSK9) inhibitors. Nicotinic acid is only effective in patients with concomitant

hypertriglyceridemia. **Mipomersen** decreases Lp(a) levels by 25% in patients with familial hypercholesterolemia and severe hypercholesterolemia. The PCSK9 inhibitors, alirocumab and evolocumab, were FDA approved in 2015 to treat hyperlipidemia by reducing Lp(a).

Small LDL particle size carries an increased risk of CAD and endothelial dysfunction. The smaller particles are more easily oxidized, bind arterial wall proteoglycans with more affinity, and bind the LDL receptor with less affinity, thereby reducing their clearance from the blood stream. These mechanisms contribute to their **proatherogenic** nature. Also, the presence of small, dense LDL particles is associated with decreased high-density lipoprotein, which is itself a risk factor for atherosclerotic cardiovascular disease.

High-Density Lipoprotein (HDL)

HDL is mainly composed of protein and phospholipids, with very little cholesterol or triglycerides. It scavenges the unesterified cholesterol from cell breakdown. **HDL** contains apo AI, apoAII, and apo CII.

Apo AI (expressed by the *apo AI* gene) helps esterify the scavenged cholesterol. Then, it is transferred to IDL (intermediate-density lipoprotein) or LDL (low-density lipoprotein) and removed via the liver. In this way, the HDL is a sort of reverse transport system. Do not confuse apo AI in HDL with apo(a) in Lp(a)—they are completely different lipoproteins.

ABCA1 is a transmembrane protein expressed by the *ABCA1* gene that helps to move cholesterol from inside the cell to the cell membrane. ABCA1 is expressed when cholesterol loads onto the cell surface and is removed when the apolipoproteins pick up the cholesterol.

Problems arise in HDL levels when something goes wrong with apo AI or *ABCA1* (protein or gene). Low HDL is common in cases of premature CAD and may be isolated or occur in combination with elevated triglycerides. Low HDL is often caused by low apo AI—due to decreased apo A synthesis or increased apo A breakdown.

HDL acts as a reservoir for apo CII. So, when HDL is low, the apo CII level falls. Because CII activates LPL, this leads to decreased processing of VLDL and chylomicrons by LPL in the muscle and fat. The end result can be hypertriglyceridemia, as in familial hypertriglyceridemia.

Hereditary Dyslipidemias

Dyslipidemias can be classified as familial/primary or acquired/secondary. **Monogenic** causes of familial dyslipidemias include mutations in the LDL receptor, the PCSK9 (proprotein convertase subtilisin/kexin Type 9) enzyme, and the microsomal triglyceride transfer protein. Common causes of acquired/secondary dyslipidemia include diabetes mellitus Type 2, hypothyroidism, and nephrotic syndrome. Most dyslipidemia is **polygenic** in origin, contributing to the variable response rates to different lipid-lowering therapies. However, regardless of

the genetic etiology of a particular dyslipidemia, clinical management is based on clinical history, family history, cardiovascular risk assessment, and, most importantly, serum LDL cholesterol.

Many cases of premature coronary artery disease (CAD) are related to familial dyslipidemia. Start screening for lipid disorders at 20 years of age using the basic fasting lipid panel. Some experts look for the less common familial dyslipidemias by measuring apo B100, apo AI, and Lp(a) when they observe CAD in a patient with a normal lipid profile or if there is a strong family history of CAD and/or cardiovascular events.

Low-Density Lipoprotein (LDL)-Associated Dyslipidemias

Familial combined hyperlipidemia (FCHL) is the most common dyslipidemia. 1% of the population is autosomal dominant for FCHL, and up to 10% of those with premature CAD have FCHL. It is the most common cause of lactescent (milky) plasma. FCHL has an extremely variable presentation, with varying elevations of LDL and VLDL. In FCHL, there is increased production of both apo B100 and VLDL, and the increased VLDL stresses the pathways toward increased LDL production. The LDL levels in FCHL are usually less than those in familial hypercholesterolemia (< 230 mg/dL [5.96 mmol/L]).

Familial hypercholesterolemia (FH) is an autosomal dominant disorder which presents as **premature** atherosclerosis and tendon xanthomas on physical exam. Homozygous FH (1:1,000,000 incidence) is **uncommon**, and patients present with an extremely high LDL (usually > 400 mg/dL [10.36 mmol/L]). Patients with **homozygous** FH have **no functional LDL receptors**, so they are typically **unresponsive to statins**. Heterozygous FH is more common, with an incidence of 1:500. Patients with **heterozygous** FH have baseline LDL cholesterol levels > 200 mg/dL (5.18 mmol/L) and have **variable response to statins**.

Diagnosis is suggested by family history of premature CAD, tendon xanthomas, unusually elevated LDL levels, and an LDL:apo B ratio < 1.2 (normal is > 1.4).

Familial defective apolipoprotein B100 is an autosomal dominant genetic disorder that causes a problem on the LDL particle at the apo B100 ligand. Like **heterozygous** FH, LDL levels are 2–2.5× higher than normal. **Distinguish** between these 2 disorders with **genetic testing**.

Hyperapobetalipoproteinemia is also caused by **excess** production of **apo B**, but **LDL** levels are **normal**. Suspect this in patients with premature CAD, especially if they have prominent **xanthelasma** (yellowish deposits under the skin, often around the eyelids). Laboratory workup shows a normal LDL level but increased apo B with LDL:apo B < 1.2.

Polygenic hypercholesterolemia is another cause of premature CAD that clusters in families. LDL is increased, but the genetic specifics are unclear.

Other Familial Dyslipidemias

Familial hyperchylomicronemia (hypertriglyceridemia) contrasts with FCHL (familial combined hyperlipidemia) in that the apo B and VLDL (very-low-density lipoprotein) levels are normal but VLDL size is larger and less dense. Like FCHL, inheritance is autosomal dominant. It results in significant elevation in triglycerides. These patients may experience acute pancreatitis, especially when triglycerides are > 1,000 mg/dL. The higher the triglycerides level, the higher the risk for pancreatitis.

Dysbetalipoproteinemia is autosomal recessive and presents with high IDL (intermediate-density lipoprotein), meaning elevated triglycerides and cholesterol. The IDL has an abnormal apo E, which interferes with the attachment of IDL on the LDL receptor in the liver. Only patients who are homozygous for the defect and are diabetic, obese, or alcoholic have significant IDL elevation.

High-Density Lipoprotein (HDL)-Associated Dyslipidemias

Familial hypoalphalipoproteinemia is autosomal dominant and results from a mutation in the gene for apo AI (*APOA1*) or for the genes *ABCA1* or *LCAT*. It results in an isolated low HDL. It affects 6% of Japanese patients with low HDL.

Familial HDL deficiency is also autosomal dominant and is caused by mutations in the *ABCA1* gene. The mutation alters intracellular transport of cholesterol, increasing catabolism of apo AI. It results in an isolated low HDL with premature CAD.

Tangier disease is also due to an *ABCA1* mutation leading to increased catabolism of apo AI. Patients heterozygous for the mutation have low HDL (50% of normal), and homozygous patients have no HDL. In homozygotes, very defective cholesterol handling and diffuse deposition of foam cells causes hepatosplenomegaly, neuropathy, and premature CAD.

TREATMENT OF HYPERLIPIDEMIA

PREVIEW | REVIEW

- What is the primary endpoint of lipid screening done for primary prevention of atherosclerotic cardiovascular disease (ASCVD)?
- Per American College of Cardiology/American Heart Association ASCVD guidelines, name the 4 statin benefit groups.
- How is a high-intensity statin defined? A moderate-intensity statin?
- Which fats are the "good" fats? The "bad" fats?
- Which class of drugs is recommended 1st line to reduce low-density lipoprotein?
- What are the major side effects of statins?
- What are side effects of bile resins?

- What is the main action of the fibrate drugs?
- What are relative contraindications to niacin?
- What increases high-density lipoprotein (HDL)?
Lowers HDL?

The treatment goal for hyperlipidemia can be:

- **Primary** prevention of ASCVD and its complications (e.g., MI [myocardial infarction], ischemic stroke, acute limb ischemia) in patients who do not have known clinical ASCVD
- **Secondary** prevention of recurrent cardiovascular events (e.g., MI, ischemic stroke, acute limb ischemia) in patients who do have known ASCVD

Dozens of randomized trials have confirmed the benefit of treating dyslipidemia for primary prevention of ASCVD. LDL cholesterol is the most important cardiovascular (CV) risk factor because it has the strongest correlation with outcomes, and lowering it (as primary prevention) reduces CV risk.

Our discussion of lipids is based on the 2018 ACC/AHA Guidelines on Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Disease Risk in Adults.

General Concepts of Primary Prevention

Start screening with a fasting lipid panel at 20 years of age, with follow-up in 5 years if normal or yearly if borderline and < 2 coronary artery disease risk factors are present. If abnormal, start treatment and follow up in 4–6 weeks.

The primary screening target is LDL (low-density lipoprotein). LDL is usually calculated from total cholesterol, HDL, and VLDL or triglycerides:

$$\text{LDL} = \text{total cholesterol} - \text{HDL} - \text{VLDL}$$

or

$$\text{LDL} = \text{total cholesterol} - \text{HDL} - (\text{triglycerides} / 5)$$

Note: This calculation is valid only if triglycerides are < 400 mg/dL [4.52 mmol/L]. If triglycerides are > 400 mg/dL [4.52 mmol/L], measure LDL directly because calculated LDL will underestimate the true level.

Measuring LDL is important to determine the need for treatment and assess response to therapy. Non-HDL cholesterol is a secondary target in patients with hypertriglyceridemia > 200 mg/dL (2.26 mmol/L):

$$\text{Non-HDL} = \text{total cholesterol} - \text{HDL}$$

The non-HDL result is theoretically equivalent to the sum of the remaining atherogenic lipoproteins, LDL + Lp(a) + IDL + VLDL, and may do a better job of predicting plaque formation than LDL alone in those patients with elevated LDL and triglycerides.

After obtaining the fasting lipid profile, identify the patient's risk category using the ASCVD risk estimator (see 2018 ACC / AHA Guidelines on Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Disease (ASCVD) Risk in Adults on page 13-38).

2018 ACC / AHA Guidelines on Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Disease (ASCVD) Risk in Adults

Recommendations from these guidelines:

- Encourage therapeutic lifestyle changes in all patients.
- Estimate 10-year ASCVD risk, using the ASCVD Risk Estimator (available at tools.acc.org/ascvd-risk-estimator-plus) to guide decisions on use of statins for primary prevention.
- There are 4 groups for whom there is strong evidence a statin should be initiated or continued:
 - Clinical ASCVD—treat with a high-intensity statin (see the discussion of statin intensity, below).
 - LDL $\geq$ 190 mg/dL (4.92 mmol/L), including those with familial hypercholesterolemia. Treat with a high-intensity statin. These patients are high risk based on LDL alone—no need to estimate their 10-year ASCVD risk!
 - Patients 40–75 years of age with diabetes mellitus and LDL of 70–189 mg/dL (1.81–4.90 mmol/L)—treat with a moderate- or high-intensity statin.
 - Patients 40–75 years of age with 10-year risk of ASCVD $\geq$ 7.5% and LDL of 70–189 mg/dL (1.81–4.90 mmol/L)—treat with a moderate- or high-intensity statin.
- Statin intensity is defined as:
 - High-intensity statin therapy (e.g., atorvastatin 40–80 mg daily, rosuvastatin 10–20 mg daily) lowers LDL cholesterol by approximately 50%.
 - Moderate-intensity statin therapy (e.g., atorvastatin 10–20 mg daily, simvastatin 20–40 mg daily) lowers LDL cholesterol by 30–50%.
 - Low-intensity statin therapy (e.g., simvastatin 10 mg daily, pravastatin 10–20 mg daily) lowers LDL cholesterol by < 30%.
- For those with LDL of 70–189 mg/dL (1.81–4.90 mmol/L) and a 10-year ASCVD risk of 5–7.5%, the guidelines give a weaker recommendation—it is reasonable to consider moderate-intensity statin.
- No recommendation was made for the initiation or continuation of statin therapy in patients with NYHA Class II–IV heart failure and patients receiving maintenance hemodialysis (insufficient data).

- Groups at high risk for adverse effects include age > 75, renal/hepatic dysfunction, unexplained ALT (alanine aminotransferase) elevation > 3 $\times$ the upper limit of normal, and previous statin intolerance or muscle disorders.

Dietary Therapy

Dietary changes are always the 1st line of treatment for the hyperlipidemias. Total fat consumption should be < 30% of daily calories. More specifically, saturated fat should be < 7% of daily calories. Cholesterol intake should be < 200 mg a day for patients with ASCVD and < 300 mg daily for others.

Regarding types of fats:

- Partially hydrogenated vegetable oils (trans fats; e.g., margarines) raise LDL (low-density lipoprotein) and lower HDL—**doubly bad!**
- Saturated fats increase both LDL and HDL—the net effect is mixed; it is best to avoid very high or very low saturated fat intake.
- Polyunsaturated fats decrease LDL and VLDL and increase or maintain HDL levels. These are **good** fats!
- Monounsaturated fats (e.g., olive, peanut, canola oils) decrease LDL but not HDL—**good!**
- Omega-3 fatty acids decrease only VLDL (triglycerides)—**pretty good**.
- Table 13-5 summarizes this information.

Drugs for Dyslipidemias

Statins are 1st line drugs for LDL reduction. They decrease both cardiovascular events and cardiovascular mortality by about 25% and overall mortality by 15%. Prior to 2011, niacin was frequently used to increase HDL, but the AIM-HIGH trial published in that year showed that increasing HDL with niacin does not improve outcomes. Gemfibrozil and cholestyramine decrease cardiac events but not overall mortality. See Figure 13-22 on page 13-35 and Table 13-6 on page 13-40.

HMG-CoA reductase inhibitors are the **statins**: lovastatin, pravastatin, simvastatin, fluvastatin, atorvastatin, pitavastatin, and rosuvastatin. These are the **primary** cholesterol-lowering drugs. The HMG-CoA reductase enzyme is the rate-limiting step of lipid metabolism.

Table 13-5: Dietary Fat and Lipid Profile

Type of Fat	LDL	HDL	LDL:HDL	Verdict
Partially hydrogenated vegetable oils (trans fats)	Increase	Decrease	Increase	Doubly bad!
Saturated fats	Increase	Increase	Same or decrease	Mixed—avoid very high or very low intake
Polyunsaturated fats	Decrease	Increase or maintain	Same or decrease	Good!
Monounsaturated fats	Decrease	May increase	Decrease	Good!

Statins inhibit this enzyme and, thereby, **up-regulate** the **LDL receptors**—as do the bile acid sequestrants.

Statins decrease LDL and may decrease VLDL. There are only **modest** gains in HDL with statins. The JUPITER Trial in 2008 showed that statins have antiinflammatory properties as well. Therefore, improved cardiovascular outcome with statins is not solely secondary to their LDL-lowering effects. This class of drugs has been a revolutionary discovery in the field of cardiology. Put **all** persons with **established ASCVD** on a statin long-term, if they can tolerate it.

Statins may cause **myalgias**, elevated creatine kinase, and, rarely, rhabdomyolysis. These are uncommon side effects and other causes of the symptoms should be excluded before stopping statin therapy. It is important to emphasize the need to continue statin therapy if the symptoms are mild and can be tolerated. There is **no** need for routine monitoring of liver function tests. However, if patients develop new nausea, abdominal pain, or other signs/symptoms of hepatotoxicity, consider checking liver transaminases.

The risk of **myopathy** with statins increases significantly when used in combination with cyclosporine, gemfibrozil (fenofibrate is okay), erythromycin, and ketoconazole.

Statins can cause mild **hyperglycemia**. Statins may cause **memory loss** and **confusion** in some people. The FDA added blood sugar and cognitive changes to the warnings in 2012. Both are generally reversible after stopping the drug.

Ezetimibe is an inhibitor of intestinal cholesterol absorption. It is a 2nd line LDL-lowering drug (after statins). It is used as adjuvant therapy in combination with statins or as monotherapy in patients who cannot tolerate statins. Ezetimibe is approved for use alone or in combination with a statin or fenofibrate to **reduce LDL** and **apo B** in patients with primary or mixed hyperlipidemias. It is also approved for use with atorvastatin or simvastatin to reduce LDL in patients with familial homozygous hypercholesterolemia. Alone, ezetimibe can reduce LDL by up to 17%; in combination with a statin, it provides a further 14% reduction in LDL over the effect of the statin. Avoid using ezetimibe with gemfibrozil. Moderate or severe hepatic impairment is a contraindication.

The IMPROVE-IT trial, published in 2015, was the first study to directly assess clinical outcomes with ezetimibe + simvastatin vs. simvastatin alone. After 7 years, the combination of ezetimibe and simvastatin caused a small reduction in adverse cardiovascular outcomes (2% absolute risk reduction) when compared to simvastatin alone.

Bile acid resins (cholestyramine, colestipol, and colesevelam) are also 2nd line LDL-lowering drugs. Similar to ezetimibe, bile acid resins are used primarily as adjuvant therapy in combination with statins, or monotherapy in patients who cannot tolerate statins. Resins decrease LDL, slightly increase HDL, and may increase triglycerides. By binding bile acids in the intestine, and thereby preventing their reabsorption, they cause up-regulation of the LDL

receptors in the liver, which increases the processing of serum LDL needed to synthesize replacement bile acids. Although the HDL level remains the same, the LDL:HDL ratio decreases.

Bile acid resins may also increase the synthesis of VLDL, potentially increasing triglycerides. Side effects of these resins are mostly gastrointestinal (nausea, vomiting, constipation, and bloating). The resins impair absorption of other oral drugs, so patients should take other medicines at least 1 hour before or 4 hours after the resins.

Fibric acid derivatives (i.e., fibrates; mainly gemfibrozil and fenofibrate) are used **primarily** to treat **hypertriglyceridemia**. These drugs decrease VLDL and raise HDL. Their main mechanism of action is **increasing** the activity of **LPL** (lipoprotein lipase) on **VLDL**—thus increasing its rate of conversion to IDL (intermediate-density lipoprotein). Some of this IDL is then converted to LDL, occasionally causing an increase in LDL. They also increase production of apo AI and AII, which increases HDL and increases excretion of cholesterol into the bile.

Fenofibrate is better than gemfibrozil at lowering LDL. Unlike gemfibrozil, it does **not** inhibit statin breakdown (thus does not increase risk for statin myopathy). Fenofibrate is the drug of choice when combining a fibrate with a statin.

The 2010 ACCORD trial included diabetic patients who were treated with a simvastatin vs. simvastatin + fenofibrate to determine if the addition of the fibric acid derivative reduced rates of nonfatal MI, stroke, or cardiovascular death. The addition of fenofibrate **did not change** these endpoints. So, high-risk patients should generally be treated using a statin only.

Nicotinic acid (a.k.a. niacin) is by far the least expensive agent of those listed. It lowers triglycerides and cholesterol (LDL) and increases HDL. It is the **most effective drug** available for **raising HDL** (up to 30%). It lowers triglycerides by **blocking** the **production** of **VLDL** (and therefore LDL). While frequently used to increase HDL in the past, the AIM-HIGH trial in 2011 showed that increasing HDL with niacin does not improve clinical outcomes. Important metabolic side effects include **hyperuricemia** and **insulin resistance**; gout and diabetes mellitus are relative contraindications. Bothersome side effects include flushing (most common), dry skin, and nausea/abdominal pain. Give 325 mg aspirin 30 minutes before the dose to block the flushing reaction. This reaction usually disappears after 1–2 weeks.

The omega-3 fatty acids (eicosapentaenoic acid and docosahexaenoic acid) have showed conflicting data in improving clinical outcomes in patients with ASCVD. However, the REDUCE-IT trial in 2019 showed that **icosapent ethyl** (highly purified eicosapentaenoic acid ethyl ester, a type of omega-3 fatty acids) resulted in significant **improvement** in clinical outcome in patients with **elevated triglyceride** despite being on statins (i.e., their risk is being reduced even beyond statin). In 2019, the FDA approved icosapent ethyl to reduce risk of cardiovascular events in

patients with elevated triglyceride levels. Side effects of icosapent ethyl include arrhythmias (such as atrial fibrillation and atrial flutter), bleeding, and allergic reactions (if allergic to fish or shellfish). In general, omega-3 fatty acids in high doses decrease platelet and neutrophil aggregation, decrease blood pressure, and decrease triglycerides (VLDL) but increase LDL. Very high doses may decrease restenosis rate after coronary angioplasty. Generally, if a patient has ASCVD, adding fatty fish (e.g., salmon, mackerel, herring, sardines, albacore tuna) to the diet 2x/week or a daily fish oil supplement is recommended.

Proprotein convertase subtilisin/kexin Type 9 (PCSK9) inhibitors (alirocumab and evolocumab) are monoclonal antibodies approved by the FDA in 2015 for the treatment of elevated LDL. PCSK9 is a serine protease produced predominantly in the liver that leads to the degradation of hepatocyte LDL receptors and increased LDL cholesterol levels. Inhibiting degradation of LDL receptors with this class of drugs increases LDL uptake from serum. Early studies support huge efficacy in LDL-lowering, safety, and cardiovascular mortality and morbidity benefits. A large clinical trial (FOURIER) combining a PCSK9 inhibitor and optimal statin therapy was stopped early when the addition of the PCSK9 therapy showed significant benefit. The 2018 ACC/AHA guidelines suggest using PCSK9 inhibitors in patients with very high ASCVD risk (i.e., a history of multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions) whose LDL ≥ 70 mg/dL or non-HDL ≥ 100 mg/dL despite maximal LDL-lowering therapy. These drugs are administered subcutaneously every 2–4 weeks.

Bempedoic acid is a novel nonstatin drug to lower LDL cholesterol that was approved by the FDA in February 2020. This agent is an inhibitor of ATP citrate lyase, a key enzyme involved in the cholesterol biosynthesis pathway.

It is indicated for the treatment of adults with heterozygous familial hypercholesterolemia or established ASCVD who require additional lowering of their LDL. It can be used alone or as a combination therapy with ezetimibe or a statin. Tendon rupture is a potential adverse effect.

Summary (see [Table 13-6](#)):

- Statins block HMG-CoA reductase. Ezetimibe inhibits intestinal cholesterol absorption. Nicotinic acid decreases triglycerides by blocking synthesis of VLDL. Fibrates increase LPL action on VLDL.
- Statins and nicotinic acid are the only drugs that both decrease LDL and increase HDL.
- Ezetimibe is used in conjunction with either a statin or fenofibrate to reduce LDL and/or apo B.
- Both fibric acid derivatives (e.g., gemfibrozil, fenofibrate) and nicotinic acid decrease triglycerides; but, whereas nicotinic acid also decreases LDL (good), gemfibrozil may increase LDL (bad). Fenofibrate increases LDL less than gemfibrozil.
- Combining gemfibrozil with statins significantly increases the risk of myositis. Use fenofibrate if you need to combine with a statin.
- What **increases** HDL? Nicotinic acid, fibrates, statins, omega-3 fatty acids, moderate alcohol intake, exercise, smoking cessation, losing weight if obese, and **reducing** intake of trans fats.
- What **lowers** HDL? β -blockers (except labetalol), smoking, weight gain, and eating a diet high in partially hydrogenated (trans) fats.
- Which interventions have no effect on HDL? Bile resins. Monounsaturated fats (peanut, olive, and canola oils) have no effect or may raise HDL only slightly.

Table 13-6: Summary of Lipid-Lowering Drugs

Drug Class	Most Common Drugs	Use	Side Effects
HMG-CoA reductase inhibitors (statins)	Atorvastatin, rosuvastatin	Drug of choice for LDL reduction	Myalgias, myositis, elevated transaminases
Cholesterol uptake inhibitors	Ezetimibe	Alternative drug for LDL reduction	Elevated transaminases
Bile resins	Cholestyramine, colesevelam, colestipol	Alternative drug for LDL reduction	Gastrointestinal symptoms (nausea/vomiting, constipation, bloating)
PCSK9 inhibitors	Evolocumab and alirocumab	Alternative drug for LDL reduction	Subcutaneous injection site irritation
Fibric acid derivatives	Gemfibrozil, fenofibrate	Drug of choice for triglyceride reduction	Abdominal pain, gall bladder disease, malignancy
Nicotinic acid (niacin)		Alternative drug for LDL and triglyceride reduction Increases HDL	Flushing, dry skin, nausea/vomiting, abdominal pain
Omega-3 fatty acids	Icosapent ethyl	Triglycerides reduction	Arrhythmias (atrial fibrillation and flutter), bleeding, allergic reactions
Bempedoic acid		Alternative drug for LDL reduction	Tendon rupture

LIPIDS IN ACUTE CORONARY SYNDROMES (ACSs)

PREVIEW | REVIEW

- What happens to the lipid panel in acute coronary syndromes?

The cardiovascular benefit of statins goes beyond just LDL reduction. They stabilize plaques, reduce inflammation and thrombogenicity, and reverse endothelial dysfunction.

Give **all** patients with ACSs a high-dose **statin** regardless of the LDL level. If the patient is already taking a statin, increase the dose for the acute event. Continuing statins during an ACS hospitalization improves outcomes.

Remember: A recent myocardial infarction or any serious illness may affect the lipid panel. These effects include decreasing LDL and HDL levels and raising or lowering triglyceride levels. So, do not use the fasting lipid panel for ACS drawn at admission to guide treatment. Start a statin at a high dose. Recheck the fasting lipid panel 8 weeks later for a better idea of the patient's true lipid profile.

PERIPHERAL ARTERIAL DISEASE (PAD)

PREVIEW | REVIEW

- What are the causes of arteriosclerotic peripheral arterial disease (PAD)?
- What is Buerger disease?
- What is claudication?
- What is the difference between claudication and pseudoclaudication?
- What is the first test to establish the diagnosis of lower extremity PAD? What result is considered abnormal?
- Which antiplatelet therapy is recommended for patients with PAD?

CAUSES OF PAD AND INTERMITTENT CLAUDICATION

PAD, previously called peripheral vascular disease (PVD), has many causes, including the following:

- Arteriosclerosis is the most common cause of PAD in middle-aged and older patients. The biggest risk factors for arteriosclerotic PAD are **diabetes** (5× greater chance) and **smoking**. Other modifiable risk factors include hypertension, hyperlipidemia, and hyperhomocysteinemia. Note: Patients with arteriosclerotic PAD are at increased risk of myocardial infarction (MI) and stroke because the involvement of one vascular bed (e.g., peripheral arteries) means a higher likelihood for involvement of other vascular beds (e.g., coronary arteries, carotid arteries).

- Arteritis (e.g., connective tissue disease, Takayasu arteritis): Vasculitides are discussed in the **Rheumatology** section.
- Trauma (e.g., jackhammer hands)
- Thromboangiitis obliterans (a.k.a. Buerger disease): Classically seen in young, male smokers, it involves medium and small arteries and often affects arteries of the wrists (positive Allen test) and hands. Due to the diffuse, distal nature of this vascular disease, there is rarely a revascularization option. Calcium channel blockers can reduce symptoms of painful or cold fingers and toes. However, no therapy will be effective without smoking cessation. See **Figure 13-23**.
- Entrapment: Think especially of thoracic outlet syndrome and popliteal artery entrapment. Thoracic outlet syndrome results in upper extremity claudication due to compression of nerves or blood vessels at the thoracic outlet. Muscle enlargement from weight lifting, trauma, rare tumors, and the rare cervical rib can all cause thoracic outlet syndrome. Popliteal artery entrapment occurs primarily in young men. Symptoms are intermittent claudication of the calf or foot arch with walking.



Figure 13-23: Thromboangiitis obliterans (a.k.a. Buerger disease) affecting the toes. Note the dusky color.
Source: James Heilman, MD

Claudication is muscle pain, including aches, cramping, and fatigue, due to muscle ischemia from PAD. Just as angina is pain from heart ischemia, claudication is angina in the extremities—you can think of claudication as angina of the legs (arm claudication is rare). Because of blockages in the arteries that supply blood, and the resulting decreased blood flow, anything that increases the oxygen demand of the extremities (i.e., exercise) can illicit symptoms of claudication.

It is important to differentiate vascular claudication from lumbar spinal stenosis (or other neurogenic causes; **Table 13-7 on page 13-42**); the latter causes **pseudoclaudication**. Lumbar spinal stenosis is relieved by sitting down (flexing the spine) but not by standing still. It is exacerbated by anything that extends the spine, such as standing or walking (especially downhill). Vascular claudication is relieved by both sitting down or standing still (i.e., resting). Neither disease causes nocturnal leg cramps. When the distance to onset of claudication or the severity abruptly changes, consider thrombosis in situ or an embolic event.

Table 13-7: Causes of Lower Extremity Pain					
	Description of Pain	Location	Precipitant	Onset of Symptoms	Relief
Claudication	Achy, cramping, fatigue	Depending on level of artery blockage, can be in calves or thighs	Exercise	Predictable relationship to exertion	Stop walking
Spinal Stenosis	Similar to claudication; may have tingling or weakness	Buttock, thigh, and hip	Walking or standing (not related to activity but rather stature of spine)	Variable	Sitting or walking while pushing a cart (i.e., flexing the spine)
Arthritis	Aching pain (also joints may be tender, unlike with claudication)	Joints of knees and hips	Exercise (use of affected joints)	Variable	Rest, non-weight-bearing
Venous Insufficiency	Fatigue, heavy sensation to legs	Feet and lower legs	Prolonged standing	Variable	Leg elevation, compression therapy, exercise

DIAGNOSIS OF PAD

On physical examination, look for diminished peripheral pulses (including popliteal, posterior tibial, dorsalis pedis, and even radial and ulnar). This finding correlates with the severity of PAD in that extremity.

PAD is more common in the lower extremities than in the upper extremities. Significant stenosis in the lower extremities can occur at a high, middle, or low level (Figure 13-24):

- **High level**—the common or external iliac arteries
- **Middle level**—the common femoral, superficial femoral, or popliteal arteries
- **Low level**—the anterior tibial, peroneal, or posterior tibial arteries

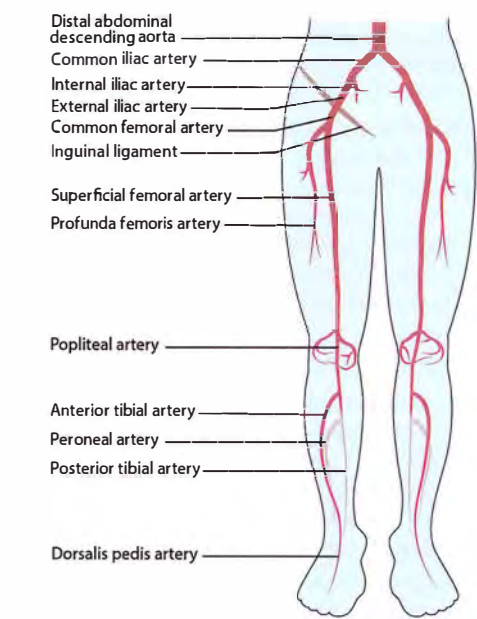


Figure 13-24: Arteries of lower extremities

In the upper extremities, significant stenosis that limits blood flow is typically at the level of the subclavian arteries (Figure 13-25).

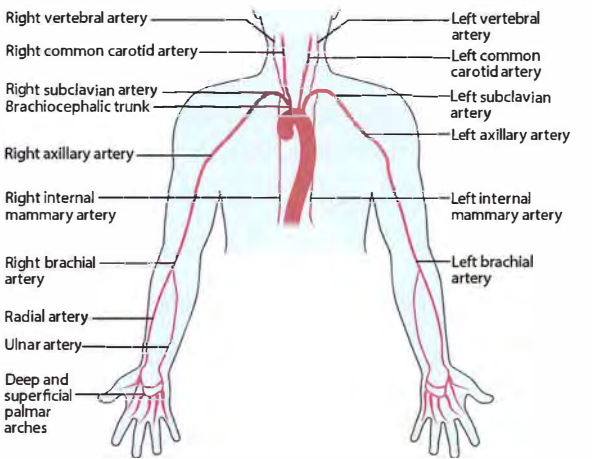


Figure 13-25: Arteries of upper extremities

Use the resting ankle-brachial index (ABI; ankle:arm blood pressure [BP] ratio) to establish the diagnosis of lower extremity PAD in those with ≥ 2 of the following: exertional leg symptoms, diminished or absent pulses, nonhealing lower extremity wounds, and age ≥ 65 years (age ≥ 50 years if history of smoking/diabetes). Understanding this index is simple. The pressure in the brachial artery, measured with a standard BP cuff, should equal the aortic pressure (remember, upper extremity PAD is very uncommon). If there is significant stenosis in the arteries in the lower extremities, the BP in the lower extremity will be lower than the aortic (or brachial) pressure, which makes the ankle-brachial index low. The ABI classification is noncompressible > 1.40 , normal 1.00 – 1.40 , borderline 0.91 – 0.99 , and abnormal ≤ 0.90 . An ABI measurement ≤ 0.90 indicates definite PAD. ABI of 0.41 – 0.90 indicates mild-to-moderate PAD. ABI ≤ 0.40 indicates severe stenosis. Note: Measure the brachial pressure in both arms and use the higher number. If one of the upper extremities may have a significant stenosis, the brachial pressure in

that arm will be lower than the true aortic pressure (hence, ABI will be falsely normal). The higher brachial pressure will be closer to the aortic pressure.

If resting ABI is normal but history is very concerning for PAD, Doppler ultrasound is a useful diagnostic tool. It identifies the anatomic location and degree of PAD stenosis by visualizing the artery with ultrasound and measuring flow velocities with Doppler.

Exercise tolerance tests (ETTs) are also recommended to follow up a normal resting ABI with concerning history; they objectively measure the functional limitation of claudication and response to therapy. Remember that the stenosis in the lower extremity may not be flow-limiting at rest, but with exercise, the aortic pressure rises significantly when the blocked artery cannot deliver all the blood the muscle needs. In these cases, exercise ABI is more sensitive for detection of PAD than resting ABI. Also, ETTs with preexercise and postexercise ABI values can differentiate arterial claudication from nonarterial claudication (pseudoclaudication).

When initial diagnostic testing is abnormal, define arterial anatomy with additional imaging studies. Magnetic resonance angiography (MRA) of the extremities (with gadolinium enhancement) is useful to diagnose anatomic location and degree of PAD stenosis. Computed tomographic angiography (CTA) can be considered as an alternative to MRA. Contrast angiography in the catheter lab (cath lab) provides detailed information about arterial anatomy and is recommended for evaluation of revascularization candidates with lower extremity PAD.

In summary, if the patient has symptoms of claudication, start with resting ABI. If resting ABI is normal but history and examination is very concerning for PAD, use Doppler ultrasound or exercise ABI. If these are abnormal, then define anatomy with either MRA, CTA, or peripheral angiography in the cath lab.

TREATMENT OF PAD

Recommendations:

- **Statin** in all patients
- Keep BP < 130/80 mmHg; β -blockers are effective and not contraindicated.
- Proper foot care
- Smoking—counsel to stop smoking, offer behavioral and pharmacologic treatment (varenicline, bupropion, and nicotine replacement therapy); ask smokers/former smokers about tobacco use at every visit.
- **Antiplatelet therapy** with aspirin 75–325 mg/day or clopidogrel 75 mg/day decreases cardiovascular events. Dual-antiplatelet therapy (aspirin plus clopidogrel) can be used in patients who develop acute limb ischemia or receive stenting of the peripheral arteries.
- Anticoagulation with warfarin is of **no benefit**.
- Exercise 30–45 minutes at least 3 days/week.

- **Cilostazol**, a phosphodiesterase inhibitor, increases cyclic adenosine monophosphate (cAMP) in platelets and blood vessels and reversibly inhibits platelet aggregation. This agent is used to increase walking distance—use only if left ventricular (LV) function is normal because phosphodiesterase inhibitors increase mortality in patients with NYHA Class III or IV heart failure.

Although anticoagulation with warfarin is not beneficial, the combination of low dose rivaroxaban with aspirin was shown to improve outcome in PAD (COMPASS Trial).

Note: Pentoxifylline is not beneficial and should not be used in PAD or claudication.

If PAD is due to Buerger disease, stop tobacco use. If Takayasu arteritis is present, treat the disease with steroids (refer to the [Rheumatology](#) section for additional information).

Revascularization: Many forms of PAD can be effectively treated with percutaneous intervention (**angioplasty** and **stents**—just like in the coronary arteries). Revascularization can also be done surgically (bypass grafting). Both forms of revascularization can relieve symptoms and ischemia.

ACUTE LIMB ISCHEMIA (ALI)

With **acute** peripheral arterial occlusion, rapid evaluation and intervention are necessary to avoid limb loss. Think of PAD as the limb equivalent of coronary artery disease, and ALI as the limb equivalent of ST-elevation myocardial infarction. This can occur due to either a plaque disruption resulting in a thrombus formation and occlusion of flow in the artery of the limb, or embolization of a thrombus from elsewhere (e.g., left ventricle, as in some cases of heart failure; left atrial appendage, as in atrial fibrillation [A-fib]; thrombus from a mechanical valve or aorta). Patients present with sudden onset of unremitting limb pain. The onset of pain is abrupt and severe enough that they are specific about the time and circumstances of onset. ALI is identified by the 6 Ps: **pain**, **pallor**, **pulselessness**, **paresis**, **poikilothermia** (coolness), and **paralysis**.

Urgent evaluation can include imaging with ultrasound, CTA, or catheter-based angiography. Consultation should be obtained from vascular surgery and/or interventional cardiology to establish a revascularization strategy. If the limb is immediately threatened (i.e., sensory loss, pain at rest, absent pulses), urgent surgical intervention may be appropriate. Heparin protects the collateral circulation during evaluation by preventing further thrombus formation around the clot that caused the ALI. Embolectomy/thrombectomy is the treatment of choice. After revascularization, ongoing pain with evidence of myonecrosis (often in conjunction with renal failure) suggests compartment syndrome. Compartment syndrome occurs because of the edema from tissue injury in the affected limb. Perform manometry to exclude compartment syndrome.

Most arterial emboli to the lower extremities can come from either the **heart** or the **aorta** (aortic aneurysms can form thrombi inside them). Perform echocardiography (echo) to identify cardiac sources of emboli. Perform ultrasound of the aorta to exclude abdominal aortic aneurysm as a possible source. ECG and possibly Holter monitoring should also be performed to exclude A-fib. Suspect thromboembolization rather than in situ thrombus formation when multiple arterial beds are affected (e.g., leg, bowels, brain).

RENAL ARTERY STENOSIS (RAS)

Atherosclerotic disease of the aorta may encroach upon the ostium of the renal arteries. RAS is an important cause of secondary hypertension—suspect it in people with early or late onset of hypertension and for those with sudden worsening of chronic hypertension (see the **Nephrology** section). Revascularization of renal arteries is a controversial topic. The 2013 ACC/AHA PAD guidelines recommend percutaneous revascularization of RAS **only** in patients with ≥ 1 of the following:

- 1) Recurrent heart failure despite medical therapy
- 2) Uncontrolled unstable angina despite medical therapy
- 3) Sudden-onset flash pulmonary edema
- 4) Accelerating decline in renal function
- 5) Bilateral RAS
- 6) Solitary viable kidney with RAS

Bulky aortic disease may also compromise flow to the mesenteric arteries. Ischemic bowel disease (ischemic colitis) is discussed in full in the **Gastroenterology** section.

CAROTID ARTERY DISEASE

PREVIEW | REVIEW

- Which of these adverse cardiovascular events is most likely to occur in a patient with atherosclerotic disease of the carotid artery: myocardial infarction, stroke, or transient ischemic attack?
- When is carotid endarterectomy indicated?

CAROTID ARTERY ATHEROSCLEROSIS

Atherosclerosis within the carotid artery occurs most frequently within the common carotid bifurcation and proximal internal carotid artery. Patients with **atherosclerotic** carotid artery disease are more likely to have an MI than a transient ischemic attack (TIA) or stroke!

Carotid artery atherosclerosis (a.k.a. carotid stenosis) can be symptomatic or asymptomatic. Symptoms can include weakness or numbness in the face or an extremity (contralateral to the stenotic vessel), dysarthria, and vision loss. Carotid duplex **ultrasound** is the best initial diagnostic

test to detect hemodynamically significant carotid stenosis in both symptomatic and asymptomatic patients. Use magnetic resonance angiography (MRA) or computer tomographic angiography (CTA) when ultrasound cannot be obtained or yields equivocal/nondiagnostic results.

Symptomatic patients who have experienced nondisabling ischemic stroke or TIA symptoms within 6 months should undergo carotid endarterectomy (**CEA**) if:

- 1) the diameter of the lumen of the ipsilateral internal carotid artery is reduced by $> 70\%$ when evaluated by noninvasive imaging or is reduced by $> 50\%$ when evaluated by catheter angiography, **and**
- 2) the anticipated rate of perioperative stroke/mortality is $< 6\%$.

Carotid artery stenting is an alternative to CEA for these same patients. The choice between these 2 methods of revascularization is based on patient and anatomic characteristics.

Therapy for primary prevention of stroke in atherosclerotic carotid disease is the same as in atherosclerosis in general—control modifiable risk factors (e.g., diabetes, hypertension, smoking), antiplatelet therapy (mainly aspirin), and statin therapy. For secondary prevention of stroke (i.e., prevention of recurrence of stroke), antiplatelet therapy regimen can be 1 of the following:

- Monotherapy with aspirin
- Monotherapy with clopidogrel
- Combination therapy with low-dose aspirin plus extended-release dipyridamole

CEREBRAL EMBOLIC DISEASE

PREVIEW | REVIEW

- What is the most common cause of cerebral embolic events?

OVERVIEW

The causes of cerebral embolic events of cardiac origin (and the approximate percentage of events they cause):

- Atrial fibrillation (45%)
- Acute myocardial infarction (15%)
- Ventricular aneurysm (10%)
- Mechanical valve prosthesis (10%)
- Valvular heart diseases, including endocarditis (10%)
- Other cardiac abnormalities (10%)

Other cardiac abnormalities include patent foramen ovale (PFO) or persistent atrial septal defect, which allows an intermittent right-to-left shunt and paradoxical emboli from the venous system (if deep vein thrombosis is present) into the arterial system, and dilated cardiomyopathy, which allows formation of a mural thrombus.

The **noncardiac** causes of **embolic** cerebral events are aortic and carotid atherosclerosis.

Nonembolic causes of cerebral ischemic attacks or strokes are thrombosis, systemic hypoperfusion, and blood disorders (especially clotting disorders).

Patients with ischemic cerebral vascular accidents (CVAs) should be evaluated for the source of ischemia:

- The majority of patients with CVA have an embolic source for their stroke. Perform carotid artery ultrasound and transthoracic echocardiography in all patients with CVA to exclude the cardiac and carotid artery abnormalities outlined above as sources of emboli.
- Perform ECG to exclude atrial fibrillation (A-fib). If ECG is normal, consider telemetry or a Holter monitor because paroxysmal A-fib can be the cause of emboli.
- A minority of CVAs are due to obstructive disease of intracranial cerebral vessels. CT angiography of the vessels of the neck and brain identifies intracranial lesions if present.
- In young patients without a source for carotid or cardiac embolus on initial evaluation, transesophageal echocardiography with bubble study may be considered to exclude PFO.

TRANSIENT ISCHEMIC ATTACK (TIA)

TIA is defined as any period of central nervous system (CNS) ischemia without infarction, regardless of symptom duration. Ischemic **stroke** is defined as ischemia with infarction. The CNS includes the brain, spinal cord, and retina. (Read more on TIAs in the [Neurology](#) section.)

Workup and treatment in general is the same as those for carotid artery atherosclerosis (refer to [Carotid Artery Atherosclerosis](#)).

Medical treatment of TIA: If there is a history of TIA but no history of cardioembolic stroke, no significant lesion is found, and the patient does not have A-fib, the cause is likely atherosclerosis; therefore, place the patient on antiplatelet therapy—**aspirin (ASA) + dipyridamole**, ASA alone, clopidogrel alone, or ASA + clopidogrel in the short term followed by monotherapy.

AORTIC DISEASE

PREVIEW | REVIEW

- What are the tests of choice for diagnosing aortic dissection?
- At what size is surgery indicated for a thoracic aortic aneurysm?
- At what size is surgery indicated for an abdominal aortic aneurysm?

AORTIC DISSECTION

Aortic dissection is an intimal tear in the aorta, resulting in a dissecting hematoma that can cause severe pain (due to tearing the aortic wall). As the dissection flap progresses distally (bleeding into the wall), it may occlude the branches coming from the aorta and compromise flow in them. Dissection of the ascending aorta can involve the carotid artery and cause a stroke; aortic dissection extending to the renal arteries can occlude flow to the kidneys, causing acute kidney failure. Aortic dissection can be acute or chronic, but should always be evaluated by a surgeon. Acute aortic dissection is a surgical emergency and should be diagnosed immediately and managed promptly.

Figure 13-26 demonstrates how flowing blood extends the separation of the aortic wall layers (i.e., dissects it further).

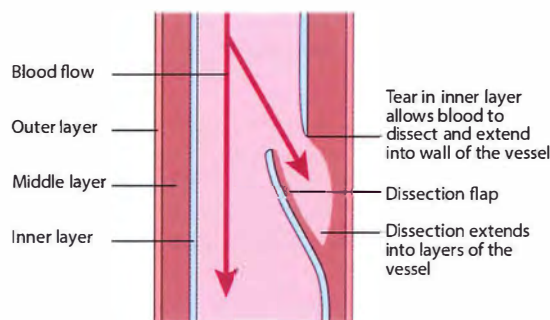


Figure 13-26: Aortic dissection

Systemic hypertension, cystic medial necrosis, bicuspid aortic valve, coarctation of the aorta, and the 3rd trimester of pregnancy are predisposing factors for aortic dissection. Aortic dissection is a major cause of death in those with **Marfan** syndrome; therefore, they should have surveillance screening imaging to assess any dilation in the aorta that could lead to dissection.

There are several classification systems for aortic dissection, but there are 2 systems that are commonly used (**Figure 13-27**).

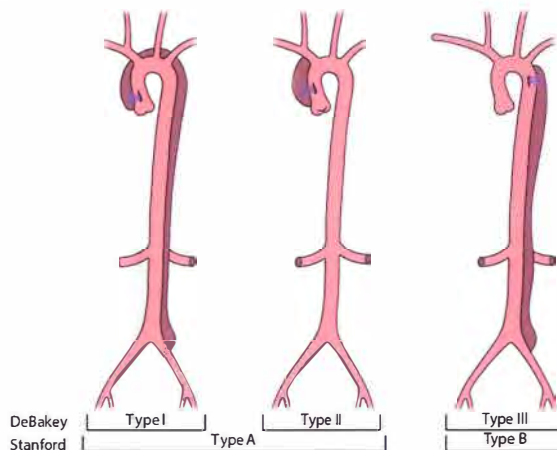


Figure 13-27: Common classifications of aortic dissection

The traditional **DeBakey** classification of aortic dissection lists 3 types:

- **Type I**—tear occurs in the ascending aorta and dissection includes the aortic arch and descending aorta.
- **Type II**—tear occurs in the ascending aorta and dissection involves the ascending aorta alone.
- **Type III**—tear occurs in the descending aorta, commonly just after the left subclavian artery, and involves only the descending aorta (before renal arteries = IIIa, to or beyond renal arteries = IIIb).

The **Stanford** classification is more commonly used to categorize aortic dissections and lists 2 types:

- **Type A**—tear is in the **ascending** arch and includes any dissection involving the ascending aorta (regardless of whether the aortic arch or descending aorta is involved).
- **Type B**—tear is in the **descending** aorta so is limited to the descending aorta only (i.e., distal to the left subclavian artery).

Proximal dissection (Stanford Type A) can cause aortic regurgitation, hemopericardium with tamponade, and myocardial infarction (MI) due to involvement of a coronary artery (usually the right coronary artery). Dissections typically present with severe **anterior** chest pain and/or severe **interscapular** back pain. Patients often describe the pain of aortic dissection as a ripping or tearing sensation down the back.

On physical exam, look for pulse differentials (e.g., between upper extremities, between upper and lower extremities), blood pressure differentials, a new diastolic murmur indicating acute aortic regurgitation, or signs of cardiac tamponade (indicating hemopericardium). However, if there is clinical suspicion for aortic dissection, do not rely on physical examination findings, as they are very unreliable and can be normal despite an extensive dissection.

Diagnosis: Low clinical suspicion and a **negative D-dimer level rules out dissection!**

Transesophageal echocardiography (TEE) or CT angiography (CTA) are the diagnostic tests of choice for suspected proximal thoracic aortic dissection (Stanford Type A). For all others, chest or cardiac CT and/or MRI are the diagnostic procedures of choice. Chest x-ray can show a wide mediastinum, but it is not a sensitive or specific test. If the initial diagnostic test is unrevealing and you still suspect dissection, get a 2nd test using a different imaging modality. You cannot afford to miss this diagnosis! There is very high mortality with aortic dissection, and mortality increases by the hour.

Ascending (Stanford Type A) aortic dissections are surgical emergencies. Consult a surgeon immediately.

Descending aortic dissections (Stanford Type B) are typically treated medically unless evidence of end-organ damage develops (e.g., acute kidney injury, gastrointestinal ischemia, limb compromise), which suggests continuing dissection and the need for

emergent surgery. Studies have shown that this type of dissection does worse with surgical repair. To medically manage aortic dissection, lower elevated blood pressure **immediately**. Administer β -blockers 1st to minimize reflex tachycardia, and then treat with a vasodilator (such as nitroprusside). Avoid hydralazine because it can increase heart rate and worsen the dissection.

In summary, remember that any dissection before or within the aortic arch (Stanford Type A) can involve the carotids, and these have high mortality; therefore, consult a surgeon immediately. Treatment is emergent surgical repair. Any dissection that is beyond the left subclavian artery (Stanford Type B) can be managed with medical therapy only, unless there is end-organ damage.

Note: Stanford Type A (but not Stanford Type B) aortic dissection can sometimes extend into the coronary arteries and obstruct blood flow, causing ST-elevation myocardial infarction (STEMI). Recognize that Stanford Type A aortic dissection is a **surgical emergency** and should never be missed, even if other findings suggest STEMI (e.g., ECG changes, troponin elevation). Catheter manipulation within the aorta during coronary angiography can result in progression of the aortic dissection. Additionally, starting treatment for STEMI with the usual anticoagulation and dual antiplatelet therapy (DAPT) can be fatal if aortic dissection is missed—anticoagulation and DAPT would result in further progression of dissection. Therefore, always consider Type A aortic dissection in patients presenting with acute coronary syndrome (ACS). If dissection is suspected, immediately get a CTA or TEE. If aortic dissection is present, then consult a surgeon immediately for emergent surgery. If aortic dissection is ruled out, proceed with treatment of ACS (i.e., antiplatelet and anticoagulation) and coronary angiography.

AORTIC ANEURYSMS

The causes of thoracic and abdominal aortic aneurysms can be broadly categorized as degenerative diseases, inherited or developmental diseases, infections, vasculitis, and trauma. **Rupture** is the biggest threat.

Abdominal aortic aneurysm (AAA) has additional complications, including **atheroembolism**. Signs of atheroembolism are livedo reticularis, then blue toes, then ischemic ulceration. (Remember, though, that most emboli to the lower extremities originate from the heart!) Hypertension from renovascular disease (i.e., renal artery stenosis) can occur if AAAs are **not** treated.

Thoracic Aortic Aneurysms

The aorta is dilated in both aneurysm and dissection; however, these are 2 distinct pathologies. In dissection, the involved segments of the aorta are dilated because there is bleeding into the aortic wall with formation of an intramural hematoma. In aneurysm, the vascular lumen itself is dilated. The walls of the involved segment of the aorta become thinner (because they are stretched) and, thus, are at risk for rupture. Remember,

the more dilated the aorta (or any vessel), the thinner its walls, and the higher the risk for rupture. That is why you should do serial monitoring of the aneurysm, looking for changes in size. There are various risk factors for forming aortic aneurysms, including:

- **Cystic medial necrosis**—the most common pathology in **ascending aortic** aneurysms
- **Atherosclerosis**, which usually causes aneurysms of the **aortic arch** and **descending thoracic aorta**

The average growth rate of thoracic aneurysms is 0.1–0.2 cm per year. In [Figure 13-28](#), notice how the aortic walls are thinner in the area of aneurysm because the affected segment is stretched. It should be no surprise that the larger the aneurysm, the thinner the walls, and the higher the risk of rupture.

For chronic, stable **thoracic** aortic aneurysm, surgery is indicated at a width of **5.5 cm** in the ascending aorta (5 cm if patient has Marfan's) and **6 cm** in the thoracic descending aorta.

Surgery is indicated if the aneurysm is small but enlarging rapidly (> 10 mm in a year), causing symptoms, compressing surrounding structures, or is of traumatic origin.

For nonruptured aneurysms, treat patients with β -blockers. Nonruptured aneurysms related to Marfan's should be treated with an angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) in addition to β -blockers.

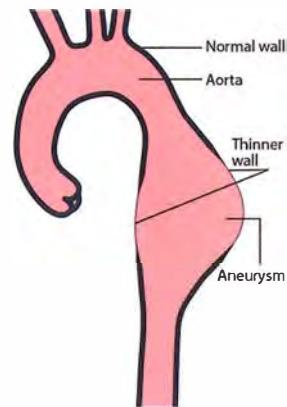


Figure 13-28: Thoracic aortic aneurysm

Know that **acute MI** and other CAD-related problems cause the majority of perioperative mortality for AAA repair. Perform CAD screening with a nuclear stress test if the patient has ≥ 2 CAD risk factors (listed under [Risk Factors for CAD on page 13-34](#)). Use perioperative β -blockers in patients with CAD undergoing surgical repair of AAA.

Open and endovascular repair are both options for infrarenal AAA and/or common iliac aneurysms in good surgical candidates. Endovascular repair includes placing a covered stent within the aneurysm that protects the thin aneurysmal walls from aortic pressure ([Figure 13-29](#)).

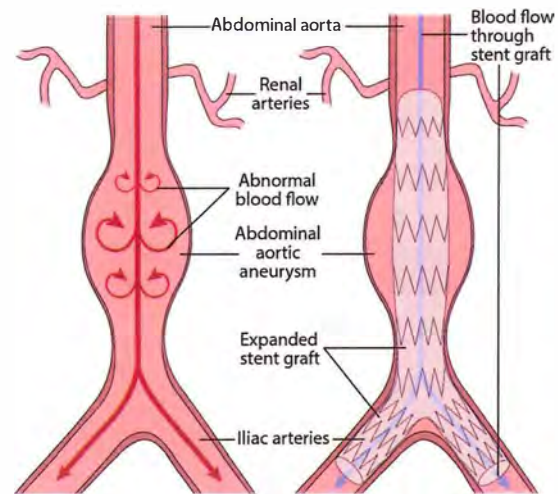


Figure 13-29: Endovascular aortic repair (EVAR)

Endovascular repair requires periodic long-term surveillance imaging to monitor for endoleak (persistent arterial perfusion of the aneurysmal sac after endovascular repair), to monitor for shrinkage/stability of the excluded aneurysm sac, and to determine the short- and long-term success of the procedure and whether the patient needs further intervention.

Abdominal Aortic Aneurysm (AAA)

Screening is covered in the [General Internal Medicine](#) section.

AAA is more common in men with a history of smoking. These aneurysms tend to rupture rather than dissect. Treat blood pressure and lipids the same as you would for patients with coronary artery disease (CAD); advise patients to stop smoking and recommend smoking cessation interventions.

According to the 2013 ACC/AHA peripheral artery disease compilation guidelines, asymptomatic aneurysms 4–5.4 cm should be monitored with ultrasound or CT every 6–12 months. Aneurysms that are ≥ 5.5 cm or symptomatic (abdominal/back pain + pulsatile mass + hypotension) should be surgically repaired. An AAA that expands **> 0.5 cm** in **6 months** should undergo surgical repair as well. Unless there is a contraindication, place all AAA patients on β -blockers during the observation period.

COARCTATION OF THE AORTA (COA)

COA is a congenital anomaly that is characterized by stenosis in the thoracic aorta distal to the left subclavian artery ([Figure 13-30 on page 13-48](#)). Because aortic pressure distal to the coarctation is lower, the kidneys are hypoperfused and secrete renin in an attempt to raise blood pressure, which causes persistent hypertension. Cardiac output responds **normally** to exercise. Blood pressure is higher in the upper extremities than in the lower. **Brachiofemoral delay**, the femoral pulse occurring after the brachial pulse, is present in COA. People with COA have a high risk of developing subsequent aortic disease, including aneurysms and dissection, even after correction of the lesion. A **bicuspid aortic valve** is often seen (~ 50%) in COA patients. Patients with COA have a higher incidence of intracerebral aneurysms. See more on COA under Congenital Heart Diseases, [Coarctation of the Aorta on page 13-83](#).

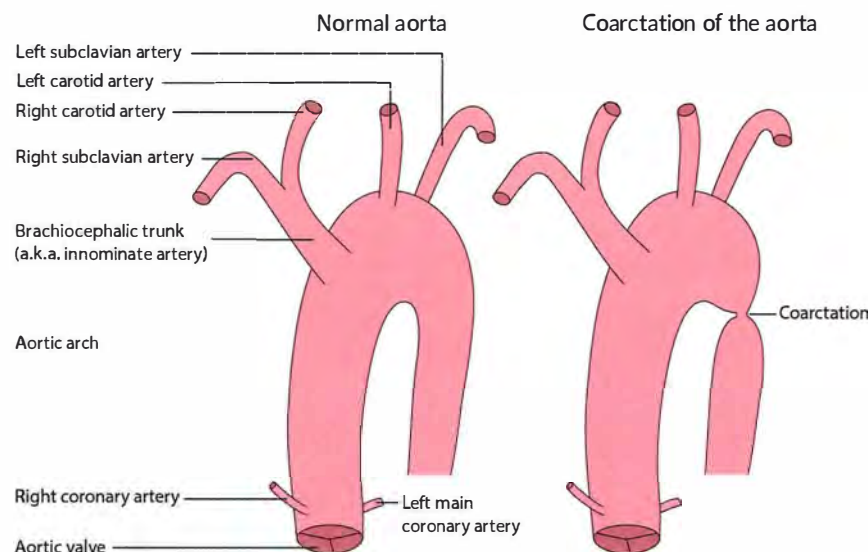


Figure 13-30: Coarctation of the aorta

VALVULAR HEART DISEASE

SPECIFIC VALVE LESIONS

PREVIEW | REVIEW

- What are the common presenting symptoms of aortic valve stenosis?
- What are the indications for valve replacement in patients with aortic valve stenosis?
- Name 2 conditions that cause chronic aortic regurgitation.
- What is the usual treatment for acute aortic regurgitation with associated heart failure?
- When the mitral stenosis is more severe, is the second heart sound to opening snap interval shorter or longer?
- Describe the murmur of mitral stenosis (timing, pitch, and location).
- Hemoptysis is seen with which valve defect?
- Describe the murmur sometimes heard with mitral valve prolapse. Does that murmur's intensity decrease or increase with standing? With Valsalva maneuver?
- Is carcinoid tumor more likely to cause tricuspid or mitral valve disease?
- In patients with tricuspid regurgitation, what abnormality is seen on the jugular venous waveform?
- True or false? Pulmonic stenosis is virtually always acquired.

- Ebstein anomaly is occasionally seen with which structural and electrical abnormalities?
- Describe the abnormal heart sounds found in aortic stenosis, chronic aortic regurgitation, and mitral stenosis.

The 2014 AHA/ACC Valvular Heart Disease Guidelines stage all valvular heart disease as:

- Stage A: at risk
- Stage B: progressive (mild-to-moderate severity)
- Stage C: severe but asymptomatic
- Stage D: severe and symptomatic

Stage D (and sometimes C) requires valve repair/replacement.

Refer to [Table 13-8 on page 13-50](#) and [page 13-51](#) as you study these valve lesions. It is important for both hospitalists and clinicians to be able to identify a specific valvular defect based on physical exam findings.

Aortic Stenosis (AS)

AS is generally due to **age-related calcific valve degeneration**. Congenital **bicuspid aortic valves** usually start getting calcified and stenotic between 40 and 70 years of age, while the normal **trileaflet aortic valves** become stenotic at > 75 years of age. A bicuspid aortic valve is the most common congenital valve disorder (1–2%). Less frequently, rheumatic heart disease can also cause AS, usually together with mitral valve disease.

Presenting signs and symptoms include one or more of the classic triad of heart failure, angina, and syncope with exercise.

Physical Exam

With significant AS, the carotid pulse has a decreased amplitude (weak) and slowed upstroke (delayed), which is commonly referred to as **parvus et tardus**, and the heart has a sustained apical impulse. Therefore, delayed and weak carotid upstroke is consistent with AS. Associated heart sounds include:

- A mid-to-late-peaking, diamond-shaped systolic ejection murmur at the right upper sternal border or suprasternal notch that radiates to the neck
- An S₄ gallop
- Often a decreased or **absent** aortic component of S₂ due to decreased mobility of the aortic valve leaflets
- A paradoxical S₂ split with severe AS (because the stenotic aortic valve closes after the pulmonic valve)

Occasionally, an AS murmur can be so loud that it is transmitted to the apex, where it can be confused with the systolic murmur of mitral regurgitation (the Gallavardin effect).

The systolic ejection murmur of AS is louder with squatting, whereas the murmur of hypertrophic obstructive cardiomyopathy (HOCM) decreases. This makes sense because squatting increases preload and stroke volume. Therefore, there will be more flow across the stenotic aortic valve (thus, murmur intensifies). Whereas in HOCM, there is less left ventricular outflow tract obstruction (thus, murmur decreases). Note: Hypertrophic cardiomyopathy (HCM) is the umbrella term for both obstructive and nonobstructive forms. HOCM is the more common presentation and the one in which the practitioner hears a murmur. In the Cardiology section, we use both of these terms to discuss hypertrophic cardiomyopathy.

An **ejection click** sounds like a guitar string being plucked immediately after S₁. This ejection click is classic and common in **bicuspid** aortic valve patients but is not heard with age-related calcific AS. Ejection clicks can also be heard in patients with pulmonic stenosis but will show respiratory variation.

With aortic stenosis, a systolic thrill can sometimes be felt over the upper precordium and the suprasternal **notch**. This thrill is a palpable sensation similar to the purring of a cat.

Diagnosis

Doppler echocardiography (echo) is very accurate in detecting **severe** AS.

A left heart cath is typically used to diagnose AS if there is a discrepancy between clinical and echo findings or to detect concomitant coronary artery disease (CAD). Patients with AS have a high rate of CAD: It is present in 1/3 of those 40–60 years of age and 2/3 of those > 60 years of age. During this procedure, the pressure inside the left ventricle (LV) and aorta are measured simultaneously. If there is AS, there will be a gradient between the LV and aorta, as the LV has to generate more pressure to push blood into the aorta through the stenotic aortic valve.

AS severity is usually assessed by mean valve pressure gradient (in mmHg) or maximum velocity across the valve (in m/second). As blood travels through a tight area, its velocity increases. The tighter the valve, the higher the pressure gradient across it and the higher the blood velocity. Criteria for grading severity of AS are as follows:

- Mild AS is < 20 mmHg.
- Moderate AS is 20–39 mmHg.
- Severe AS is ≥ 40 mmHg (or **peak blood velocity of ≥ 4.0 m/second**).

Low flow states (e.g., heart failure) give artificially low pressure and velocity readings. In this case, determine severity by valve area:

- **Not** severe AS is > 1 cm².
- Severe AS is ≤ 1 cm².

AS prognosis: Patients with symptomatic, severe AS have at least a 10% risk of sudden death. Without surgical intervention, clinical symptoms predict **median survival**, given by the mnemonic S:ASH.

Survival in AS:

- Angina—5 years
- Syncope—3 years
- Heart failure—2 years

Treatment

In AS, there is no medical therapy. It is a mechanical problem; so, the only solution is replacing the valve. However, the key is correctly timing the replacement. Do aortic valve replacement (AVR) for **all severe, symptomatic** (Stage D) AS patients—i.e., with a gradient ≥ 40 mmHg, velocity ≥ 4.0 m/second, or valve area ≤ 1 cm². AVR is also indicated for **asymptomatic** patients (Stage C) with **very severe AS** who have **very high gradients** (≥ 50 mmHg), **ejection fraction (EF) < 50%**, or those who are undergoing **other cardiac surgery**.

Transcatheter aortic valve replacement (TAVR) is recommended for patients with prohibitive risk for surgical AVR and a predicted post-TAVR survival > 12 months.

Use caution when treating ventricular failure due to AS with vasodilators. **Medical therapy alone is not effective.**

Without surgical intervention, severe AS results in high mortality and sudden cardiac death.

Note: AS is almost always chronic. Acute AS is extremely rare (such as an acute aortic root abscess that is obstructing the opening of the aortic valve leaflets).

Chronic Aortic Regurgitation (AR)

Chronic AR occurs as a result of **valve deformity** (e.g., bicuspid valve, rheumatic fever, endocarditis, degenerative valve disease) or an abnormal **aortic root** (e.g., dilation seen in Marfan syndrome, senile aortic disease, giant cell arteritis, relapsing polychondritis, syphilis). Dilation of

Table 13-8: Heart Defects and Associated Sounds

Valve Defect	Murmurs*	Clicks*	Change in Heart Sounds	Pulse Waveforms; a/v Waves
AS	S: SEM at RUSB, mid-to-late peaking, diamond-shaped	S: ejection click if congenital or bicuspid	Absent S ₂ (occ); S ₄ ; paradoxically split S ₂	Slowed carotid upstroke
Chronic AR	S: occasional early systole SEM D: 1) high pitched, decrescendo early to holodiastolic (regurgitation through the valve); 2) Austin Flint: low, rumbling diastolic resembling MS (regurgitant stream striking the anterior mitral narrowing in mitral valve opening)		S ₃ if severe	Corrigan or water-hammer pulse (rapidly increasing and falling)
Acute AR	D: short diastolic murmur		S ₃ if severe	Thready pulse
MS	D: diastolic rumble	D: opening snap (the only click that occurs in diastole!)	S ₁ is enhanced, sometimes "snapping"; may be silent if severely calcified.	Large left (pulmonary venous) a waves and y descent (seen on PCWP tracing, but not seen on physical exam)
Chronic MR	Holosystolic constant murmur	There is no click in chronic MR.	S ₃ if severe; S ₄	
MVP with murmur	S: Late SEM follows click, changes with hemodynamic maneuver.	S: midsystolic click (click-murmur syndrome)		
Acute MR	S: pansystolic decrescendo murmur at apex		S ₃ if severe	Large left (pulmonary venous) v waves
TS	D: diastolic at LSB			Giant right (jugular) a wave
Chronic TR	S + D: systolic at LLSB			Large right (jugular) v waves
PS	SEM, maximal at LUSB with radiation to the back	S: ejection click	Persistently/widely split S ₂	
VSD	S: loud holosystolic at LLSB with thrill			
ASD—ostium secundum	S: SEM at LSB (increased flow across pulmonic valve)		Fixed split S ₂	
ASD—ostium primum	S: SEM at LSB (increased flow across pulmonic valve); +/- TR or MR murmur		Fixed split S ₂	
COA	Midsystolic to continuous murmur (depending on severity) in the upper back			
HOCM	S: harsh midsystolic murmur		S ₄	Brisk carotid upstroke that is bifid in 2/3
PDA	S + D: continuous machinery-like murmur at LUSB		Paradoxically split S ₂	

Table Notes

Remember that S₄ is also heard in ischemic heart disease, diabetic cardiomyopathy, and hypertensive heart disease with concentric hypertrophy.

Note: Right-sided murmurs sound louder on **I**nspiration, **L**eft on **E**xpiration; all right-sided valve problems can rarely be caused by carcinoid.

Cannon **a** waves occur in complete heart block and with ventricular pacing.

Mitral valve pathologies affect the venous waveform in the pulmonary veins (which are assessed with PCWP tracing, not physical examination).

Tricuspid valve pathologies affect the venous waveform in the superior and inferior venae cavae (which can be assessed on physical examination of the jugular vein and liver or with right atrial pressure tracing).

* S = systolic, D = diastolic

† Squatting or lying down or raising legs if already supine

Table 13-8: Heart Defects and Associated Sounds (continued)

Valve Defect	Murmur Louder with:	CXR	Other
AS	Squatting†; expiration, after PVCs	LVH	Sustained apical impulse Etiology: bicuspid valve SSx: Classic triad is LVF, angina, and syncope with exercise.
Chronic AR	Squatting†; expiration	LVH	Etiology: congenital, endocarditis, or dilated aortic root from Marfan's, VSD, arteritis, polychondritis, syphilis
Acute AR	Squatting†; expiration	Normal	Cardiogenic shock and pulmonary edema Consider aortic dissection.
MS	Squatting†; expiration	LAE	Etiology: virtually always rheumatic fever SSx: hemoptysis, secondary pulmonary HTN
Chronic MR	Increasing afterload (sustained handgrip and expiration); no changes with standing or Valsalva	LAE	Etiology: pathologies that dilate the MV annulus (functional MR like in HF) or degeneration of MV
MVP with murmur	Standing or Valsalva: Murmur is longer—moves earlier into systole.	LAE	Etiology: congenital, ischemia
Acute MR	Squatting†; expiration	Normal	Etiology: endocarditis, MI with papillary muscle ischemia or rupture, chordae tendineae rupture SSx: pulm edema
TS	Squatting†; inspiration	RAE	TS is rare. Etiology: usually rheumatic fever but also congenital; rarely, carcinoid causes TS (together with TR) SSx: venous congestion
Chronic TR	Squatting†; inspiration	RVE	Etiology: usually dilation from pulmonary HTN; other—rheumatic fever, endocarditis (IVDA), carcinoid SSx: liver pulsations, JVD
PS	Inspiration	RVH; enlarged pulmonary artery	Etiology: Virtually always congenital—rarely caused by rheumatic fever and carcinoid; congenital type typically does not progress.
VSD	Handgrip	RVE + LVE	Consider in new MI with new systolic murmur
ASD—ostium secundum		RVE; shunt vascularity	ECG: right axis deviation, RBBB
ASD—ostium primum		RVE	ECG: left axis deviation, RBBB
COA		Rib notching, loss of aortic notch	
HOCM	Standing, Valsalva; sustained handgrip decreases murmur.	LVE	Apical impulse may have double- or triple-taps.
PDA		Calcification of ductus arteriosus	

AR = aortic regurgitation
AS = aortic stenosis
ASD = atrial septal defect
COA = coarctation of the aorta
D = diastolic
HF = heart failure
HOCM = hypertrophic obstructive cardiomyopathy
HTN = hypertension
IVDA = IV drug abuse

JVD = jugular venous distention
LAE = left atrial enlargement
LBBB = left bundle-branch block
LSB = left sternal border
LUSB = left upper sternal border
LV = left ventricle
LVE = left ventricular enlargement
LVF = left ventricular failure
LVH = left ventricular hypertrophy
MI = myocardial infarction

MR = mitral regurgitation
MS = mitral stenosis
MVP = mitral valve prolapse
PCWP = pulmonary capillary wedge pressure
PDA = patent ductus arteriosus
PE = pulmonary embolism
PS = pulmonic stenosis
RAE = right atrial enlargement
RBBB = right bundle-branch block

RUSB = right upper sternal border
RV = right ventricle
RVE = right ventricular enlargement
RVH = right ventricular hypertrophy
S = systolic
SEM = systolic ejection murmur
TR = tricuspid regurgitation
TS = tricuspid stenosis
VSD = ventricular septal defect

the aortic root causes the aortic valve leaflets to pull away from each other and prevents them from coapting well.

Patients with AR may be asymptomatic and typically have good exercise tolerance. Exercise induces peripheral vasodilation, reducing afterload and augmenting forward flow. Exercise also causes tachycardia, which reduces regurgitation by shortening the time for regurgitation during diastole.

Chronic AR causes LV volume overload, which eventually causes LV dilation and a drop in LV systolic function. Once this happens, symptoms of heart failure occur (i.e., exertional dyspnea and angina).

Physical Findings

Physical exam with chronic AR has several classic physical findings:

- A decrescendo, **diastolic, high-pitched** blowing murmur is caused by regurgitation through the valve:
 - It is loudest at the **left** sternal border (3rd space) if due to the aortic leaflet and at the **right** sternal border (RSB) if due to aortic root disease (because the root is closer to the RSB).
 - The high-pitched blowing sound of this murmur indicates **high flow** and **high pressure gradient** between the aorta (diastolic pressure around 80 mmHg) and the left ventricle (diastolic pressure around 5 mmHg). In contrast, the diastolic murmur of mitral stenosis (MS) is a low-flow diastolic rumble because it has a lower pressure gradient (left atrial pressure is around 10 mmHg, and left ventricular pressure is around 5 mmHg).
- Occasionally, you hear an Austin Flint murmur, which **sounds similar** to the low-flow rumble of MS. It is thought to be due to the high-pressure regurgitant jet striking the anterior mitral leaflet and pushing it into a closed position, which impedes mitral valve inflow. This murmur does not have the associated presystolic accentuation that is seen in MS.
- A wide and bounding carotid Corrigan pulse and water-hammer in the limbs is 2° to elevated systolic and low diastolic components of blood pressure (BP).
- There are many other exam findings seen with chronic AR that have eponyms and are all related to pulsations; e.g., Becker sign = visible pulsations of the retinal arteries; de Musset sign = bobbing of the head with the pulse; Müller sign = bobbing of uvula during systole.

Chest x-ray shows an enlarged LV and may show dilation of the ascending aorta. **Aortic angiography** can be performed at the time of cardiac cath to diagnose AR—although it is more frequently diagnosed with echocardiography.

Monitor patients with chronic AR using serial echocardiography to follow **LV size** and **function**.

Perform surgery if the patient is:

- Symptomatic (Stage D valvular disease)
- Asymptomatic (Stage C valvular disease) but with evidence of LV dysfunction (the 50-50 rule), which includes either:
 - LVEF < 50%, or
 - LV enlargement with LV end-systolic diameter ≥ 50 mm.

Unlike AS, **prognosis** with chronic AR is generally good—AR can be well tolerated even at advanced stages. The LV may recover after surgery even if there was evidence of dysfunction (per the 50-50 rule).

Treatment

Medical therapy for severe AR can involve vasodilators to decrease afterload if the patient is hypertensive. If blood pressure is normal, routine decrease of afterload does not improve outcomes and can cause harm. For a patient with hypertension, ACEIs/ARBs are typically used for afterload reduction. You can use diuretics to treat **symptoms** caused by volume overload and heart failure.

Aortic valve replacement (AVR) surgery is indicated if the patient meets the criteria for Stage D valvular disease or Stage C valvular disease with LV dysfunction (the 50-50 rule). Intraaortic balloon pump placement is contraindicated in patients with AR because it increases aortic regurgitation.

Acute Aortic Regurgitation (AR)

Native valve acute AR can be caused by a flail leaflet due to:

- Endocarditis
- Type A aortic dissection
- Trauma

Prosthetic valve acute AR can be caused by:

- Tissue valve leaflet rupture
- Mechanical valve closure problem (e.g., thrombosis)
- Paravalvular regurgitation due to infection

Patients with acute AR present with severe pulmonary edema and low cardiac output (CO). Because the CO and BP are **low**, there is **no** bounding arterial pulse. The diastolic murmur is **short** because it ends when the ventricular pressure rises to the level of the low aortic pressure. The LV in these patients does not have time to compensate for the LV volume overload.

The fastest, most sensitive, and most specific way to diagnose acute AR is with echocardiography. Transthoracic echocardiography (TTE) is adequate to confirm AR, but transesophageal echocardiography (TEE) may be needed to determine the underlying cause of AR (e.g., a perivalvular abscess). TEE may be preferred when you suspect acute AR in a patient with cardiogenic shock, because urgent cardiothoracic surgical consult will be needed,

and TEE provides the image guidance needed for valve replacement.

Patients with significant **acute AR** and heart failure (HF) need **immediate AVR**.

Notice how hemodynamics differ between chronic AR and acute AR. Acute pathologies cause acute changes in hemodynamics and do not allow time for the cardiovascular system to compensate; therefore, patients with acute AR do not do well. Remember, the 50-50 rule applies to patients with chronic AR only.

Mitral Stenosis (MS)

MS is relatively rare in the U.S. The most common cause is **rheumatic fever**. Other causes are systemic lupus erythematosus, rheumatoid arthritis, and severe valve calcification. **Atrial fibrillation** (A-fib) is very common in MS due to left atrial stretching and dilation. MS can cause HF (mostly right rather than left ventricular failure), but sometimes 2° pulmonary hypertension is the main complication.

Physical Findings

Patients have a diastolic murmur with a diastolic **opening snap** (OS) caused by the sudden tensing of the calcified/stiff mitral leaflets. Distinguish the OS of MS from a split 2nd heart sound (S₂) based on location: an OS is best heard at the apex, while a split S₂ is best heard at the upper sternal border. The time interval between the S₂ and the OS (the S₂-OS interval) is inversely related to the severity of the MS. The more severe the MS, the higher the left atrial (LA) pressure; thus, the earlier the mitral valve is forced open in diastole, and the smaller the S₂-OS interval.

Prognosis: MS has a relatively benign course. It may take 20 years until MS becomes symptomatic after the episode of rheumatic fever.

Diagnosis

As mentioned in **Heart Sounds on page 13-2**, the S₁ is accentuated and can also have a snapping quality. The diastolic murmur is often described as a rumble and is best heard at the left 5th interspace at the midclavicular line. It suggests low flow, in contrast to the high-pitched, high-flow diastolic murmur heard in aortic regurgitation.

The chest x-ray shows the following triad:

- 1) Prominent pulmonary artery vascularity
- 2) An enlarged LA
- 3) Normal-sized LV (because MS affects the LA but not the LV)

A biphasic P wave in V1 on the ECG is seen with an enlarged left atrium (**Figure 13-44 on page 13-90**). Do an echo to confirm the diagnosis. Hemoptysis can occur with MS; it is due to rupture of the pulmonary bronchial vessels distended by pulmonary venous congestion.

Treatment

Medical treatment of MS involves diuresis and heart rate control. Controlling heart rate is important in MS, as higher heart rates mean higher flow rate across the stenotic mitral valve (blood volume remains relatively the same during tachycardia, but the diastolic period is shorter, resulting in a higher flow rate). Heart rate control can be achieved with β -blocker or calcium channel blocker therapy.

All nonpregnant patients with A-fib due to MS should be anticoagulated with **warfarin**. Because of the teratogenic effects of warfarin in pregnancy (if dose is > 5 mg/day), use heparin instead. Direct oral anticoagulant agents (rivaroxaban, apixaban, dabigatran, and edoxaban) are not indicated for A-fib in MS.

Percutaneous mitral balloon valvotomy (PMV) is recommended for patients with symptomatic severe MS (Stage D valvular disease; mitral valve area $\leq 1 \text{ cm}^2$).

Surgical mitral valve replacement or repair is less desirable but is an alternative for patients who are not PMV candidates or fail PMV. Mitral valve surgery is also considered for patients with **moderate** stenosis who are undergoing other cardiac surgery.

Note: MS is a chronic pathology. Generally, there is no acute MS other than very rare and unusual exceptions (such as a massive thrombus in the left atrium that is obstructing flow to the left ventricle).

Chronic Mitral Regurgitation (MR)

Chronic MR can be due to rheumatic heart disease, mitral valve prolapse (discussed in **Mitral Valve Prolapse (MVP) on page 13-54**), annulus dilatation from left ventricular dilatation, prior episode of endocarditis, and/or ischemic effects on the papillary muscle (from coronary artery disease or myocardial infarction [MI]).

Physical Findings

Chronic MR presents differently from acute MR. Because the left atrium in chronic MR becomes enlarged over time, it provides less resistance to the backflow of blood across the incompetent mitral valve and can accommodate large regurgitant volumes. This results in a **constant intensity, holosystolic** murmur instead of decrescendo (as in acute MR). It is best heard at the apex and radiates towards the axilla. Atrial fibrillation (A-fib) is common. In both severe chronic **and** acute MR, the S₁ is soft or absent and S₂ is widely split. (The aortic valves close early because of decreased volume ejected from the left ventricle.) An S₃ is common in severe MR. Increasing afterload with handgrip increases the MR murmur.

The left ventricular ejection fraction (LVEF) in chronic MR is frequently normal or high because LV outflow now has 2 routes of exit during systole: forward through the aorta (high resistance) and backward through the regurgitant mitral valve into the left atrium (low resistance).

Because of the increased preload on the left ventricle, it starts to dilate and decompensate over time, leading to heart failure. Increased preload results in increased backup pressure into the pulmonary circulation and pulmonary hypertension. Patients with chronic MR present with symptoms of heart failure (HF; e.g., orthopnea, dyspnea on exertion, decreased exercise tolerance, fatigue).

Note: Dilated mitral annulus in HF can result in MR. On the other hand, increased preload and LV workload from MR can result in worsening HF. Therefore, it is not surprising that both HF and MR present together and patients with MR have symptoms of HF.

Diagnosis

Just like in chronic AR, monitor patients with chronic MR using serial echocardiography to follow **LV size** and **function**.

Perform surgery if the patient is:

- Symptomatic (Stage D valvular disease)
- Asymptomatic (Stage C valvular disease) but evidence of LV dysfunction, which includes either:
 - LVEF < 60%, or
 - LV enlargement with LV end-systolic diameter ≥ 40 mm.

Notice that cutoffs for replacing a mitral valve in chronic MR are slightly different than those in chronic AR. In chronic AR, use the 50-50 rule (LVEF < 50% or LV end-systolic diameter ≥ 50 mm). In chronic MR, use the 60-40 rule (LVEF < 60% or LV end-systolic diameter ≥ 40 mm). If you ever forget which rule is which, remember that LVEF in MR should be higher (because of decreased afterload), and 60-40 rule is for MR.

Chronic MR has a much worse **prognosis** than chronic AR. Chronic MR results in wasted LV workload (backflow of blood into the left atrium rather than into the aorta) and increased LV workload (increased preload). It usually leads to LV dysfunction. Additionally, it results in pulmonary hypertension and, consequently, causes right ventricular dysfunction. Therefore, overall prognosis is poor. Chronic MR can be the worst among all the chronic valvular pathologies, whether stenotic or regurgitant.

Treatment

Treat significant chronic MR with **diuretics** and **afterload reducing agents** (ACEIs/ARBs), but only if there is hypertension. Just like in chronic AR, afterload reduction does not change outcome of chronic MR. β -blockade can help by prolonging diastole.

Repair (if possible) is preferable to replacement in patients with Stage C and D valvular disease. Percutaneous valve repair devices (such as MitraClip and Carillon Mitral Contour System) may be good options in patients with severely symptomatic chronic MR who are poor surgical candidates. However, even with repair, prognosis remains poor once LV dysfunction develops (per the 60-40 rule).

Mitral Valve Prolapse (MVP)

MVP is the most common valvular problem seen in practice (incidence up to 2.4%) and is more common in women. There are different causes of MVP. Some are associated with connective tissue disorders (e.g., Marfan's, osteogenesis imperfecta, Ehlers-Danlos). Most MVPs are considered a normal variant; in these, the chordae tendineae are elongated, causing a billowing of the otherwise normal mitral valve leaflets. Most patients are asymptomatic throughout life, but some may present with severe MR after rupture of the chordae or with endocarditis. On the other hand, myxomatous changes in the mitral valve leaflets (determined by echo) invariably progress to chronic MR. Many symptoms (e.g., dyspnea, panic attacks, chest pain) previously attributed to MVP have been shown to occur with no greater frequency than in individuals without MVP. Patients with MVP should receive reassurance of its generally benign course and be advised to follow a healthy lifestyle. β -blocker agents may help with symptom management. However, if the accompanying (chronic) MR is severe, it can lead to LV dysfunction. Therefore, monitor with echo and treat patients with severe chronic MR in the setting of MVP just like any other patient with severe chronic MR. Use the 60-40 rule discussed in **Diagnosis**. MV repair can be performed for symptomatic severe MR.

Physical exam with MVP: With MVP, there is usually a mid-systolic click followed by a mid-to-late systolic murmur. As the LV contracts during systole, its systolic pressure starts to rise to eject the blood into the aorta. Normally, its papillary muscles contract to tether their chordae tendineae and prevent the mitral valve leaflets from prolapsing into the left atrium. However, in MVP, because some of the chordae tendineae are elongated, they allow the mitral valve leaflet (usually posterior leaflet) to prolapse in the left atrium at midsystole. So, MR due to MVP usually starts in midsystole, rather than at the beginning of systole like in most chronic MR. Additionally, immediately before the MR starts at midsystole, there is a **midsystolic click**. This is believed to be the sound of the overstretch and tension of elongated chordae tendineae, which happens suddenly at midsystole. (Think of it as the sound you make when you suddenly and quickly overstretch a thread.) This mid-systolic click is present in MVP, but not other causes of chronic MR. If there is also MR, the click is followed by a mid-to-late systolic murmur (**click-murmur syndrome**). Whereas, in chronic MR, the murmur is holosystolic (from the beginning to end of systole) and there is no click.

The murmur of MVP is like the murmur in hypertrophic obstructive cardiomyopathy (HOCM) in that decreased preload **increases** the intensity of the murmur. The click and murmur become louder and move **earlier** into systole with standing or Valsalva, both of which decrease preload and, hence, LV volume. (An earlier click means a longer murmur.) This gives the clue for how you can tell the difference between an ejection click (aortic or pulmonic stenosis) and the midsystolic click of MVP—an **ejection click** is **fixed**, whereas the **midsystolic click** **varies in timing**.

with **changes in the patient's position**. Stand the patient up, and the midsystolic click sounds just like an ejection click. Squatting or supine position does the opposite: It **increases** preload, increases LV size, and causes the click to occur later, thereby shortening the murmur. **Dynamic** auscultation is **required** to diagnose MVP clinically.

The reason the timing of the click in MVP varies with changes in preload makes sense if you think about it. With increased preload, the LV is stretched more during diastole. Because of the increased inner dimensions of the LV, the elongated chordae tendineae are taut, and do not allow the mitral valve leaflet to prolapse into the left atrium. Later in systole, after the LV has ejected much of its blood, the LV inner dimension is smaller, and the elongated chordae tendineae will then allow the mitral leaflet to prolapse into the left atrium. At that point, the click and MR murmur are audible.

Acute Mitral Regurgitation (MR)

Acute MR commonly presents with acute-onset pulmonary edema.

Causes of **native** valve acute MR include:

- Flail leaflet (due to endocarditis or trauma)
- Papillary muscle ischemia or rupture (e.g., MI, trauma)
- Chordae tendineae rupture (e.g., endocarditis, acute rheumatic fever, trauma, degeneration, spontaneous)

Causes of **prosthetic** valve acute MR include:

- Tissue valve leaflet rupture
- Mechanical valve closure problem (e.g., thrombosis)
- Paravalvular regurgitation due to infection

Physical exam with acute MR: **decrecendo systolic** murmur at the **apex**. It can be difficult to hear. Echocardiogram shows a hyperactive LV with normal-to-high ejection fraction and a normal-sized left atrium. There are large, left-sided *v* waves on pulmonary capillary wedge pressure tracing. There are crackles in the lungs due to pulmonary edema.

Initially manage with afterload reduction and diuresis. Unlike severe AR, **intraaortic balloon pump** can be helpful for patients in heart failure from acute MR. **Emergent surgery** is usually the only treatment.

Notice how hemodynamics differ between chronic MR and acute MR. Acute pathologies cause acute changes in hemodynamics and do not allow time for the cardiovascular system to compensate; therefore, patients with acute MR do poorly. Remember the 60-40 rule applies to patients with chronic MR only.

Tricuspid Stenosis (TS)

TS is rare. Causes are rheumatic fever (usual), congenital, carcinoid syndrome (rarely), and endocarditis.

Physical exam with TS: A diastolic murmur presents along the left sternal border that increases with inspiration (as do all right-sided murmurs). This murmur has a giant *a* wave caused by backflow during atrial contraction against a stenotic tricuspid valve. There may be ascites and lower extremity edema.

The ECG shows the tall, peaked P waves in II and V1 (evidence of the right atrial hypertrophy) but no evidence of right ventricular hypertrophy. Chest x-ray shows an enlarged right atrium.

Treat the underlying disease and consider tricuspid valve surgery for patients with Stage C or D valvular disease.

Chronic Tricuspid Regurgitation (TR)

Chronic TR is often a functional result of **RV** (right ventricular) **dilation**, which can be caused by end-stage left ventricular failure, pulmonary embolism, pacemaker/implantable cardioverter-defibrillator leads (which prevent coaptation of tricuspid leaflets), or other causes of pulmonary hypertension. Chronic TR can also be caused by rheumatic heart disease, endocarditis, carcinoid, and congenital disease (Ebstein anomaly). Endocarditis affecting the tricuspid valve is typically seen in IV **drug abusers**, and it is often caused by *Staphylococcus*; also consider *Candida*.

Carcinoid tumor can result in damage to the tricuspid valve leaflets and significant TR. Carcinoid tumor more commonly affects right-sided heart valves (i.e., tricuspid and pulmonic valves) and typically implies a **hepatic tumor** if valvular involvement is present. The reason left-sided valves (i.e., mitral and aortic valves) are usually not involved is because the pulmonary vascular bed is generally quite effective in removing the active 5-HIAA products that lead to valve damage. If there is left-sided valvular involvement, suspect a huge tumor burden (with high hormonal levels that overwhelm the pulmonary vasculature) or metastases to the lungs themselves.

Physical exam with chronic TR: Patients have a holosystolic murmur along the lower left sternal border (increases with inspiration) that does **not** radiate to the axilla. Severe TR can cause a parasternal heave, liver pulsations (because the regurgitant blood is going back to the hepatic vein via the inferior vena cava), venous distention, ascites, and lower extremity edema (signs of RV failure). There are large, jugular *v* waves, reflecting the backflow through the tricuspid valve during ventricular contraction.

Diagnose with echocardiography. Treat the underlying disease. Antibiotic treatment is usually sufficient for endocarditis; the valve rarely needs to be replaced, **unless** the cause is *Candida*. Surgery is also indicated with severe destruction of the valve (Stage D valvular disease). Tricuspid surgery is considered in patients with Stage C (severe asymptomatic) TR who are undergoing other cardiac surgery.

Acute Tricuspid Regurgitation (TR)

Acute TR is extremely rare. It can occur after perforation of tricuspid leaflet (e.g., acute endocarditis) or destruction of one of its chordae tendineae (e.g., during performance of endomyocardial biopsy).

Pulmonic Stenosis (PS)

PS is virtually always **congenital**, and it typically does **not** progress! It is a fairly common congenital valve anomaly in adults. **Rarely**, it is caused by rheumatic heart disease or carcinoid tumor. It can cause right ventricular hypertrophy (due to increased afterload).

Physical exam with severe PS: Patient presents with an ejection click and a crescendo-decrescendo systolic murmur that changes in intensity with respiration.

If needed, the stenotic pulmonic valve can be treated with percutaneous balloon valvuloplasty.

Pulmonic Regurgitation (PR)

PR is typically secondary to pulmonary hypertension (e.g., primary pulmonary hypertension, secondary pulmonary hypertension due to cor pulmonale or mitral stenosis), but it may be a primary valve lesion (e.g., congenital, rheumatic heart disease, endocarditis, carcinoid tumor). The murmur of PR is diastolic, high pitched, and best heard over the 2nd and 3rd intercostal spaces. It classically is louder during inspiration, just like all right-sided murmurs.

Ebstein Anomaly

With Ebstein anomaly, the tricuspid septal leaflet is positioned lower in the ventricle than normal (**apically displaced**)—so the right atrium appears huge and the right ventricle small. TR murmur is common. A sound like a flapping sail may be heard due to the abnormally displaced septal leaflet. It is occasionally seen with ASD and with WPW syndrome. See [Atrial Septal Defect \(ASD\)](#) on page 13-82 and [Wolff-Parkinson-White \(WPW\)](#) on page 13-64.

Final Pearls about Murmurs

Know:

- Aortic stenosis—suprasternal notch thrill, systolic murmur, paradoxically split S₂
- Chronic aortic regurgitation—early diastolic, blowing, decrescendo murmur heard best at left sternal border, 3rd intercostal space, with patient leaning forward and exhaling; also, low-pitched late-diastolic rumble (Austin Flint)
- Mitral stenosis—opening snap; low-pitched, diastolic murmur at the apex

One last time: Valsalva decreases the murmur of aortic stenosis, increases the murmur of hypertrophic cardiomyopathy, and increases the murmur of mitral valve prolapse.

INFECTIVE ENDOCARDITIS (IE)

PREVIEW | REVIEW

- Are blood cultures more frequently positive with right-sided or left-sided endocarditis?
- Which of these require antibiotic prophylaxis: previous coronary artery bypass graft, ventricular septal defect, mitral valve prolapse (MVP) without murmur, MVP with murmur, prosthetic valve? Are your answers based on the 2017 AHA/ACC guidelines focused update?
- Does atrial septal defect require antibiotic prophylaxis before a dental procedure?

Endocarditis is infection of the inner part of the heart—usually, one or more heart valves. Fever is the most common symptom. Occasionally, endocarditis presents only with signs of embolic events, such as black toes or septic emboli to other organs. It can also present as an illness of smoldering, nonspecific symptoms (e.g., weight loss, fevers, chills, night sweats) or heart failure due to valvular insufficiency.

Classic physical exam findings include new regurgitant heart murmurs, Osler nodes (tender nodules on the pads of the digits), Janeway lesions (nontender erythematous/hemorrhagic macular/nodular lesions on the palms or soles), splinter hemorrhages ([Figure 13-31](#)), and Roth spots.



Figure 13-31: Splinter hemorrhage on fingernail in endocarditis

Blood cultures are positive in right- and left-sided endocarditis with equal frequency (95%). This is because there is a **constant level of bacteremia** in endocarditis, whereas with most other bacterial causes of fever, the bacteremia **precedes** the temperature spike.

Diagnosis of endocarditis is by the **Duke** criteria. Transesophageal echocardiography (TEE) is frequently used to help make the diagnosis.

Endocarditis can affect native valves or prosthetic valves. Endocarditis occurring within 2 months of prosthetic valve placement means the valve was seeded when it was implanted. This is harder to treat (especially if *Staphylococcus epidermidis*) than endocarditis that develops from transient bacteremia seeding the valve later. If there is no response to 1 round of adequate antibiotics, **replace** the valve.

If it has been > 2 months since the prosthetic valve placement, antibiotic treatment is generally sufficient. The valve must also be replaced if there is evidence of valve dehiscence or ring infection, or extension of

infection into adjacent heart tissue, which can manifest as a new heart block or a new bundle-branch block.

Surgery is indicated in endocarditis for refractory heart failure (usually from acute valve regurgitation), extension of the infection to the myocardium (or perivalvular abscess), failure of medical therapy, large vegetations with systemic emboli, or recurrent emboli despite adequate therapy.

More information on the causes, diagnosis, and prophylactic treatment of IE is in the [Infectious Disease](#) section.

Antibiotic Prophylaxis

Know the following from the 2017 AHA/ACC valvular heart disease guidelines focused updates on infective endocarditis.

Risk of infective endocarditis from medical procedures is very low; in fact, endocarditis is more likely to occur from bacteremia caused by brushing teeth than from medical procedures! In addition, antibiotics are not very effective for preventing endocarditis. Therefore, their use has been limited to only high-risk populations.

Indications for Prophylaxis

Know this well!

Prophylaxis is **no longer indicated** for routine gastrointestinal (GI)/genitourinary (GU) surgeries in the absence of active infection. Prophylaxis prior to dental procedures is indicated **only** for patients with specific cardiac conditions with **highest risk** for IE:

- Prosthetic valves
- Previous episode of endocarditis
- Congenital heart disease (CHD) if the following are present:
 - Unrepaired cyanotic CHD
 - Repaired CHD within 6 months of procedure
 - Repaired CHD with residual defects
- Cardiac transplant patients with valve regurgitation

You need to start prophylaxis in these patients if the dental procedure involves manipulation of gingival tissue, manipulation of the periapical region of teeth, or perforation of the oral mucosa (e.g., dental implants, tooth extractions, bone and gum grafting, root planing, scaling). Routine teeth cleaning does not warrant IE prophylaxis. Additionally, give antibiotics in the populations listed above if the patient is scheduled for an invasive procedure on **infected** tissue (e.g., surgery on skin or soft tissue with active infection, a procedure on GI or GU tract with ongoing GI or GU infection), or undergoing bronchial biopsy. There is **no indication** for IE prevention in patients who are undergoing vaginal or cesarean delivery or routine GI or GU procedures (e.g., colonoscopy, cystoscopy).

Prophylaxis is **no longer indicated** for bicuspid aortic valve, any atrial septal defect, ventral septal defect, native valvular stenosis or regurgitation, mitral valve prolapse (with or without murmur), or HOCM. The only exceptions that **do** require prophylaxis are those listed above: unrepaired cyanotic CHD, CHD repair within 6 months of procedure, and repaired CHD with a residual defect.

Antibiotic Selection for Prophylaxis

Know the following prophylaxis protocols ([Table 13-9](#)).

Table 13-9: Endocarditis Prophylaxis — Dental Procedures

Situation	Antibiotic	Regimen
Oral prophylaxis	Amoxicillin	2 g orally
Unable to take oral medications	Ampicillin or Cefazolin* or ceftriaxone	2 g IM/IV 1 g IM/IV
Allergic to penicillin	Clindamycin or Cephalexin* or Azithromycin or clarithromycin	600 mg orally 2 g orally 500 mg orally
Both allergic to penicillin and unable to take oral meds	Clindamycin or Cefazolin* or ceftriaxone	600 mg IM 1 g IM/IV

Note: Antibiotics (PO or IV) are given 30–60 minutes before the procedure.
*Cephalosporins should not be used if the PCN allergy is an immediate-type hypersensitivity reaction.

RHEUMATIC FEVER

PREVIEW | REVIEW

- Following acute rheumatic fever, how many years on average does it take for valvular dysfunction to occur, if it does?

Acute rheumatic fever (ARF) is a syndrome that occurs 2–4 weeks after acute group A streptococcal pharyngitis. In patients with pharyngitis, always swab throats for a strep screen.

ARF is rare in the U.S. and developed countries (<2 cases/100,000), but rheumatic fever remains common outside of the U.S. (> 470,000 cases/year worldwide). It occurs more frequently in overcrowded areas and is the most common cause of mitral and tricuspid **stenosis** worldwide. It can also cause AS, but the aortic valve is rarely involved alone and most commonly presents with MS. If you see both MS and AS, think of rheumatic fever as a cause.

[Table 13-10](#) on [page 13-58](#) lists the diagnostic criteria for rheumatic fever. Rheumatic fever is distinguished from rheumatoid arthritis by the **lack** of typical joint deformities and a **negative** rheumatoid factor. The associated carditis typically has **no** symptoms referable to the heart!

Table 13-10: Modified Jones Criteria for the Diagnosis of Rheumatic Fever

Major	Minor
Carditis (usually MR, TR, and/or AR)	Previous rheumatic fever
Polyarthrititis	Arthralgias
Chorea (nonrhythmic, involuntary movements)	Fever
Erythema marginatum	Acute phase reactants (high sed rate or WBC)
Subcutaneous nodules	ECG changes: prolonged PR interval

Diagnosis requires 2 major criteria or 1 major and 2 minor criteria and evidence of a preceding group A strep infection (positive strep test or rising or elevated [> 250 Todd units] ASO titers).

Treat group A *Streptococcus* with intramuscular (IM) or oral penicillin and consider ongoing prophylactic parenteral penicillin. In adults, administer 1.2 million units benzathine penicillin IM on diagnosis. For patients with evidence of carditis, this should be repeated monthly for 10 years or up to 21 years of age, whichever is longer. If there is residual heart disease, it should continue until 40 years of age. For patients with rheumatic fever without carditis, therapy is recommended to continue for 5 years or to 21 years of age, whichever is longer.

Up to 72% of children with ARF develop chronic valvular disease. Symptoms of valvular dysfunction occur, on average, 20 years following acute infection. See the [Rheumatology](#) section for more on ARF.

VALVE SURGERY

PREVIEW | REVIEW

- What are the major prognostic factors after valve surgery?

In general, valve surgery is indicated for any valve problem if the patient is **symptomatic at rest** (Stage D valvular disease) or asymptomatic with severe disease (Stage C valvular disease). Even though perioperative mortality is high, valve surgery is better than no surgery in patients with severe valve disease and ventricular failure, since the natural history in these cases is 100% early mortality.

Bioprosthetic valves are less durable (especially in young patients and those on hemodialysis) but do not require anticoagulation. These are indicated for patients > 70 years of age and those with contraindications to anticoagulation (e.g., chronic bleeding problems, ulcers). They also are often given to women of childbearing age to avoid the need for anticoagulants during pregnancy.

Mechanical valves are more durable than bioprosthetic valves. These are used for younger patients and **do** require anticoagulation. Either bioprosthetic or mechanical valves are reasonable in patients between 60 and 70 years of age.

Percutaneous balloon valvuloplasty is the procedure of choice in pulmonic stenosis and rheumatic mitral stenosis—but **not** aortic stenosis. This is because aortic stenosis has a very high short-term restenosis rate (6–12 months).

If surgery is required for mitral regurgitation (MR), do valve reconstruction **whenever possible** because it has better outcomes and less morbidity than mitral valve (MV) replacement. Reconstruction is valve repair and/or annuloplasty with an annuloplasty ring (because valve annulus can be dilated); it is especially useful for MV prolapse, ruptured chordae, flail leaflets, endocarditis, and annular dilation. **Valve replacement is usually necessary in MR due to rheumatic fever.**

Percutaneous transcatheter MV repair is possible using various devices (e.g., MitraClip device, Carillon Mitral Contour System). This procedure is ordinarily reserved for patients who are high risk for traditional repair. Similarly, percutaneous transcatheter aortic valve replacement (TAVR) is available for patients who are at high risk for surgery.

The major prognostic factors after valve surgery are **ejection fraction**, severity of **symptoms**, and **type** of valve surgery (valve repair is better than replacement). Echocardiography is best for checking for prosthetic valvular function. **TEE** is especially useful for checking MV prostheses. Fluoroscopy is also a useful tool for documenting leaflet motion in patients with mechanical valves, if valve dysfunction is suspected.

Regarding anticoagulation for mechanical valves, the only approved agent is warfarin. Direct oral anticoagulant agents (rivaroxaban, apixaban, dabigatran, and edoxaban) are not appropriate for mechanical valves. When anticoagulating for **mechanical aortic** valves, keep international normalized ratio (INR) at an average of 2.5 (if no additional risk factors for emboli) or 3.0 (if additional risk for emboli). For mechanical MVs, keep INR at an average of 3.0. Additional risk factors for thromboemboli that should be considered in the INR target include atrial fibrillation (A-fib), hypercoagulable state, left ventricular dysfunction, and prior thromboembolic event. A mechanical MV has a higher risk for a thrombus formation than a mechanical aortic valve (hence the higher INR goal for mechanical MVs). Use unfractionated heparin or low molecular weight heparin for all MV patients having warfarin withheld for surgery. Use aspirin 75–100 mg in all prosthetic valves, whether they are bioprosthetic or mechanical.

In summary, regarding antithrombotic therapy in prosthetic valves:

- Mechanical mitral valve—use aspirin 75–100 mg plus warfarin with average INR goal of 3.0.
- Mechanical aortic valve with risk factors for thromboembolism (such as A-fib, pulmonary embolism, deep vein thrombosis, hypercoagulable states)—use aspirin 75–100 mg plus warfarin with average INR goal of 3.0.
- Mechanical aortic valve with no risk factors for thromboembolism—use aspirin 75–100 mg plus warfarin with average INR goal of 2.5.

- Bioprosthetic valves (all of them, whether in mitral or aortic position)—use aspirin 75–100 mg.

Note: The valve used in TAVR is a bioprosthetic valve.

Figure 13-32 shows different prosthetic valves. Those used for valve replacement include mechanical types (of various designs) and bioprosthetic types (xenografts [i.e., grafts from nonhuman tissue] and allografts [i.e., grafts from human tissue]).

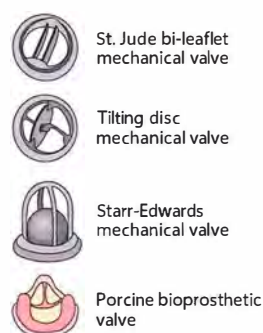


Figure 13-32: Prosthetic valve types

ARRHYTHMIAS

MECHANISMS OF ARRHYTHMIAS

The 3 usual mechanisms of abnormal rhythms are **reentry**, **triggered activity**, and **automaticity**. Reentry is the most common, causing atrioventricular node reentrant tachycardia (AVNRT), atrial flutter, and most ventricular tachycardias. AVNRT is the most common type of reentrant tachycardia and the most common supraventricular tachycardia (SVT). Be able to diagnose all rhythms based on ECG; some case studies are provided in [ECG – Analysis Summary on page 13-108](#).

BRADYARRHYTHMIAS

Slow heart rhythms can result from inadequate sinus node activation or a block of conduction at or below the atrioventricular (AV) node. Although bradycardia is normal in athletes, look for a pathologic cause when it is present in nonathletes. Get a 12-lead ECG to identify heart block (see [ECG – Analysis Summary on page 13-108](#)). Hypothyroidism is an important cause of bradycardia: Think of this in patients with weight gain, cold intolerance, and delayed reflexes. Medications that block the AV node may cause bradycardia; these include β -blockers, nonhydropyridine calcium channel blockers (e.g., diltiazem, verapamil), and adenosine. Digoxin toxicity causes bradycardia; think of this in a patient on digoxin with worsening renal function.

Patients with severe symptomatic bradycardia should be admitted and placed on telemetry. Admit the patient to a coronary care unit (CCU) if the ECG shows any of the following, as they are at risk for complete heart block:

- 2:1 AV block
- Long PR interval and wide QRS
- High-grade Mobitz 2 block
- Alternating right and left bundle-branch block

In the case of sinus node dysfunction, give atropine if hypotension develops or the patient becomes symptomatic.

Note that atropine does not work below the AV node, and therefore, generally does not help Mobitz 2 or complete heart block. The most likely source of block in these cases is **infranodal**, which does not respond to atropine. IV dopamine or isoproterenol, however, may temporarily improve AV nodal conduction in these cases. The definitive treatment for Mobitz 2 and complete heart block is a placement of a pacemaker. If permanent pacing is delayed (e.g., urgent surgery), use temporary or transcutaneous pacing. If transcutaneous pacing is used, be sure there is capture of the heart. The presence of muscular response does not, by itself, mean the heart is responding.

SICK SINUS SYNDROME

Sick sinus syndrome causes several sinoatrial node problems, including sinus **bradycardia**, sinus pauses/sinus arrest, and tachy-brady syndrome (typically baseline sinus bradycardia or sinus pauses with intermittent episodes of rapidly conducting atrial fibrillation/atrial flutter). These patients generally do **not** need electrophysiologic testing. Because prognosis is good, there are only 2 indications for treatment with a pacemaker:

- 1) Patient is symptomatic.
- 2) Patient has tachy-brady syndrome, and treatment of tachyarrhythmias might precipitate or worsen bradycardia.

HEART BLOCK

1st degree heart block: PR interval > 200 ms. Often caused by medications (e.g. digoxin, β -blockers) and generally requires no treatment.

2nd degree heart block (Mobitz 1, Wenckebach): gradually increasing prolongation of PR interval until QRS drops; return PR interval is shorter than last conducted PR interval. Grouped beating is seen on ECG. It can occur in periods of high vagal tone during sleep (obstructive sleep apnea) or in endurance athletes. It generally does not require treatment unless it is causing symptoms.

2nd degree heart block (Mobitz 2): abrupt loss of P-wave conduction to the ventricle with no evidence of gradual prolongation of the PR interval. Thus, there is no warning prior to the dropped beat. Generally, it indicates higher-grade AV block, and associated **symptoms** can necessitate **pacemaker** placement.

3rd degree heart block (complete heart block): None of the P waves are conducted to the ventricles, and there is often a regular, narrow junctional (40–60 bpm) or wide ventricular (20–40 bpm) escape rhythm. Look for cannon *a* waves due to lack of AV synchrony.

Permanent pacing is indicated if there is a Mobitz 2 or complete heart block—especially if symptomatic. See [Arrhythmias and Conduction Abnormalities on page 13-30](#) for more detailed pacing criteria after myocardial infarction (MI).

Complete heart block can be at the AV node or infranodal. AV node block typically has narrow QRS complexes, has escape focus rate > 40 bpm (usually 40–60 bpm), and is responsive to atropine. Infranodal block (involving the His-Purkinje system) usually has widening of the QRS complex.

Common causes of heart block are acute or chronic myocardial ischemia and infarction, cardiomyopathies, and fibrosis of aging. Other causes to consider, especially in young people with heart block, include Lyme disease, congenital heart disease, myocarditis, or infiltrate disease such as sarcoidosis or amyloidosis.

SUPRAVENTRICULAR ARRHYTHMIAS

PREVIEW | REVIEW

- What is the most effective immediate treatment for atrial flutter?
- What procedure can cure the most common types of atrial flutter with 85–95% success rate?
- In which circumstance is immediate DC cardioversion indicated for atrial fibrillation (A-fib)?
- What can happen after DC cardioversion to the patient who has A-fib with a slow rate? What intervention prevents this complication?
- According to the 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation, what is the recommended heart rate goal for most patients with A-fib treated with a rate control strategy?
- Which medication should you use to prevent postoperative A-fib in patients undergoing cardiac surgery?
- How is the CHA₂DS₂-VASc score calculated? At what score should you treat with warfarin/direct oral anticoagulants (unless contraindicated)?
- In which patient group is multifocal atrial tachycardia found?
- What is the treatment for acute A-fib in Wolff-Parkinson-White syndrome?

Sinus Tachycardia

Patients with sinus tachycardia (defined as a sinus rhythm of > 100 bpm) typically have an underlying pathology as an instigator. Fever, infection, pain, hypoxia, anemia, ongoing bleeding, and pulmonary embolism are possible causes. In addition to history and physical exam, start the workup for sinus tachycardia with an ECG, complete blood count (CBC), basic metabolic panel (BMP), and a thyroid-stimulating hormone test (TSH; to exclude hyperthyroidism).

Atrial Flutter

Typical (Type I) atrial flutter, the common form, has a characteristic atrial rate of 300 bpm (240–340 bpm), commonly with a 2:1 AV block. Look for atrial flutter in any ECG with a heart rate of 150 bpm; atrial flutter waves at 300 bpm with 2:1 AV block gives a heart rate of 150 bpm. At this rate there is usually no hemodynamic compromise unless there is coexistent coronary artery disease or heart failure.

Atrial flutter can be:

- **counterclockwise** rotation around the right atrium (most common), characterized by **negative** saw-tooth flutter waves in ECG leads II, III, and aVF (with positive deflection in V1) or
- **clockwise**, characterized by **positive** flutter waves in ECG leads II, III, and aVF (with prominent negative deflection in V1).

These 2 atrial flutter types share the same right atrial reentrant circuit around the cavotricuspid isthmus (circuit running between the inferior vena cava and the tricuspid valve).

Atrial flutter is generally an indication of underlying disease, most often either organic heart disease or pulmonary disease. Flutter is a relatively unstable rhythm and often spontaneously converts to either atrial fibrillation or a normal sinus rhythm.

AV block is usually 2:1 with a ventricular rate 50% of the atrial rate. If it is $\geq 3:1$, the cause is either medications or advanced AV conduction system disease. Atrial flutter (like atrial fibrillation) can cause systemic embolization, most notably transient ischemic attack (TIA)/stroke. Thus, **anticoagulation** needs to be considered in both disorders.

Vagal maneuvers or adenosine cannot terminate atrial flutter; however, they can slow the ventricular rate and assist diagnosis. Rule out pulmonary emboli (often multiple) and hyperthyroidism—especially if there is no history of heart or lung disease.

The most effective treatment for atrial flutter is synchronized direct current (DC) cardioversion. Always cardiovert if the patient is hemodynamically compromised. If the patient is hemodynamically stable and has not been anticoagulated, do transesophageal echocardiography (TEE) prior to cardioversion to exclude a clot (see [Anticoagulation for A-fib on page 13-63](#)).

Do not repeat DC cardioversion if the patient repeatedly reverts to atrial flutter.

Antiarrhythmic drugs can be used for medical cardioversion in nonemergent cases. IV **ibutilide** is **most effective** and is 1st line for pharmacologic cardioversion for atrial flutter; however, it can cause QT prolongation (8%) and torsades de pointes. Make sure K⁺ and Mg²⁺ levels are normal prior to administering ibutilide to minimize risk of torsades.

Procainamide, flecainide, and propafenone can be used as well, and can be given in an outpatient setting. See [Antiarrhythmic Therapy on page 13-67](#).

In patients with atrial flutter and preexcitation syndrome (Wolff-Parkinson-White syndrome [WPW]), **never give** digoxin, calcium channel blockers, or β -blockers. See [Wolff-Parkinson-White \(WPW\) on page 13-64](#). Blocking the AV node can lead to 1:1 conduction through the accessory pathway, which is extremely dangerous.

Radiofrequency ablation is a definitive treatment that can **cure** the most common types of atrial flutter (success rate 85–95%).

Atrial Fibrillation (A-fib)

A-fib is the most common sustained arrhythmia. The ventricular rhythm is irregularly irregular, with a ventricular rate of 120–180 bpm in the absence of drug therapy. Many patients with A-fib have structural heart disease. It is common with hypertension, heart failure, valvular heart disease, coronary artery disease, chronic lung disease, and obstructive sleep apnea.

A-fib can be classified as **first detected** (only 1 diagnosed episode), **paroxysmal** (terminates spontaneously or with intervention within 7 days), **persistent** (continuous for > 7 days), or **permanent** (> 12 months with no plan to restore sinus rhythm).

The symptoms of A-fib vary widely between patients.

Some patients are asymptomatic; others have severe, functionally disabling symptoms. The diagnosis of A-fib is usually made by ECG. With paroxysmal A-fib, ECG may be normal; in this case, order ambulatory ECG (Holter) monitoring. Always work up new-onset A-fib with an echocardiogram, TSH, and CMP to check electrolytes. These initial results will guide further testing.

With **new-onset** A-fib or in A-fib not responsive to the usual treatment (described in [Treatment of A-fib](#)), consider hyperthyroidism, untreated or undertreated obstructive sleep apnea, hypomagnesemia, alcoholism/cocaine abuse, excessive caffeine (including energy beverages), and nicotine as possible causes.

A-fib complications include **embolic** events—mainly stroke—and tachycardia-induced **cardiomyopathy**.

Treatment of A-fib

Rhythm Control vs. Rate Control

Remember that any hemodynamically unstable tachycardia, including atrial fibrillation, should be cardioverted emergently! This includes patients with severe ongoing myocardial ischemia, symptomatic hypotension, angina, or heart failure.

For stable A-fib, you have 2 choices for treatment:

- 1) Rhythm control (restoration and maintenance of sinus rhythm)
- 2) Rate control (control of ventricular response)

There are no significant differences in mortality or morbidity between the 2 treatments. Rate control is the common strategy for asymptomatic or minimally symptomatic patients, while rhythm control is often selected for significantly symptomatic and younger patients.

A-fib Rhythm Control — DC Cardioversion

DC cardioversion is the most effective method to restore sinus rhythm. Pharmacologic cardioversion is less likely to be successful, and outcomes vary based upon the antiarrhythmic drug used and clinical scenario. If possible, DC cardioversion should be carried out under sedation with appropriate cardiac and hemodynamic monitoring.

Again, **emergent/urgent DC cardioversion** is recommended for patients with hemodynamic instability (angina pectoris, MI, shock, or pulmonary edema), ongoing myocardial ischemia, symptomatic hypotension, angina or heart failure, and WPW syndrome with rapid ventricular rate.

Important points regarding DC cardioversion:

- With **slow** A-fib, consider inserting a temporary pacemaker **before** DC cardioversion because the patient could have sinus node disease and may have asystole after cardioversion.
- If time of A-fib onset is unknown or A-fib is known to be present > 48 hours, you must do TEE (to rule out left atrial thrombus) or at least 3 weeks of anticoagulation prior to cardioversion, due to the risk of thromboembolism.
- **TEE-guided cardioversion** allows you to rule out thrombus at the time of cardioversion. It is especially useful when the time of onset of the A-fib is unclear. It is fast and cost effective.
- Just as with atrial flutter, do **not** continue DC cardioversion if the patient repeatedly goes right back into A-fib shortly after being shocked.

Note: In what other scenarios do you not shock a patient with an abnormal tachycardic atrial rhythm (but who is stable hemodynamically)? Digitalis intoxication and hypokalemia.

A-fib Rhythm Control — Pharmacologic Cardioversion

When attempting **pharmacologic cardioversion**, the drug used is based on **duration** of symptoms:

- For A-fib > 7 days:
 - 1st line: dofetilide (must be initiated in the hospital)
 - 2nd line: amiodarone (oral or IV) or ibutilide (IV)
- For A-fib < 7 days:
 - 1st line: dofetilide, flecainide, ibutilide, or propafenone (previously, dronedarone; see caution, below)
 - 2nd line: amiodarone (Exception: If < 48 hours and **poor** cardiac function, amiodarone is 1st line.)

As with DC cardioversion, when A-fib has been present for more than 48 hours or duration is unknown, you must first rule out atrial thrombus with TEE or do anticoagulation for 3 weeks prior to pharmacologic cardioversion.

Caution: Do **not** prescribe dronedarone to patients who have:

- Class IV heart failure or those who have had decompensated heart failure in the past month, especially if LVEF < 35% (it increases mortality in these patients),
- been taking dabigatran for anticoagulation with a creatinine clearance < 30 mL/min (this may increase the serum concentration of dabigatran to dangerously high levels),
- a history of pulmonary toxicity on amiodarone, or
- elevated LFTs.

Maintenance Drugs for Rhythm Control

Pharmacological therapy can be useful to maintain sinus rhythm in patients with recurrent paroxysmal or permanent A-fib. Before initiating antiarrhythmic drug therapy, treat precipitating or reversible causes of A-fib (e.g., thyroid disorders, electrolyte abnormalities). Drug selection is based on the presence of structural heart disease (safety) and, to a lesser degree, on efficacy:

- No or minimal heart disease: Use flecainide, propafenone, sotalol, dofetilide, or dronedarone; if ineffective, then use amiodarone or catheter ablation (see below).
- Heart failure (ejection fraction [EF] < 35%): Use amiodarone or dofetilide (definitely **not** dronedarone!); if ineffective, use catheter ablation.
- Coronary artery disease: Use dofetilide, dronedarone, or sotalol; if ineffective, then use amiodarone or catheter ablation. Avoid Class Ic agents (e.g., flecainide, propafenone) if EF is markedly diminished, due to increased mortality in this population.
- Hypertension:
 - Left ventricular hypertrophy (LVH) present: Use amiodarone; if ineffective, then use catheter ablation.
 - LVH not present: Use flecainide, propafenone, or sotalol. If these fail, then go to amiodarone, dofetilide, or catheter ablation.

Use of Class Ic agents (e.g., flecainide, propafenone) for A-fib: The unopposed use of Class Ic agents (i.e., without concomitant AV nodal blocking agents) can organize atrial fibrillation into atrial flutter conducting to the ventricles much more rapidly. This rapid conduction could degenerate into ventricular tachycardia (VT) or ventricular fibrillation (VF). To avoid this potentially fatal event, always use Class Ic agents with AV nodal agents such as β -blockers, nondihydropyridine calcium channel blockers, or digoxin (see [Drugs on page 13-67](#) under Antiarrhythmic Therapy).

Dofetilide and sotalol require hospital monitoring to initiate therapy.

Catheter ablation (which includes radiofrequency ablation and cryothermal ablation) can help maintain sinus rhythm for selected patients with symptomatic, paroxysmal A-fib who have failed treatment with an antiarrhythmic drug, have a normal or mildly dilated left atrium, normal or mildly reduced left ventricular (LV) systolic function, and no severe pulmonary disease. Catheter ablation is less useful (yet can be considered) in treatment of patients with symptomatic persistent A-fib.

A-fib Rate Control

The 2014 ACC/AHA/HRS Guideline for the Management of Patients with Atrial Fibrillation states that a strict rate-control strategy (resting heart rate < 80 bpm) is reasonable for management of symptomatic A-fib. However, a lenient rate-control strategy (resting heart rate < 110 bpm) may also be okay if symptoms are controlled and LV function is normal. Uncontrolled tachycardia may, over time, result in a reversible decline in ventricular performance.

Use β -blockers (e.g., atenolol, metoprolol) or nondihydropyridine calcium channel blockers (e.g., verapamil, diltiazem) for rate control at rest and with exercise. Digoxin is useful to control the heart rate at rest in patients with A-fib with HF, patients with LV dysfunction, or sedentary individuals. Digoxin can have a synergistic effect for rate control when combined with β -blockers or nondihydropyridine calcium channel blockers. Be sure to watch for bradycardia after conversion because the drugs used to slow the rapid response may excessively slow the sinus rate.

A-fib with HF: In the acute setting in patients without preexcitation (i.e., WPW), use IV β -blockers (e.g., esmolol, metoprolol, propranolol) or diltiazem to slow ventricular rate, or amiodarone or digoxin to slow ventricular rate and possibly restore sinus rhythm. Use nondihydropyridine calcium channel blockers (e.g., verapamil, diltiazem) **with caution** in patients with hypotension or HF because of negative inotropic effects.

Remember: An accessory pathway, a.k.a. preexcitation, is usually indicated by a short PR interval and a delta wave on ECG (see [Wolff-Parkinson-White \(WPW\) on page 13-64](#)).

If exertional symptoms related to A-fib are present, assess heart rate control during exercise, adjusting pharmacological treatment to keep the rate in physiological range.

Radiofrequency ablation of the AV node with subsequent **permanent** pacing is a treatment option for patients with refractory A-fib and for those who cannot tolerate the medications needed for rate or rhythm control. This strategy provides definitive rate control but does **not** cure the underlying atrial fibrillation—hence, patients still require anticoagulation.

In many patients, A-fib originates as abnormal impulses arising in the **pulmonary veins**. Radiofrequency ablation,

with the goal of electrical isolation of the pulmonary veins, is becoming increasingly popular in treating recurrent, drug-refractory, symptomatic A-fib, although it is not yet established as 1st line therapy. Some patients may require repeat procedures and will often continue to require antiarrhythmic therapy and anticoagulation, at least in the short term.

Postoperative A-fib

For patients undergoing cardiac surgery, give an oral β -blocker to prevent postoperative A-fib (unless contraindicated). For those who develop postoperative A-fib, achieve rate control with AV nodal blocking drugs (β -blockers, calcium channel blockers, or digoxin). Make sure K^+ and Mg^{2+} levels are normal. Remember, fever and acute pain can exacerbate an underlying propensity for A-fib. Routine postoperative amiodarone is not indicated for the prevention of A-fib but is reasonable if postoperative A-fib persists despite initial treatment.

Anticoagulation for A-fib

Before and After Cardioversion

If it has been **< 48 hours** since the onset of A-fib, most patients can be safely cardioverted without any preceding anticoagulation.

As noted earlier, if it has been **> 48 hours** since the onset of A-fib (or duration of A-fib is unknown) and the patient is **stable**, you **must** achieve adequate anticoagulation $\times$ 3 weeks before you attempt cardioversion. As an alternative to preceding anticoagulation, it is reasonable to perform TEE, and if there is no identifiable thrombus, perform a cardioversion.

After cardioversion: Treat with low molecular weight or unfractionated heparin until INR = 2–3 on warfarin. As an alternative to heparin/warfarin, one of the direct oral anticoagulants (DOACs) can be considered (see [Anticoagulation](#)).

Anticoagulation

Antithrombotic therapy to prevent thromboembolism is recommended for all patients with A-fib (irrespective of rate or rhythm control strategy), except for those with lone A-fib (< 60 years of age without heart disease and without risk factors) or those with contraindications to anticoagulation. The selection of the antithrombotic agent should be based upon the absolute risk of stroke vs. bleeding. Patients with rheumatic mitral stenosis or prior thromboembolism are at highest risk. Patients with high fall risk or with end-stage kidney disease on dialysis are at increased risk of bleeding complications. Warfarin has been considered the safest agent in renal failure patients, but some of the DOACs have been used safely in non-randomized trials. For patients with nonvalvular A-fib (without rheumatic mitral stenosis or prosthetic valves), the **CHA₂DS₂-VASc** scoring system is often used for risk stratification (see [Table 13-11](#) and [Table 13-12](#)).

Table 13-11: The CHA₂DS₂-VASc Scoring System

CHA ₂ DS ₂ -VASc Abbreviation	Points
Congestive HF during last year or EF < 35% (any history)	1
Hypertension (prior history)	1
Age $\geq$ 75 years	2
Diabetes mellitus	1
Stroke/TIA/thromboembolic event	2
Vascular disease (prior MI, PAD, or aortic plaque)	1
Age 65–74 years	1
Sex category = female	1
Maximum Score	9

Table 13-12: Risk of Stroke Associated with CHA₂DS₂-VASc Scores

CHA ₂ DS ₂ -VASc Score	Unadjusted Ischemic Stroke Rate (% Per Year)
0	0.2%
1	0.6%
2	2.2%
3	3.2%
4	4.8%
5	7.2%
6	9.7%
7	10.8%
8	11.2%
9	12.2%

Medications based on CHA₂DS₂-VASc score:

- 0 points = aspirin (ASA) alone
- 1 point = oral anticoagulation or ASA
- $\geq$ 2 points = oral anticoagulation

Oral anticoagulation can be achieved with vitamin K antagonists such as warfarin or with direct oral anticoagulants (DOACs)—e.g., dabigatran, rivaroxaban, apixaban, edoxaban. DOACs do not require monitoring INR; however, they should not be used in patients with prosthetic valves, rheumatic mitral stenosis, severe chronic kidney disease (with the exception of apixaban and edoxaban), and advanced liver disease.

Multifocal Atrial Tachycardia (MAT)

MAT is mainly diagnosed by ECG criteria of an irregular atrial rate > 100 bpm with P waves of at least 3 distinct morphologies.

MAT is usually seen in patients with pulmonary disease and can be a result of **theophylline** use. MAT can also be caused by very low K^+ or Mg^{2+} .

Therapy is directed at the underlying illness. If medications are necessary, calcium channel blockers or amiodarone might be useful. Digoxin is of no use in MAT! It can actually worsen it, in addition to causing digoxin-toxic arrhythmias.

Supraventricular Tachycardia (SVT)

SVT is a narrow QRS complex tachycardia originating above the ventricles. Rate is typically 150–250 bpm (although it can be slower or faster). SVT can be a wide complex if there is an underlying bundle-branch block or in the case of antidromic WPW (see Wolff-Parkinson-White (WPW)). Most SVTs are due to a reentrant mechanism. The most common SVT is AV node reentrant tachycardia (AVNRT). The presence and position of P waves with respect to QRS can help distinguish the different SVT types:

- If no P wave is seen (buried in QRS) or is seen at the end of the QRS (very short RP interval), the patient likely has AVNRT. Representing 60–70% of regular SVT, AVNRT is the most common reentrant tachycardia.
- If a P wave is somewhere in the ST segment (short RP interval, usually < 70 ms), consider AV reentrant tachycardia ([AVRT]; 20–30% of regular SVT).
- If a P wave is seen after a T wave (long RP interval), atrial tachycardia (10% of regular SVT) is most likely.

For acute management of SVT, treatment options include vagal maneuvers, β -blockers, adenosine, or calcium channel blockers.

For long-term therapy, either radiofrequency ablation or medical therapy is an effective 1st line option. Situations where ablation is preferred include hemodynamic instability, severe symptoms, failed medical therapy, high-risk occupations (e.g., pilots, bus drivers), and patient preference. If medical therapy is chosen, β -blockers, calcium channel blockers, or digoxin are 1st line options, followed by antiarrhythmic drugs (typically flecainide or propafenone if there is no structural heart disease).

Wolff-Parkinson-White (WPW)

In WPW (a.k.a. preexcitation syndrome), ECG shows tachycardia with a short PR interval (< 0.12 seconds) due to a delta wave. QRS duration is > 0.12 seconds because of the fusion between the impulse that uses the normal conduction system and the impulse that uses the abnormal (accessory) pathway, which bypasses the AV node. This bypass tract (accessory pathway) conducts faster than the AV node. This portion of the electrical current reaches the ventricle sooner than the current from the AV node, producing the delta wave on the ECG. This impulse preexcites the ventricle—hence the alternative name preexcitation syndrome. Occasionally, the accessory pathway is concealed and the delta wave is not visible. An unusual cause of WPW can involve Ebstein anomaly of the tricuspid valve (more under Ebstein Anomaly on page 13-56).

Arrhythmias related to WPW include:

- Orthodromic AVRT—a narrow QRS complex regular tachycardia, which uses the AV node antegrade and accessory pathway node retrograde. Note that the retrograde P wave will be > 100 ms behind the R wave (RP interval), differentiating it from AVNRT.
- Antidromic AVRT—wide QRS complex regular tachycardia, which uses the accessory pathway node antegrade and AV node retrograde
- Atrial fibrillation—irregularly irregular with a wide QRS complex tachycardia. A-fib impulses are conducted along the accessory pathway antegrade.

Treatment of accessory pathways: Many patients have a completely asymptomatic accessory pathway and no dysrhythmias. Patients with an accessory pathway and symptoms of tachycardia (a.k.a. WPW syndrome) can be treated with vagal maneuvers, adenosine, β -blockers, or calcium channel blockers—same as any SVT! In these cases, the impulses are moving down the normal conduction system and returning via the accessory pathway to complete the circuit. Never treat acute A-fib in WPW with digoxin, verapamil, β -blockers, and especially adenosine. Although verapamil, β -blockers, and digoxin increase the refractory period in the AV node, they can preferentially enhance conduction down the accessory pathway and precipitate ventricular fibrillation (V-fib). Adenosine will block the AV node altogether, making V-fib an even higher risk.

Instead, treat acute A-fib in WPW with IV procainamide, ibutilide, or amiodarone. Shock if there are any signs of hemodynamic deterioration in any WPW tachyarrhythmia; especially watch those with ventricular rate > 285 bpm because they are at greatest risk of V-fib.

Definitive treatment is by electrophysiology-guided radiofrequency ablation of the accessory pathway. Without treatment, WPW syndrome carries a low but definitive risk of sudden death.

VENTRICULAR ARRHYTHMIAS

PREVIEW | REVIEW

- On an ECG, premature ventricular contractions (PVCs) are often followed by what type of pause?
- Ventricular tachycardia (VT) is defined as ≥ 3 sequential QRS complexes of ventricular origin occurring at what heart rate?
- List the ECG criteria consistent with VT.
- With which type of tachycardia should you never use verapamil?
- Implantable cardioverter-defibrillators are recommended for primary prevention in which situations with ischemic and nonischemic cardiomyopathy?
- Which antiarrhythmic drugs can cause torsades de pointes by prolonging the QT interval?
- What is the treatment for torsades de pointes?

Premature Ventricular Contractions (PVCs)

PVCs are common and are seen in up to 75% of people who undergo Holter monitoring. Palpitations are the most common symptom, though many patients are completely asymptomatic. Dizziness can occur if the stroke volume is low due to decreasing ventricular filling. Note that the first step in evaluating a person with episodic palpitations is to put them on a 24-hour Holter monitor. This often identifies the cause of the palpitations. Other causes of palpitations include nonsustained ventricular tachycardia and premature atrial complexes.

On ECG, PVCs often have a **compensatory** pause; that is, the time between P waves on either side of the PVC = 2 PP intervals. The compensatory pause occurs because PVCs do not reset the sinoatrial node, so the underlying sinus rhythm continues unaltered before and after the PVC.

PVCs are classified as simple or complex. Simple PVCs occur **after** the T wave, are single, uniform in morphology, and have a constant interval between the PVC and the preceding P wave (coupling interval). Complex PVCs occur in pairs or triplets, may occur within the T wave, have different morphologies, and have different coupling intervals. Asymptomatic or minimally symptomatic, simple PVCs do **not** need to be treated if LV function is normal and there is no structural heart disease. Complex PVCs (pairs, triplets) also do **not** need to be treated if the patient is **asymptomatic** and has **no** heart disease! Symptomatic PVCs in an otherwise normal heart are treated only if the symptoms persist and are intolerable. Tolerance of symptoms varies widely. In the case of underlying heart disease, PVCs need to be investigated further and treated depending on severity of disease and symptoms.

Without treatment, most patients have spontaneous resolution or improvement. If you do attempt treatment (β -blockers are 1st line), the PVCs should decrease by 80% for the treatment to be considered successful—otherwise, stop treatment.

Frequent PVCs (> 10/hour) in a patient who has had an MI and has an ejection fraction of < 35–40%, indicates a **high risk of sudden cardiac death**—especially if they are sequential.

Ventricular Tachycardia (VT)

ECG Findings

Study tip: Now is a good time to review ventricular tachycardias vs. SVT with wide QRS complexes due to aberrant conduction (WPW or bundle-branch block; refer to **Supraventricular Tachycardia (SVT)** and **Wolff-Parkinson-White (WPW)**).

Ventricular tachycardia (VT) is defined as ≥ 3 sequential QRS complexes of ventricular origin at a rate of ≥ 100 bpm. Based on duration and symptoms, VT can be defined as **nonsustained** (duration of < 30 seconds) or **sustained** (duration of > 30 seconds or causes hemodynamic collapse in < 30 seconds). VT can be monomorphic or polymorphic.

Monomorphic VT is generally regular in rate and appearance. It needs to be differentiated from SVT with aberrant conduction, pacing, and QRS changes due to severe hyperkalemia. The majority of patients with **monomorphic** VT have **structural** heart disease (particularly ischemic heart disease). VT occurring in otherwise structurally normal hearts is considered idiopathic and has much better prognosis. The most common idiopathic VT is right ventricular outflow tract (RVOT) VT.

Know the ECG criteria for VT:

- AV dissociation
- Fusion and capture beats
- Northwest axis (between -90° and $+/-180^\circ$; see **Figure 13-35 on page 13-85**)
- Positive or negative concordance in precordial leads (Recall concordance is when QRS complexes in all 6 precordial leads are monophasic with the same polarity.)
- Absence of rS complex in all precordial leads
- If rS is present, r to S time > 100 ms
- QRS width of > 140 ms with an RBBB pattern
- QRS width > 160 ms with an LBBB pattern

If a patient with a history of structural heart disease develops a wide QRS complex regular tachycardia, VT is significantly more likely than SVT.

VT can also be bidirectional, with the complexes alternating in direction; this is usually due to **digitalis** intoxication but also can be seen **after MI** and in a relatively rare genetic condition called catecholaminergic polymorphic ventricular tachycardia.

Polymorphic VT generally has an irregular ventricular rate and polymorphic QRS morphology. QRS complexes appear to twist around an isoelectric axis. Duration of polymorphic VT is typically brief; however, it can be sustained and can degenerate into VF. It can occur in patients with prolonged QT interval (torsades de pointes) or in patients with normal QT interval (usually in the setting of ischemia/MI).

Treatment

For sustained **monomorphic** VT, do the following:

- Stable—give IV amiodarone.
- Hemodynamically compromised—shock first (electrical cardioversion); if refractory, give IV amiodarone/procainamide.
- VT with **acute MI**—most use amiodarone first. IV lidocaine can be useful.

For sustained **polymorphic** VT, do the same as monomorphic, except:

- IV β -blockers if ischemia is suspected or cannot be excluded
- Urgent cath if ischemia is suspected

- Do not use IV amiodarone if there is QT prolongation.
- Assess for torsades de pointes. (See [Torsades de Pointes](#).)

Never use verapamil with any wide-complex tachycardias in the emergency setting. 30% of those with ventricular tachycardia will rapidly deteriorate!

For RVOT VT, do the following:

- Terminate acutely with adenosine.
- Use β -blockers or calcium channel blockers (CCBs) for long-term management. (Remember to avoid CCBs for other wide-complex tachycardias.)

Implantable Cardioverter-Defibrillators (ICDs)

ICDs can be used for secondary (after event occurs) or primary prevention (patients at high risk) of ventricular fibrillation (VF) and sustained VT.

The following are indications for ICD placement from the 2013 ACCF/HRS/AHA/ASE/HFSA/SCAI/SCCT/SCMR Appropriate Use Criteria for Implantable Cardioverter-Defibrillators and Cardiac Resynchronization Therapy:

- Survivors of cardiac arrest due to VF or hemodynamically unstable sustained VT, after evaluation has excluded any completely reversible causes
- Patients with structural heart disease and spontaneous sustained VT (> 30 seconds), whether hemodynamically stable or unstable
- Patients with syncope of undetermined origin with:
 - long QT syndrome,
 - Brugada pattern (concave down ST-segment elevation > 2 mm in > 1 of V1-V3 followed by a negative T wave), or
 - catecholaminergic polymorphic VT.
- Patients with LVEF $\leq$ 35% due to prior MI who are at least 40 days post-MI and are in the NYHA functional Class II or III; or, with LVEF < 30% and in the NYHA functional Class I
- Patients with LVEF $\leq$ 35% due to nonischemic dilated cardiomyopathy (DCM) and who are in the NYHA functional Class II or III
- Patients with nonsustained VT due to prior MI, LVEF $\leq$ 40%, and inducible VF or sustained VT at electrophysiologic study

Torsades de Pointes

Know this topic! Torsades de pointes is a common type of **polymorphic** VT. It occurs in patients with prolonged QT interval (congenital or acquired). Acquired forms are most often drug induced.

Drugs that can cause torsades de pointes are:

- Class Ia antiarrhythmic drugs (e.g., quinidine, procainamide, disopyramide)
- Class III antiarrhythmics (e.g., sotalol, dofetilide)
- Haloperidol

- Antidepressants (e.g., most tricyclic antidepressants, citalopram, escitalopram, venlafaxine, mirtazapine)
- Antibiotics (e.g., macrolides, fluoroquinolones)
- Antihistamines (e.g., astemizole, terfenadine)
- Antifungal agents (e.g., ketoconazole)

Torsades de pointes can be triggered by bradycardia, very low K^+ , or very low Mg^{2+} in patients with prolonged QT.

Treat torsades de pointes with:

- DC cardioversion (for sustained episodes)
- Mg^{2+} sulfate 2–4 grams IV over 10–15 minutes
- Correction of hypokalemia
- Correction of bradycardia (isoproterenol or pacing)

Never treat with Class Ia or Class III antiarrhythmic drugs.

To prevent recurrence of torsades de pointes: 1) discontinue any offending medications, 2) prevent bradycardia with isoproterenol or overdrive pacing, and 3) supplement K^+ and Mg^{2+} .

Nonsustained Ventricular Tachycardia (NSVT)

NSVT is defined as asymptomatic VT (> 3 sequential PVCs with HR > 100 bpm) lasting for < 30 seconds.

NSVT increases risk of death in patients with heart disease, particularly ischemic cardiomyopathy. NSVT patients are at risk of sustained VT and sudden death when:

- they have ischemic cardiomyopathy (LVEF < 40%) and
- **sustained VT** can be **induced** at electrophysiologic testing.

These patients benefit from ICD implantation.

Patients with NSVT without structural heart disease have good prognosis and they do not require further management.

Ventricular Fibrillation (VF)

VF is a fatal arrhythmia. It initially may look like polymorphic VT with its rapid irregular rate and polymorphic complexes, but there is no true twisting around an axis, and it will quickly become fine with less amplitude. **Acute cardiac life support (ACLS) must be initiated immediately, with urgent defibrillation.** Survival depends on rapid recognition of the rhythm, defibrillation, and reversal of any inciting factors, such as electrolyte abnormalities, acute MI, acute hypoxia, pulmonary embolism, electrocution, pericardial tamponade, drugs, or acidosis.

PACEMAKERS

PREVIEW | REVIEW

- Under which conditions is permanent pacing recommended?

Permanent pacing is indicated for patients with:

- Symptomatic bradycardia (including chronotropic incompetence if symptomatic and not reversible)
- Sinus node dysfunction (sick sinus syndrome)
- High-grade AV block

Even in the absence of symptoms, permanent pacing is appropriate in patients with complete heart block and advanced (i.e., **not** Wenckebach) Type 2 second-degree AV block (particularly with wide QRS).

The most common pacemaker (Table 13-13) is **DDD**, which stands for dual-chamber paced, dual-chamber sensed, and dual response to sensing: triggered and inhibited. Most clinicians use DDD unless the patient is in chronic, slow atrial fibrillation. The DDD is the most physiologic and provides better exercise tolerance. The addition of R as the 4th letter in the code indicates that the pacing rate is responsive to exercise (i.e., rate-modulated), which makes it even more physiologic.

Standard pacemakers pace only the right heart (atrium, ventricle, or both). With biventricular pacing, also known as cardiac resynchronization therapy, both the right and the left ventricles are paced. This is accomplished by placing a lead in the coronary sinus to pace the left ventricle. Biventricular pacing improves long-term LV function in patients with LBBB and reduced EF, and it is indicated in this patient group—even if asymptomatic.

Pacemaker syndrome (lightheadedness and/or syncope) can occur with single-chamber ventricular pacing and is commonly **cured** by dual-chamber (DDD) pacers, which restore the ventricular timing.

Pacemaker-mediated tachycardia can occur when paced ventricular complexes are sensed by the atrial lead and then trigger subsequent ventricular paced beats; this cycle can continue indefinitely.

ANTIARRHYTHMIC THERAPY

PREVIEW | REVIEW

- How long do you have to wait for an antiarrhythmic to reach steady-state therapeutic levels?
- When is it not okay to use verapamil? When is it okay?
- Which antiarrhythmic drug can cause lupus?
- Name the side effects seen with amiodarone.

- Which test is the best indicator of digoxin toxicity?
- For which condition is radiofrequency ablation the treatment of choice?

Drugs

There are 4 classes of drugs used in antiarrhythmic therapy:

- **Class I:** Sodium channel blockers that slow electrical conduction in the heart
 - **Ia:** **quinidine, procainamide, disopyramide**—slow conduction velocity, prolong action potential duration, and can prolong QT interval. Use this class of drugs for atrial fibrillation and SVT.
 - **Ib:** **lidocaine, tocainide, mexiletine, phenytoin**—shorten action potential duration slightly with no significant QT prolongation. These drugs have traditionally been used to treat ventricular arrhythmias
 - **Ic:** **flecainide** and **propafenone**—slow conduction velocity without effect on action potential duration or QT interval. This class of drugs is not approved for ventricular arrhythmias.
- **Class II:** **β -blockers**—decrease heart rate and blood pressure by blocking impulses that can cause irregular heart rhythm and decreasing hormonal effects (e.g., adrenaline) on the heart.
- **Class III:** **amiodarone, sotalol**, and the relatively new agents **dofetilide** and **dronedarone**—prolong the action potential by **potassium** channel blockade. These agents can cause QT prolongation. Side effects of dronedarone are discussed under [Major Side Effects of Antiarrhythmic Drugs \(AADs\)](#) on page 13-68.
- **Class IV:** **calcium channel blockers**, especially verapamil and diltiazem—slow inward current. They decrease heart rate and blood pressure like Class II.

Notes:

- With antiarrhythmic drugs (AADs), always wait 4–5 half-lives before determining whether a drug is effective.
- **All** AADs have a **proarrhythmic** potential.
- Per the 1989 CAST study, there is evidence that Class Ic AADs (e.g., flecainide) decrease survival in patients post-MI with reduced EF and PVCs.
- The only AAD that has a proven mortality benefit after an ST-elevation MI is a β -blocker.

Table 13-13: Permanent Pacemaker Abbreviation Codes

1st letter = chamber(s) paced—V/A/D (ventricle, atrium, or dual [V + A])

2nd letter = chamber(s) sensed—V/A/D/O (ventricle, atrium, dual [V + A], or none)

3rd letter = mode(s) of response—T/I/D/O (triggered, inhibited, dual [T + I], or none)

4th letter = programmability—P/M/C/R/O (programmable rate and output, multiprogrammable, communicating, rate-modulated, or none)

5th letter = arrhythmia control—P/S/D/O (pacing, shock, dual [P + S], or none)

- **Mexiletine** is effective in most patients who respond to lidocaine for ventricular arrhythmias.
- Quinidine **increases** digoxin levels.
- Even though amiodarone causes QT prolongation it rarely causes torsades de pointes.
- **Avoid** verapamil with:
 - A-fib or atrial flutter occurring in WPW
 - Wide-complex tachycardias
 - β -blockers—relative contraindication because they are both negative chronotropes and negative inotropes
 - Hypertrophic obstructive cardiomyopathy (HOCM) with hypotension or severe dyspnea at rest
- Okay to use verapamil in these cases:
 - Rate control in A-fib or atrial flutter in an otherwise healthy heart
 - MAT
 - SVT (2nd choice after adenosine)
 - Symptomatic hypertrophic cardiomyopathy (but look above regarding avoiding verapamil in HOCM with hypotension or severe dyspnea at rest)
 - Severe, concentric LVH
 - Hypertension

Digoxin and Adenosine

Digoxin is **not** in the above classes of antiarrhythmics, but it has antiarrhythmic effects and occasionally is used for this. Digoxin works by inhibiting membrane ATPase. It increases contractility and slows AV conduction and HR. Digoxin is usually reserved for treating severe heart failure.

Adenosine is also **not** in the above groups. Adenosine slows conduction in the AV node and is used for conversion of SVT (AV node reentry) to normal sinus rhythm. It also induces coronary artery vasodilation and is used in cardiac perfusion imaging. It depresses LV function, but it has such a **short half-life** it can be used even in patients with decreased LV function.

Major Side Effects of Antiarrhythmic Drugs (AADs)

Know this topic! All AADs are potentially arrhythmogenic. Especially remember the following:

- **Class Ia:**
 - **Quinidine**—prolongs the QRS complex and the QT interval, occasionally leading to torsades de pointes. Also can cause diarrhea, autoimmune thrombocytopenic purpura (rare), and cinchonism (hearing loss, tinnitus, and psychosis).
 - **Procainamide**—prolongs QRS and QT, and also causes blood dyscrasias, such as agranulocytosis, neutropenia, and thrombocytopenia, in ~ 0.5% of patients. Procainamide also causes **drug-induced lupus**. It must be used with **caution in HF patients** because it has a mild myocardial depressive effect.

- **Disopyramide**—prolongs QRS and QT and can cause torsades de pointes. It is anticholinergic and vagolytic, so it causes urinary retention, constipation, and dry mouth. Disopyramide has a negative inotropic effect, so avoid in patients with HF. This drug is occasionally used in patients with HOCM.
- Because Class Ia agents prolong both the QRS and QT intervals, avoid them in patients with 2nd or 3rd degree heart block.
- **Class Ib: lidocaine**—seizures
- **Class Ic:** Flecainide was shown in the CAST trial to increase mortality or cardiac arrest compared to placebo when given to patients with previous MI.
- **Class II:** β -blockers can cause fatigue, decreased libido, and erectile dysfunction. They must be tapered slowly; stopping a β -blocker abruptly can precipitate angina.
- **Class III** can cause prolonged QT, QRS, and torsades de pointes:
 - **Amiodarone** is the most effective, but also, due to the extremely high **iodine** content, the most toxic antiarrhythmic drug. It causes corneal deposits (in 98% of patients!), thyroid disease (both hyper- and hypothyroidism), pulmonary fibrosis, gray skin, and sun sensitivity. Mild transaminitis occurs in 25% of patients; LFTs should be monitored and amiodarone stopped if LFTs increase more than 2-fold. **Pulmonary fibrosis** from amiodarone can be fatal (~ 10% mortality). It ordinarily occurs in the 1st year of treatment. It tends to occur in older patients (> 40 years old) and in those with low carbon monoxide diffusing capacity. Pulmonary fibrosis is unlikely at dosages < 200 mg/day. Amiodarone also causes a less common **acute** form of pulmonary toxicity. Again, amiodarone: hepatic toxicity, extremely long half-life (40–55 days), hyper/hypothyroidism, gray skin, pulmonary fibrosis.
 - **Dronedarone** is recommended by the 2014 ACC/AHA/HRS Guidelines and the 2016 ESC Guidelines as a 1st line agent for recurrent paroxysmal or persistent A-fib without LVH or HF. It is contraindicated in patients with Class IV HF or decompensated HF within 4 weeks, especially if EF is < 35% (2 $\times$ increase in HF mortality in this setting).
 - **Dofetilide** blocks the cardiac ion channel carrying the delayed rectifier K^+ current (I_{Kr}). It is used to treat highly symptomatic A-fib and can be used in patients with CAD and HF. Dofetilide must be started as an inpatient by approved prescribers. Dose reduction is required for patients with chronic kidney disease. It can cause significant QT prolongation requiring dose reduction or discontinuation. Do **not** use dofetilide with the following medications: cimetidine, verapamil, ketoconazole, trimethoprim, prochlorperazine, megestrol, or thiazide diuretics; these agents can increase dofetilide levels.

Risk of **digoxin toxicity** is highest in elderly patients, and in those with **low K⁺, low Mg²⁺, low pO₂** (low, low, low), or impaired kidney function. Symptoms of digoxin toxicity are nonspecific and can include confusion, nausea, vomiting, vague abdominal pain, or visual changes. The toxicity of digoxin is best determined by changes in the ECG or symptoms, not by blood levels. The most common ECG changes are bradycardia and prolonged PR interval. Note: In patients with chronic atrial fibrillation, the development of a **regular** pulse could be a manifestation of digoxin toxicity.

Patients with digoxin toxicity should receive digoxin-binding antibodies to remove it from the circulation. They should be monitored in an intensive care setting. Digoxin levels are not reliable after digoxin antibodies are administered. Note that dialysis will not remove digoxin.

Electrophysiologic Testing

Electrophysiologic (EP) studies are used to identify and characterize SVTs and VTs, often as a precursor to radiofrequency ablation. This involves putting catheters in the heart from the femoral veins, or sometimes the subclavian veins, to measure electrical conduction and perform programmed stimulation to assess arrhythmia inducibility.

Radiofrequency Ablation

Radiofrequency ablation is the treatment of choice for **WPW syndrome**.

It is also used for the following if the patient **prefers** it over drug therapy or the condition is **not responsive** to meds:

- AVNRT
- Atrial tachycardia
- Atrial flutter
- Idiopathic VT

Radiofrequency ablation is also used to treat atrial fibrillation by performing pulmonary vein isolation, or by destroying the AV node and placing a ventricular pacemaker. Complications of ablation can include perforation, cardiac tamponade, heart block, and groin bleeding.

SYNCOPE

PREVIEW | REVIEW

- What is the most common cause of syncope?
- Explain how you approach the diagnostic workup in a patient with probable neurocardiogenic (neurally mediated or vasovagal) syncope.
- What are the tests used to work up high-risk patients with syncope?

Syncope is sudden transient loss of consciousness with loss of postural tone, followed by spontaneous recovery. It is important to differentiate syncope from other types of loss of consciousness, such as seizures or narcolepsy. In this topic, we discuss types and causes of syncope, then outline evaluation and management options.

Neurocardiogenic syncope (a.k.a. vasovagal syncope): Symptoms include dizziness, lightheadedness, and fatigue, with prodromal features such as diaphoresis, pallor, palpitations, nausea, hyperventilation, and yawning. Myoclonic jerks can occur when the patient is unconscious, sometimes mimicking seizure.

Subtypes of neurocardiogenic syncope:

- **Vasovagal syncope**, as in the common faint, is the most common cause of syncope. It is triggered by intense emotion, pain, prolonged standing, alcohol, or heat exposure. Vasovagal episodes are typically preceded by a prodrome that includes nausea, vomiting, flushing, tunnel vision, and diaphoresis. Extremely elderly patients may not have a classic prodrome.
- **Situational reflex syncope** is brought on by specific scenarios such as cough, micturition, straining, or squatting. These triggers provoke reflex vasodilation and bradycardia leading to syncope.
- **Carotid sinus hypersensitivity** may be responsible for up to 40% of falls in the elderly and is diagnosed with a pause > 3 seconds during carotid sinus massage (CSM). Absolute contraindications to CSM include MI within 3 months and TIA/CVA (transient ischemic attack/cerebrovascular accident) within 3 months. Relative contraindications to CSM include previous VT/VF or carotid bruit.

Arrhythmias: Bradycardia, SVT, or VT can all cause syncope.

Nonarrhythmic causes of syncope include severe aortic stenosis, hypertrophic cardiomyopathy (HCM), pulmonary embolism, drug toxicity, and seizure.

Orthostatic hypotension: Syncope from orthostatic hypotension can be caused by volume depletion or autonomic dysfunction. With volume depletion, the blood pressure drops and the HR rises with standing. With **autonomic dysfunction**, blood pressure falls but there is no increase in heart rate with standing (or during the vertical phase of tilt-table testing.)

To treat autonomic dysfunction, try **nonpharmacologic** therapy first (e.g., support hose, increased dietary salt or salt tablets, avoid hot tubs). Medications include **midodrine** and **fludrocortisone**. Midodrine is a prodrug for desglymidodrine, an α -agonist that stimulates the α -adrenergic receptors of both **arteriolar and venous** vessels. Fludrocortisone is a mineralocorticoid agonist (opposite of spironolactone) that promotes retention of Na⁺ and water. Side effects of fludrocortisone include supine hypertension and edema.

Structural heart disease: Anatomic causes include depressed EF (causing VT/VF), aortic stenosis, HCM, atrial myxoma, pulmonary embolism, pulmonary HTN, and myocardial ischemia.

Medications: Check the patient's history for new medications. Common medications causing syncope include cardiovascular, neurologic, antiparkinsonian, and antidepressant medications. Medications for BPH (prazosin, terazosin, and tamsulosin) are a classic cause of syncope. For this reason, these meds are usually given at bedtime.

Recreational substances: Caffeine use can aggravate neurocardiogenic syncope due to its diuretic effect, stimulation of cardiac baroreceptors, and tendency to replace noncaffeinated beverages. Ask about intake of coffee, tea, soda, and energy drinks. All stimulant-containing drinks and pills should be discontinued. Alcohol also has a diuretic effect, and excessive use should be avoided.

A thorough history, physical exam, **supine and upright blood pressure**, and **ECG** are essential parts of the initial evaluation. If the history is typical for vasovagal syncope, and this is the **first** episode in a young patient with **no** suspected heart disease, further evaluation is not usually needed. However, patients in high-risk occupations or risk factors for heart disease should be worked up after the 1st episode of syncope. Further workup for patients with recurrent syncope and high-risk patients includes:

- Do a **carotid sinus massage** if the patient is elderly and has no contraindications to CSM (listed above).
- Perform **echocardiography** if syncope is preceded by palpitations (suggesting arrhythmia) or occurs following a cough (to rule out HF).
- Use **tilt-table test** to diagnose neurocardiogenic syncope—the patient is strapped to a table that rotates from a flat position to a vertical position, kept flat for 5 minutes, and then rotated into the vertical position for 45 minutes while monitoring HR and BP. Sometimes, pharmacologic provocation (nitroglycerine or isoproterenol) is used to increase susceptibility to the test.

If the diagnosis remains uncertain, stratify to determine whether the patient is at increased risk of death (typically patients with severe structural heart disease or clinical or ECG features suggesting arrhythmic syncope).

Admit high-risk patients for additional workup, which can include coronary angiogram and EP study.

Management: Initial measures to prevent recurrent syncope include avoidance of precipitating factors and volume depletion. Remind patients to remain hydrated, avoid caffeine and stimulants, and (if no hypertension) use salt. Patients should also be taught to sit or lie down at the onset of symptoms and to initiate physical isometric maneuvers (leg-crossing and handgrip). The

value of pharmacologic agents (e.g., β -blockers, fludrocortisone, midodrine) is less certain. Frequent episodes, despite initial management, require evaluation with continuous ambulatory electrocardiography. Patients with severe cardioinhibitory response (i.e., bradycardia, prolonged PR interval, AV block) during syncope could benefit from pacemaker placement.

SUDDEN CARDIAC ARREST (SCA) AND SUDDEN CARDIAC DEATH (SCD)

SCA occurs when the heart fails to effectively beat, interrupting blood flow to the brain. If the patient dies as a result, it is called sudden cardiac death (SCD). Generally, this is due to ventricular fibrillation or very rapid ventricular tachycardia. These arrhythmias are usually caused by underlying heart disease.

Risk factors for SCA/SCD include:

- A previous myocardial infarction
- A family history of sudden death
- Some congenital heart defects (both before and after surgical repair)
- Reduced ejection fraction
- Nonsustained ventricular tachycardia
- Unexplained syncope

Workup for SCA should include ECG, routine labs (BMP and CBC), echocardiography, and possibly stress test. Other valuable tests include ambulatory rhythm monitoring (Holter, event monitor, implantable loop recorder), cardiac catheterization, electrophysiology study, and in some cases, genetic testing.

In young patients with SCA, consider:

- Long QTc syndrome
- Brugada syndrome
- Progressive heart block
- Hypertrophic cardiomyopathy (particularly in athletes)
- Anomalous coronary artery disease
- Congenital heart disease
- Genetic mutations (e.g., short QT syndrome, catecholaminergic polymorphic ventricular tachycardia, idiopathic ventricular fibrillation)
- Drug intoxication
- Wolff-Parkinson-White syndrome with atrial fibrillation

SCA/SCD prevention (secondary prevention)—anyone who survives SCA should undergo placement of an implantable cardiac defibrillator (ICD) unless contraindicated (e.g., life expectancy < a year, high infection risk). The exception is patients who have SCA in the setting of acute myocardial infarction or acute coronary syndrome. These patients require reevaluation after revascularization and recovery.

Antiarrhythmic therapy is less effective than ICD therapy for prevention of SCA/SCD. In fact, antiarrhythmic medications actually increase mortality in patients with ischemic cardiomyopathy. These drugs can be used in combination with ICDs to help decrease ventricular tachycardia/VF burden, but keep the potential for proarrhythmia in mind.

β -blockers are safe and may reduce symptoms of ectopy, block catecholamine-sensitive conditions such as long QTc syndrome and other inherited mutations, and slow the rate of arrhythmias.

Primary prevention (preventing SCA/SCD before it occurs)—ICDs are recommended prophylactically in patients with:

- Ischemic cardiomyopathy (LVEF < 35%)
- Hypertrophic cardiomyopathy with syncope, or with septal thickness > 3 cm
- Long QTc syndrome and syncope
- Brugada syndrome
- Unexplained syncope and inducible ventricular arrhythmias in the EP lab
- Sustained documented ventricular tachycardia

Patients with reduced ejection fraction **not** due to coronary artery disease do not benefit from ICD implantation.

CARDIOMYOPATHIES

PREVIEW | REVIEW

- List some of the causes of dilated cardiomyopathy.
- What are the risk factors for sudden cardiac death (SCD) in patients with hypertrophic cardiomyopathy (HCM)?
- What are the 3 main medications used in the treatment of HCM?
- What are some causes of restrictive cardiomyopathy?
- Which auscultatory findings are the same and which are different in restrictive cardiomyopathy vs. constrictive pericarditis?

OVERVIEW

The term cardiomyopathy refers to disease of the heart muscle. This term technically refers to heart muscle disease of unknown cause, but many also use the term to indicate significant left ventricular (LV) dysfunction caused by underlying heart disease.

Heart diseases that can cause LV systolic heart failure (HF) include:

- Ischemic heart disease (ischemic cardiomyopathy)
- Hypertensive heart disease
- Valvular heart disease

Dilated (or nonischemic) cardiomyopathy is heart muscle disease not due to underlying heart disease. An ischemic workup (e.g., stress test, coronary angiography) is usually recommended to rule out ischemic cardiomyopathy. 20–30% of patients with a dilated cardiomyopathy will have no discernible cause—idiopathic dilated cardiomyopathy. **Causes of dilated cardiomyopathy include:**

- Infections—viral (e.g., coxsackievirus B, HIV); Chagas disease (Latin America)
- Toxins and drugs—chemotherapeutic agents (especially the anthracyclines doxorubicin and daunorubicin), alcohol, cocaine
- Metabolic causes—diabetes, thyroid diseases, acromegaly
- Connective tissue and inflammatory diseases
- Genetic dilated cardiomyopathy (usually autosomal dominant)
- Tachycardia and stress-induced (takotsubo) cardiomyopathy
- Infiltrative diseases (e.g., sarcoidosis)
- Peripartum cardiomyopathy
- Left ventricular noncompaction (increased LV trabeculae)

Hypertrophic cardiomyopathy is a genetic disease causing thickening of the heart muscle and heart failure with preserved ejection fraction.

Restrictive cardiomyopathy is usually due to infiltrative diseases such as amyloidosis, hemochromatosis, and sarcoidosis.

We cover hypertensive heart disease (see [Pulmonary Hypertension on page 13-84](#) and [Right Ventricular Failure on page 13-79](#)), valvular heart disease (see [Right Ventricular Failure on page 13-79](#)), and ischemic heart disease (see [Angina on page 13-12](#)) elsewhere in this section.

DILATED CARDIOMYOPATHY (DCM)

Patients with **DCM** have ventricular dilation and depressed myocardial contractility of one or both ventricles (ejection fraction < 40%). Systolic function is impaired, with or without overt heart failure symptoms. Atrial and ventricular arrhythmias are common and patients are at increased risk for sudden cardiac death. African Americans have nearly a 3-fold higher risk for developing DCM than Caucasians.

The prognosis of patients with symptomatic HF and DCM is poor: 50% mortality at 5 years. Heart failure due to dilated cardiomyopathy is treated similarly to other causes of HF (see [Heart Failure \(HF\) on page 13-74](#)).

Stress cardiomyopathy (a.k.a. takotsubo cardiomyopathy, apical ballooning syndrome, broken heart syndrome) often presents with sudden onset of chest pain suggesting an acute coronary syndrome. ECG typically reveals anterior ST segment elevations of acute myocardial infarction. However, angiography reveals normal coronaries. Left ventriculogram or echocardiogram typically

shows apical ballooning with akinesis of the apical and distal anterior wall. An emotional or stressful life event may precipitate the presentation. Most patients with stress cardiomyopathy will recover to normal LV function, although in-hospital mortality is the same as acute coronary syndrome. Systolic function typically recovers in 2–4 weeks. As with DCM, treat according to current heart failure guidelines (see [Treatment for HF on page 13-76](#)).

Peripartum cardiomyopathy is a severe idiopathic cardiomyopathy that can cause systolic HF in previously healthy young women. It can occur toward the end of pregnancy through the first 5 postpartum months. The best diagnostic test to confirm the diagnosis is a transthoracic echocardiogram (TTE). The heart is usually dilated, but not always. Most patients recover within 3–6 months of onset. There is a high risk of recurrence with subsequent pregnancies. For more information on peripartum cardiomyopathy, see the [Women's and Men's Health](#) section.

HYPERTROPHIC CARDIOMYOPATHY (HCM)

HCM is the most common genetic cardiovascular disease. It has an **autosomal dominant** pattern of inheritance, most commonly due to mutations in sarcomere genes. In HCM, the left ventricle is thickened, but not dilated ([Figure 13-33](#)), in the absence of other cardiac or systemic conditions (e.g., HTN, aortic valve stenosis). HCM is the most common cause of sudden cardiac death in young patients (< 35 years of age), especially competitive athletes.

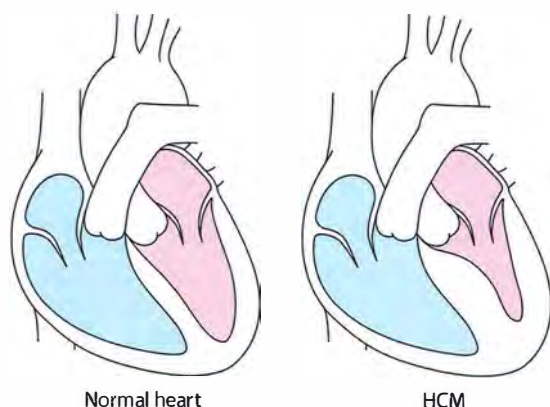


Figure 13-33: Hypertrophic cardiomyopathy

HCM can lead to:

- LV outflow tract obstruction
- Diastolic dysfunction (heart failure with preserved ejection fraction [EF])
- Myocardial ischemia
- Mitral regurgitation

Patients with HCM usually present with heart failure, chest pain (typical or atypical), or exertional syncope. Others with HCM can be asymptomatic and are recognized because of abnormal physical exam (e.g., murmur).

Physical exam in HCM: The patient usually has a harsh, crescendo-decrescendo systolic murmur, typically in the

left 3rd intercostal space, which increases with Valsalva and decreases with sustained handgrip, squatting, and passive leg raise (see [Table 13-8 on page 13-50 and page 13-51](#)). A holosystolic murmur of mitral regurgitation can sometimes be heard from systolic anterior motion of the mitral valve due to a suction-like effect of the outflow obstruction. The carotid pulse has a **brisk upstroke**—but, because outflow obstruction occurs late in systole, it is **bifid** in 2/3 of HCM patients. The briskness of the upstroke distinguishes it from aortic stenosis. Palpation at the apex can surprise you with a double- or triple-tap impulse.

The ECG with HCM is abnormal in > 90% of patients. Most common abnormalities include LVH, ST-T changes with T-wave inversion in the lateral precordial leads, and Q waves in inferior and lateral leads.

Diagnosis is with echocardiography. Cardiac MRI can be considered if the diagnosis is uncertain or for assessment of cardiac anatomy prior to septal ablation or surgical myectomy. There is no single classic morphologic form, and virtually all possible patterns of hypertrophy have been described (although septal hypertrophy is most common). Some patients have dynamic obstruction related to systolic anterior motion of the mitral valve. Left ventricular outflow tract (LVOT) obstruction can occur: This is called **obstructive HCM**. Approximately 25% of patients with HCM have a high resting LV outflow gradient (> 30 mmHg). Routine genetic testing is not recommended in patients with HCM but can be considered in first-degree family members of a proband with a known genetic mutation.

The majority of patients with HCM have normal life expectancy with little or no disability; however, subgroups of patients are at risk for complications including sudden death, progressive heart failure, and atrial fibrillation.

Risk factors for sudden cardiac death in HCM (and potential indications for implantable cardioverter-defibrillator [ICD]):

- Prior cardiac arrest or sustained ventricular arrhythmia
- Massive LVH (myocardial thickness > 30 mm anywhere in the LV)
- Personal history of syncope (due to arrhythmia)
- Family history of SCD due to HCM in 1st degree family member
- NSVT
- Apical LV aneurysm
- End-stage HCM with reduced EF (< 50%)
- Abnormal BP response to exercise (< 20 mmHg increase in BP rest to peak, or fall in BP with exercise)
- Extensive late gadolinium enhancement (LGE) on cardiac MRI

Treatment for HCM includes the following:

- **β-blockers** (obstructive and nonobstructive HCM) and **verapamil** (obstructive HCM) **improve diastolic filling** by slowing heart rate and are 1st choice to treat angina.

- **Disopyramide** can be used with β -blockers for obstructive HCM when other drugs fail to achieve symptom control.
- **IV phenylephrine** (or another pure vasoconstrictor) is recommended for treating acute hypotension in HCM patients who do not respond to IV fluids.
- **ICD placement** is recommended for HCM patients with prior sudden cardiac arrest, ventricular fibrillation, or hemodynamically significant VT. ICD is reasonable if there is a history of sudden cardiac death in ≥ 1 first-degree relative(s), LV wall thickness ≥ 30 mm, or ≥ 1 recent unexplained syncopal episode(s).
- **Septal reduction therapy** via open-heart surgery (septal myectomy) or percutaneous, transcatheter injection of ethanol reduces obstruction in patients with severe symptoms from LVOT obstruction refractory to medical treatment. **Septal myectomy** is preferred for patients with severe drug-refractory heart failure symptoms (New York Heart Association Class III and IV).

RESTRICTIVE CARDIOMYOPATHY

Restrictive cardiomyopathy must be differentiated from constrictive pericarditis (see [Constrictive Pericarditis on page 13-80](#)) because the signs and symptoms can be similar (dyspnea, fatigue, and right-sided heart failure). Constrictive pericarditis is a pericardial problem; restrictive cardiomyopathy is a myocardial problem. While constrictive pericarditis can often be quickly treated with good results, restrictive cardiomyopathy is **not** reversible.

Arrhythmias, such as atrial fibrillation, occur early in the course of restrictive cardiomyopathy.

Causes of restrictive cardiomyopathy include:

- Infiltrative diseases (e.g., amyloidosis, sarcoidosis, Gaucher disease)
- Storage diseases (e.g., hemochromatosis, Fabry disease, glycogen storage diseases)
- Familial disorders
- Other causes including diabetic cardiomyopathy, scleroderma, endomyocardial fibrosis, radiation

Physical exam findings in restrictive cardiomyopathy include S_3 or S_4 , a mitral and/or tricuspid regurgitation murmur (see [Table 13-8 on page 13-50 and page 13-51](#)), and inspiratory increase in jugular venous pressure (i.e., Kussmaul sign). Constrictive pericarditis will also have these findings, but in addition, a paradoxical pulse (inspiratory fall in systolic blood pressure) may be present in $\sim 1/3$ of cases. A pericardial knock during early diastole is pathognomonic for constrictive pericarditis.

With restrictive cardiomyopathy (which is a form of HF), BNP levels are markedly elevated (e.g., $8\times$ max normal). With constrictive pericarditis, there is little or no actual HF, and BNP levels are typically just above normal.

On echocardiography, restrictive cardiomyopathy shows thickened myocardium, sometimes with granularity

(suggesting an infiltrative process). Batrial enlargement, normal or small LV cavity, preserved systolic function, and diastolic dysfunction with a restrictive filling pattern are other common echo findings. Despite left ventricular hypertrophy, the ECG may show normal or low voltage (especially with amyloidosis).

Other useful imaging tests include:

- Chest or cardiac CT—look for pericardial calcification in constrictive pericarditis.
- Cardiac catheterization with pressure recordings—elevated filling pressure is common in restrictive cardiomyopathy but rare in constrictive pericarditis.
- Cardiac magnetic resonance (CMR)—late gadolinium enhancement (LGE) identifies fibrosis, scars, or infiltration from restrictive cardiomyopathy. Patterns of LGE can suggest amyloidosis (diffuse subendocardial LGE) or sarcoidosis (patchy enhancement).
- **Thoracotomy** is occasionally done to ensure that you do not miss a treatable constrictive pericarditis (treatment = pericardiectomy).

Treat restrictive cardiomyopathy with diuretics and management of underlying etiology.

MYOCARDITIS

Myocarditis can cause dilated cardiomyopathy. Myocarditis is an inflammatory disease of the myocardium typified by mononuclear cell infiltration. Myocarditis has a variety of infectious and noninfectious causes. Infectious etiologies include viruses, bacteria (e.g., *Rickettsia*, *Chlamydia*), fungi, and helminths. The most common viral agents are enteroviruses (coxsackievirus), parvovirus B19, and human herpes virus 6. Noninfectious causes include toxins (e.g., alcohol, chemotherapeutic agents), hypersensitivity reactions, and systemic diseases including sarcoidosis, inflammatory bowel diseases, collagen vascular diseases, and thyrotoxicosis. Myocarditis may present acutely, subacutely, or chronically with HF and depressed ejection fraction. Consider myocarditis in patients without risk factors for other causes of cardiomyopathy.

The clinical presentation of myocarditis is highly variable. Patients may present with signs and symptoms of an acute coronary syndrome, acute heart failure, or with a life-threatening arrhythmia, cardiogenic shock, and sudden cardiac death. See [Pulmonary Artery Catheterization \(PAC\) on page 13-11](#) and the [Pulmonary Medicine](#) section for more on shock. Troponin levels may be elevated in myocarditis, but they do not follow the typical pattern of myocardial infarction; rather, levels are high but stable over time. Echocardiogram may demonstrate poor LV function but cannot differentiate myocarditis from other causes of cardiomyopathy.

Definitive diagnosis is by endomyocardial biopsy. Patients with viral myocarditis presenting with symptoms of HF should be treated with the usual guidelines-directed medical therapy (see [Treatment for HF on page 13-76](#)).

HEART FAILURE (HF)

OVERVIEW

PREVIEW | REVIEW

- In the 2013 ACC/AHA classification, what are the 2 major types of heart failure?
- Define Stage A through Stage D heart failure (ACC/AHA classification). What are the goals of therapy for each of these stages?
- What is the sequence of drugs used to treat heart failure (HF) based on ACC/AHA stages?
- What are the most common causes of low-output HF?
- Which factors result in a poor prognosis in HF?
- What are the hormonal pathways that contribute to the development of HF?
- When are β -blockers started in the treatment of HF?
- With which type of HF do aldosterone antagonists prolong survival?
- True or false? Digoxin can reduce HF hospitalizations in patients with heart failure with reduced ejection fraction (HFrEF).
- In which population is hydralazine + isosorbide dinitrate beneficial?
- True or false? Ivabradine can be beneficial in stable HF patients to decrease hospitalizations for HF.
- Which patients with chronic HF should receive anticoagulation?
- Cardiac resynchronization therapy is indicated for which HF patients?
- Know all drugs used for emergency treatment of severe HF!
- What does dopamine do at low doses (< 2 mcg/kg/min)? At doses of 2–5 mcg/kg/min?
- True or false? Mechanical circulatory support is beneficial in selected patients with Stage C HFrEF in whom definitive management (cardiac transplantation) or cardiac recovery is anticipated or planned.
- What is the treatment for acute pulmonary edema?

Heart failure is a complex clinical syndrome resulting from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill or to eject blood.

The lifetime risk of developing HF is 20% for Americans ≥ 40 years of age. African American males have the highest risk for HF and the highest 5-year mortality rate (Atherosclerosis Risk in Communities [ARIC] Study—ongoing).

Left ventricular ejection fraction (LVEF) is important in the classification of HF.

The 2013 ACC/AHA definitions are as follows:

- Heart failure with **reduced** ejection fraction (HFrEF): EF $\leq 40\%$, systolic HF
- Heart failure with **preserved** ejection fraction (HFpEF): EF $> 50\%$, diastolic HF

Cardiac output (CO) is maintained in **mild** HF, usually at the expense of increased left ventricular end-diastolic volume (LVEDV) and increased heart rate.

Numerous adaptations occur in response to HF in the peripheral circulation, kidneys, skeletal muscle, and other organs. The changes contribute to the clinical manifestations of heart failure, and ultimately become maladaptive.

In response to exercise, LVEDV and **plasma** norepinephrine rise in patients with HF **more** than in controls, but the resulting CO increase does **not** rise in proportion to O_2 consumption—so the patient has dyspnea on exertion and is easily fatigued. Activation of the adrenergic system and the renin-angiotensin-aldosterone system are ultimately maladaptive and contribute to HF progression.

NYHA Classification

New York Heart Association (NYHA) classification of heart failure is a **functional** classification based on how much the patient is limited during physical activity:

- **Class I**—no limitation in physical activity
- **Class II**—slight limitation of normal physical activity (fatigue, palpitations, dyspnea, and/or angina)
- **Class III**—marked limitation of physical activity. Slight activity causes symptoms.
- **Class IV**—symptoms may be present at rest. Unable to carry on any physical activity without discomfort.

ACC / AHA Staging and Management

The 2013 ACC/AHA staging system for HF considers heart failure a progressive and irreversible disorder and has goals of therapy for each stage (A through D). Note that the ACC/AHA classification is quite different than the NYHA functional classification, in that there is no moving backwards to prior ACC/AHA stages. Know the definition, goal of therapy, and medications for each stage of HF.

Stage A HF patients are at high risk for heart failure but with no structural heart disease or symptoms of HF. This stage includes patients with any of the following:

- Hypertension (HTN)
- Atherosclerotic disease
- Diabetes
- Obesity
- Metabolic syndrome
- Use of cardiotoxins (such as anthracycline)
- Family history of cardiomyopathy

So yes, you read this right: Just having HTN means you have Stage A heart failure!

Treatment goals for Stage A are to treat the underlying disorder (e.g., HTN, atherosclerotic disease) and control/avoid other risk factors that can lead to or contribute to HF, such as hyperlipidemia, obesity, diabetes mellitus, tobacco use, and known cardiotoxic agents (e.g., excess alcohol, illicit drugs). Regular physical activity is recommended in all HF patients.

Stage A drugs include ACEIs/ARBs and statins when indicated. Hypertension and lipid disorders should be controlled as per current guidelines (see [Hypertension \(HTN\) on page 13-12](#) and [2018 ACC / AHA Guidelines on Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Disease \(ASCVD\) Risk in Adults on page 13-38](#)).

Stage B HF patients have structural heart disease but without signs or symptoms of heart failure. This stage includes patients who have a history of a previous myocardial infarction (MI), those with LV remodeling from left ventricular hypertrophy (LVH), low LVEF, or asymptomatic valvular heart disease.

Goals of Stage B therapy are to prevent HF symptoms and prevent further cardiac remodeling.

Stage B drugs are ACEIs/ARBs, β -blockers, and statins if there is a history of MI/ACS. Use ICD if indicated and revascularization as appropriate.

Stage C HF patients have structural heart disease with prior or current symptoms of HF. These are patients with structural heart disease as described above in Stage B, and who additionally have (or had) signs and symptoms of HF (e.g., dyspnea, fatigue, decreased exercise tolerance).

Goals for Stage C therapy are symptom control, patient education, improved health-related quality of life, and prevention of hospitalization and mortality.

Stage C drugs include:

- Loop diuretics; recommended for volume-overloaded NYHA II-IV patients
- Renin-angiotensin-aldosterone system inhibitors (ACEI or ARB) for all patients with chronic HFrEF to reduce morbidity and mortality
- Combination ARB + neprilysin inhibitor (to replace ACEI or ARB monotherapy) in patients with chronic symptomatic HFrEF (further reduces morbidity and mortality)
- 1 of 3 β -blockers proven to reduce mortality (bisoprolol, carvedilol, and metoprolol succinate)
- Hydralazine/isosorbide dinitrate for symptomatic African American NYHA III-IV patients (after optimal treatment with ACEI/ARB and β -blockers)
- Aldosterone antagonist for NYHA II-IV patients (if estimated GFR > 30 mL/min and K^+ < 5 mEq/L [5.00 mmol/L])
- Ivabradine for NYHA Class II-III patients receiving maximally tolerated β -blocker in sinus rhythm with a heart rate $\geq$ 70 bpm at rest

Use ICD and/or cardiac resynchronization therapy (CRT) if indicated, and revascularization or vascular surgery as appropriate.

Stage D HF patients have marked symptoms at rest and frequent hospitalizations despite maximal medical therapy.

Goals for Stage D therapy are to control symptoms, improve health-related quality of life, reduce hospital readmissions, and establish the patient's end-of-life goals.

Stage D drugs are the same as those for Stage C.

Options for Stage D patients include consideration of "extraordinary measures"—including heart transplant, chronic inotropes, temporary or permanent mechanical circulatory support (ventricular assist devices), experimental surgery or experimental drugs—as well as palliative care, hospice, and ICD deactivation.

Patients with cardiogenic shock should receive temporary IV inotropic support to maintain systemic perfusion and preserve end-organ performance until definitive therapy (coronary revascularization, mechanical circulatory support, or heart transplantation) is performed or the acute precipitating problem resolves.

Patients with advanced heart failure may present with signs and symptoms of low cardiac output including shortness of breath, marked fatigue, exercise intolerance, weight loss, refractory fluid retention, hypotension, and signs of inadequate perfusion (worsening renal function).

The most common causes of HF with reduced EF (HFrEF) are:

- Coronary artery disease (40–60%)
- Dilated cardiomyopathy (30%)
- Valvular disease (15%)
- Hypertension (10%)

HF is the most common diagnosis in hospitalized elderly patients. Only 50% of patients with HF die from actual pump failure; ~ 40% die from arrhythmias!

Determining Prognosis in HF

Factors corresponding to a worse prognosis in severe HF include:

- Lower ejection fraction
- Hyponatremia
- Chronic kidney disease
- Anemia
- Elevated troponin
- High B-type natriuretic peptide (BNP)
- Increased width of QRS
- Persistent sinus tachycardia
- Poor functional capacity (NYHA III and IV)
- High catecholamine levels

Mechanism of HF

Heart failure with reduced ejection fraction (HFrEF) results in **decreased** CO. Decreased CO can be due to systolic dysfunction, diastolic dysfunction, or both. (Note that diastolic dysfunction can occur with normal CO.) After a certain point, decreased CO from any type of HF causes decreased renal perfusion. This stimulates the release of renin, which converts angiotensinogen to angiotensin I. Angiotensin I is converted to angiotensin II in the lungs. Angiotensin II then stimulates the secretion of aldosterone, which causes renal Na^+ and water retention, **increasing filling pressure** (moving the Starling curve to the **right**).

Let's see if we have all of that: Low CO $\rightarrow$ low renal perfusion $\rightarrow$ high renin $\rightarrow$ high angiotensin I $\rightarrow$ high angiotensin II $\rightarrow$ high aldosterone $\rightarrow$ retention of Na^+ and water $\rightarrow$ high filling pressure $\rightarrow$ exacerbation of HF (Figure 13-34). To compensate for reduced stroke volume, heart rate is increased in response to increased sympathetic tone and increased catecholamines levels. Higher catecholamine levels indicate worse prognosis.

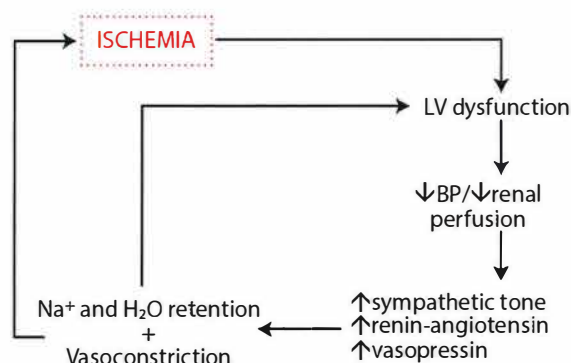


Figure 13-34: Spiral of worsening HF

ADH is normally released from the hypothalamus in response to high plasma osmolality. In HF, ADH can be released in response to decreased effective tissue perfusion. The high ADH state in heart failure causes hyponatremia, which is associated with a poor prognosis.

Atrial (or A-type) natriuretic peptide (ANP) and brain natriuretic peptide ([BNP]; a.k.a. B-type natriuretic peptide) are released from the heart myocytes; the release is stimulated by stretching of the atrium (for ANP and BNP) and the ventricle (for BNP). ANP and BNP increase renal excretion of Na^+ and water, cause vasodilation, and inhibit the effects of aldosterone. These peptides offset the effects of renin, angiotensin, and ADH—but cannot antagonize them adequately.

In **severe** heart failure, the BNP increases **20- to 100-fold**. High levels of these peptides (especially BNP) correlate directly with a poor prognosis in HF. BNP is also elevated in restrictive cardiomyopathy but not constrictive pericarditis and is used to differentiate between these disorders.

In ~ 50% of patients with HF, the ejection fraction is preserved (HFpEF, formerly known as **diastolic dysfunction**). Myocardial ischemia, severe concentric LVH,

hypertrophic cardiomyopathy, and diabetic cardiomyopathy can cause diastolic dysfunction, at least initially. With diastolic dysfunction, the CO is often normal; HF develops from increased filling pressure (decreased relaxation due to increased stiffness). So, the problem is not that the ventricle is not squeezing enough but rather that it is not relaxing enough. This is reflected in elevated left and right end-diastolic pressure (LVEDP and RVEDP), tachycardia, and an S_4 .

Treatment for HF

General Measures

See [ACC / AHA Staging and Management on page 13-74](#) for treatment based on ACC/AHA stage. Exercise training in patients with stable chronic HF can result in an 11% reduction in combined all-cause death or hospitalization (based on the 2009 HF-ACTION trial). We will now discuss individual drugs and how they affect/improve survival in heart failure.

(Note: In our discussion, the term **class** refers to NYHA classification; the term **stage** refers to the ACC/AHA classification.)

Pharmacologic management of HFrEF is aimed at reducing ventricular preload and afterload and diminishing, inhibiting, and/or antagonizing neurohormonal **vasoconstrictor** activation. This contrasts with historical treatment strategies, which aimed to directly increase cardiac contractility.

Optimal HF treatment aggressively targets the major risk factors, including hypertension, diabetes, obesity, metabolic syndrome, hyperlipidemia, and coronary artery disease (CAD). Use therapies that promote regression of LVH or reverse remodeling of the dilated heart; these include inhibitors of catecholamines and the renin-angiotensin-aldosterone pathway.

Angiotensin-Converting Enzyme Inhibitors (ACEIs) and Angiotensin II Receptor Blockers (ARBs)

ACEIs (e.g., lisinopril, benazepril) or ARBs (e.g., valsartan, losartan) are 1st line therapy for HF. ACEIs block formation of angiotensin II. ARBs **block the effect** of angiotensin II. Both ACEIs and ARBs decrease systemic vascular resistance, pulmonary capillary wedge pressure, right atrial pressure, and end-diastolic and end-systolic dimensions; and they improve cardiac performance, as evidenced by increased CO and stroke volume and by improved fractional shortening, as determined by echocardiography. Hence, they decrease tachycardia due to HF. They also decrease the incidence of ventricular arrhythmia and prolong survival. In addition, they **reverse the remodeling** in the myocytes that causes progression of heart failure.

ACEIs and ARBs are equally effective—the 2 are commonly grouped in discussion as ACEIs/ARBs. Do not use ACEIs and ARBs together!

Often, renin-angiotensin-aldosterone system (RAAS) inhibition is provided by angiotensin receptor neprilysin

inhibitors (ARNIs), which are also 1st line therapy for HFrEF (see [Angiotensin Receptor Neprilysin Inhibitors \(ARNIs\)](#) on page 13-78).

Per the 2017 AHA/ACC Focused Update on the 2013 Guidelines for the Management of Heart Failure, inhibition of the RAAS system with ACEIs, ARBs, or ARB + neprilysin inhibitor (e.g., sacubitril/valsartan) is recommended for all patients with chronic heart failure with reduced ejection fraction to reduce morbidity and mortality.

Monitor patients on ACEIs/ARBs/ARNIs for renal impairment and hyperkalemia. Important side effects include angioedema and acute kidney injury in patients with bilateral renal artery stenosis. ACEIs/ARBs/ARNIs are contraindicated in pregnancy.

Commonly used ARBs:

- Candesartan (Atacand)
- Valsartan (Diovan)
- Irbesartan (Avapro)
- Olmesartan (Benicar)
- Eprosartan (Teveten)
- Losartan (Cozaar)
- Telmisartan (Micardis)

Candesartan and valsartan are preferred since they have the strongest trial data supporting their use.

β-Blockers

β-blockers are a standard treatment for HFrEF. In HF, the sympathetic nervous system is overstimulated. This raises norepinephrine levels, which can cause cardiac remodeling, lead to arrhythmias, and increase mortality risk. Mortality is clearly improved by 3 specific β-blockers: carvedilol (~ 65% relative risk reduction), metoprolol succinate (~ 66%), and bisoprolol (~ 35%).

For this reason, the 2013 ACCF/AHA Guidelines for the Management of Heart Failure recommend initiation of β-blockade at any stage of heart failure, after an ACEI has been initiated. Carvedilol is a nonselective β-blocker that also has some α-blocker effect, which is dosed twice daily. Extended-release metoprolol succinate and bisoprolol are β-1 selective β-blockers and are dosed once daily. Use β-blockers in conjunction with ACEIs in Class I-IV heart failure. β-blockers need to be started cautiously in patients with decompensated heart failure.

Diuretics

Give loop diuretics if needed for volume control (i.e., to decrease edema and pulmonary congestion) for Stage C HF. Remember: Therapy with ACEIs/ARBs and β-blockers should begin before patients even have symptoms (Class B heart failure).

Diuretics are effective in treating volume overload in both HF with reduced EF and HF with preserved EF. Loop diuretics have no mortality benefit, unlike ACEIs/ARBs, β-blockers, and aldosterone antagonists.

Promptly treat HF patients admitted with significant fluid overload with IV loop diuretics. In those already receiving outpatient loop diuretics, the initial IV dose should be more than their chronic oral daily dose and be given as either intermittent boluses or continuous infusion. Adjust diuretic dose for dyspnea relief and to reduce edema, but avoiding hypotension.

If maximal IV loop diuretic is inadequate, a thiazide or thiazide-like diuretic (e.g., metolazone) can be added, which results in a synergistic effect. This combination can result in severe hypokalemia and prerenal acute kidney injury, so close monitoring is necessary.

Aldosterone antagonists (a.k.a. mineralocorticoid antagonists) reduce morbidity and prolong survival in NYHA II-IV heart failure with reduced EF < 35%:

- **Spirolactone** decreases mortality by 30% at 24 months in patients with Class IV HF or Class III with a history of Class IV in the previous 6 months (1999 RALES trial).
- **Eplerenone** is similar to spironolactone but with greater specificity for the mineralocorticoid receptor—thus fewer side effects (e.g., gynecomastia). Eplerenone decreases mortality by 15% at 16 months in patients with recent MI, EF < 40%, and evidence of HF or diabetes mellitus (2003 EPHEUS trial). Monitor patients closely for hyperkalemia.
- NYHA Class II patients benefit from aldosterone antagonists only if they have prior HF hospitalizations and elevated plasma natriuretic peptides.

More notes on diuretics:

- **Thiazides** block Na⁺ and Cl⁻ reabsorption in the distal tubule. Examples include hydrochlorothiazide and metolazone. Thiazides are effective for hypertension but not edema—except when used together with a loop diuretic, which will enhance diuresis.
- **Furosemide, bumetanide, torsemide, and ethacrynic acid** are loop diuretics. They block Na⁺ reabsorption in the ascending limb of the loop of Henle. Bumetanide can also have some action on the proximal tubule. Loop diuretics are best for treating edema.
- **Triamterene** and **amiloride** block Na⁺ reabsorption in the cortical collecting tubule. Like the aldosterone antagonists, they are potassium-sparing diuretics—they tend to increase K⁺ levels. With chronic kidney disease, use spironolactone or triamterene with caution (especially in combination with ACEI/ARB) because they can cause hyperkalemia.

Much more information on diuretics is in the [Nephrology](#) section.

Digoxin

Digoxin decreases hospitalizations for HF in patients with HFrEF. It is sometimes used in patients who remain symptomatic despite the use of other therapies. In HF, digoxin appears to reset the baroreceptors and dampen the renin-angiotensin effects; it has very little inotropic effect. It also

is used to control the ventricular rate in patients with HF and atrial fibrillation. Digoxin has no mortality benefit. Many drugs increase digoxin levels; see Table 13-14.

Table 13-14: Drugs That Increase Digoxin Levels

Alprazolam
Amiodarone
Macrolide and tetracycline antibiotics
Cyclosporine
Diphenoxylate or propantheline (decrease bowel motility)
Indomethacin
Itraconazole (antifungal)
Omeprazole
Propafenone (Class Ic antiarrhythmic)
Quinine
Spironolactone

Hydralazine and Isosorbide Dinitrate

Hydralazine is an afterload reducer (arterial vasodilator); it also increases heart rate. Hydralazine is frequently used with nitrates to get the added benefit of decreased preload.

The combination of hydralazine and isosorbide dinitrate is recommended to reduce morbidity and mortality in African Americans with NYHA III–IV HFrEF, as adjunctive therapy to ACEIs (or ARBs) and β -blockers (2004 A-HeFT). The combination can also be helpful in patients with current or prior symptomatic HFrEF who cannot be given ACEIs/ARBs (e.g., drug intolerance, hypotension, chronic kidney disease).

Ivabradine

Ivabradine, approved by the FDA in 2015, reduces hospitalizations from worsening HF.

The 2017 ACC/AHA Heart Failure Focused Update recommends consideration of ivabradine in patients who meet all the following criteria:

- have stable, chronic HF (EF $\leq$ 35%) with symptoms (NYHA Class II–III),
- are in sinus rhythm at a rate of $\geq$ 70 bpm, and
- are taking maximally tolerated dose of β -blocker.

Angiotensin Receptor Neprilysin Inhibitors (ARNIs)

The 2017 ACC/AHA Guidelines recommend valsartan/sacubitril in place of ACEI/ARB in patients with chronic symptomatic HFrEF NYHA Class II–III to further reduce morbidity and mortality. Neprilysin is an enzyme that degrades natriuretic peptides and other vasoactive peptides. The combination of ARB (valsartan) and neprilysin inhibitor (sacubitril) was shown to be superior to ACEI (enalapril) alone in patients with chronic HFrEF. ARNIs

can be used as initial therapy or in place of an ACEI/ARB in patients with persistent symptoms. ARNIs should not be added to ACEIs or ARBs and should not be started in patients with a history of angioedema.

Anticoagulation

For patients with chronic HF and permanent, persistent, or paroxysmal atrial fibrillation plus an additional risk factor for cardioembolic stroke (e.g., HTN, diabetes mellitus, previous stroke/TIA, age 65 or older, vascular disease), give individualized anticoagulation (e.g., warfarin, dabigatran, apixaban, rivaroxaban, edoxaban).

Clinical practice guidelines—the 2013 ACCF/AHA Guidelines for the Management of Heart Failure and the 2017 ESC Guidelines for the Management of Acute Myocardial Infarction—also recommend anticoagulation in HF patients with a cardioembolic source, such as a history of systemic/pulmonary embolism or a mobile left ventricular thrombus. In the absence of the above-mentioned indications, anticoagulation is not recommended in patients with HFrEF.

Decompensated HF patients admitted to hospital should receive venous thromboembolism prophylaxis.

Other Therapy

The 2013 ACCF/AHA Guidelines for the Management of Heart Failure recommend an ICD for primary prevention of sudden cardiac death (and to reduce total mortality) in patients with nonischemic dilated cardiomyopathy or ischemic heart disease who are $\geq$ 40 days post-MI and either:

- EF $\leq$ 35% and NYHA II/III symptoms on optimal medical therapy or
- EF $\leq$ 30% and NYHA I symptoms on optimal medical therapy.

ICD candidates must also have an expected survival $>$ 1 year. See [Implantable Cardioverter-Defibrillators \(ICDs\) after STEMI on page 13-31](#) for Class I indications for ICD therapy.

Ventricular dyssynchrony is caused by electrical disturbances that cause the heart to pump blood inefficiently. It typically occurs in patients with severe HF (NYHA III/IV), severely decreased ejection fraction (LVEF $\leq$ 35%), and QRS exhibiting LBBB configuration with QRS duration $\geq$ 120 ms.

Cardiac resynchronization therapy (CRT) involves pacing both right and left ventricles, and is recommended for patients with EF $\leq$ 35%, sinus rhythm, LBBB with a QRS duration of $\geq$ 150 ms, and NYHA II, III, or ambulatory with NYHA IV symptoms despite optimal medical therapy.

Emergency Treatment for Severe HF

Know: With severe ventricular failure, patients may require short-term treatment with inotropes (dopamine, dobutamine, and milrinone).

Dobutamine is an inotropic agent that does not have the vasoconstrictor activity of dopamine and has some vasodilatory effects.

Milrinone is an inotropic/vasodilator agent with phosphodiesterase inhibitor activity (peak III cAMP—an isoenzyme of cyclic adenosine monophosphate). It is indicated for short-term IV treatment of HF. It does **not** cause thrombocytopenia (unlike amrinone) or tachycardia.

Dopamine:

- At **< 2 mcg/kg/min** dopamine stimulates the **dopaminergic** receptors and causes mesenteric dilation.
- At **2–5 mcg/kg/min**, it has a predominantly **β-agonist** effect (positive inotrope) and increases renal perfusion.
- At **> 10 mcg/kg/min**, it mainly has an **α-agonist** effect and causes vasoconstriction. Never use **> 10 mcg/kg/min** for only an inotropic effect!

Mechanical circulatory support (MCS) is beneficial in selected patients with **Stage D HFrEF** in whom definitive management (e.g., cardiac transplantation) or cardiac recovery is anticipated or planned. Nondurable MCS (percutaneous and extracorporeal ventricular assist devices) are reasonable as a bridge to recovery/decision in carefully selected HFrEF patients who have acute, profound hemodynamic compromise. Durable MCS can be used to prolong survival for carefully selected HFrEF patients.

Revascularization (coronary artery bypass graft or percutaneous coronary intervention) is indicated for patients on optimal medical therapy with angina and suitable anatomy, especially left main stenosis (> 50%) or left main–equivalent disease. For end-stage HF, cardiac transplant is the best option. There is a 65% 5-year survival and a 55% 10-year survival!

Harmful for HFrEF patients:

- Definitely avoid or withdraw most antiarrhythmics, calcium channel blockers (except amlodipine), non-steroidal antiinflammatory drugs (NSAIDs), and thiazolidinediones (e.g., rosiglitazone, pioglitazone).
- Long-term use of positive inotropic drugs is potentially harmful, except as palliation for patients with end-stage (Stage D) disease who cannot be stabilized with optimal medical therapy.

Immediate treatment for acute pulmonary edema:

- Patient should be sitting with legs dangling, if possible, to decrease venous return.
- Give supplemental O₂ if hypoxemic (pulse ox < 90%).
- Give IV furosemide (improves symptoms via venodilation even before the diuresis).
- IV nitroglycerin or nitroprusside can be used if systolic BP is > 100 mmHg.
- Consider dobutamine if systolic BP < 90 mmHg.
- CPAP/BiPAP for ventilation is preferred over intubation.

HIGH-OUTPUT HF

PREVIEW | REVIEW

- What are some causes of high-output heart failure?

High-output ventricular failure is seen with **peripheral shunting** (large atrioventricular [AV] fistulas, severe hepatic hemangiomatosis, and Paget disease) and low systemic vascular resistance, as seen in sepsis. You can also see it in patients with hyperthyroidism, beriberi, carcinoid, or anemia. These patients may have a **normal, rather than high**, CO measurement by the time of diagnosis—because of the **worsening** ventricular failure!

RIGHT VENTRICULAR FAILURE

“The most common cause of **right** heart failure is **left** heart failure!” is what you heard on rounds. And, indeed, right ventricular failure (RVF) is mainly caused by pulmonary hypertension, most often secondary to left ventricular failure (LVF). RVF is also seen with large RV infarctions and cor pulmonale. Remember: If the patient has signs of RVF (jugular venous distention and liver congestion) but pressures are equal in all chambers in diastole, think external compression (constriction or effusion).

As LVF progresses, orthopnea usually worsens, but it may then actually improve temporarily as RV function worsens due to the pulmonary hypertension.

PERICARDIAL DISEASES

PREVIEW | REVIEW

- What are some causes of nonconstrictive pericarditis? What ECG changes can you see?
- What ECG changes do you see in pericarditis?
- What treatments can be helpful in recurrent pericarditis?
- What are the 2 clinical hallmarks of constrictive pericarditis?
- How is brain natriuretic peptide used to differentiate constrictive pericarditis from restrictive cardiomyopathy?
- In which conditions are the measured diastolic pressure of all 4 chambers equal?
- Name the 3 hallmarks of cardiac tamponade.

NONCONSTRICTIVE PERICARDITIS

Acute nonconstrictive pericarditis is an inflammatory process involving the pericardial sac. The pericardium is made up of two layers: the visceral pericardium, adherent to the myocardium, and the parietal pericardium. The visceral and parietal pericardium is separated by

the pericardial space, which normally contains a small amount of fluid. Conditions that cause inflammation of the pericardium can lead to an increased amount of fluid in the pericardial space (a pericardial effusion). A pericardial effusion can inhibit the heart from filling with blood, causing cardiac tamponade.

Although pericarditis can be caused by a number of different etiologies, in most cases, no identifiable cause is found (idiopathic). Most idiopathic cases are presumed due to a virus, which is the most common cause of pericarditis.

Causes of nonconstrictive pericarditis include:

- Infection—viral (most common), bacterial (e.g., tuberculosis), and fungal
- Autoimmune—systemic lupus erythematosus (SLE), rheumatoid arthritis
- Neoplasm—cancers can metastasize to the pericardium.
- Metabolic—uremia, hypothyroidism
- Drugs—hydralazine, procainamide
- After pericardial injury—following blunt chest trauma or cardiac surgery
- After myocardial infarction (Dressler syndrome)
- After radiation

Patients with acute pericarditis typically present with chest pain. The chest pain is described as sharp and is frequently pleuritic (varies in intensity with respiration). Many individuals will note that the pain improves with sitting up and leaning forward. Other features of acute pericarditis include a pericardial friction rub on physical examination and typical ECG changes (see below). A pericardial effusion may be present but is not universal.

The diagnosis of acute pericarditis is made if **at least two** of the following signs and symptoms are present:

- Typical chest pain (sharp, pleuritic, and positional)
- Pericardial friction rub (this finding can be transient and is sometimes absent)
- Typical ECG changes including diffuse ST-segment elevation and/or PR depression
- New or worsening pericardial effusion

Pericarditis can also cause transient increases in troponin (secondary to associated myocarditis).

The **ECG** may show diffuse **concave-up** ST elevation (vs. localized, **concave-down** ST elevation in an acute MI [myocardial infarction]) and, occasionally, depressed PR segments, especially in lead II. ECG changes occur in 4 stages:

- Stage 1—diffuse ST-elevation segments with upward concavity and PR depression
- Stage 2—normalization of ST segments (after several days)
- Stage 3—inverted T waves
- Stage 4—weeks or months after onset of acute pericarditis, ECG returns to normal.

Treat pericarditis by stopping any possible causative drugs and giving NSAIDs. Do not treat idiopathic pericarditis

with steroids because there can be a relapse when they are stopped. Treatment with colchicine has been shown to reduce recurrence.

Recurrent pericarditis is acute pericarditis that recurs within weeks to months of the initial episode. Recurrent pericarditis can be accompanied by a pericardial friction rub, ECG changes, and/or a pericardial effusion. The cause of recurrent pericarditis is thought to be autoimmune, as the initial causative agent is usually resolved and no longer active. Recurrent pericarditis can cause thickening of the pericardium and lead to constrictive pericarditis. This can cause restriction of blood flow into the heart and lead to symptoms of fluid retention. Recurrent pericarditis can also become refractory, which is very difficult to treat and may take many years to resolve.

Treat recurrent pericarditis with colchicine and/or NSAIDs. Do **not** use glucocorticoids, as they increase morbidity and recurrence rates. Pericardiectomy often does not have good results and is tried only after medical treatment options have been exhausted.

CONSTRICTIVE PERICARDITIS

Constrictive pericarditis occurs when resorption of pericardial effusion is followed by obliteration of the pericardial cavity with scarring. Ventricular filling is normal during early diastole but falls abruptly when the elastic limit of the pericardium is reached.

Constrictive pericarditis may follow:

- Viral or idiopathic pericarditis
- Traumatic hemopericardium
- TB
- Cardiac surgery
- Mediastinal irradiation
- Purulent infection
- Histoplasmosis
- Rheumatoid arthritis
- SLE
- Neoplastic disease (especially breast cancer, lung cancer, and lymphoma)
- Chronic renal failure with uremia treated by chronic dialysis

Constrictive pericarditis must be differentiated from restrictive cardiomyopathy (see [Restrictive Cardiomyopathy on page 13-73](#)) because the signs and symptoms can be similar—dyspnea, fatigue, and right-sided heart failure.

On physical exam, listen for a loud presystolic knock just after S₂. This is caused by rapid, early diastolic filling of the L.V. Pulsus paradoxus can occur but is usually mild.

There are 2 hallmarks of constrictive pericarditis on **neck vein examination**:

- 1) **Kussmaul sign**. Because the heart is encased in an inflexible “shell,” the negative pressure during inspiration is transferred to the venous inflow tract, resulting in a **lack** of normal decrease in jugular

venous distention (JVD) during inspiration. When severe, JVD can even increase during inspiration.

- 2) Large, right-sided *x* and *y* descents. This is seen as a brisk collapse of the jugular veins during diastole.

Constrictive pericarditis can cause calcification of the pericardium (~ 50%). You can see this best on the lateral chest x-ray because it is typically found over the right ventricle, but you also can see it on the posteroanterior view and on CT. A lateral chest x-ray that shows calcification over the right ventricle is pathognomic for constrictive pericarditis.

CT and MRI are best for measuring pericardial thickness, but echocardiography is also used. A pericardial thickness of **>5 mm** is suggestive of, but not sufficient for, diagnosis. The pericardium can be of normal thickness in ~ 20–25% of cases of constrictive pericarditis.

Brain natriuretic peptide (BNP) plasma levels can help differentiate between constrictive pericarditis and restrictive cardiomyopathy. BNP increases with heart failure (HF). With restrictive cardiomyopathy (which is a form of HF), BNP levels are markedly elevated (e.g., 8× max normal). With constrictive pericarditis, there is little or no actual HF, and BNP levels are typically just above normal.

In both tamponade and constrictive pericarditis, cardiac cath shows the **same pressure** during **diastole** in **all 4 chambers**. You can often differentiate tamponade and constrictive pericarditis at the bedside using several hallmark signs (Table 13-15).

Symptomatic constrictive pericarditis must be treated with an open thoracotomy and **pericardiectomy**. Unfortunately, this resolves the problem only 50% of the time!

Think of **constrictive pericarditis** in the cancer survivor who has undergone **prior radiation therapy** to the chest and now presents with progressive dyspnea, typically occurring over several months to years.

PERICARDIAL EFFUSION

Pericardial effusion is generally diagnosed by echocardiography, but CT and MRI are the most accurate, especially if there is tamponade due to **localized pockets** of effusion. Chest x-ray may show an enlarged cardiac silhouette, although in rapidly developing effusions, patients can present before sufficient volume accumulates to alter the heart's appearance on x-ray. Electrical alternans is seen on ECG, with alternating amplitude of the QRS complex, due to the heart swinging in the pericardium.

Check blood work to exclude liver dysfunction, hypothyroidism, and coagulopathy as potential causes for the effusion.

Pericardial **biopsy** can help diagnose TB. An endomyocardial biopsy to identify infiltrative heart disease may be required to diagnose restrictive heart disease and may help distinguish restriction from constrictive pericarditis (where the myocardium will not show infiltration).

Surgical drainage is preferable in traumatic **hemopericardium**, postsurgical effusion, and when bacterial infection (including TB) is suspected as a cause of the effusion. Pericardiocentesis is often used to **treat** viral, idiopathic, neoplastic, hypothyroid, and renal failure-related effusion. Pericardiocentesis is usually only diagnostically helpful if there is a malignancy.

TAMPONADE

Know! Tamponade occurs when a pericardial effusion leads to critical cardiovascular compromise. There is obstruction to the inflow of blood to the ventricles and equalization of pressures in all 4 cardiac chambers. The most common causes are trauma, cancer, uremia, and acute pericarditis. When there is **rupture** of the **free wall** of the **heart**, as in trauma or post-MI, tamponade develops quickly; otherwise, it generally develops slowly.

Table 13-15: Distinguishing Tamponade and Constrictive Pericarditis

Findings	Tamponade	Constrictive Pericarditis
Duration of symptoms	Hours to days	Months to years
Chest pain, friction rub	Absent	Often present
Pulsus paradoxus	Present	Mild or absent
Kussmaul sign	Absent	Usually present
Diastolic knock	Absent	Often present
Pericardial calcification	Absent	Often present
Thickened pericardium on CT/MRI	Absent	Present
Pericardial effusion	Present	Absent
Jugular venous waveforms	Prominent x descent	Prominent x and y descents
Diastolic pressures	Equal	Equal
Echocardiography	Pericardial effusion, collapse of RV/RA	Marked respiratory variation in transmitral flow
History	Cancer, uremia, recent cardiothoracic surgery, chest trauma	TB, previous XRT, remote cardiothoracic surgery

The 3 hallmarks of acute tamponade:

- 1) Hypotension and muffled heart sounds
- 2) Pulsus paradoxus (Systolic BP drops ≥ 10 mmHg during inspiration.)
- 3) Jugular venous distention with no collapse during diastole (i.e., an attenuated y descent)

Tamponade causes soft, distant heart sounds. Compare and know the differences between this and constrictive pericarditis (see [Constrictive Pericarditis on page 13-80](#)).

Treatment of tamponade is surgery or pericardiocentesis.

CONGENITAL HEART DISEASE

PREVIEW | REVIEW

- What is the most common congenital heart abnormality found initially in adults?
- True or false? Ostium secundum atrial septal defect (ASD) often has right axis deviation and/or right bundle-branch block (RBBB) on ECG.
- When should surgery be performed for ASD?
- Which type of cyanosis would you expect to see in someone with a patent ductus arteriosus?
- What is the most common congenital heart defect in children?
- What are the 2 most common causes of sudden cardiac death in an exercising young person? What 3rd cause should you consider in a young woman?

ATRIAL SEPTAL DEFECT (ASD)

ASD is a hole in the atrial septum, the wall that separates the right and left atria. This allows shunting of blood from the left atrium (high pressure) to the right atrium (low pressure). ASD is classified into 3 types based on the location of the defect: secundum, primum, and sinus venosus. Most patients with an ASD will be asymptomatic until volume overload of the right heart causes symptoms of right heart failure. A flow murmur may be present before the onset of symptoms.

Ostium Secundum ASD

Secundum ASDs comprise 70% of all ASDs. Secundum ASD is the **second most common** form of congenital heart disease diagnosed in adulthood ($F > M$), after bicuspid aortic valve. With a large secundum ASD, there is a systolic ejection murmur at the left sternal border (2° to increased flow across the pulmonic valve), occasionally a diastolic murmur (from increased flow across the tricuspid valve), and a **fixed split S₂**. The left-to-right shunt causes diastolic overloading of the right ventricle and increased pulmonary blood flow with inspiration and expiration.

ECG shows **right axis deviation** and/or **right bundle-branch block (RBBB)**. Chest x-ray shows an enlarged right ventricle (RV) with shunt vasculature. Notice all of the **right-sided stuff** with ASD—makes sense because ASD causes a volume load on the right side of the heart. Patients can develop 2° atrial fibrillation.

Ostium Primum ASD

Ostium **primum** ASD is seen most commonly in **Down syndrome**. Patients may have a loud pansystolic murmur 2° to mitral and/or tricuspid regurgitation. The regurgitation occurs because the ostium is low on the septum, interfering with the function of the atrioventricular (AV) valves or left mitral valve. ECG may show 1° degree AV block, **left axis deviation**, and RBBB.

Sinus Venosus ASD

Sinus venosus ASD is seen with anomalous pulmonary venous return because it occurs high on the septum. It is a cause of 10% of ASDs.

Treatment of ASD

For all types of ASD, surgical or percutaneous closure essentially cures the problem. NYHA functional Class III/IV patients can revert to functional Class I with excellent survival! See [NYHA Classification on page 13-74](#). Standard treatment had been open surgical closure, but now most secundum ASDs are closed **percutaneously**. Closure is indicated if there is a **> 2:1 left-to-right** shunt, even if the patient is asymptomatic. In this case, the ASD would eventually cause an increase in pulmonary vascular resistance and associated complications.

Severe fixed pulmonary hypertension is considered a contraindication to surgical or percutaneous repair of the ASD. **Eisenmenger syndrome** (right-to-left cardiac shunt, pulmonary arterial disease, and cyanosis) is also a contraindication to ASD closure.

PATENT DUCTUS ARTERIOSUS (PDA)

Adult patients with PDA are usually asymptomatic, although heart failure and infectious endocarditis can occur. Females are affected more than males. PDAs are typically discovered early by detection of the distinct murmur.

PDA causes a **continuous**, machinery-like murmur at the LUSB. As pulmonary pressures **rise**, the murmur becomes **less continuous**. **Differential** cyanosis (e.g., cyanotic toes, normal fingers) with pulmonary hypertension can occur.

If the patient develops pulmonary hypertension, consider Eisenmenger syndrome (more under [Eisenmenger Syndrome on page 13-84](#)).

Chest x-ray shows calcification of the ductus arteriosus in adults.

Surgical or percutaneous closure has excellent results in patients with heart failure or pulmonary hypertension

symptoms and in asymptomatic patients with moderate-to-large PDAs. Surgery is not advised in severe, irreversible pulmonary hypertension.

PULMONIC STENOSIS

Balloon valvuloplasty is the procedure of choice for treating pulmonic stenosis. It has favorable long-term clinical and hemodynamic results.

VENTRICULAR SEPTAL DEFECT (VSD)

VSDs are the most common congenital heart defect in children. They are uncommon in adults because most either close spontaneously or are surgically closed in childhood. 80% of small VSDs close spontaneously in the first 10 years of life. Large VSDs typically require surgery (although even 10% of these eventually close spontaneously). Expect to hear a holosystolic murmur at the left lower sternal border. Larger VSDs cause softer murmurs; smaller VSDs cause louder murmurs. Any adult with a residual VSD should have a Qp:Qs (pulmonic to systemic blood flow) measurement. This measurement is usually made by right heart catheterization but can be estimated by echocardiography. Those with Qp:Qs of $\geq 2:1$ should be referred for closure to avoid progression to Eisenmenger syndrome (for more information, see [Eisenmenger Syndrome on page 13-84](#)).

COARCTATION OF THE AORTA

Coarctation of the aorta is a condition in which there is a narrowing of the aorta, usually just distal to the left subclavian artery (although, rarely, between the left subclavian and the left carotid artery). Increased pressure proximal to the narrowing leads to left ventricular pressure overload. Know that a bicuspid aortic valve occurs in ~ 50% of patients with coarctation of the aorta! Other associated anomalies include mitral valve problems, left ventricular myocardium problems, and membranes in the left atrium. Notice that all of the heart problems seen with coarctation of the aorta are left-sided! The classic physical findings are either a delayed femoral/brachial pulse (a distinct delay between the brachial pulse and the femoral pulse) or an absent femoral pulse. Patients can have upper-body hypertension and can get hypertensive aneurysmal dilatation and rupture of the circle of Willis. Look for **rib notching** on chest x-ray due to large collateral vessels eroding the ribs. Many patients with Turner syndrome have coarctation of the aorta and a bicuspid aortic valve.

ANOMALOUS CORONARY ARTERY

Coronary anomalies are the 2nd most common cause of sudden death associated with strenuous exercise in competitive athletes (1st is hypertrophic cardiomyopathy).

Premortem detection is extremely difficult and requires a high index of suspicion. This can present as exertional chest pain or exertional syncope in a young,

otherwise healthy individual. Syncope after exercise can occur in healthy people, but syncope during exercise is never normal.

In many cases of anomalous coronary artery there is a benign retroaortic course. However, problems can occur when the left main or left anterior descending coronary artery courses between the 2 great vessels, the pulmonary artery and aorta. At rest, there is plenty of room for the vessel to pass without compromise; however, in extreme exercise, the CO can increase 4- to 8-fold. This expands the elastic pulmonary artery and aorta, resulting in compression of the coronary artery as it courses between the great vessels. This compression creates coronary ischemia and arrhythmias.

While invasive coronary catheterization is the diagnostic gold standard, coronary CTA or MRA are excellent and highly accurate noninvasive imaging methods to identify anomalous coronary arteries.

TETRALOGY OF FALLOT

Tetralogy of Fallot (TOF) is the most common cyanotic congenital heart disease. A minority of cases have a known genetic defect—usually 22q11.2 deletion syndrome (10–16%) or trisomy 21 (3–8%). TOF comprises the following 4 defects:

- 1) Large VSD
- 2) Right ventricular outflow tract obstruction
- 3) Overriding aorta
- 4) Right ventricular hypertrophy (RVH)

A helpful mnemonic to remember the 4 components of tetralogy of Fallot is V-ROAR-V: **V** for **VSD**, **R** for right ventricular outflow obstruction, **OA** for overriding aorta, and **RV** for **RVH**. Virtually all those born with TOF undergo repair and have a normal life expectancy.

SUDDEN DEATH IN EXERCISING YOUNG PEOPLE

Etiologies of sudden death in exercising young people:

- Hypertrophic cardiomyopathy (HCM; 36%)
- Coronary anomalies (17%)—especially in the 30- to 40-year-old age group
- Possible HCM (8.2%)
- Myocarditis (5.9%)
- Arrhythmogenic RV cardiomyopathy (4.3%)
- Ion channelopathies including long QT syndrome (LQTS; 3.6%)
- Primary pulmonary hypertension (especially in women)

OTHER

Marfan syndrome causes decreased strength of the aorta (with aortic regurgitation and dissection) and mitral regurgitation. Cystic fibrosis can eventually cause

pulmonary hypertension. Rubella (eradicated from the Americas) causes congenital pulmonic stenosis, PDA, and multiple pulmonary artery stenoses. Bicuspid aortic valve is discussed in [Aortic Stenosis \(AS\)](#) on page 13-48.

PULMONARY HEART DISEASE

PREVIEW | REVIEW

- What is the only effective treatment for Eisenmenger syndrome?

CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD) AND SLEEP APNEA

The most common causes of pulmonary heart disease are **COPD** and **sleep apnea** syndrome. These 2 are covered extensively in the [Pulmonary Medicine](#) section, so we will cover the other causes here.

EISENMENGER SYNDROME

Eisenmenger syndrome occurs in patients with a large intracardiac shunt, when the pulmonary vascular resistance becomes greater than systemic vascular resistance. At that point, the shunt becomes **right-to-left** instead of the usual left-to-right. It is a result of severe pulmonary hypertension, which can develop in patients with large left-to-right shunts of virtually any type: VSDs, PDAs, and ASDs. **Cyanosis** is common. Eisenmenger's is an absolute contraindication to pregnancy (more in the [Women's and Men's Health](#) section). Heart-lung transplant is the only effective treatment for Eisenmenger syndrome.

CHRONIC THROMBOEMBOLIC OBSTRUCTION

Chronic thromboembolic obstruction mainly occurs as a result of **impaired fibrinolytic resolution** of **acute** pulmonary embolism (PE), leading to organization, incomplete recanalization, and chronic obstruction of the pulmonary vascular bed. Most patients **treated** for acute pulmonary thromboembolism do **not** develop chronic pulmonary hypertension. Chronic thromboembolic obstruction can also result from other causes of secondary pulmonary hypertension such as large **left-to-right shunts** and **chronic left ventricular (LV) failure**.

Progression of this disease probably results from pulmonary arteriolar changes (rather than more PEs); these are similar to the changes that develop with large septal defects. The high pulmonary vascular resistance causes right ventricular (RV) failure. Surgical removal of the thromboembolic material results in significant improvement. In patients with deep vein thrombosis (DVT) who have failed or are unable to take anticoagulants, vena cava filters may be used.

PULMONARY HYPERTENSION

The WHO has divided pulmonary hypertension (PH) into 5 different groups, based on etiology:

- 1) Pulmonary arterial hypertension (PAH) is a rare progressive disease of the arteries of the lung. It is diagnosed by a right heart cath showing a mean pulmonary artery pressure ≥ 20 mmHg (nl = 12–16 mmHg) with a pulmonary capillary wedge pressure ≤ 15 mmHg (nl = 8–12 mmHg). This indicates high pulmonary artery and right heart pressures with normal left heart pressure.
 - Idiopathic
 - Familial
 - Drugs and toxins
 - Associated with other conditions:
 - Connective tissue disorders
 - Congenital systemic-to-pulmonary shunts
 - Portal hypertension
 - HIV infection
 - Associated with significant venous or capillary involvement:
 - Pulmonary veno-occlusive disease
 - Pulmonary capillary hemangiomatosis
 - Persistent pulmonary hypertension of the newborn
 - Other (e.g., thyroid disorders, glycogen storage disease, Gaucher disease, hereditary hemorrhagic telangiectasia, hemoglobinopathies, chronic myeloproliferative disorders, splenectomy)
- 2) PH with **left heart disease**
 - Left-sided atrial or ventricular heart disease
 - Left-sided valvular heart disease
- 3) PH associated with **lung diseases and/or hypoxemia**
 - Chronic obstructive pulmonary disease
 - Interstitial lung disease
 - Sleep disordered breathing
 - Alveolar hypoventilation disorders
 - Chronic exposure to high altitude
 - Developmental abnormalities
- 4) PH due to chronic thrombotic and/or embolic disease
 - Thromboembolic obstruction of proximal pulmonary arteries
 - Thromboembolic obstruction of distal pulmonary arteries
 - Nonthrombotic pulmonary embolism (e.g., tumor, parasites, foreign material)
- 5) Miscellaneous
 - Sarcoidosis
 - Histiocytosis X
 - Lymphangiomatosis
 - Compression of pulmonary vessels (e.g., adenopathy, tumor, fibrosing mediastinitis)

The initial tests in suspected PH are ECG and echocardiography. Echo can provide an estimate of pulmonary

artery pressure and is necessary to exclude less obvious cardiac causes of secondary pulmonary hypertension. PAH includes the sporadic idiopathic pulmonary hypertension that commonly occurs in **young women** (though men can be affected as well). Idiopathic PAH is refractory, and results in death within 5–10 years.

Treatment: Calcium channel blockers (in patients who show significant reduction in pulmonary arterial pressures during cardiac catheterization with the admission of a vasodilator) and sildenafil may be helpful. Endothelin antagonists (e.g., ambrisentan) and prostanoids (e.g., epoprostenol) can also be of use. Heart-lung transplant is occasionally used.

It is important to appropriately determine PH class, because treatments may differ between groups. For example, chronic thromboembolic pulmonary hypertension may respond to surgical removal of the thromboembolic material. A heart catheterization rules out secondary causes such as right-to-left shunt, PH due to lung disease, or chronic left ventricular (LV) heart failure. A perfusion lung scan rules out PE. Pulmonary capillary wedge pressure (PCWP) is increased only in the pulmonary hypertension caused by, or concurrent with, LV heart failure. A discussion of PAH can be found in the [Pulmonary Medicine](#) section.

PAH and Eisenmenger syndrome (particularly deadly if cyanosis is present) are absolute contraindications to pregnancy.

THE ELECTROCARDIOGRAM (ECG)

THE 12-LEAD ECG

PREVIEW | REVIEW

- Does a positive deflection on ECG tracing indicate the depolarization wave is moving toward or away from the lead?

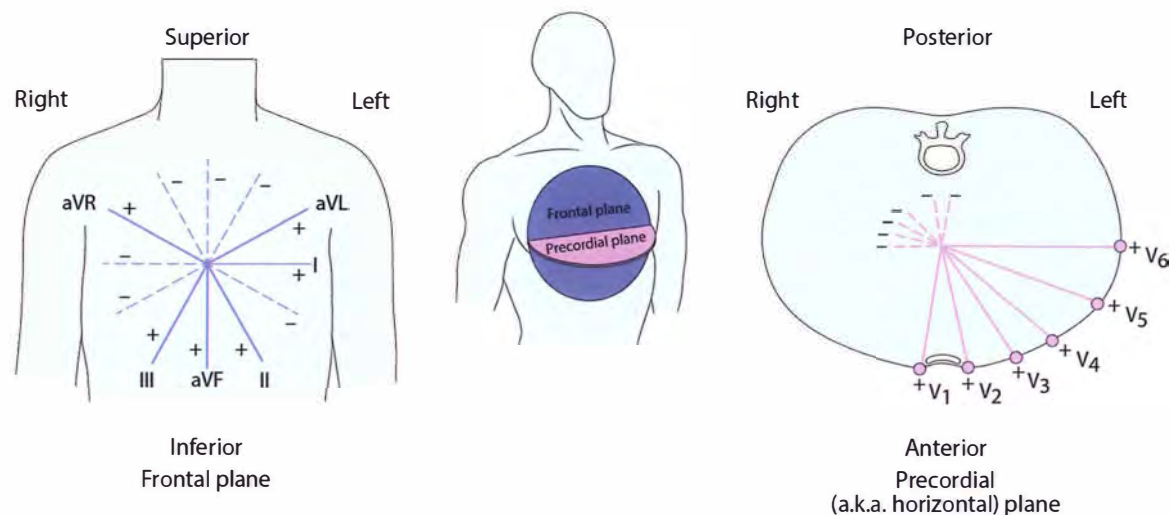


Figure 13-36: Frontal and precordial (a.k.a. horizontal) planes

First, we will briefly go over the basics of ECGs. Refer to [Figure 13-35](#) as we go through this.

A lead tracing is positive if the wave of depolarization spreads toward the positive pole of that lead, and it is negative if it spreads away from the positive pole. The tracing is zero if the wave is maximal at a 90° angle to it. For instance, if lead II is zero, look for the maximum projection to be at lead aVL (either + or –). [Figure 13-35](#) is important, so keep referring to it as you review this topic.

With the 12-lead ECG, the wave of depolarization is recorded on both the frontal plane—using limb leads I, II, and III, and the leads aVR, aVL, and aVF (which are mathematically derived from the previous 3 leads)—and the horizontal plane—using precordial leads V1, V2, V3, V4, V5, and V6. See [Figure 13-36](#). Because the frontal and horizontal planes are 2 orthogonal planes, the 12-lead ECG gives a 3-dimensional representation of the electrical activity of the heart. The projection of the electrical activity of the heart onto the frontal plane is recorded by the frontal leads I, II, III, aVR, aVL, and aVF. On the horizontal plane, it is recorded via electrodes placed in

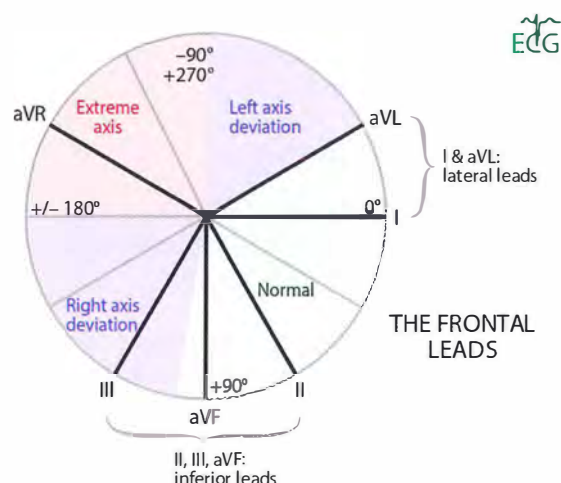


Figure 13-35: Axis determination diagram

the V1–V6 position (the precordial leads). Occasionally, V3R and V4R (placed the same as V3 and V4, except on the right side of the chest) are used to better monitor the right side of the heart (e.g., to detect right-ventricular ischemia). Depolarization moving toward the lead causes a positive deflection (P wave and QRS complex), as does repolarization moving away from the lead (T wave).

The frontal leads give inferior-superior-left-right information. For example, II, III, and aVF cover the inferior area. ST variations/Q waves occur in these leads with inferior wall ischemia and infarction.

The horizontal leads relay anterior-posterior-lateral information. Think of V1 as looking at the right side of the heart while V6 looks at the left side. The QRS in V1 is positive when the right ventricle is depolarizing (and negative when the left ventricle [LV] is depolarizing), whereas the QRS in V6 is positive when the LV is depolarizing.

ECG — AXIS DEVIATIONS

PREVIEW | REVIEW

- Know how to very quickly determine the axis of an ECG. Brand [Figure 13-35 on page 13-85](#) into your brain!
- What are the causes of left axis deviation?
- What are the causes of right axis deviation?
- Does right axis deviation always warrant additional workup in an adult?

All the electrical activity in the heart has an axis. There is an axis for the P wave, QRS complex, and ST segment. In this topic, we will focus on the basics of P-wave and QRS-complex axes.

P-WAVE AXIS

The P wave reflects the depolarization of atrial tissue. Depolarization usually starts in the sinoatrial node (found in the high right atrial wall) and propagates by **slow** myocyte-to-myocyte conduction. Think about the conduction of depolarization as the wave you generate when you throw a stone into a pond; it starts in the center and expands outward. The conduction starts from the right atrium (where the sinoatrial node is located), then propagates to the left atrium. As a result, the P-wave axis is from right to left in a **horizontal** plane. Since the sinoatrial node is high in the right atrium, the depolarization also should conduct downward toward the base (where the atrioventricular node is located). As a result, the P-wave axis is from top to bottom in a **frontal** plane. As you correctly concluded, the P-wave axis moves from top-right to bottom-left. This means the normal P-wave axis is between 0° and $+75^\circ$, in the bottom right quadrant (0° to $+90^\circ$) of the circle in [Figure 13-35 on page 13-85](#). This is illustrated in [Figure 13-37](#). Because this axis overlies lead II, P wave is best seen in this lead.

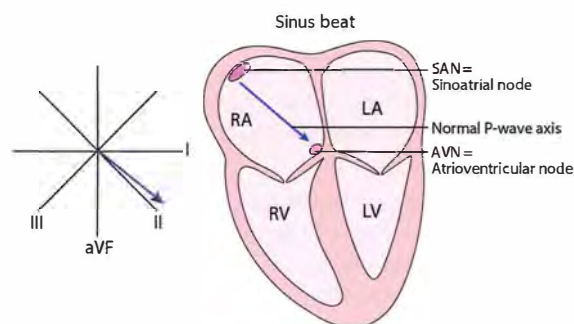


Figure 13-37: Sinus beat

QRS-COMPLEX AXIS

The QRS complex reflects depolarization of the ventricles. Ventricular depolarization usually starts at the atrioventricular node (in the base) and moves toward the apex. Thus, the QRS axis is from top to bottom in a frontal plane. Because the left ventricle has larger mass than the right ventricle, the QRS axis is shifted from right to left. Therefore, the QRS axis (like the P-wave axis) moves from top right to bottom left (see [Figure 13-38](#)). The normal mean QRS axis is between -30° and $+100^\circ$. If the QRS axis is $> +100^\circ$, right axis deviation is present; if a QRS axis $< -30^\circ$, left axis deviation is present. A quick, fairly accurate method to determine QRS axis is to look at I and aVF (because these are the ones that divide the circle into the 4 quadrants). If both are prominent, you can quickly tell in which quadrant the mean vector lies. Visualize the following:

- I (+) and aVF (+) suggests normal
- I (+) and aVF (–) suggests left axis deviation
- I (–) and aVF (–) suggests extreme right axis deviation
- I (–) and aVF (+) suggests right axis deviation

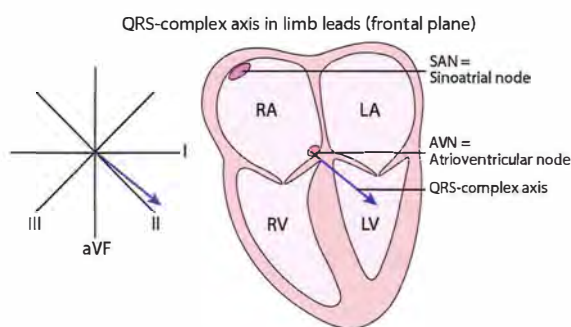


Figure 13-38: QRS-complex axis

[Figure 13-39](#) illustrates how this looks. In lead I, the R wave is 8-mm tall and S wave is 2-mm deep. So, the net vector in lead I is $+8 - 2 = +6$. Meanwhile, in lead aVF, the Q wave is 2-mm deep and the R wave is 3-mm tall, resulting in a net vector in lead aVF of $-2 + 3 = +1$. Since both leads I and aVF are positive, the QRS-complex axis is normal.

What about the P-wave axis? The P wave is positive in lead I and positive in lead aVF, thus the P-wave axis is

also normal. Note how P wave is much better visualized in lead II than in other leads.

Left axis deviation is usually due to left anterior hemiblock (a.k.a. fascicular block) and is a marker for coronary artery disease (CAD)—as are all fascicular blocks.

Right axis deviation is often a normal finding in children and young adults. Pathological causes include left posterior hemiblock, right ventricular hypertrophy, and acute or chronic right ventricular overload syndromes (e.g., pulmonary hypertension, pulmonary embolism, pulmonic stenosis). If an adult is incidentally found to have right axis deviation, do further workup.

ECG — DETERMINING HEART RATE

PREVIEW | REVIEW

- Describe one way to determine heart rate from a 12-lead ECG.

The ECG is recorded on 1-mm² graph paper, with a thicker line every 5 mm. See Figure 13-40. Because the paper moves at 25 mm/second, **each thicker line** is 1/5 of a second—or 0.2 seconds (**200 ms**)—and **each thin line** represents 0.04 seconds (**40 ms**). The interval covering **5 thicker lines** (or “big squares”) is **1 second**.

There are a couple quick ways to determine the heart rate. The RR interval is one way, although any prominent wave of the standard QRS can be used to determine the interval. Using a calculator, a quick and accurate method for determining heart rate is $1,500/\text{RR interval in mm}$. So, if the beat interval is 28 mm, the rate is $1,500/28 = 54$ bpm. A less accurate, but easier, method is to divide 300 by the number of big squares in the RR interval. If the beat interval is 28 mm, this is not quite 6 big squares. You divide 300 by 6 and get 50, **but** you know the heart rate is actually a little faster because the interval is **not quite** 6 big squares. A derivative method is taught in Dale Dubin’s book *Rapid Interpretation of EKG’s*, in which you memorize 2 sets of triplicates: 300–150–100 and 75–60–50. These represent heart rates corresponding to RR intervals of 1, 2, 3, 4, 5, and 6 big squares.

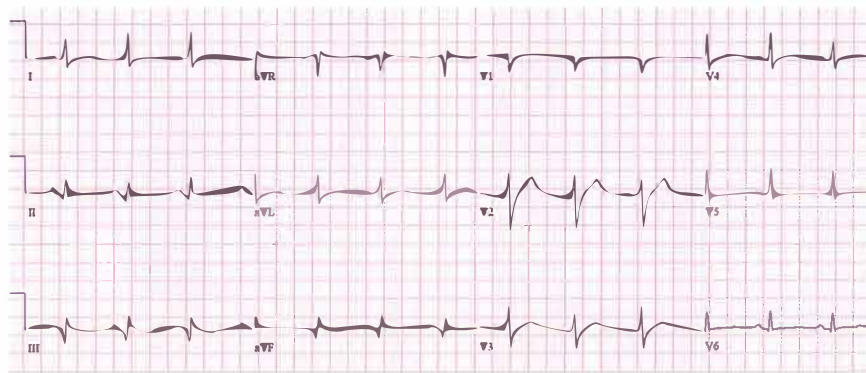


Figure 13-39: Normal QRS-complex axis (positive QRS complexes in both lead I and lead aVF)

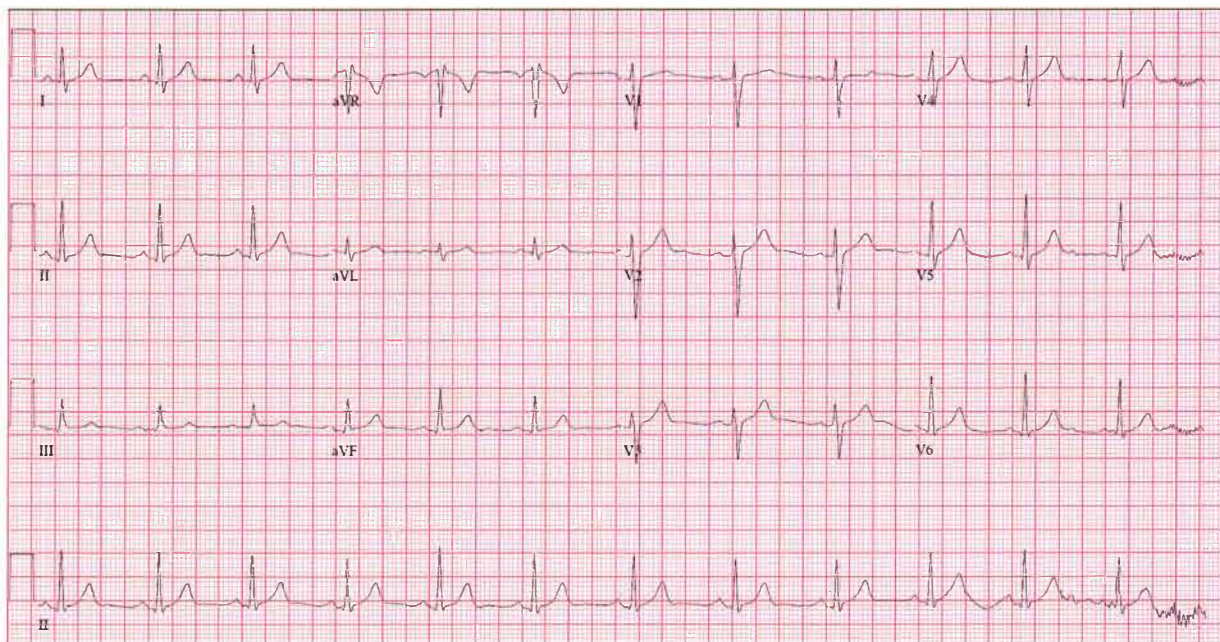


Figure 13-40: Normal ECG

Remember that the methods described above can be used only if the rhythm is regular with a fixed RR interval. If the rhythm is irregular, the RR interval is variable and the rate is over- or underestimated, depending on whether you choose the shorter or longer RR interval.

In irregular rhythm (e.g., atrial fibrillation), you can count the QRS complexes in the entire rhythm strip (which is 10 seconds) then multiply by 6. This method also works if the rhythm is regular. In the ECG above (Figure 13-40 on page 13-87), the rhythm is regular, and there are 12 QRS complexes; therefore, the rate is $12 \times 6 = 72$ bpm.

Normal rate is 60–100 bpm. Sinus tachycardia is defined as a sinus rhythm of > 100 bpm; sinus bradycardia is < 60 bpm. So, an RR interval < 3 big squares indicates tachycardia; > 5 big squares indicates bradycardia.

ECG — INTERVALS

PREVIEW | REVIEW

- Despite the much larger mass of the ventricles compared to the mass of the atria, why is the QRS-complex duration (normally < 100 ms) not significantly longer than the P-wave duration (normally 80–110 ms)?
- Why does left or right bundle-branch block cause widening of the QRS complex?
- Why does ventricular beat (such as premature ventricular contraction) cause widening of the QRS complex?
- Why does ventricular rhythm (such as ventricular tachycardia or ventricular escape rhythm) have a wide QRS duration?
- Why does ventricular pacing cause widening of the QRS-complex duration?
- Why does Wolff-Parkinson-White syndrome cause widening of QRS-complex duration?
- Name the causes of prolonged QT intervals.

PR INTERVAL

The PR interval indicates the time between the beginning of atrial depolarization (beginning of P wave) and the beginning of ventricular depolarization (beginning of QRS). Normal duration is 120–200 ms (3–5 small squares). Longer than 200 ms (1 big square) is the definition of 1st degree atrioventricular block. Shorter than 120 ms (3 small squares) may indicate Wolff-Parkinson-White syndrome (WPW; delta wave); more information is located in [QRS Duration](#).

QRS DURATION

QRS duration is normally < 100 ms (i.e., 1/2 a big square). QRS > 120 ms (i.e., 3 small squares) can be caused by left or

right bundle-branch blocks, ventricular beat (ventricular premature contraction), ventricular rhythm, ventricular pacing, and WPW syndrome. QRS duration 100–120 ms is often due to an incomplete bundle-branch block.

The conduction in the atria relies mostly on the myocyte-to-myocyte conduction, which is slow. In contrast, the conduction in the ventricles relies on the specialized conduction system (His bundle and its left and right bundle branches), which is much faster. Therefore, the larger mass in the ventricles is depolarized more quickly than the atria.

The left bundle branch divides into the anterior and posterior fascicles and then continues to additional smaller branches called Purkinje fibers. The right bundle branch does not have fascicle branches. Instead, the right bundle branch transitions directly into Purkinje fibers. See Figure 13-41.

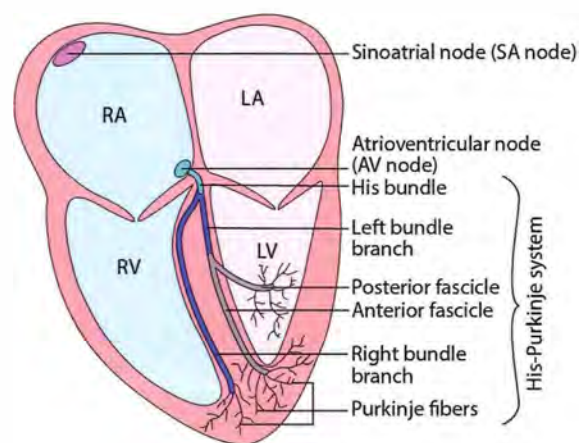


Figure 13-41: The ventricular conduction system

Left or right bundle-branch block causes widening of the QRS complex when ventricles start to rely on the **slow** myocyte-to-myocyte conduction instead of the fast conduction system (left or right bundle). The more the conduction system is compromised, the wider the QRS complex becomes.

Ventricular beats, such as premature ventricular contractions (**PVCs**), also cause widening of the QRS complex. With a PVC, ventricular depolarization originates in the ventricular tissue (outside the conduction system), then propagates to the rest of the ventricle. Depolarization is by **slow** myocyte-to-myocyte conduction, rather than the fast conduction that occurs when the atrioventricular node normally depolarizes the His bundle and then continues to the left and right bundle branches.

Ventricular rhythms, such as **ventricular tachycardia (VT)** or **ventricular escape rhythm**, have a wide QRS duration for the same reason as PVCs (see above). Ventricular depolarization originates in the ventricles and proceeds by **slow** myocyte-to-myocyte conduction. If the ventricular focus depolarizes only once, it causes a PVC. If it depolarizes multiple times, it causes VT (usually a faster depolarization rate at > 100 bpm) or ventricular escape rhythm (usually a slower depolarization rate at 30 bpm).

Ventricular pacing causes widening of the QRS-complex duration because the pacer is placed in the ventricle and, thus, paces and depolarizes a specific focus in the ventricle. Then, just like in PVC or VT, the depolarization uses the **slow** myocyte-to-myocyte conduction. In cases where the pacer paces the His bundle, the QRS complex is usually narrow because the depolarization occurs through the fast conduction system.

WPW syndrome causes widening of QRS-complex duration because there is an **accessory pathway** that **directly** connects the atria to the ventricles. Atrial depolarization of the atria conducts to the ventricles using this accessory pathway, bypassing the normal pathway (i.e., the atrioventricular [AV] node to His bundle to bundle branches). Normally, the AV node delays conduction of depolarization from atria to ventricles (this delay causes the PR interval). However, in WPW, there is **no delay** in the accessory pathway, and it conducts immediately, shortening the PR interval. The delta wave seen at the beginning of the QRS complex is due to the conduction in the accessory pathway using **slow** myocyte-to-myocyte conduction. Meanwhile, the AV node starts to conduct after its normal delay, and ventricular depolarization occurs via the **fast** conduction system. In [Figure 13-42](#), notice how the delta wave is wide with slurred take-off (using the slow myocyte-to-myocyte conduction) while the rest of the QRS complex suddenly becomes narrow and sharp (the conduction system takes over). Because of the delta wave, the QRS-complex duration becomes wide.

QT INTERVAL

The QT interval corrected for rate (QT_c) is normally 340–470 ms, depending on gender and age. $QT_c = QT / \sqrt{RR}$; that is, the QT interval (in ms or seconds) divided by the square root of the beat interval in **seconds**. Again, the RR interval in this calculation **must** be in seconds. (Consider the

difference between dividing by the square root of 0.7 and the square root of 700!) When scanning ECGs, a rule of thumb is: The QT interval normally is < 50% of the RR interval—do the calculation for QT_c if it appears longer or very short (< 1/3 of the RR interval).

Note: We use the **corrected** QT interval instead of the QT interval because QT interval is not a fixed duration; it changes with heart rate (just like how durations of systole and diastole change with heart rate). With a faster heart rate, the QT interval has to become shorter (to allow the next depolarization to start immediately). With slower heart rate, the QT interval has to become wider (less consumption of energy). The corrected QT interval is useful because it is corrected for heart rate.

With prolonged QT_c , there is a tendency to develop **polymorphic ventricular tachycardia**. If the prolonged QT_c is due to **bradycardia**, the polymorphic ventricular tachycardia is then called **torsades de pointes** (which means “twist of points” in French); see [Figure 13-43](#) and notice how the arrhythmia looks like a twisted ribbon.

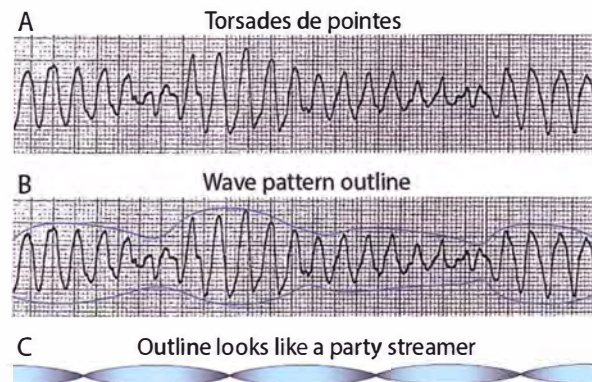


Figure 13-43: Torsades de pointes — a form of polymorphic ventricular tachycardia due to prolonged QT_c from bradycardia



Figure 13-42: Wolff-Parkinson-White (a.k.a. preexcitation) syndrome. Note the short PR interval because of the delta wave. Slurred take-off of delta waves (marked in red) cause widening of QRS-complex duration.

Prolonged QT_c has many causes:

- Long QT syndrome
- Tricyclic overdose
- Hypocalcemia
- Hypomagnesemia
- Hypokalemia
- Starvation
- Central nervous system insult (such as large stroke or intracranial hemorrhage)
- Hypothermia
- Type Ia and III antiarrhythmics (e.g., quinidine, procainamide = Class Ia; e.g., amiodarone, sotalol = Class III)
- Opioids, such as hydrocodone and methadone
- Antipsychotics, including chlorpromazine, haloperidol, and thioridazine
- Liquid protein diet
- Some medications, such as erythromycin and estradiol

Short QT_c can be caused by hyperkalemia, hypercalcemia, and digoxin.

Long QT syndrome (LQTS) is a hereditary condition caused by different channelopathies. These patients can be at risk for life-threatening arrhythmias. Patients with LQTS should be instructed to avoid strenuous exercise (which can precipitate arrhythmias) and avoid drugs that prolong the QT interval (see above). LQTS is usually treated with a β -blocker.

Syncope and sudden cardiac death (death from a cardiac cause) are major concerns in patients with LQTS. These patients should avoid exercise. Though syncope and sudden cardiac death can occur in WPW as well, the risk is much higher LQTS patients.

ECG — WAVEFORMS AND SEGMENTS

PREVIEW | REVIEW

- What are the P-wave findings for right atrial hypertrophy? For left atrial hypertrophy?
- What are the 5 causes of an R wave in lead V1?
- What does poor R-wave progression across the precordial leads indicate?
- When are peaked T waves seen?
- What do focal, flipped T waves signify?
- U waves indicate a predisposition to which serious condition?
- What are the common causes of U waves?
- What is the significance of an inverted U wave?
- Name the 3 main causes of ST-segment elevation.
- What are the causes of ST-segment depression?

P WAVE

The P wave results from the depolarization of the atria. The normal P wave is < 2.5 mm in height and < 120 ms (3 small squares) in duration, and the normal axis is 0° and +75°. For simplicity, you can think of it as almost the same as the axis of QRS complex, within the bottom right quarter (0° to +90°) of the circle in [Figure 13-35](#) on [page 13-85](#). Do not confuse P-wave duration (from beginning of P wave to end of P wave; normally 80–110 ms) with PR interval (from beginning of P wave to beginning of QRS complex; normally 120–200 ms). See [Figure 13-44](#).

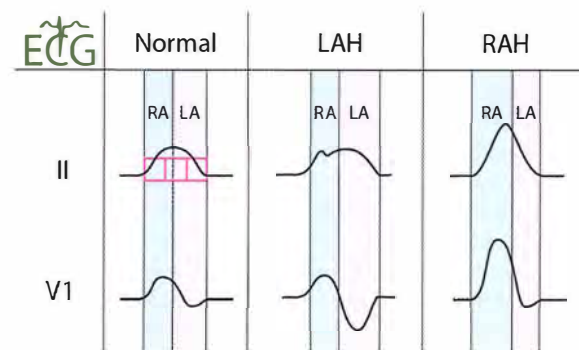


Figure 13-44: P wave in atrial enlargement

Most information from the P wave can be derived from II, aVR, and V1. As the wave of depolarization spreads from the SA node high in the right atrium and through the right and then left atrial myocardium, the mean vector is downward and to the patient's left—so the normal P wave is positive in II and negative in aVR.

If the atria are depolarized from a different focus, say a paroxysmal atrial contraction in the bottom of the left atrium ([Figure 13-45](#)), the P-wave axis is superior (from bottom to top) and rightward, which is the opposite of the normal P-wave axis. Note how the normal P wave is very positive in lead II because its normal axis overlies lead II, while an ectopic P wave can have a superior axis and, thus, can be negative on lead II.

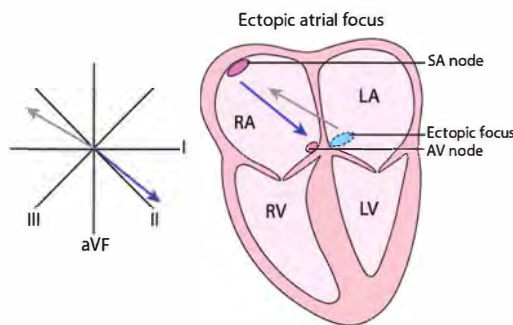


Figure 13-45: Axis of atrial depolarization. Note the difference in axis between normal sinus P wave (blue arrow) and an ectopic atrial P wave (gray arrow).

Seeing a P wave before each QRS complex does not necessarily mean the rhythm is sinus in origin. Refer to [Figure 13-46](#) and [Figure 13-47](#). The ECGs are very similar, but do they both show sinus rhythm? No. The P wave is inverted in the inferior leads in the 1st ECG (indicating

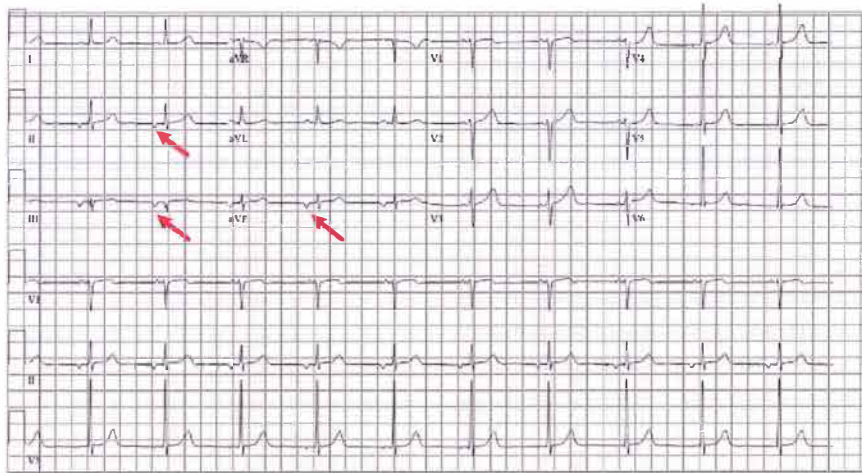


Figure 13-46: Ectopic atrial rhythm. Note the negative P waves in inferior leads due to abnormal (superior) P-wave axis. Even though there is a P wave before each QRS complex (see rhythm strip at the bottom of the ECG), this does not automatically indicate a sinus rhythm.

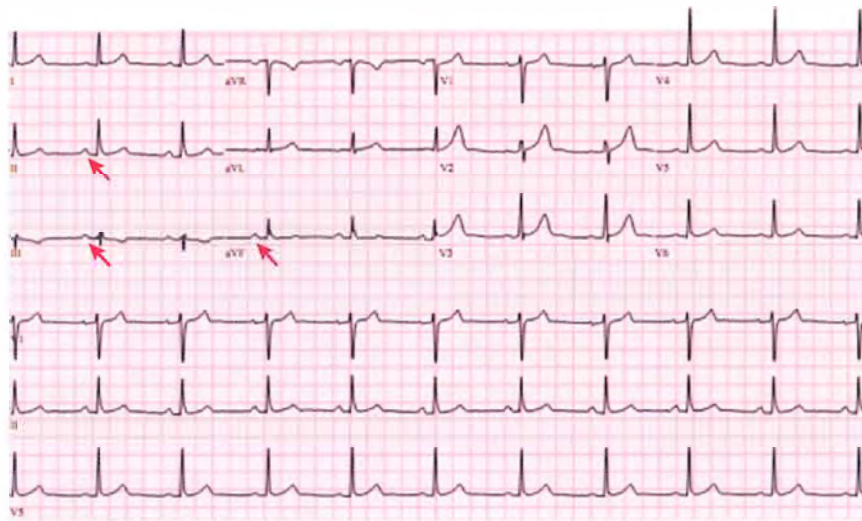


Figure 13-47: Sinus rhythm. Note the positive P waves in inferior leads due to normal P-wave axis.

ectopic atrial rhythm), while it is normal (upright) in the 2nd one (indicating sinus rhythm).

Because atrial depolarization traverses from the patient's right to left, the left/initial side of the P wave represents the right atrium, while the right/terminal side of the P wave represents the left atrium (mid-P wave is both).

The normal P wave is positive in lead II and positive or biphasic in V1. Biphasic means the wave is initially a positive wave, then becomes negative (see the lower left waveform in Figure 13-44). This is because the wave of depolarization through the atria is initially toward V1 in the right atrium (initial part of P wave) and somewhat away from V1 in the left atrium (latter part of P wave).

With **right atrial enlargement** (a.k.a. right atrial hypertrophy; RAH), the right atrial (initial) portion of the P wave is widened and therefore overlaps onto the left atrial (latter) portion of the P wave. The P wave width stays normal (< 120 ms), but look for an increased P-wave amplitude in II and V1 (the positive portion). The P wave being **peaked** in II is more important than its being tall.

Decreased P-wave amplitude is seen in severe hyperkalemia. If you cannot see P waves and the rhythm seems to be regular and narrow but too fast to be junctional (i.e., QRS complexes are present at > 60 bpm), it is possible that the patient has hyperkalemia and P-wave amplitude is too low to be visible. Consider this in a patient with other findings suggestive of hyperkalemia, such as peaked T waves and being on hemodialysis.

With **left atrial enlargement** (a.k.a. left atrial hypertrophy), the latter part of the P wave is enlarged, resulting in a wide P wave with a shortened or absent PR interval (i.e., < 120 ms). Other typical findings are a widened, notched P wave in II and an enlargement of the negative portion of the P wave in V1. The most **sensitive** ECG finding for left atrial enlargement is a negative P wave in V1, with a duration of > 40 ms (1 small square). On the other hand, the most **specific** ECG finding is a notched P wave (usually in II) with an interpeak distance of > 40 ms (see the upper middle waveform in Figure 13-44).

Chronic obstructive pulmonary disease (COPD): Because of the hyperexpanded lungs, there is not much room within the mediastinum, the heart assumes a more vertical position, and there is resultant right axis deviation of the P wave. A $+90^\circ$ P-wave axis is highly suggestive of COPD. Also, the pulmonary hypertension can result in RAH with associated P-wave changes.

R WAVE

The R wave is always the positive deflection in the QRS complex. The Q wave is the negative deflection that precedes R wave, and the S wave is the negative deflection that follows R wave. If there is no R wave and the entire QRS complex is negative, then this can be referred to as QS wave (Figure 13-48).



Figure 13-48: Two of the various morphologies of QRS complex

The R wave should be negligible (or very small) in lead V1 because the QRS-complex axis is away from V1. The presence of a noticeable R wave in V1 alerts you to one of the following:

- Right bundle-branch block (RBBB)
- Right ventricular hypertrophy (With an enlarged right ventricle, the QRS axis shifts rightward, toward V1.)
- WPW pattern
- Prior posterior ST-elevation myocardial infarction
- Duchenne muscular dystrophy (rarely seen in adults, as affected individuals die in childhood)

In Figure 13-49, notice how the R wave increases in amplitude from V1 to V4/V5 (depending on where the leads are placed on the chest wall) then decreases in amplitude slightly in V6. This is normal R-wave progression in which the QRS-complex axis points at V5. In Figure 13-50, notice the normal QRS axis is away from V1 (thus, the negative R wave in that lead) and mostly toward V4 (thus, the large R wave in that lead). V5 and V6 still have positive R waves but with less amplitude than V4.

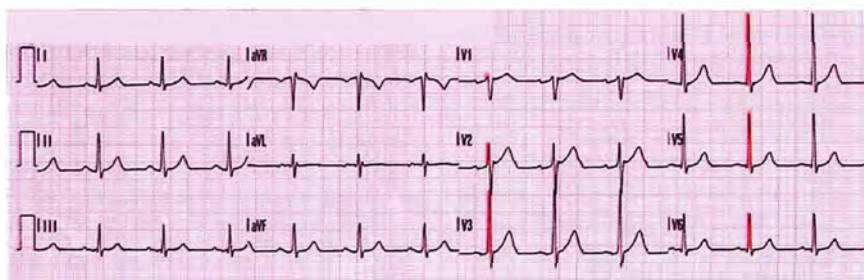


Figure 13-49: ECG showing normal R-wave progression

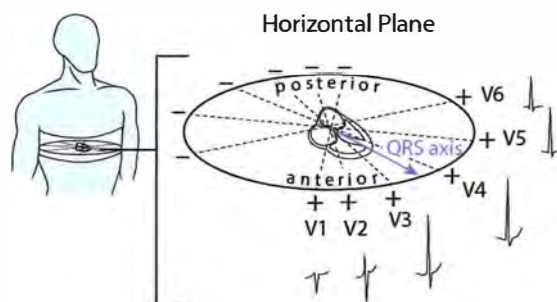


Figure 13-50: R-wave axis and normal R-wave progression

When the R wave does not become progressively taller from V1 to V4-V5, poor R-wave progression is present. Poor R-wave progression can indicate prior anterior myocardial infarction (MI). After MI, the damaged myocardial tissue is replaced by scar. Scar tissue does not depolarize; so, there is a loss of electrical activity in that area. Therefore, R waves in precordial leads do not have normal voltage (i.e., amplitude).

T WAVE

The T-wave axis is ordinarily in the same direction as the QRS axis.

Causes of peaked T waves:

- Hyperkalemia
- Acute myocardial infarction (early stage, before ST segments start to deviate)
- Intracerebral hemorrhage

Focal, flipped (i.e., inverted) T waves may accompany:

- Ischemia
- RBBB, right ventricular hypertrophy (RVH), and elevated right ventricular pressure (in V1-V2)
- Left ventricular hypertrophy (LVH)
- Left bundle-branch block (LBBB; in lateral leads I, aVL, V6)

Diffuse, flipped T waves may accompany:

- Pericarditis
- Diffuse ischemia; after resuscitation
- Metabolic abnormalities
- Intracerebral hemorrhage

U WAVE

The U wave is not a common finding and occurs just after the T wave. It is typically small and is best seen in V2–V3. If seen, it is usually a < 1-mm, rounded deflection in the same direction as the T wave. A **prominent U wave** indicates an increased tendency for **polymorphic ventricular tachycardia**. Prominent U waves are present with **hypokalemia**, **bradycardia**, **digoxin**, and **amiodarone**.

Inverted U waves are significant—even if the rest of the ECG is normal! Causes are **ischemia**, **hypertension**, **mitral** or **tricuspid valve disease**, and **RVH**. Inverted U waves occur in up to 60% of patients with an anterior MI, up to 30% of patients with an inferior MI, and up to 30% of patients with **angina**.

ST SEGMENT

This is important! Know this **very well**!

ST-segment deviation (elevation or depression; [Figure 13-51](#)) is evaluated relative to the isoelectric line, which is commonly the preceding **TP segment** (end of the T wave to the beginning of the P wave). If the isoelectric line is not clear (artifact or labored breathing that causes the line to shift up and down), you can use the **onset of Q wave** as a reference. Notice that the isoelectric line is wandering and changing in [Figure 13-52](#). Because of respiratory variations (marked in green), it is difficult to identify a reliable TP segment (marked in blue) to use as reference. In this situation, use the onset of Q wave as a reference—in this case, to correctly conclude that there is no ST deviation (marked in red). Using the TP segment as a reference can lead to the erroneous conclusion that there is ST depression.

ST-segment deviation is measured in millimeters. The more deviated the ST segment (whether ST elevation

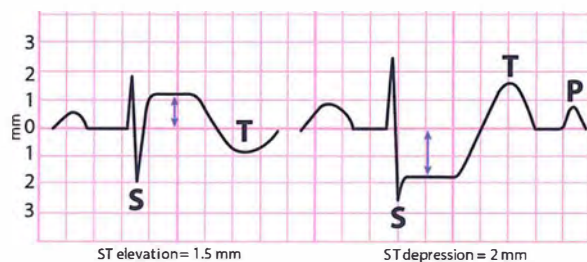


Figure 13-51: ST-segment deviation (elevation and depression)

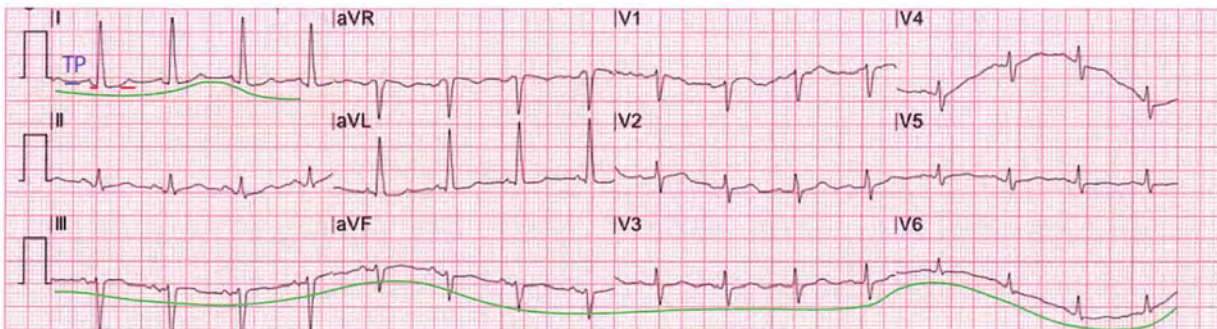


Figure 13-52: No identifiable isoelectric line

or ST depression), the more severe the ischemia and resulting myocardial infarction. The larger the number of leads showing ST-segment deviation (whether ST elevation or ST depression), the larger the area of involved myocardial tissue.

Note: ST elevation can be present in healthy individuals. Patients < 40 years of age may commonly have it (called early repolarization); therefore, a different cutoff is used for this population (see below).

ST segment **elevation** can have 2 distinct morphologies ([Figure 13-53](#)):

- Concave upward, which is seen in pericarditis (not a life-threatening condition, thus, a happy face) and early repolarization (normal variant)
- Convex upward, which is seen in ST-elevation myocardial infarction and coronary vasospasm (both life-threatening conditions, thus, a sad face)

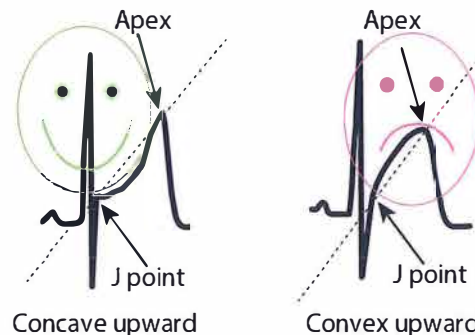


Figure 13-53: Morphologies of ST-segment elevation—concave up is benign (happy face) and convex up can be life-threatening (sad face)

Early repolarization (a.k.a. benign early repolarization): This is a common cause of ST elevation. It is a **normal** variant in those < 40 years of age ([Figure 13-54](#) on page 13-94 and [Figure 13-55](#) on page 13-94). Do not confuse this normal ST-segment elevation with the abnormal ST-segment elevation in ST-elevation myocardial infarction (STEMI). Criteria for early repolarization include:

- Age < 40 years (avoid making this diagnosis in patients older than 70 years of age)
- ST elevation in precordial leads (mainly V2–V5) but no reciprocal ST depression that suggests STEMI
- ST elevation is concave upward (happy face).

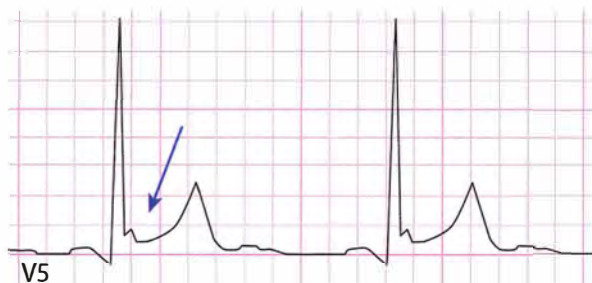


Figure 13-54: ST elevation due to benign early repolarization. Notice the notching at the end of R wave (arrow).

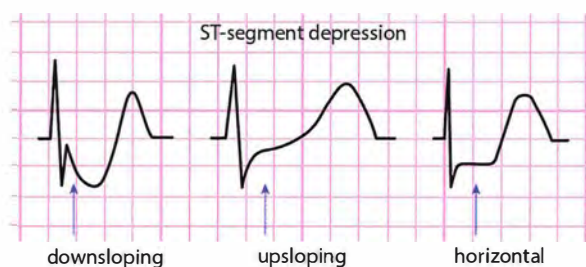


Figure 13-56: Morphologies of ST-segment depression



Figure 13-55: ST elevation due to benign early repolarization in a 38-year-old male

- There is elevated J point (junction between end of QRS and beginning of ST segment).
- ST elevation is $< 25\%$ of the height of the T wave in lead V6.
- There is usually notching on descending limb of R wave, mostly seen in V4 and V5.

ST-segment depression can have 3 distinct morphologies (Figure 13-56). Downsloping ST depression and horizontal ST depression are indicative of ischemia or infarction. Upsloping ST depression is less specific for ischemia.

ECG is a great tool to assess for ischemia, as it is readily available. However, it is not a perfect tool. To improve specificity of ECG (i.e., supporting the diagnosis that ischemia is truly present), certain cutoffs are used for ST-segment elevation and depression. The European Society of Cardiology, American College of Cardiology, American Heart Association, and World Heart Federation Task Force released the Fourth Universal Definition of Myocardial Infarction in 2018 that provides the following guidance:

- ST-segment elevation should be present in at least two contiguous leads as follows:
 - In V2-V3, ST elevation should be ≥ 2 mm in men ≥ 40 years of age; ≥ 2.5 mm in men < 40 years of age (note the higher cutoff to improve specificity in this population); and ≥ 1.5 mm in women regardless of age. There is a lower cutoff in women to increase the sensitivity of ECG because women may have acute coronary syndrome with atypical symptoms.
 - In leads other than V2-V3, ST elevation should be ≥ 1 mm.

- ST-segment depression
 - New horizontal or downsloping ST depression should be ≥ 0.5 mm in two contiguous leads, and/or
 - T inversion should be > 1 mm in two contiguous leads with prominent R wave or R:S ratio > 1 .

There are 3 main causes of ST-segment elevation: acute STEMI, coronary vasospastic (i.e., Prinzmetal) angina, and pericarditis. It can also be present with early repolarization variant, stress-induced (i.e., takotsubo) cardiomyopathy, LBBB, left ventricular wall aneurysm, and hypothermia (J wave, a.k.a. Osborn wave; Figure 13-57).

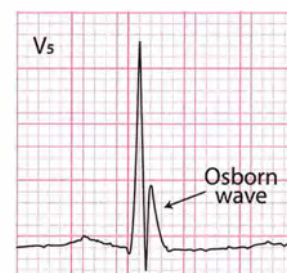


Figure 13-57: Osborn wave
Source: Jason E. Roediger, CCT, CRAT

Note: In STEMI and coronary vasospasm, ST elevation is **convex up (sad face)** and **limited** to leads covering the affected myocardial territory. In pericarditis, ST elevation is **concave up (happy face)** and **diffuse** in all leads.

In pericarditis, the diffuse concave-up ST elevation is usually followed by PR depression in all leads (except in aVR where PR is elevated). Use the depressed PR to support a diagnosis of pericarditis.

ST-segment depression occurs with:

- Subendocardial ischemia (especially if downsloping or flat), such as seen in classic angina
- Unstable angina and non-ST-elevation myocardial infarction (NSTEMI)

- Digoxin toxicity
- Acute posterior MI in V1–V2 (Remember this is STEMI with mirror sign rather than NSTEMI; refer to [Acute Coronary Syndromes \(ACSs\)](#) on page 13-17.)
- Reciprocal depression in inferior leads, which may accompany anterior STEMI
- Left ventricular hypertrophy with LV strain (ST depression with flipped T waves in the leads that meet the LVH criteria)
- Right ventricular hypertrophy (may cause right axis deviation and ST depression preceding a flipped T wave in V1)

QRS COMPLEX

During the QRS complex, both ventricles depolarize simultaneously **after** the interventricular septum depolarizes. The normal mean axis of interventricular **septum** depolarization points from the patient's left to the right across the septum (i.e., pointing toward V1 and away from V6). You see this as a small **initial** deflection that is positive in V1 (r wave) and negative in V6 (q wave). After the first part (basal segment) of the septal wall depolarizes, the conduction system directs depolarization to both left and right ventricles; the QRS-complex axis starts to shift leftward because the mass of the left ventricle is larger than the right ventricle. See [Figure 13-58](#).

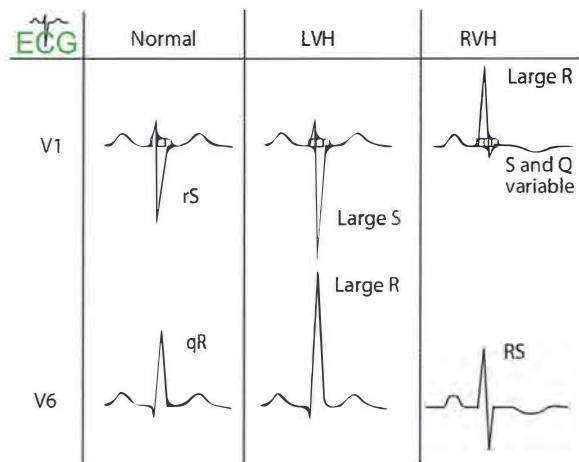


Figure 13-58: Ventricular hypertrophy

By convention, a smaller wave in the QRS complex is written in lowercase, and a larger wave is written in uppercase.

The left ventricle is normally much more massive than the right ventricle; therefore, the mean QRS axis (reflecting depolarization of the ventricles) is strongly to the patient's left. You see a large net negative deflection in V1 and positive net deflection in V6. So, in the **frontal** plane, the mean axis is between -30° and $+100^\circ$.

The normal duration of the QRS is < 100 ms.

QRS changes seen with ventricular hypertrophy and conduction disturbances are discussed in [ECG – Ventricular Hypertrophy](#).

ECG — VENTRICULAR HYPERTROPHY

PREVIEW | REVIEW

- What are the ECG criteria for left ventricular hypertrophy? Right ventricular hypertrophy?
- Which of the listed LVH criteria does the ECG in [Figure 13-59](#) on page 13-96 meet?
- Which of the listed RVH criteria does the ECG in [Figure 13-60](#) on page 13-96 meet?
- What ECG changes would you expect to see in the presence of a large pulmonary embolism causing acute cor pulmonale?

LEFT VENTRICULAR HYPERTROPHY (LVH)

LVH causes a leftward shift of the QRS-complex axis because of the increased mass of the left ventricle.

This prolonged activation results in a reversal of repolarization that proceeds from the endocardium to epicardium and is reflected by a **flipped T wave** in the septal leads (V1–V2).

There are many criteria for LVH on ECG and you do not need to know all of them. Do know that ECG criteria for LVH are specific, but not very sensitive (ECG specificity for LVH is 95%, and sensitivity is 50%). **Know the most common ECG criteria for LVH:**

- 1) R wave in aVL ≥ 12 mm or
- 2) S wave in V1 + (R in V5 or R in V6) > 35 mm or
- 3) R in aVL + S in V3 > 28 mm in males or > 20 mm in females (Cornell criteria, most accurate)

Criteria 2 is the equation that you read: “The **S** in **V1** plus the **R** in **V5** is **> 35 mm**” ([Figure 13-59](#) on page 13-96).

The ECG in [Figure 13-59](#) on page 13-96 illustrates several of the ECG criteria for LVH: 1) R wave in aVL ≥ 12 mm, 2) S wave in V1 + R in V5 = 57 mm (i.e., > 35 mm), and 3) R in aVL + S in V3 = 48 mm (thus meeting Cornell criteria for both males and females).

A left ventricular strain pattern may be present with LVH. LV strain is precordial ST-segment depression and flipped T waves in a patient with ECG criteria for LVH. Note the ST depression and T-wave inversion in leads I, aVL, V5, and V6 in the ECG in [Figure 13-59](#) on page 13-96. Generally, the ST-segment and T-wave changes of LV strain occur in the leads that meet the criteria for LVH.

RIGHT VENTRICULAR HYPERTROPHY (RVH)

In RVH, the increased mass of the right ventricle shifts the QRS-complex axis toward the right.

ECG criteria for RVH are **right axis deviation** ($> +100^\circ$) plus any of the following:

- 1) R wave in V1 ≥ 7 mm or
- 2) R:S ratio in V1 > 1 or
- 3) R:S ratio in V5 or V6 < 1

Remember to look for that R wave in lead V1!

The ECG in [Figure 13-60](#) illustrates all of the ECG criteria for RVH: right axis deviation plus 1) R wave in V1 ≥ 7 mm, 2) R:S ratio in V1 > 1 , and 3) R:S ratio in V5 or V6 < 1 . You can also see ST-segment depression and inverted T waves in the right precordial leads (i.e., V1, V2)—this is an RV strain pattern. Similar to LVH, those ST-segment and T-wave changes occur in the leads that meet the criteria for RVH ([Figure 13-60](#); note the ST depression and T-wave inversion in lead V1).

Pulmonary embolism (PE): Note that with acute, severe **pulmonary embolism** causing acute cor pulmonale, the ECG shows sinus tachycardia (the most common finding) and sometimes acute RV strain with RV and RA dilation $\pm$ ischemia. There is often an RBBB, and sometimes right axis deviation. Also look for an S1Q3T3 pattern (S wave in lead I, Q wave in lead III, and an inverted T wave in lead III), which indicates RV strain and is a somewhat specific, but not sensitive, indication of acute PE.

ECG — CONDUCTION DISTURBANCES

PREVIEW | REVIEW

- What rhythm does the ECG in [Figure 13-64](#) show? What is the origin of the ventricular rhythm (QRS complexes)?
- When do you suspect the presence of a left bundle-branch block (LBBB) or right bundle-branch block (RBBB)?
- What do you see on an ECG in LBBB? RBBB?
- Patients with anterior MI and a new bifascicular block are at high risk for what complication?

ATRIOVENTRICULAR (AV) BLOCKS

AV blocks are due to conduction disturbances at the AV node. Know the 3 degrees and their patterns.

1st degree AV block prolongs the PR interval to > 200 ms (1 big square). See [Figure 13-61](#).

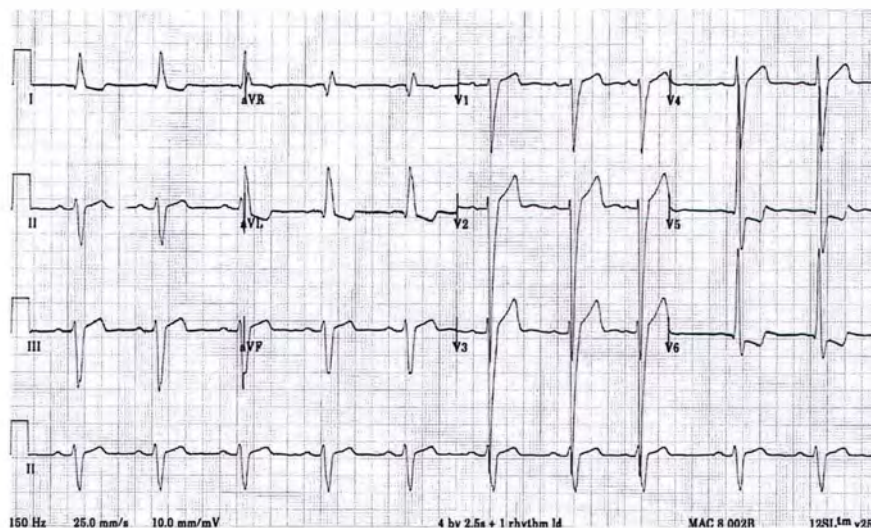


Figure 13-59: Left ventricular hypertrophy

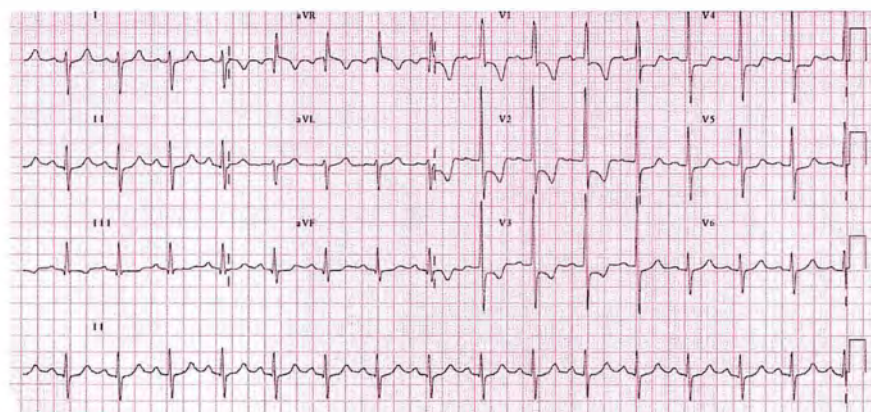


Figure 13-60: Right ventricular hypertrophy

Figure 13-61: 1st degree AV block**2nd degree AV block has 2 patterns:**

- **Mobitz Type 1 (i.e., Wenckebach)**—PR intervals become progressively longer until there is a dropped QRS (ventricular beat). The block here is usually at the level of the atrioventricular node (**intranodal** block) and QRS is usually narrow (Figure 13-62). Since the conduction system is not involved, this carries a benign prognosis. It usually does not progress to complete heart block. You can continue β -blockers with this type of AV block.
- **Mobitz Type 2**—PR intervals are normal, but periodically there is a dropped QRS. 2:1 AV block is 2 P waves for each QRS (see Figure 13-66 on page 13-98), 3:1 is 3 P waves for each QRS, and so on. The block is usually at the His bundle (**infranodal** block). Since the conduction system is involved, QRS is usually wide but sometimes is narrow (as in Figure 13-63) and it carries a poor prognosis: Mobitz Type 2 can progress to complete heart block. Avoid β -blockers in this type of AV block and consider permanent pacemaker implantation.

Figure 13-62: 2nd degree AV block, Mobitz Type 1 (Wenckebach)Figure 13-63: 2nd degree AV block, Mobitz Type 2

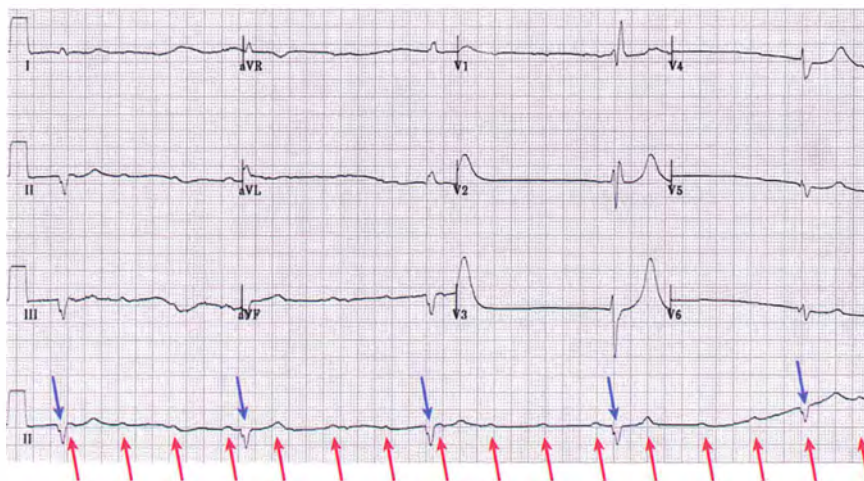
3rd degree AV block (a.k.a. complete heart block): There is no communication between the atria and ventricles (because the point of communication, the AV node, is not conducting depolarization). Each of the atria and ventricles are depolarizing on their own. Again, no depolarizations are conducted through the AV node. The P waves and QRS complexes have independent **regular** rhythms. If the QRS complex has a normal width (< 100 ms, also referred to as narrow), the rhythm is a junctional ectopic rhythm, which is usually at 40–60 bpm. If the QRS complex is wide (> 120 ms), then the rhythm is a ventricular escape rhythm, which is usually at 20–40 bpm. In Figure 13-64, notice the regular P waves (red arrows) and the **narrow** QRS complexes (blue arrows), which occur at regular intervals and independent of one another. In Figure 13-65 on page 13-98 notice the regular P waves (red arrows) and the **wide** QRS complexes (blue arrows), which occur at regular intervals and independent of one another.

In both ECGs, notice that the PP and RR intervals are constant, but there is no correlation between them. Remember, you may not be able to see all the P waves because some are buried within the QRS complexes, but if you march them out, you should be able to predict where the next P wave will be.

In Figure 13-64, the QRS complexes are narrow because ventricular depolarization is completed via the fast conduction system and originates from the His bundle (i.e., junctional escape rhythm).

In Figure 13-65 on page 13-98, the QRS complexes are wide because ventricular depolarization is completed via the slow myocyte-to-myocyte conduction system and originates from the ventricles themselves (i.e., ventricular escape rhythm). Notice how the ventricular escape rate is much slower than the junctional escape rate.

Note: The origin of complete heart block can be within the AV node (i.e., **intranodal** block). This is commonly seen in **inferior** ST-elevation myocardial infarction (STEMI). With intranodal block, QRS complexes are normal in duration (**narrow**). Complete intranodal heart block is usually **transient**, resolves within 48 hours, and does not need a

Figure 13-64: 3rd degree AV block (a.k.a. complete heart block) with **junctional** escape rhythm

permanent pacemaker. It does not increase mortality in inferior STEMI.

On the other hand, complete heart block can be at the level of the His bundle (i.e., **infranodal** block). This is more commonly seen with **anterior** STEMI and is usually accompanied by a **wide** QRS complex. The conduction system is damaged in infranodal block, while it is normal in intranodal block. This level of complete heart block is usually **permanent**, and if it does not resolve in 2 weeks, the patient will need a permanent pacemaker. In the meantime, use a temporary pacemaker. Because new infranodal block suggests extensive damage to the myocardial tissue (a damaged conduction system), **mortality** is even **higher** than in anterior STEMI without complete heart block.

2:1 AV block: This is the diagnosis when every other P wave does not conduct. When this happens, there is no method that reliably discriminates between Mobitz 1 and Mobitz 2, because you cannot see either the progressive lengthening of PR interval (Mobitz 1) or the fixed PR interval (Mobitz 2) until QRS drops. One way to begin to distinguish between them is to look at the QRS complex

(Figure 13-66); if narrow, then Mobitz 1 is more likely; if wide, then Mobitz 2 is more likely. Keep in mind that Mobitz 1 and 2 are ECG patterns, and as such, if you do not explicitly see them, they cannot inform a diagnosis. So, if there are no explicit ECG findings, use a diagnosis of 2:1 AV block without a Mobitz designation and consider an electrophysiologic study to assess the level of block.

Note the regular sinus rhythm with normal P-wave axis firing at a regular interval. Every other P wave (red arrows) does not conduct and there is a dropped QRS. Notice that the T waves (green arrows) look similar to P waves; however, if you march out the P waves, you can see that the T waves do not fit there. QRS complexes are marked in blue.

BUNDLE-BRANCH BLOCK (BBB)

Just a little after the AV node, the fast conduction pathway, known as the His bundle, splits in 2. These 2 fast conduction pathways travel down the interventricular septum; 1 pathway goes to the right ventricle, while the other pathway goes to the left ventricle, splits again, and proceeds

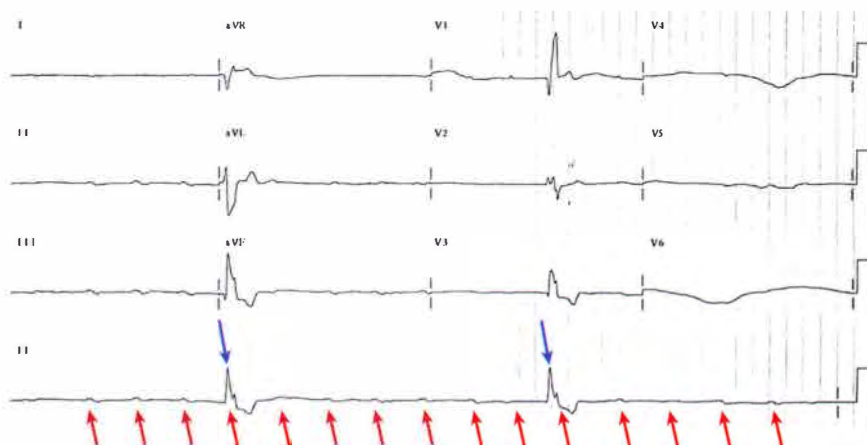


Figure 13-65: 3rd degree AV block (a.k.a. complete heart block) with **ventricular** escape rhythm

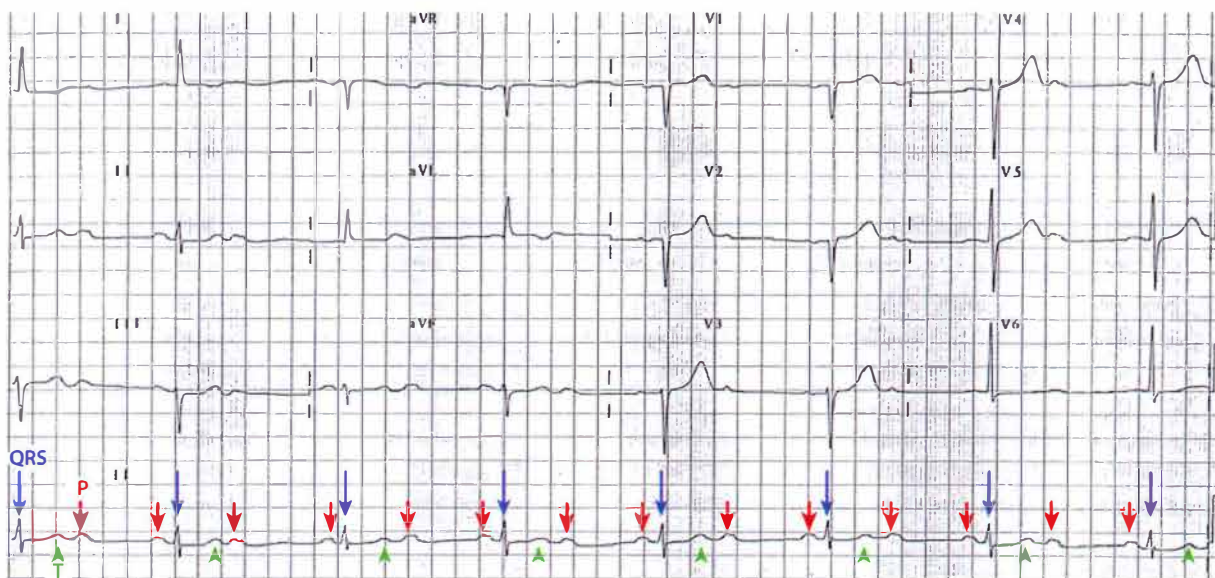


Figure 13-66: 2:1 AV block (2nd degree AV block, Mobitz Type 2)

to the anterior and posterior walls of the left ventricle. If conduction in 1 of these pathways is blocked (a BBB), the depolarization downstream to that pathway is delayed because the myocardial tissue in that area can only be depolarized via the **slow** myocyte-to-myocyte conduction (Figure 13-67).

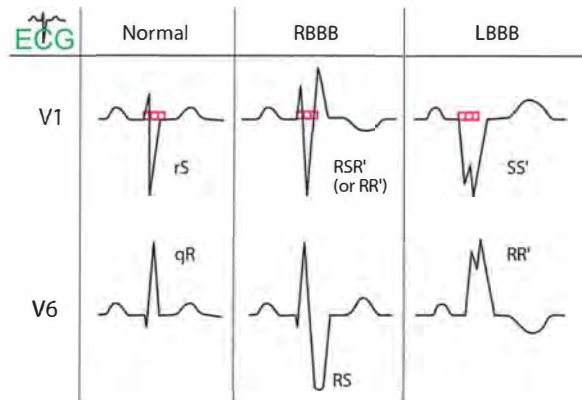


Figure 13-67: Bundle-branch block

Suspect left bundle-branch block and right bundle-branch block when you see a QRS duration of > 120 ms. If QRS is > 120 ms, then use the approaches described in **Left Bundle-Branch Block (LBBB)** and **Right Bundle-Branch Block (RBBB)** to determine which type of block is present.

Recall that lead **V1** records electrical activity on the **right** side of the heart and lead **V6** records activity on the **left** side of the heart (see Figure 13-50 on page 13-92). You can usually diagnose left and right BBB using just ECG leads V1 and V6 (Figure 13-67).

Left Bundle-Branch Block (LBBB)

In LBBB, the QRS is prolonged with a duration of > 120 ms (3 small squares). Because the left ventricle takes a long time to depolarize (relative to the right ventricle), the QRS axis shifts further leftward. Figure 13-68 is an example that illustrates the ECG findings in LBBB. First, look at V1 (right-sided lead) and V6 (left-sided lead). Because the QRS axis is very leftward, QRS complex is very negative in V1 and very positive in V6. There is also ST-segment discordance (meaning, where the QRS is negative, its ST segment is elevated; and where the QRS is positive, there is ST depression). Yes, it is that simple. Also notice there

is left-axis deviation (QRS is positive in lead I and negative in lead aVF). This further confirms the diagnosis of LBBB.

Let's summarize the simple approach to diagnose LBBB:

- 1) If the QRS complexes are wide (> 120 ms), assess for LBBB and RBBB.
- 2) Look at leads V1 (right-sided lead) and V6 (left-sided lead).
- 3) If QRS is negative in V1 and positive in V6, the QRS is shifting away from the right side and toward the left side—this supports a LBBB.
- 4) Look at the ST segments; if there is discordance (i.e., ST segment is elevated if its QRS is negative, and ST segment is depressed if its QRS is positive), this further supports LBBB.
- 5) Lastly, confirm the left axis deviation—QRS is positive in lead I and negative in aVF.

Practice on the ECG provided here.

Criteria for LBBB:

- QRS > 120 ms (3 small squares)
- Negative QRS with ST elevation in V1
- Positive QRS with ST depression in V6
- Left axis deviation

Incomplete LBBB fulfills the above criteria, except the QRS is between 100 and 120 ms.

Note: LBBB is always abnormal, and usually is caused by ischemia. As we discussed in **Classification of ACSs** on page 13-19, if you encounter a patient presenting with symptoms concerning for acute coronary syndrome and ECG shows new (or presumed new) LBBB, manage as ST-segment elevation myocardial infarction (STEMI). On the other hand, if routine ECG shows LBBB in a stable patient without symptoms, you can presume the finding is chronic and no change in management is needed—this is not a STEMI.

Right Bundle-Branch Block (RBBB)

In RBBB, like in LBBB, the QRS is prolonged with a duration of > 120 ms (3 small squares). Diagnosing RBBB is a **bit** more complex than LBBB, but you should be able to do it easily by the end of this topic. Focus on V1 and V6.



Figure 13-68: Left bundle-branch block

Remember that the normal depolarization of the inter-ventricular septum is from left to right, which creates a small R wave in V1 (right-sided lead). Also, recall that the left ventricle (LV) is more massive than the right ventricle (RV). Therefore, the **normal** QRS axis is shifted toward the left.

In RBBB, you might expect the axis to shift toward the right, but because LV mass is larger than RV mass, the slowed depolarization of the RV is too small to offset that of the LV. Slow RV depolarization remains buried in the fast LV depolarization (which uses the normal-functioning left bundle branch); hence, the axis initially stays leftward, as expected (i.e., V1 [right-sided lead] is negative and V6 [left-sided lead] is positive). However, this is only true for the **first 40–60 ms** of the QRS complex. As the LV is depolarized quickly through its normal conduction system, the RV falls behind due to RBBB. Because the LV completes depolarization while the RV is still depolarizing, the **later** part of the wide QRS shifts to the right.

In **Figure 13-69**, notice the 1st part of the QRS is normal (sharp with normal axis, red arrows in the ECG), and it shows normal progression of R wave (it becomes taller from V1 to V4/V5). The 2nd part of the QRS, however, becomes abnormal (slurred and rightward, blue arrows in the ECG) and its axis is rightward (positive R' wave in V1 and negative S wave in V6). This change in axis causes the typical rSR' or rsR' "Rabbit ears" in V1, with a small initial r wave, a large or small S wave, and a larger second R' (R stands for Rabbit and RBBB). However, overall QRS axis is normal (positive in leads I and aVF).

Review: Small waves are conventionally notated with lowercase letters and larger waves with uppercase letters. For example, rSR' pattern means a small initial r wave is followed by a large S wave and a large secondary R wave. rsR' pattern means a small initial r wave is followed by a small S wave and a large secondary R wave. R' simply means a second R wave.

RBBB by itself does **not** cause right axis deviation. Only the **second half** of the QRS shows right axis deviation; the **whole** QRS complex does **not**. Therefore, if there is RBBB with right axis deviation throughout the QRS complex, there is another abnormality, such as RVH, in addition to RBBB.

Let's summarize the simple approach to assess for RBBB:

- 1) If the QRS complexes are wide (> 120 ms), assess for LBBB and RBBB.
- 2) Look at leads V1 (right-sided lead) and V6 (left-sided lead).
- 3) If there is rSR' or rsR' pattern ("Rabbit ears") with small initial r wave then a larger second R wave, suspect a RBBB.
- 4) Ignore the 1st part of the QRS (highlighted in red in the ECG sample provided) and look at the 2nd part of the QRS (highlighted in blue). The 2nd part of the QRS has a rightward axis (i.e., positive in V1 [right-sided lead] and negative in V6 [left-sided lead]).
- 5) To confirm, look at the S wave in V6 (highlighted in blue), expect it to be slurred (due to slow conduction from RBBB). You can also confirm the finding in another left-sided lead (limb lead I).
- 6) Lastly, confirm the axis is normal (**no** right axis deviation **throughout** the QRS complex), using limb leads I and aVF. If axis is abnormal, consider another abnormality in addition to RBBB.

Criteria for RBBB:

- QRS > 120 ms (3 small squares)
- rSR' or rsR' ("Rabbit ears") in V1
- Wide/slurred S wave in leads V6 and I
- Normal QRS axis

Incomplete RBBB fulfills the above criteria, except QRS duration = 100–120 ms.

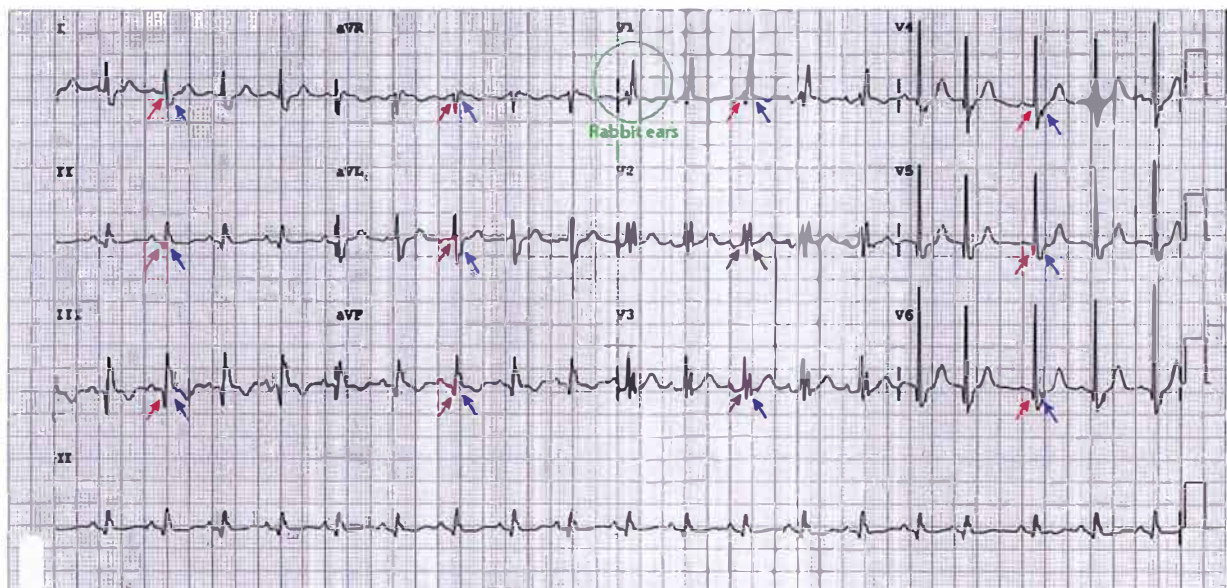


Figure 13-69: Right bundle-branch block

Intraventricular Conduction Delay (IVCD)

Nonspecific IVCD is a wide QRS (> 120 ms) that does not meet criteria for either right or left bundle-branch block.

Left Anterior Fascicular Block (LAFB)

With LAFB (a.k.a. left anterior hemiblock), QRS duration is 100–120 ms. It is an abnormal finding and seen in ischemic heart disease.

Left Posterior Fascicular Block (LPFB)

LPFB (a.k.a. left posterior hemiblock) is much rarer than LAFB, because the posterior fascicle has dual blood supply. It signifies a much worse prognosis, especially post-MI, as it indicates extensive damage to the myocardial tissue.

Bifascicular Block

Conduction abnormalities sometimes result in a combination of RBBB and either left anterior fascicular block, left posterior fascicular block, or complete LBBB. This condition is sometimes called **bifascicular block**.

Anterior MI and calcific aortic stenosis can cause bifascicular block. Remember that acute MI + a new bifascicular block indicates a high risk for progression to complete heart block.

ECG — ARRHYTHMIAS

PREVIEW | REVIEW

- What is the difference between an ectopic beat and an escape beat?
- What are the ECG findings with atrial fibrillation?
- What is the rhythm shown in the ECG in [Figure 13-70 on page 13-102](#)?
- What are the ECG findings with multifocal atrial tachycardia?
- What are the ECG findings with premature ventricular contraction?

ECTOPIC RHYTHM vs. ESCAPE RHYTHM

All heart tissue is capable of depolarizing automatically and becoming its own pacemaker. However, different tissues have different depolarization rates, and the tissue with the fastest rate will depolarize the tissue around it and take precedence. Normally, the focus with the fastest depolarizing rate in the heart is the sinoatrial (SA) node, which depolarizes at a rate of 60–100 bpm and suppresses all other foci in the heart. Atrial, non-SA-node pacemaker activity has an inherent rate of 60–80 bpm. AV junction (His bundle, not AV node) pacemaker rate

is 40–60 bpm. Ventricular pacemaker rate is 20–40 bpm (idioventricular rhythm).

Ectopic rhythm: In an ectopic rhythm, the primary pacemaker (SA node) is functioning **normally**, but there is a **faster** ectopic focus that preempts the SA node. If the SA node is depolarizing at 80 bpm (SA-SA interval of 750 ms) and there is an ectopic focus (EFo1) in the atria that wants to depolarize at 75 bpm (EFo1-EFo1 interval of 800 ms), then the SA node drives the rhythm, as it is going faster, and thus resets the ectopic focus. In other words, as the EFo1 resets and is waiting for 800 ms to fire again, it receives a command from the SA node to fire at 750 ms (i.e., 50 ms earlier), and thus cannot execute a command of its own. However, if there is a second ectopic focus (EFo2) that can depolarize faster, at 85 bpm (EFo2-EFo2 interval of 706 ms), it can suppress and reset the SA node. An **ectopic beat** occurs when an ectopic (abnormal) focus depolarizes **earlier** than expected. It can originate in the atria, AV junction, or ventricles.

Escape rhythm: In an escape rhythm, the primary pacemaker (SA node) is **not functioning normally** or its depolarization commands are **not being conducted**; thus, another focus in the heart (AV junction or ventricles) assumes the pacemaker role at a slow rate (escape).

For example, if the SA node is dysfunctional (e.g., sick sinus syndrome) and depolarizes at a very slow rate (e.g., 30 bpm; SA-SA interval of 2,000 ms), the next-fastest pacemaker takes over the rhythm. As a second example, in complete heart block (3rd degree AV block), the SA node functions normally and depolarizes at its normal rate of 80 bpm; the depolarizations, however, are not conducted to the ventricles. As a result, the ventricles start depolarizing at their own rate (e.g., 35 bpm) to **escape** from the complete heart block.

Note that ectopic beats are different from escape/pacemaker beats. Ectopic beats are abnormally early and occur despite a normally functioning SA node and conduction system. Escape beats are at the rate of inherent pacemaker activity and occur when there is dysfunction of the SA node or conduction system.

ATRIAL ARRHYTHMIAS

Atrial Fibrillation (A-fib)

ECG criteria for A-fib:

- No P waves
- Irregularly irregular rhythm (Intervals between QRS complexes are variable and follow no repetitive pattern.)

A-fib is the result of multiple ectopic foci firing continuously and randomly in a disorganized manner causing chaotic atrial activity. It is thought to be due to a micro-reentry mechanism. Because of this chaotic activity in atrial depolarization, no discernable P waves are seen. The atrial depolarization can be 400 bpm (the SA node that normally fires at 60–80 bpm does not stand a chance

against that). The atrioventricular (AV) node gets bombarded with many random depolarizations, but filters most of them and conducts only a few to the ventricular conduction system. This manifests as irregular RR intervals on ECG (Figure 13-70).

In Figure 13-70, what seems like P waves in V1 are actually artifact. The clue is that you do not see that electrical activity in other leads.

Atrial Flutter

Atrial flutter has the following characteristics on ECG:

- High atrial rate: characteristic rate ~ 300 bpm (range 240–340 bpm), typically with a 2:1 AV block
- Sawtooth-like flutter waves
- Whole number ratio of flutter waves to QRS complexes

In atrial flutter, there is a circuit around the cavotricuspid isthmus in the right atrium. If parts of this circuit get excited, depolarization travels repeatedly in a

counterclockwise direction (like a race car going around and around on a racetrack). As the depolarization travels in the circuit, it depolarizes the surrounding tissue (just like the race car spreads fumes as it goes around the track). The depolarized surrounding tissue includes the atria (evident as flutter waves; Figure 13-71) and ventricles (via the AV node, evidenced as QRS complexes). The circuit depolarizations at 300 bpm are all conducted to the atria; thus, the atrial rate is 300 bpm as well. The 300-bpm circuit depolarizations also bombard the AV node (in a more regular fashion than in A-fib), but the AV node filters out many of them and conducts only a portion. If the AV node filters out half of the depolarizations, then the ventricular rate is 150 bpm. Consider atrial flutter in your differential diagnosis when you see narrow complex tachycardia at around 150 bpm. If the AV node filters more, then there are fewer QRS complexes. Therefore, it is possible to have atrial flutter with 2:1, 3:1, 4:1, or even 6:1 block. The most common degree of block in atrial flutter is 2:1 or 3:1 block.

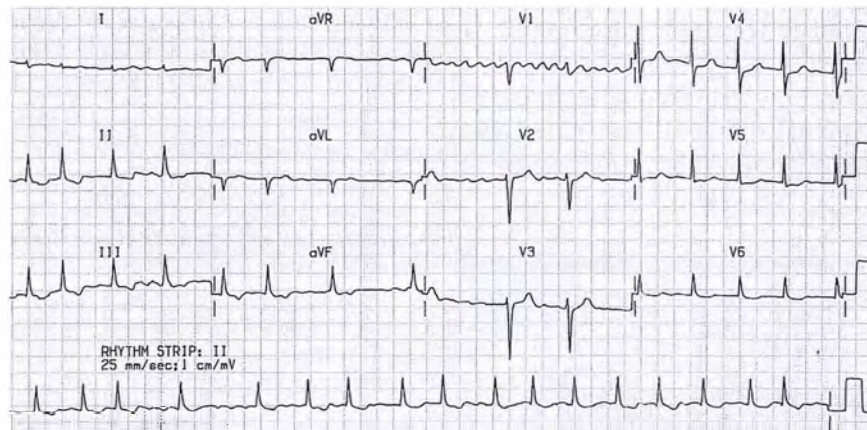


Figure 13-70: Atrial fibrillation

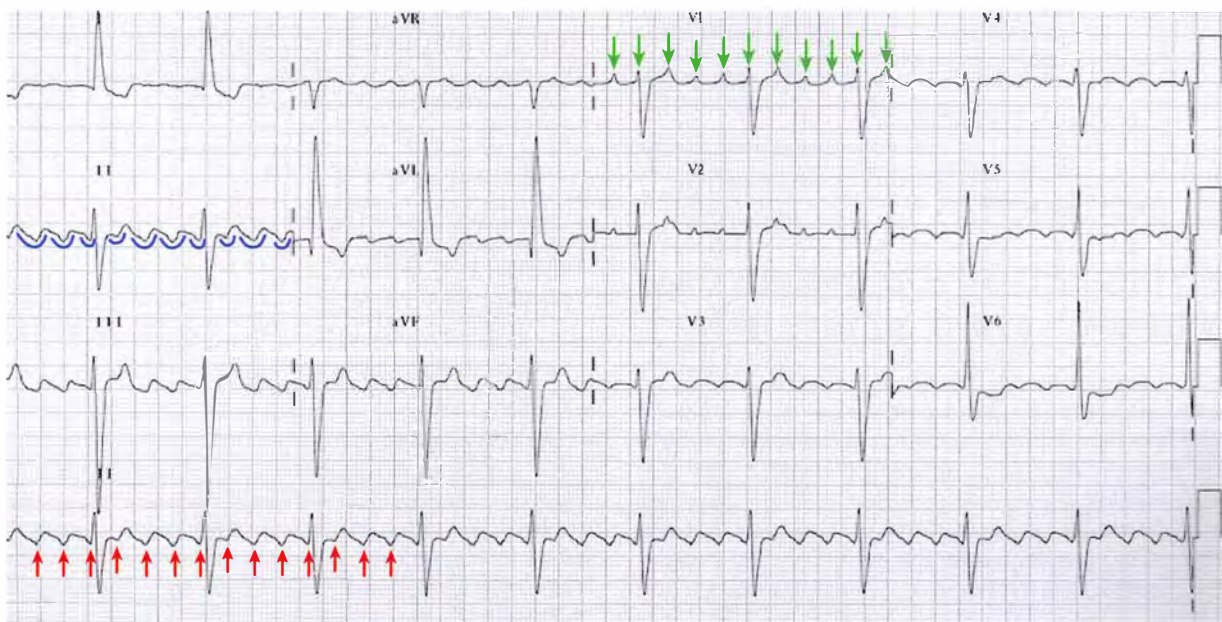


Figure 13-71: Atrial flutter with 4:1 block

Ignore all QRS complexes in Figure 13-71 and concentrate on P waves; try to visualize where they would land if there were no QRS complexes. Some flutter waves are hidden within the QRS complexes. If you do not miss the hidden flutter wave buried within the QRS complex, you can recognize this as atrial flutter with 4:1 block. The flutter waves are negative waves (marked in blue to demonstrate shape). Notice the difference in morphology of flutter waves between lead II (red arrows) and V1 (green arrows).

Note: In atrial flutter, you do not see typical P waves. Instead, you see sawteeth. Why is that?

The circuit travels around the cavotricuspid isthmus, which is at the base (bottom) of the right atrium. Therefore, when the circuit depolarizes the atria, it does so from bottom to top (superior vector). Recall that the normal P-wave axis moves from top to bottom (and from left to right). This normal top-to-bottom (inferior) P-wave axis shifts toward the inferior leads (II, III, and aVF); thus, the P wave is positive. However, in atrial flutter, the superior axis moves the atrial depolarizations away from the inferior leads (II, III, and aVF); thus, the P waves (also called flutter waves) are negative. Atrial flutter waves look like sawteeth because there is no isoelectric line between them—the depolarization around the circuit is very fast with no time to rest in between. The best leads in which to look for flutter waves are inferior leads (II, III, and aVF), but flutter waves can be seen in V1 as well.

The most common type of atrial flutter is the one described above (cavotricuspid isthmus-dependent). However, be aware that there is also another form of atrial flutter—Type II, or atypical atrial flutter, also called clockwise, left atrial, or non-cavotricuspid-isthmus-dependent atrial flutter. It has a much higher atrial rate: 340–440 bpm.

Wandering Pacemaker

Wandering pacemaker is exactly what the name implies. The pacing impulse migrates from one atrial pacemaker-excited focus to another. It is a benign condition seen mostly in young people—especially athletes. The varying foci are reflected by varying shapes of P waves (different foci have different locations in the atria and, thus, generate different P-wave axes).

Multifocal Atrial Tachycardia (MAT)

MAT is similar to wandering pacemaker, except that MAT occurs at a higher rate (hence the “tachycardia”) with more chaotic switching between pacemakers. MAT is often seen in patients with chronic obstructive pulmonary disease (COPD), hypoxia, severe hypokalemia and hypomagnesemia, or in those taking digoxin or theophylline. Atrial rate is 100–130 bpm. The rhythm is irregularly irregular. Differentiate it from A-fib by seeing discernable P waves (though they have variable morphologies).

Sinus Pause

Sinus pauses result in a long TP interval. An ectopic escape beat (different P wave) may precede the resumption of the rhythm. If an atrial pacemaker takes over the rhythm, the rate is usually 60–80 bpm. If a junctional pacemaker focus takes over the rhythm, this is termed a junctional (a.k.a. escape) rhythm. With a junctional rhythm, there is a change in the P wave—it may not be visible, or it may be a retrograde P wave (from the ventricles to the atria via the retrograde AV node conduction). In this case, the retrograde P wave is very close to the QRS (short PR interval). Junctional rate is normally 40–60 bpm.

Note: Retrograde P waves are seen in supraventricular tachycardias, such as AV nodal reentry tachycardia (AVNRT).

VENTRICULAR ECTOPIC BEATS AND HEART BLOCK

Premature ventricular contraction (PVC) ECG findings:

- The QRS complex occurs earlier than expected (premature), is wider than normal (myocyte-to-myocyte conduction) and has a different QRS axis than the normally conducted QRS complex.
- P wave is obscured in the ectopic QRS complex.
- T wave is inverted (abnormal depolarization is followed by abnormal repolarization).
- The next RR interval is longer than normal. This is called a full compensatory pause. The SA node is not reset by the ventricular depolarization (because it is unaffected by the ventricles)—hence, the P waves march out normally.

A ventricular escape beat can occur if the sinus pause is long enough and no atrial or junctional pacemakers kick in. The PVC comes early; the ventricular escape beat comes late.

Remember: Junctional escape rhythm means narrow QRS complexes (rate is 40–60 bpm), and ventricular escape rhythm means wide QRS complexes (rate is 20–40 bpm). Medication and certain illnesses can affect these rates.

ECG — MYOCARDIAL INFARCTION (MI)

PREVIEW | REVIEW

- Describe the sequence of ECG changes with the different phases of ST-elevation myocardial infarction.
- What are the top differential diagnoses for the 2 ECGs in Figure 13-73 on page 13-105?

- What ECG changes occur with a septal MI? Anterior MI? Inferior MI? Posterior MI? **Know** all these!
- What are the main 3 diagnoses that should come to mind when dealing with wide QRS-complex tachycardia?

COMMON FINDINGS

Know this topic! Common findings in STEMI (ST-elevation myocardial infarction): Within the 1st minute or so of acute **ischemia**, the T waves become **inverted** (flipped). After 1–2 minutes, they become positive and **peaked** (hyperacute; [Figure 13-72](#)). Then **injury** to the cells occurs, causing **ST-segment elevation** and sometimes T waves become flipped again. **Q waves** correlate with irreversible cell death (which occurs after hours to days). Days later, the ST segment returns to normal and T waves may become normal again.

Again:

- 1) T-wave changes (ischemia), then
- 2) ST-segment changes (injury), and then
- 3) Q waves (cell death)

Note: These changes are seen in STEMI; you do not see this pattern in NSTEMI, where the common ECG findings are ST depression and/or T wave inversion. Q waves may develop, but not necessarily.

Take a look at the following 2 ECGs ([Figure 13-73](#)). What are the top 2 differential diagnoses?

The top differential diagnoses for peaked T waves are **1) STEMI—early (ischemia) stage—and 2) hyperkalemia**. In [Figure 13-73](#), ECG 1 shows hyperkalemia: a very tented T wave with **symmetric** limbs (i.e., both uprising and downsloping limbs of T wave are steep) that ends with a point at the top. ECG 2 illustrates the early stage of anterior STEMI, before ST-segment elevation develops: T waves are tented, but limbs are not **symmetric** (the uprising limb of the T wave is less steep than the downsloping limb) and the tip is not as pointed as in hyperkalemia. Both are medical emergencies, so do not ignore them. Complete the workup!

What is the likely cause of ST elevation that persists for weeks after STEMI? Left ventricular wall aneurysm. Refer to [Figure 13-72](#).

LOCALIZATION OF MI ON ECG

If the **location** of MI is defined, this implies STEMI; NSTEMI is not localized. So, if you read “anterior MI,” this means “anterior STEMI.” The general term “MI” without localization can refer to either STEMI or NSTEMI.

When specifying the location of MI (e.g., inferior MI), the walls of the left ventricle (LV) are implied. In other words, “inferior MI” means “MI in the inferior wall of LV.” Because it is diagnosed less frequently, we explicitly specify location for right ventricle MI and refer to it exclusively as RV MI.

Left ventricular MI is localized by ECG based on the leads involved:

- Septal MI = ST elevation in V1–V2
- Anterior MI = ST elevation in V3–V4
- Anteroseptal MI = ST elevation in V1–V4
- Lateral MI = ST elevation in I, aVL, and/or V5–V6
- Anterolateral MI = ST elevation in I, aVL, and V2–V6
- Inferior MI = ST elevation in II, III, and aVF
- Inferolateral MI = ST elevation in II, III, and aVF plus I, aVL, and/or V5–V6
- Apical MI = ST elevation in II, III, aVL, and any of V1–V4
- Posterior MI = tall R in V1–V2 (mirror image of Q wave) with an R:S ratio > 1 in V1 or V2; ST depression in V1–V2 (mirror image of ST elevation)
- Inferoposterior MI = ST elevation in II, III, and aVF plus tall R in V1–V2 (mirror image of Q wave); ST depression in V1–V2 (mirror image of ST elevation)
- High lateral MI = ST elevation in I and aVL

RV infarction usually occurs with inferior MI. RV MI appears on ECG as:

- ST elevation in the **right** precordial leads, such as V1. ST elevation in V4R to V6R is fairly sensitive and specific for RV infarction (~ 90% each). It is **diagnostic** of RV infarction if the ST elevation is greater in V4R than in V1.

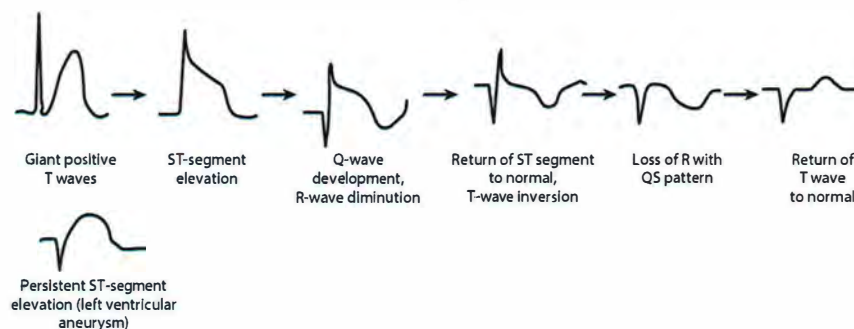


Figure 13-72: Evolution of ECG changes in STEMI over time

Be sure to remember the most common locations of STEMI (know this very well!):

- Acute anterior MI = ST elevation in V3–V4
- Acute inferior MI = ST elevation in II, III, and aVF
- Acute posterior MI = tall R in V1–V2 (mirror image of Q wave) with an R:S ratio > 1 in V1 or V2; ST depression in V1–V2 (mirror image of ST elevation)
- Acute inferoposterior MI = ST elevation in II, III, and aVF plus tall R in V1–V2 (mirror image of Q wave); ST depression in V1–V2 (mirror image of ST elevation)

Note: True isolated posterior MI without inferior MI is very rare. The majority of posterior MIs occur with inferior MI (termed inferoposterior MI).

The trick for reading the ECG with a suspected posterior MI is to hold the ECG upside-down and backwards while holding it up to a light to see the tracing. Study V1–V2. A posterior MI assumes the morphology of other

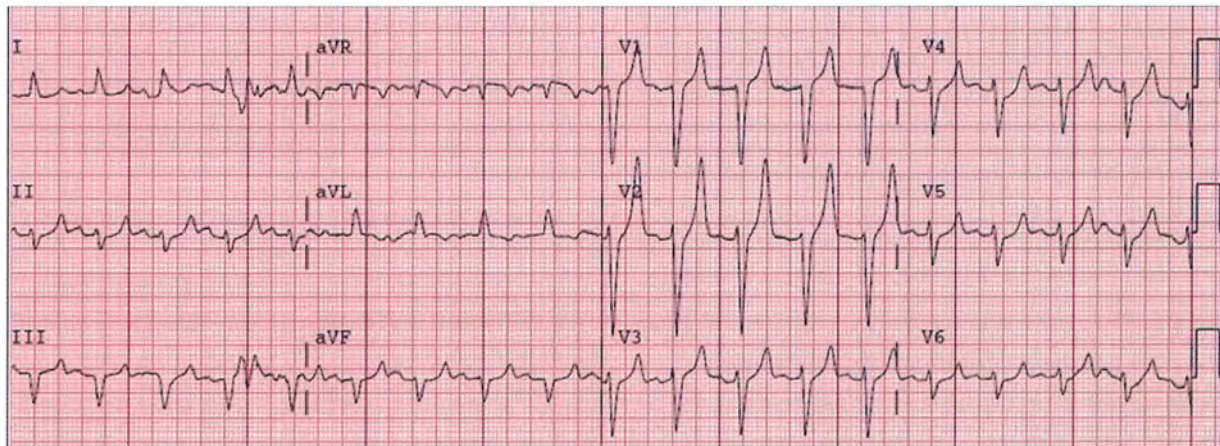
MIs with this trick. (R wave looks like Q wave and ST depression appears to be ST elevation.)

Old MI is diagnosed by Q waves without acute changes in ST segment or T waves. Localize old MI using the same leads as with acute STEMI:

- Old anterior MI = Q wave in V3–V4
- Old inferior MI = Q wave in II, III, and aVF
- Old posterior MI = tall R in V1–V2 (mirror image of Q wave)
- Old inferoposterior MI = Q wave in II, III, and aVF plus tall R in V1–V2 (mirror image of Q wave) with an R:S ratio > 1 in V1 or V2

Q waves commonly indicate old MI. However, they can also be seen in acute MI as described in [Common Findings](#). Q waves seen in acute MI (i.e., consistent clinical presentation with dynamic ST-T changes) can indicate more extensive damage to the heart, but

ECG 1



ECG 2

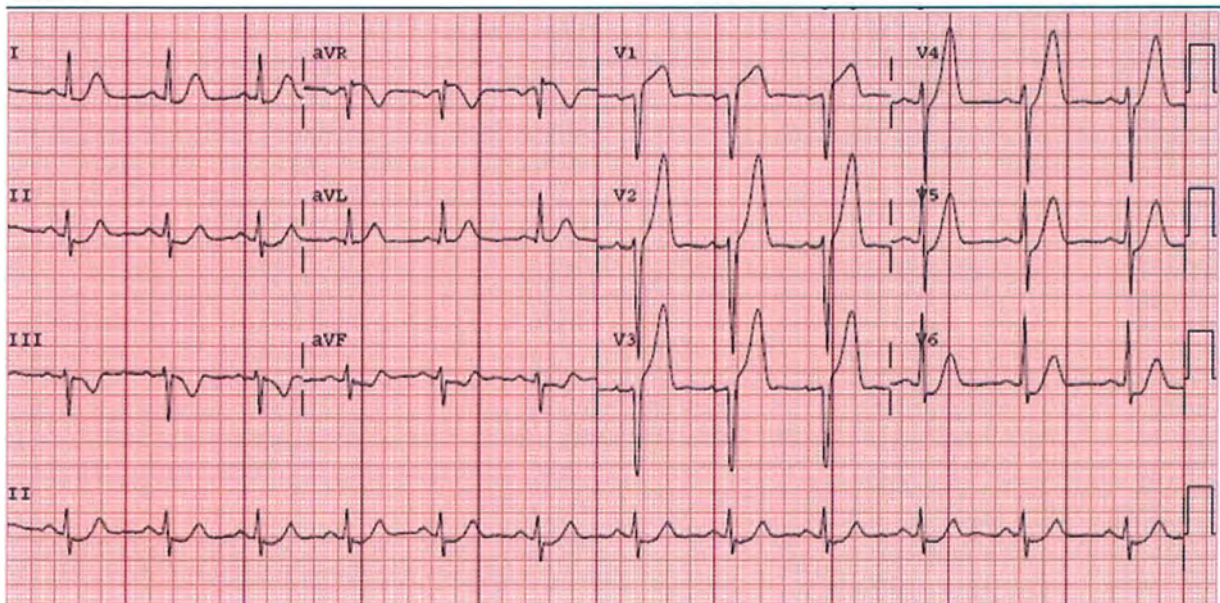


Figure 13-73: Life-threatening findings on ECG

management does not change with the presence or absence of Q waves in acute MI.

Note: In MI (old or acute) and ischemia (ST depression and/or T-wave inversion), recognize that as the area of the involved myocardium becomes larger, more ECG leads become involved. Also, more extensive ECG changes indicate more severe injury and/or ischemia. So, an inferoposterior MI is much larger than an inferior MI. An inferoposterior MI with RV involvement is worse than an inferoposterior MI without RV involvement. And a 1-mm ST depression in both inferior leads (II, III, aVF) and anterior leads (V2, V3, V4) is more severe than a 1-mm ST depression in inferior leads alone.

SITUATIONS WHERE ECG IS NONDIAGNOSTIC FOR ISCHEMIA

In several conditions that cause chronic ECG abnormalities, the ECG is insensitive for detection of ischemia or even MI. These include:

- Left bundle-branch block (LBBB) has ST elevation as a part of its morphology, which makes assessment for ischemia or MI very challenging. This is why you treat LBBB (if new or presumed to be new) as STEMI if the presentation is concerning for acute coronary syndrome (ACS). The Sgarbossa criteria can be used to assess for ST elevation in LBBB, but these are not commonly present.
- Ventricular pacing causes a LBBB morphology as well, which makes assessment for ischemia or MI very challenging.
- Wolff-Parkinson-White syndrome causes deviation of the QRS axis and repolarization abnormalities.
- Left anterior fascicular block causes a change in the QRS axis that masks inferior MI.
- Left posterior fascicular block causes a change in the QRS axis that masks lateral MI.
- Left ventricular hypertrophy causes depolarization and repolarization abnormalities (ST-segment changes), making diagnosis of ischemia difficult. This is why you do not order a treadmill ECG stress test without imaging (echocardiography or nuclear scan) in patients with LVH.

If the patient has symptoms concerning for ACS and has any of the above conditions, ECG is not sufficient to rule out ACS. Consider echocardiography to assess wall motion.

In ventricular pacing with a pacemaker, LBBB morphology reflects early depolarization of the right ventricle (RV). The pacer lead is inserted in the vein and ends up on the right side of the heart (i.e., RV). When RV is being paced, it depolarizes earlier than LV. This is like LBBB, where LV depolarizes late (after RV). So, the QRS has LBBB morphology both when LV depolarizes late (intrinsic LBBB) or RV depolarizes early (ventricular pacing).

Note: Unlike LBBB, RBBB does not change the QRS axis and does not hide MI.

WIDE QRS-COMPLEX TACHYCARDIA

There are 3 main diagnoses, listed here in order of frequency, that cause wide QRS-complex tachycardia:

- 1) **Ventricular tachycardia (VT)** is usually **regular**, but not necessarily very fast (rate of 100–180 bpm). In a patient with a history of cardiovascular disease or cardiomyopathy, this is VT in 95% of cases. Treat with emergent synchronized cardioversion if the patient is unstable (hypotension or chest pain).
- 2) **Supraventricular tachycardia (SVT) with aberrancy:** SVT is an umbrella term that includes many narrow complex tachycardias. However, if there is a baseline widening of QRS (LBBB or RBBB), then the tachycardia will also have wide QRS (i.e., aberrant conduction). SVT is usually **regular**. Treatment is AV-nodal blocking medications (e.g., adenosine, β -blockers, diltiazem).
- 3) **A-fib with Wolff-Parkinson-White (WPW) syndrome** is **irregular** (because of the A-fib). Because of the accessory pathway in WPW, the QRS is wide (with delta wave) at the baseline. Never give AV-nodal blocking medications (adenosine, β -blockers, or diltiazem) to any patient with **irregular** wide complex tachycardia, as it can degenerate into ventricular fibrillation. Treat instead with either procainamide or synchronized cardioversion.

Remember: A wide complex tachycardia in someone with known heart disease is most likely **VT**.

If you see **irregular** wide complex tachycardia, immediately think of **A-fib with WPW**. Treatment is either procainamide or cardioversion.

Remember that VT can be either **monomorphic** or **polymorphic**. Monomorphic VT is seen in patients with severe cardiomyopathy, especially those with scarred ventricles from **previous** MI (Figure 13-74). Polymorphic VT occurs in the setting of **acute** ischemia and **acute** MI (Figure 13-75).

In Figure 13-74, all the QRS complexes look the same (hence, monomorphic). In Figure 13-75, QRS complexes have different morphologies and amplitudes (hence, polymorphic). Polymorphic ventricular tachycardia can lead into ventricular fibrillation (Figure 13-76). Note the development of polymorphic VT at the beginning of the ECG (red arrow), which then degenerates into ventricular fibrillation (VF) toward the end (blue arrow).

In VF, there is no organized ventricular depolarization, no organized mechanical ventricular contraction, and consequently, no cardiac output. Treatment is cardiopulmonary resuscitation and immediate defibrillation, per the 2019 AHA Advanced Cardiac Life Support Focused Update. (The more delayed the defibrillation, the worse the outcome.)

In STEMI patients, successful reperfusion can be followed by a ventricular rhythm called accelerated idioventricular

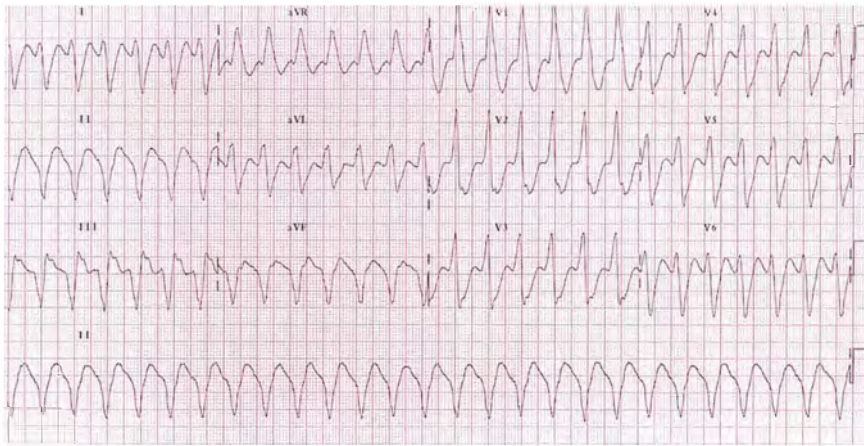


Figure 13-74: Monomorphic ventricular tachycardia

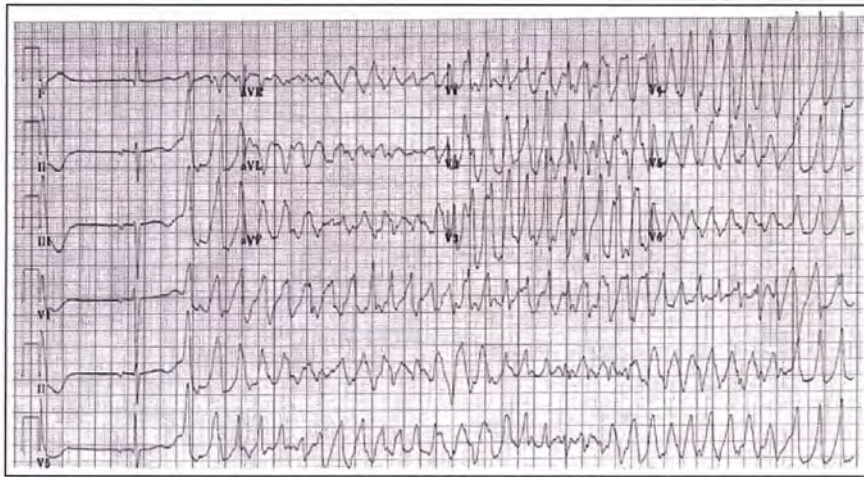


Figure 13-75: Polymorphic ventricular tachycardia

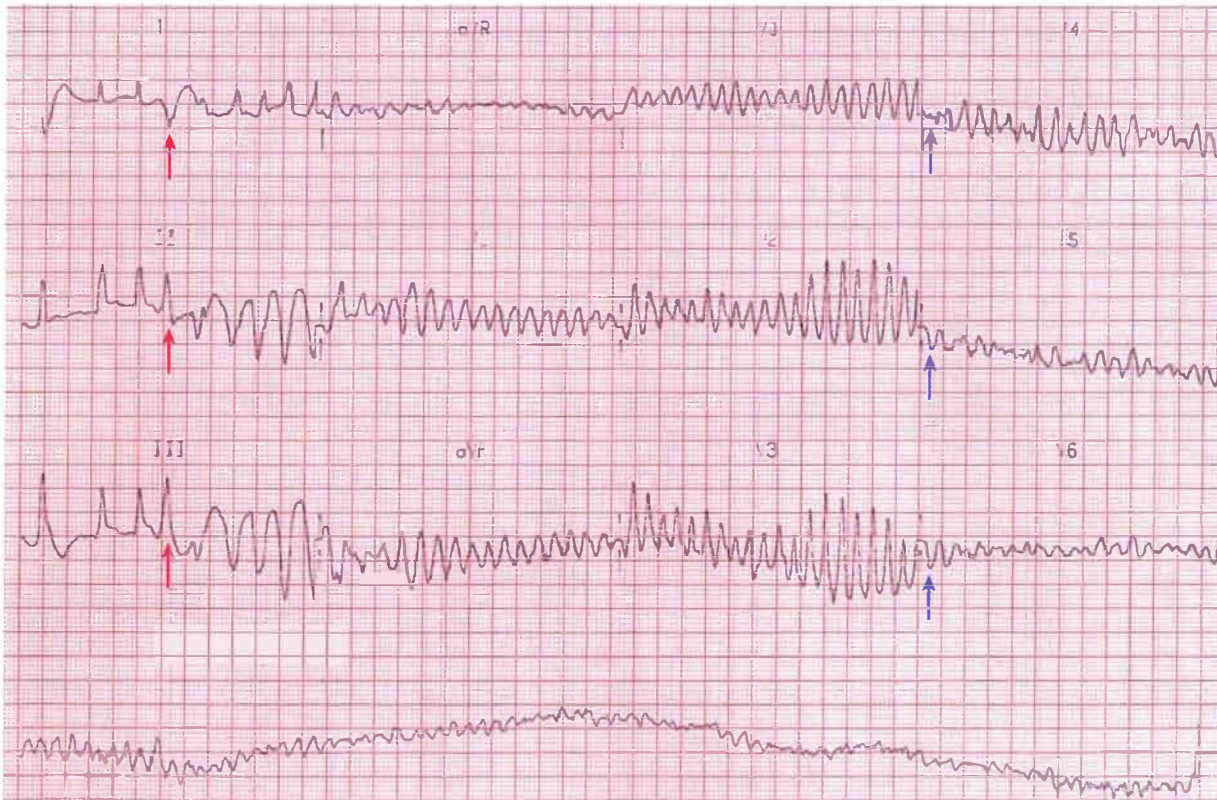


Figure 13-76: Polymorphic ventricular tachycardia leading into ventricular fibrillation

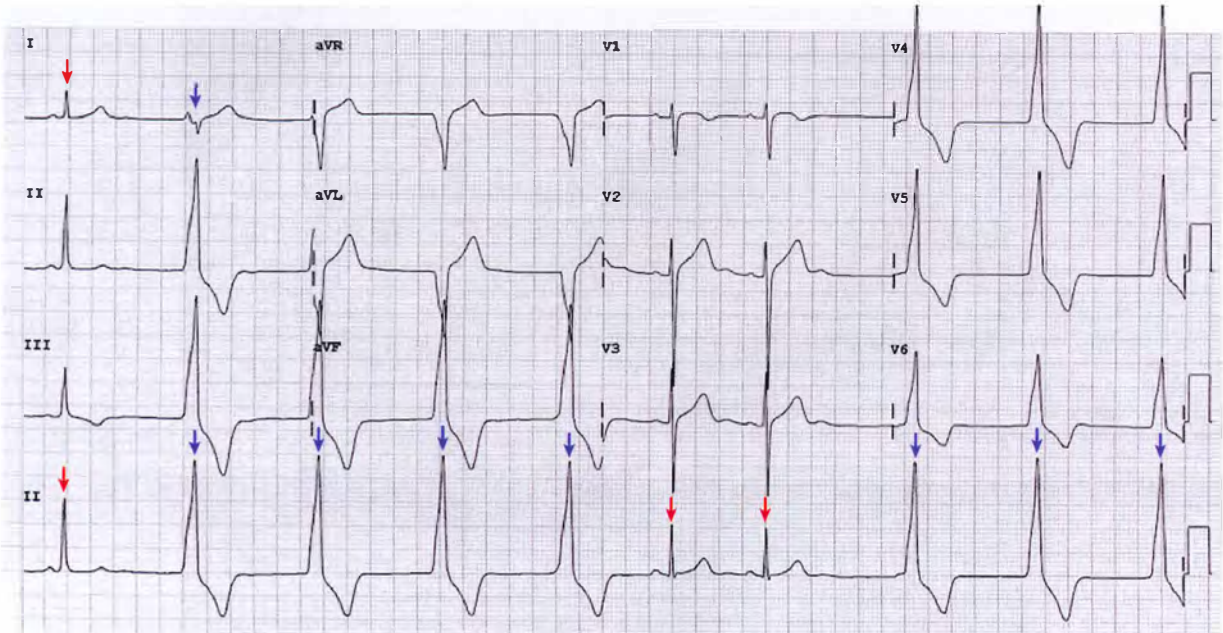


Figure 13-77: Accelerated idioventricular rhythm

rhythm (AIVR; [Figure 13-77](#)). It is a rhythm that originates in the ventricles (i.e., a wide complex rhythm just like VT), but its rate is usually 60–100 bpm (or even 120 bpm). Note the sinus rhythm with narrow QRS (red arrow) at the beginning, then 4 beats of AIVR (blue arrow), followed by 2 sinus beats, then 3 runs of AIVR. Since it is not technically “tachycardia,” it is not referred to as ventricular “tachycardia.” It is important to identify this rhythm after reperfusion therapy (especially fibrinolytic therapy) because it indicates successful therapy and predicts improved outcomes. This is one of the very rare instances when you would be excited to see someone have a ventricular rhythm (that looks like VT)! No treatment or changes in medications are needed here. It should resolve within hours.

In the ECG above ([Figure 13-77](#)), leads I, II, and III show sinus rhythm initially, with normal QRS and T wave, followed by AIVR. Note the AIVR has a wide QRS complex with abnormal axis (see how the QRS axis changes in lead I). Also notice the abnormal T wave (see how the T wave changes in lead II). The T wave is abnormal in AIVR because abnormal depolarization causes abnormal repolarization. A wide QRS complex is always concerning for VT, but this ventricular rhythm is at 54 bpm, which is too slow for VT. Therefore, this is more consistent with AIVR.

ECG — ANALYSIS SUMMARY

OVERVIEW

The key to reading ECGs is to be systematic, otherwise you will miss things. Here is a simplified, stepwise approach to analyzing the ECG:

- 1) Check the rhythm, then rate.
- 2) Determine the P-wave axis and QRS-complex axis.
- 3) Check the intervals (PR, QRS, then QT).
- 4) Check the waveforms (P wave, QRS complex, ST segment, T wave, then U wave if present).

Practice this stepwise approach in [ECG Case Studies](#). In addition, [Figure 13-78](#) provides organizational assistance and key diagnostic reminders for ECG interpretation. A copy of the figure appears below each practice ECG.

Rate = 1500/#mm or 300/#large squares
QTc = QT/(RR)

ECG

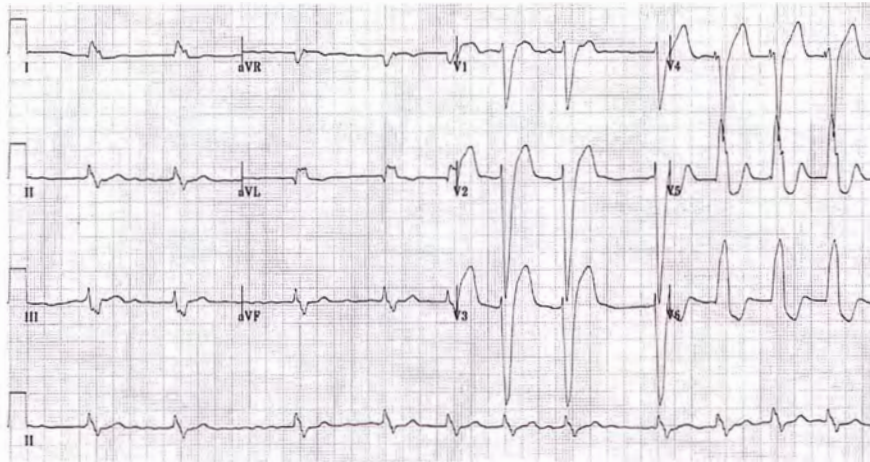
Rate _____	Waveforms:
Rhythm _____	P wave _____
Intervals: PR _____	QRS voltage _____
QRS _____	QRS axis/shape _____
QTc _____	R waves _____
	ST segment _____
	T waves _____
	U waves _____

Figure 13-78: Memory aid for ECG interpretation

Study tip: The patient’s presenting information appears to the left of each ECG. Review the scenarios and read the ECGs, then check your answer in the [Findings from ECG Case Studies](#) on page 13-120 topic.

ECG CASE STUDIES

Case 1: A 62-year-old man with previous myocardial infarction (MI) and chronic hypertension presents to the emergency department with chest pain.



Rate _____

Rhythm _____

Intervals: PR _____

QRS _____

QTc _____

Waveforms:

P wave _____

QRS voltage _____

QRS axis/shape _____

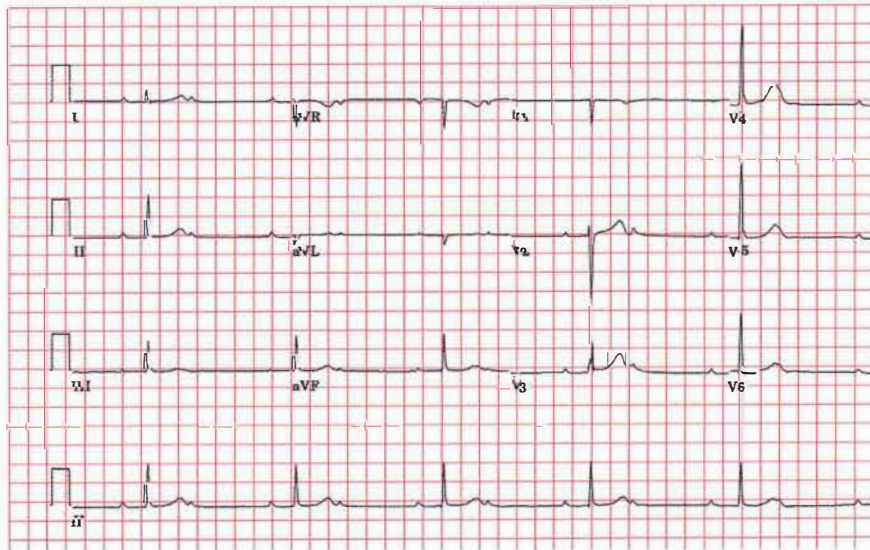
R waves _____

ST segment _____

T waves _____

U waves _____

Case 2: A 36-year-old man with a history of cocaine abuse and “slow heart rate” since his teens



Rate _____

Rhythm _____

Intervals: PR _____

QRS _____

QTc _____

Waveforms:

P wave _____

QRS voltage _____

QRS axis/shape _____

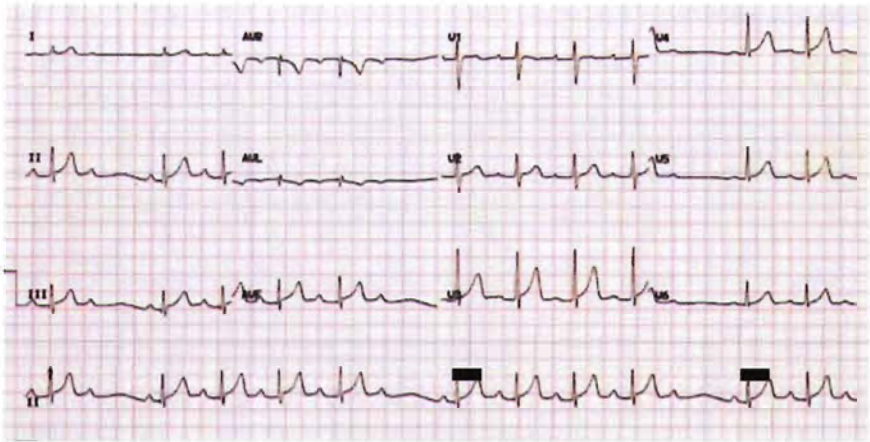
R waves _____

ST segment _____

T waves _____

U waves _____

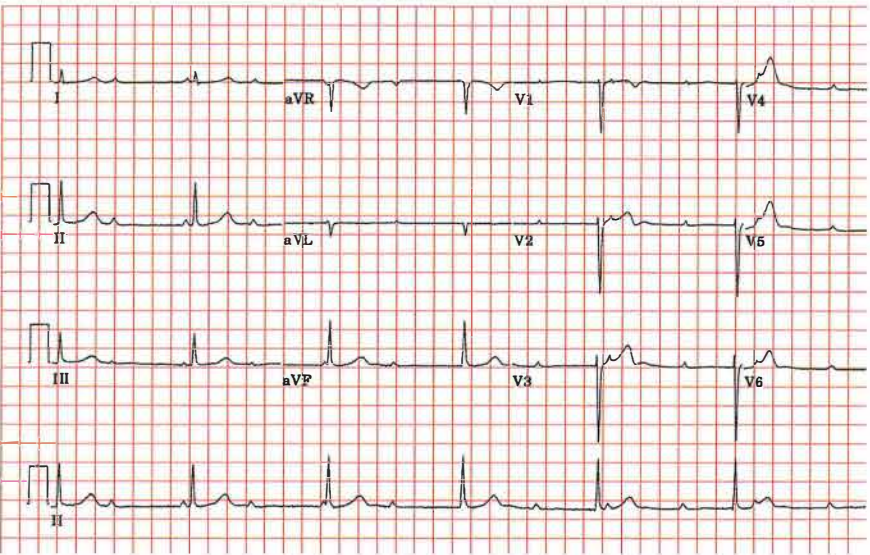
Case 3: A 68-year-old asymptomatic man



Rate _____
Rhythm _____
Intervals: PR _____
QRS _____
QTc _____

Waveforms:
P wave _____
QRS voltage _____
QRS axis/shape _____
R waves _____
ST segment _____
T waves _____
U waves _____

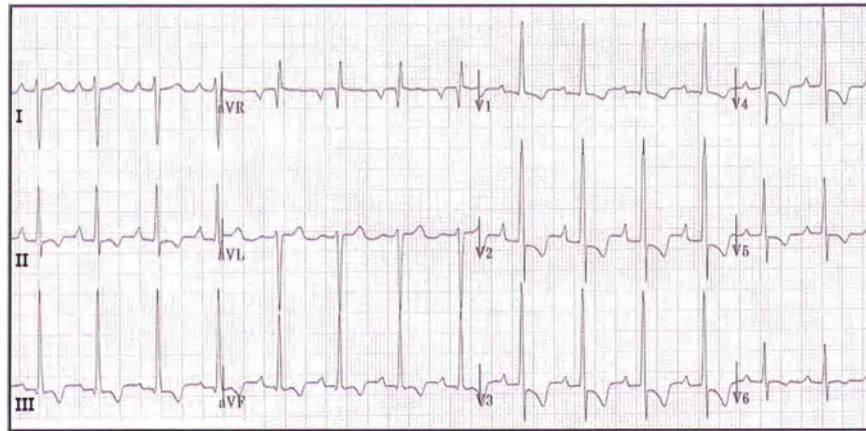
Case 4: A 61-year-old man presents with fatigue on exercise.



Rate _____
Rhythm _____
Intervals: PR _____
QRS _____
QTc _____

Waveforms:
P wave _____
QRS voltage _____
QRS axis/shape _____
R waves _____
ST segment _____
T waves _____
U waves _____

Case 5: A 54-year-old woman with COPD and dyspnea on exertion



Rate _____

Rhythm _____

Intervals: PR _____

QRS _____

QTc _____

Waveforms:

P wave _____

QRS voltage _____

QRS axis/shape _____

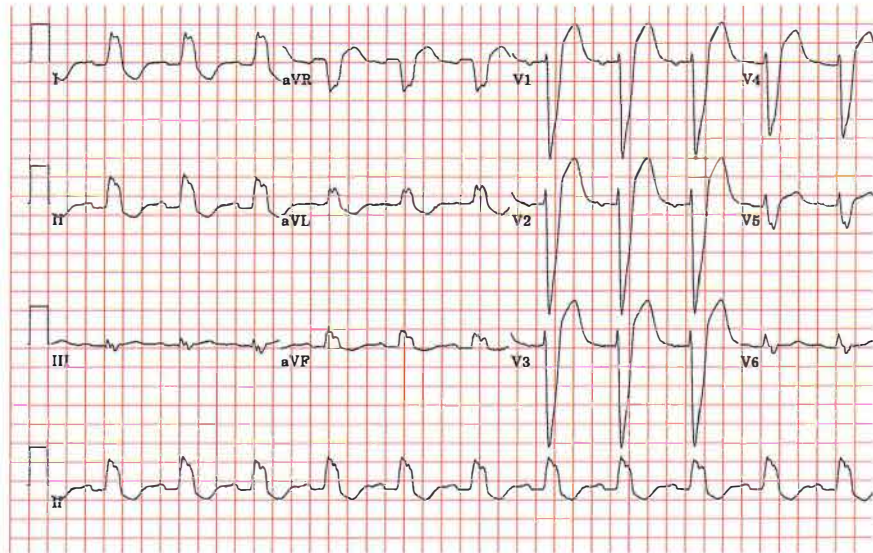
R waves _____

ST segment _____

T waves _____

U waves _____

Case 6: A 77-year-old man with a history of chronic heart failure



Rate _____

Rhythm _____

Intervals: PR _____

QRS _____

QTc _____

Waveforms:

P wave _____

QRS voltage _____

QRS axis/shape _____

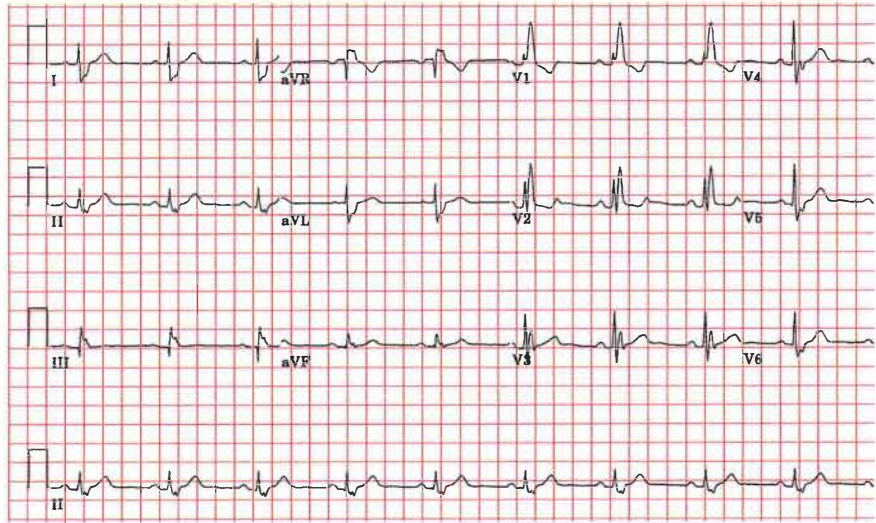
R waves _____

ST segment _____

T waves _____

U waves _____

Case 7: A 34-year-old man with a history of a cardiac murmur and prior repair of a congenital heart defect



Rate _____

Rhythm _____

Intervals: PR _____

QRS _____

QTc _____

Waveforms:

P wave _____

QRS voltage _____

QRS axis/shape _____

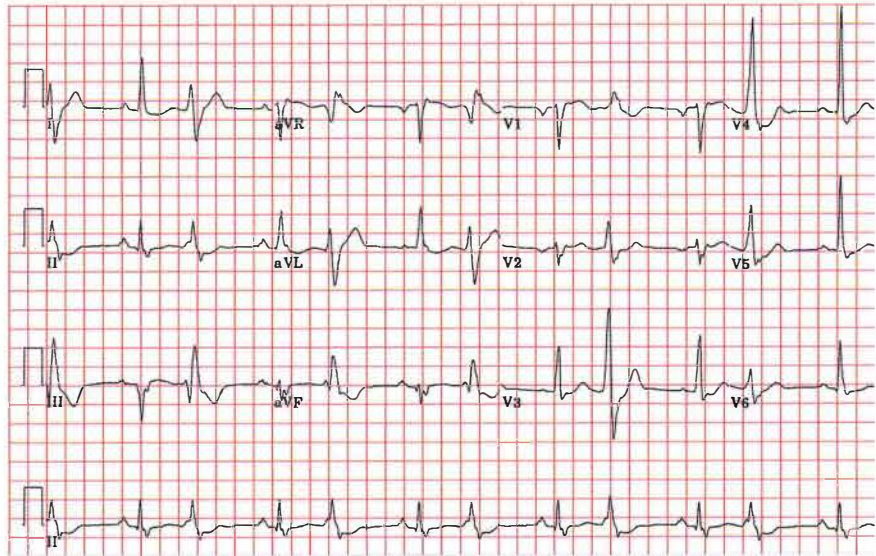
R waves _____

ST segment _____

T waves _____

U waves _____

Case 8: A 65-year-old man with recurrent palpitations



Rate _____

Rhythm _____

Intervals: PR _____

QRS _____

QTc _____

Waveforms:

P wave _____

QRS voltage _____

QRS axis/shape _____

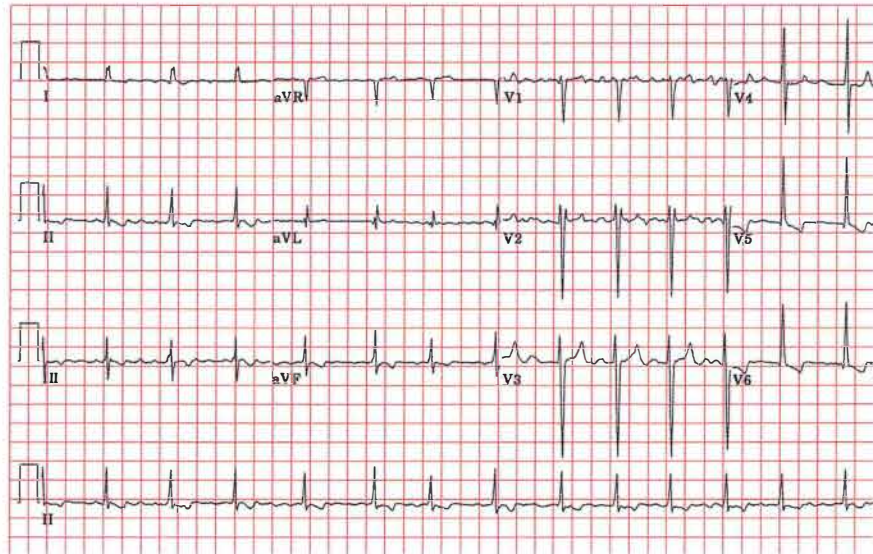
R waves _____

ST segment _____

T waves _____

U waves _____

Case 9: A 45-year-old man with a history of rheumatic fever as a child and a heart murmur



Rate _____

Rhythm _____

Intervals: PR _____

QRS _____

QTc _____

Waveforms:

P wave _____

QRS voltage _____

QRS axis/shape _____

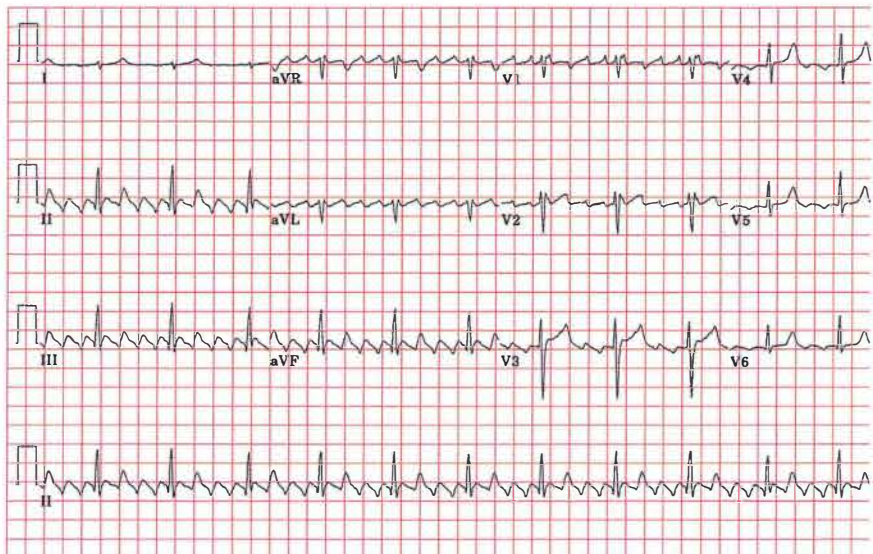
R waves _____

ST segment _____

T waves _____

U waves _____

Case 10: A 44-year-old man with a history of 2-pack-per-day smoking for 15 years



Rate _____

Rhythm _____

Intervals: PR _____

QRS _____

QTc _____

Waveforms:

P wave _____

QRS voltage _____

QRS axis/shape _____

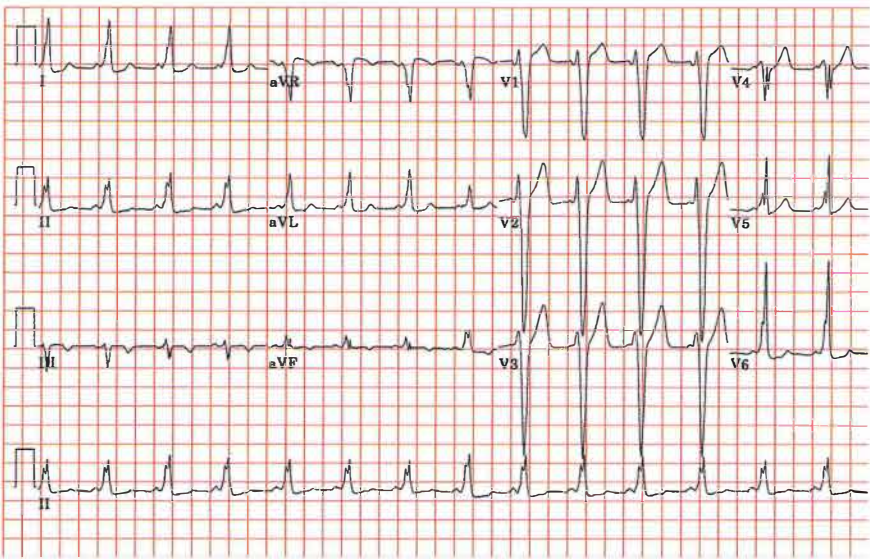
R waves _____

ST segment _____

T waves _____

U waves _____

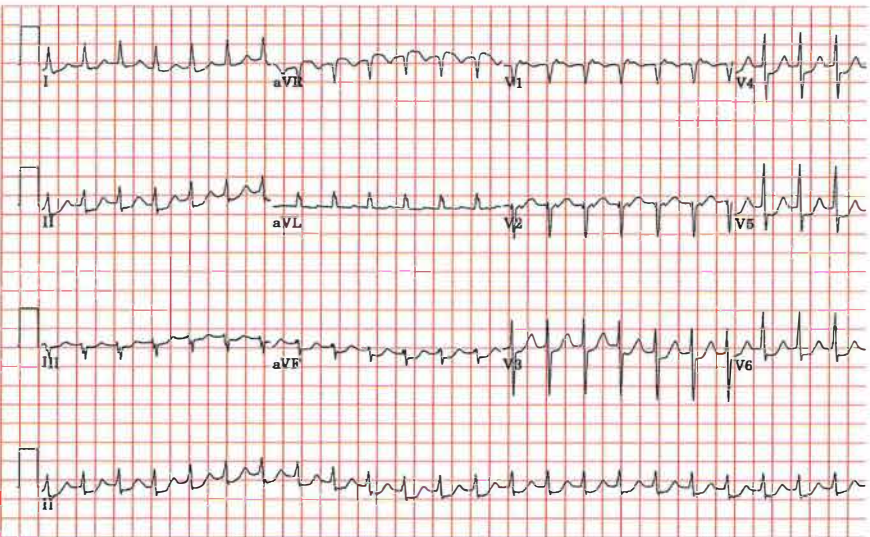
Case 11: A 34-year-old man with history of palpitations since childhood



Rate _____
Rhythm _____
Intervals: PR _____
QRS _____
QTc _____

Waveforms:
P wave _____
QRS voltage _____
QRS axis/shape _____
R waves _____
ST segment _____
T waves _____
U waves _____

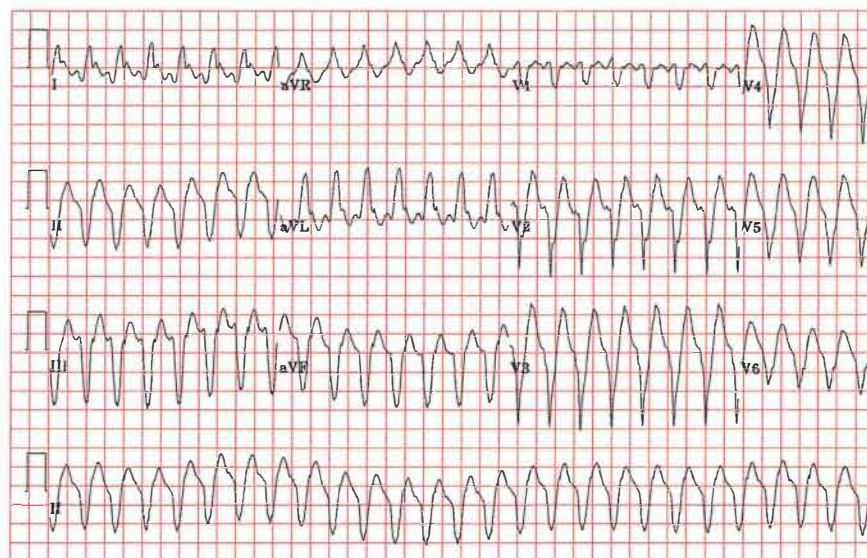
Case 12: A 74-year-old woman with recent episodes of light-headedness and palpitations



Rate _____
Rhythm _____
Intervals: PR _____
QRS _____
QTc _____

Waveforms:
P wave _____
QRS voltage _____
QRS axis/shape _____
R waves _____
ST segment _____
T waves _____
U waves _____

Case 13: A 71-year-old man with history of previous MI and coronary artery bypass surgery is admitted for chest pains and syncope.



Rate _____

Rhythm _____

Intervals: PR _____

QRS _____

QTc _____

Waveforms:

P wave _____

QRS voltage _____

QRS axis/shape _____

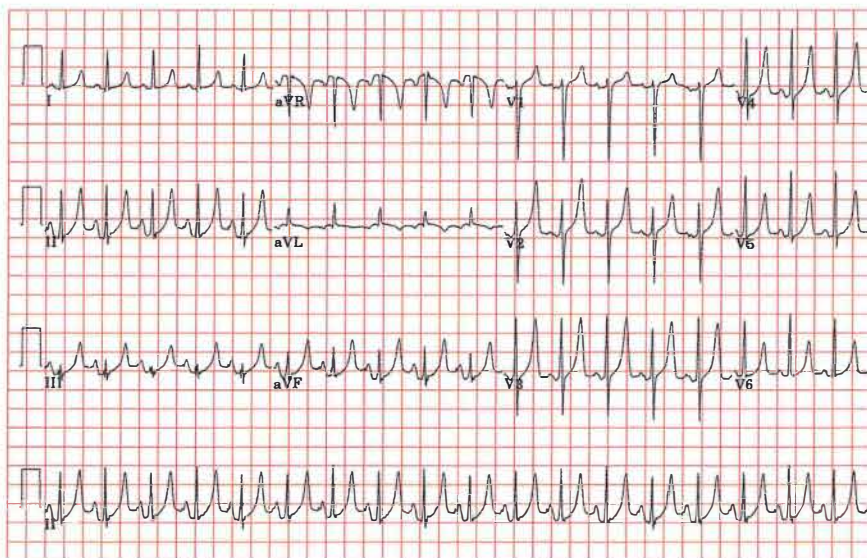
R waves _____

ST segment _____

T waves _____

U waves _____

Case 14: A 47-year-old man with Type 1 diabetes and chronic kidney disease is admitted with diabetic ketoacidosis and serum potassium of 7 mEq/L.



Rate _____

Rhythm _____

Intervals: PR _____

QRS _____

QTc _____

Waveforms:

P wave _____

QRS voltage _____

QRS axis/shape _____

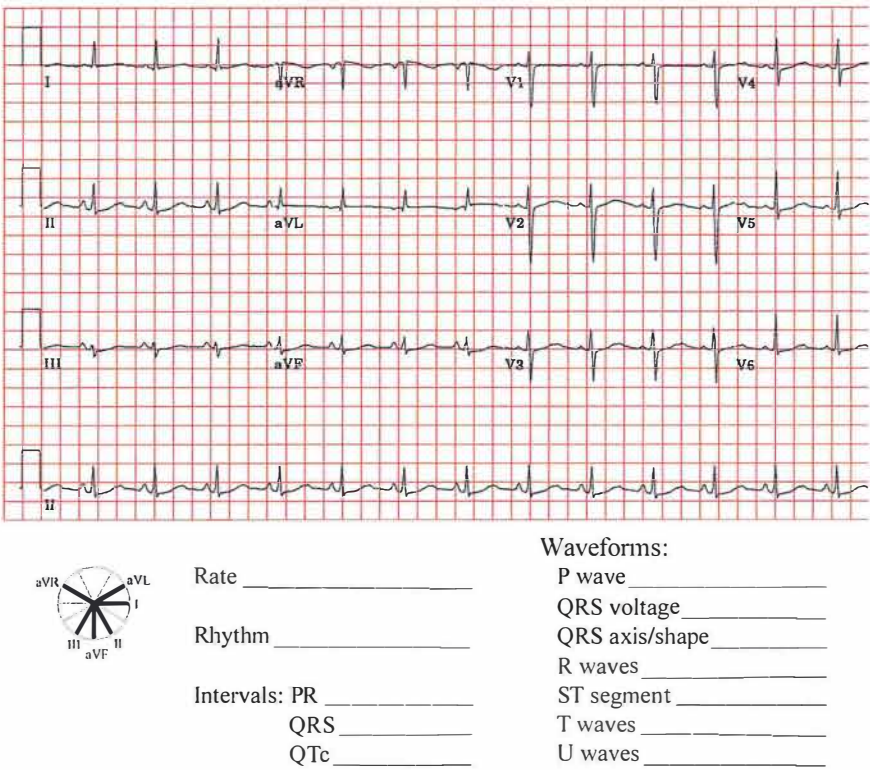
R waves _____

ST segment _____

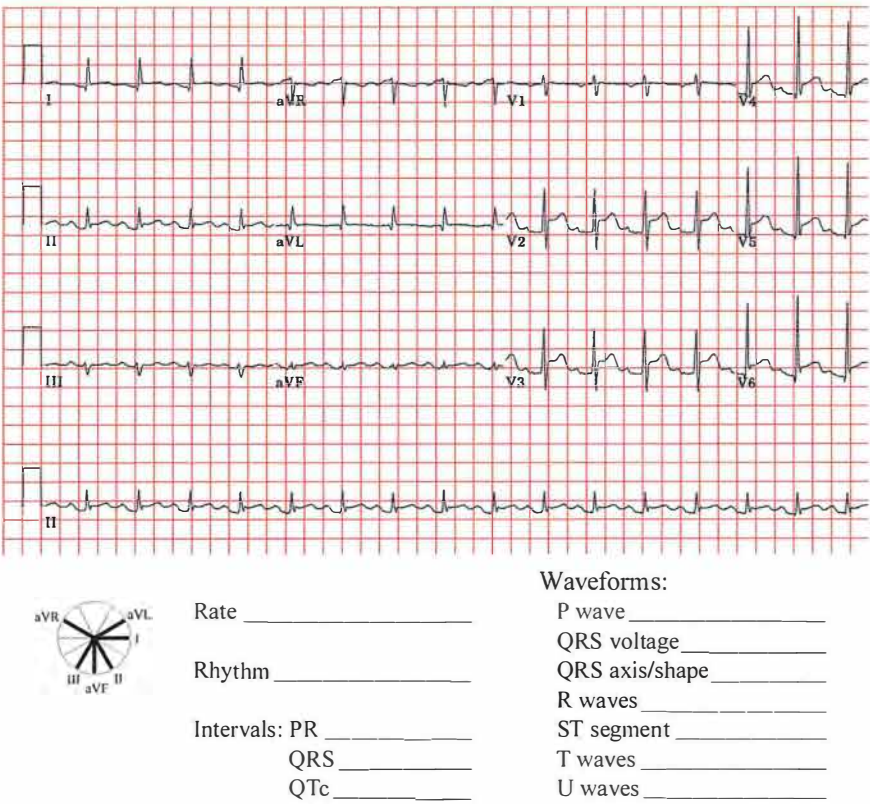
T waves _____

U waves _____

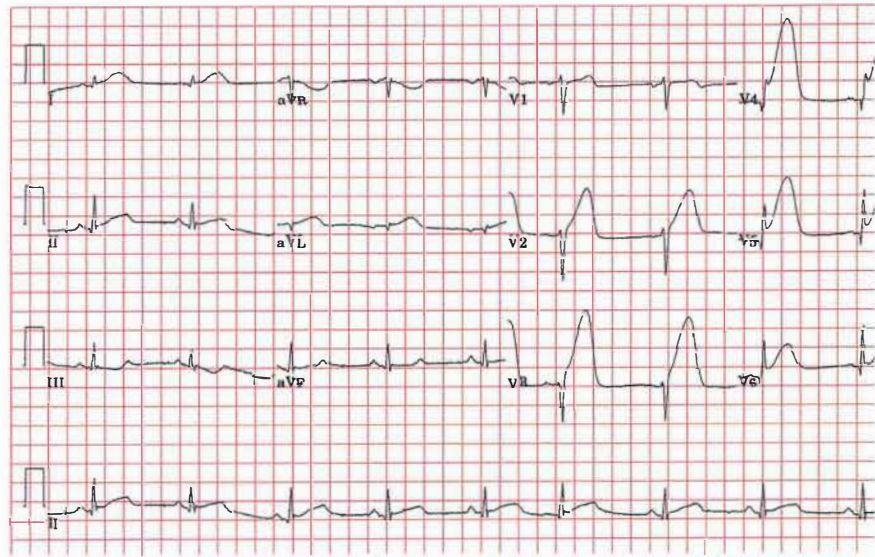
Case 15: A 39-year-old woman is successfully resuscitated from ventricular fibrillation with no evidence of acute MI.



Case 16: A 65-year-old man is admitted for pleuritic chest pain 1 week following a bout of flu-like symptoms.



Case 17: A 65-year-old man is admitted with a 2-hour episode of severe retrosternal chest pain and shortness of breath.



Rate _____

Rhythm _____

Intervals: PR _____

QRS _____

QTc _____

Waveforms:

P wave _____

QRS voltage _____

QRS axis/shape _____

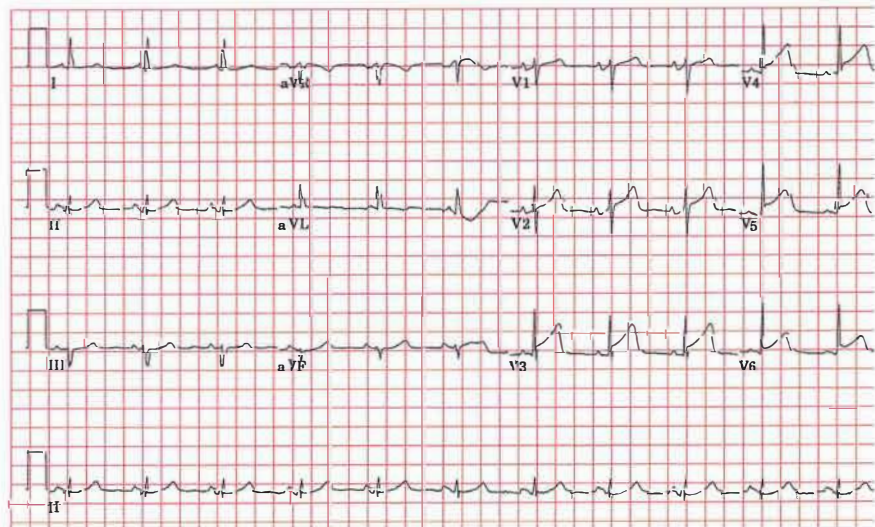
R waves _____

ST segment _____

T waves _____

U waves _____

Case 18a: An 80-year-old woman is seen in the emergency department 3 hours after waking up with severe retrosternal pressure and lightheadedness.



Rate _____

Rhythm _____

Intervals: PR _____

QRS _____

QTc _____

Waveforms:

P wave _____

QRS voltage _____

QRS axis/shape _____

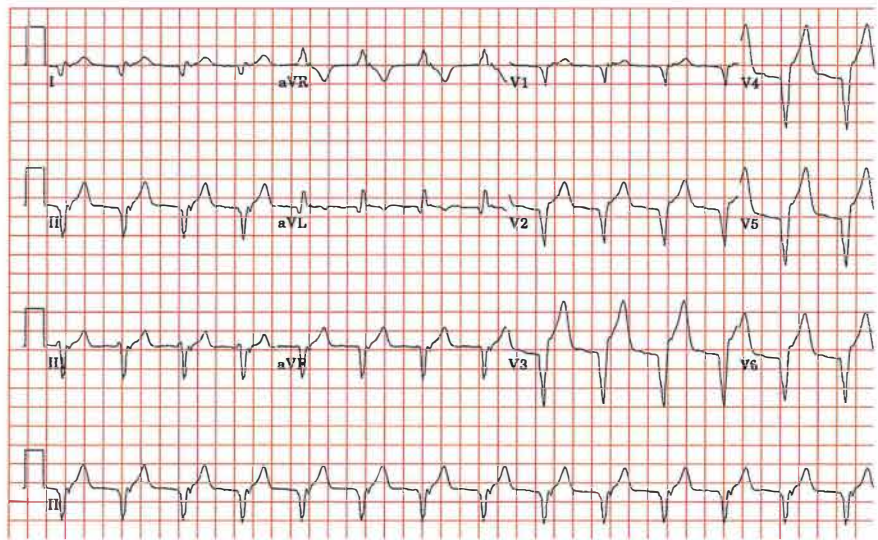
R waves _____

ST segment _____

T waves _____

U waves _____

Case 18b: For the same woman, a repeat ECG is performed 20 minutes following infusion of a thrombolytic.



Rate _____

Rhythm _____

Intervals: PR _____

QRS _____

QTc _____

Waveforms:

P wave _____

QRS voltage _____

QRS axis/shape _____

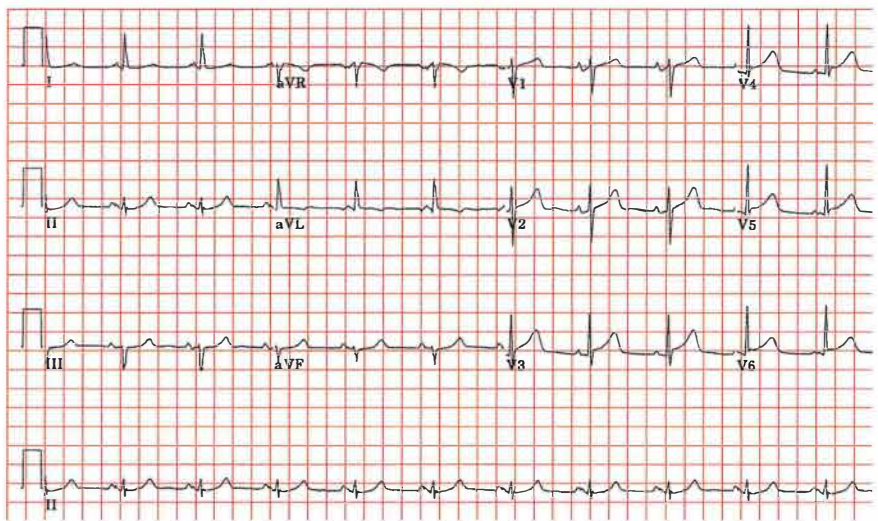
R waves _____

ST segment _____

T waves _____

U waves _____

Case 18c: 90 minutes after thrombolysis, the patient is free of chest pain.



Rate _____

Rhythm _____

Intervals: PR _____

QRS _____

QTc _____

Waveforms:

P wave _____

QRS voltage _____

QRS axis/shape _____

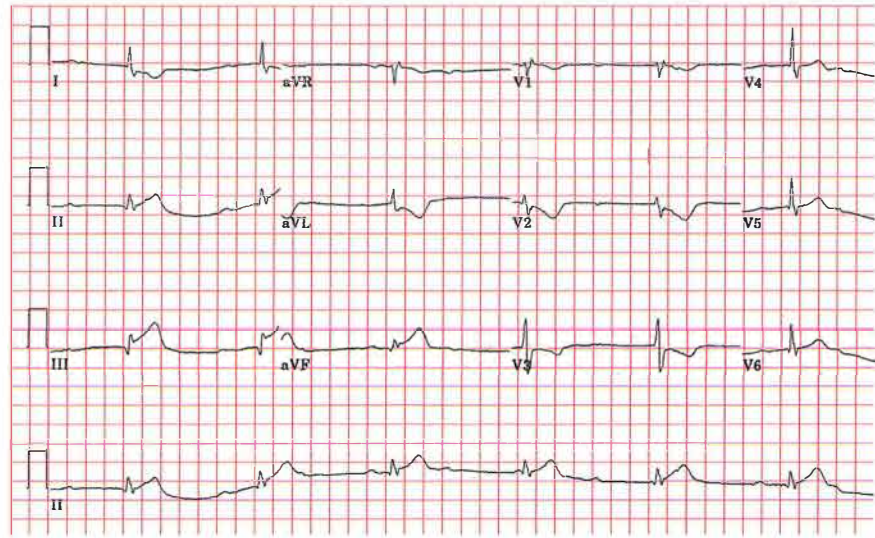
R waves _____

ST segment _____

T waves _____

U waves _____

Case 19: A 65-year-old man with severe epigastric pains, nausea, and vomiting of 2-hour duration



Rate _____

Rhythm _____

Intervals: PR _____

QRS _____

QTc _____

Waveforms:

P wave _____

QRS voltage _____

QRS axis/shape _____

R waves _____

ST segment _____

T waves _____

U waves _____

FINDINGS FROM ECG CASE STUDIES

Case 1: Atrial fibrillation with LBBB. Note the irregular rhythm with no discernable P waves or specific RR-interval patterns. QRS is wide (but no tachycardia, therefore no need to worry about Wolff-Parkinson-White [WPW] syndrome here). The wide QRS is because of left bundle-branch block (LBBB). Even though it is unknown if the LBBB is old or new, with this presentation of chest pain, you should presume it is new and treat the patient for ST-elevation myocardial infarction (STEMI).

Case 2: Sinus rhythm with 2:1 atrioventricular (AV) block. Note there is a buried P wave at the end of each T wave. QRS is narrow, so the AV block is likely at the level of the AV node (i.e., possibly Mobitz Type 1). However, you cannot reliably diagnose Mobitz Type 1 vs. Type 2 AV block when there is 2:1 conduction.

Case 3: 2nd degree Mobitz Type 1 (Wenckebach) 5:4 AV block. The 2nd P wave is not followed by a QRS. The PR interval becomes progressively longer until the depolarization from the atria (P wave) is not conducted to the ventricles (dropped QRS). The 4th PR interval is longer than the 1st PR interval, and the QRS is dropped in the following cycle.

Case 4: Sinus rhythm with complete 3rd degree AV block. There is no association between the P waves and QRS complexes (march each one out separately). QRS is narrow, so this is a junctional escape rhythm.

Case 5: Right ventricular hypertrophy (RVH). Note the sinus rhythm with tall P waves due to right atrial enlargement (RAE). There is right axis deviation. The ECG meets 2 of the criteria for RVH: 1) R wave in V1 ≥ 7 mm and 2) R:S ratio in V1 > 1 . RAE and RVH can be due to pulmonary hypertension resulting from COPD.

Case 6: Sinus rhythm with complete LBBB. Note the QRS is negative in V1 and positive in V6. But left axis deviation is not present here (may have RVH that is buried in LBBB and shifting the axis rightward against the LBBB).

Case 7: Sinus rhythm with right bundle-branch block (RBBB). Initial QRS looks normal (sharp; R progresses toward V4/V5), but the later QRS is slurred and shifted rightward (R' wave in V1 and S wave in V6). ECG shows rsR' pattern ("Rabbit ears"). The axis is normal, as you would expect in RBBB.

Case 8: Sinus rhythm with frequent premature ventricular contractions (PVCs) in bigeminy. Note the full compensatory pause after the PVC. This occurs because the SA node is not affected by the PVCs, hence does not get reset by them, and continues to fire at its own rate without interference from the ventricles.

Case 9: Atrial fibrillation (A-fib) with flipped T waves in the inferolateral leads (II, III, aVF, I, V5, and V6). There are lots of artifacts which may be mistaken for P waves, but if you check the RR intervals between all QRS complexes, you can see variability with no pattern, which is due to A-fib.

Case 10: Atrial flutter with 4:1 block. There is neither ST elevation in V3 nor peaked T waves in lead II or V4. Rather, you see the sum of flutter waves overlying T waves (thus the amplitude of the combined waves is larger).

Case 11: WPW syndrome. Note the sinus rhythm, short PR interval (QRS starts immediately at the end of P wave without an isoelectric line in lead II), and delta wave. Once you make a diagnosis of WPW, do not add more diagnoses (such as MI or left ventricular hypertrophy) because WPW changes the QRS axis, thereby making the ECG nondiagnostic for ischemia.

Case 12: Supraventricular tachycardia (specifically, AV-node reentrant tachycardia). Note the narrow QRS tachycardia (rate ~ 150 bpm) with retrograde P waves (immediately at the end of each QRS complex) evident in precordial leads V1 (positive P wave) and II (small negative deflection). Also notice the pronounced diffuse ST-segment depression (leads I, II, III, aVF, V3, V4, V5, and V6)—it is likely that the rapid rate is contributing to the ischemia (increased myocardial oxygen demand due to increased workload from tachycardia).

Case 13: Ventricular tachycardia (VT). This is a wide complex tachycardia. Given the known history of heart disease, VT should come to mind as the first diagnosis. This rhythm is very fast, 185 bpm, and necessitates immediate synchronized cardioversion before hemodynamic collapse ensues.

Case 14: Hyperkalemia. There is sinus rhythm with tall, peaked T waves with symmetric limbs.

Case 15: Prolonged QT interval. Note the sinus rhythm with no ST-T interval changes. However, there is prolonged QT of 530 ms and a QTc of 640 ms (recall $QTc = QT/\sqrt{RR}$). When measuring the QT interval, you must look at all the leads and choose the longest QT interval—in this case, use lead V2.

Case 16: Pericarditis. There is sinus rhythm with diffuse ST-segment elevation (concave up) that is consistent with pericarditis. There is PR-segment depression (best seen in lead II) and PR-segment elevation in aVR; these are also often seen with pericarditis. If ST segments had been focally elevated and convex up, this case would have been more concerning for STEMI.

Case 17: Anterolateral STEMI with 2:1 AV block. There is marked ST-segment elevation in the precordial leads consistent with acute extensive anterolateral STEMI. Associated T waves are hyperacute. When you pay attention to the end of the ST segment in lead III, you will notice a positive deflection that is a nonconducted P wave (see how the P waves march out), which is indicative of sinus tachycardia rather than sinus rhythm or sinus bradycardia. This means there is 2:1 AV block. One reason to suspect hidden P waves in this case is the critical condition the patient is expected to be in given the extensive STEMI (severe chest pain with labored breathing). Sick patients have sinus tachycardia—a physiologic response

to stress and illness. However, if we notice only the obvious P waves, we would erroneously diagnose sinus bradycardia (as if the patient is relaxing in a spa!)

Case 18a: Acute anterolateral STEMI. The ST-segment elevations in the precordial leads (V3, V4, V5, and V6) are consistent with acute anterolateral STEMI. Even though the ST segment is mildly concave up, continue to be very concerned about acute coronary syndrome because the patient presents with acute chest pain. ECG is a great tool, but not perfect!

Case 18b: Accelerated idioventricular rhythm (AIVR) with a ventricular rhythm of 90 bpm. A tracing with a wide QRS is seen with either AIVR (reperfusion arrhythmia) or VT. It is not VT because the rate is below 100 bpm. Note the change in QRS duration, the axis shift, and the retrograde P waves (negative dips at the very end of each QRS in lead II)—the ventricles are resetting the atria and their sinoatrial node!

Case 18c: Sinus rhythm with resolution of the precordial ST-segment elevation. AIVR with resolution of ST elevation and chest pain all support successful reperfusion with fibrinolytic therapy. Still, remember to transfer this patient immediately to a percutaneous coronary intervention-capable facility. She still needs to undergo invasive coronary angiography within 24 hours!

Case 19: Inferoposterior STEMI. Note the sinus rhythm (regular PP interval). There is acute inferior STEMI (ST elevation in II, III, and aVF). There is also reciprocal ST-segment depression in V1 and V2 (and even somewhat in V3) consistent with posterior STEMI. There is also complete AV block; look for the sinus P wave hidden on top of the first T wave in lead II. When you march the P waves and march the QRS complexes, you will notice that both are regular but independent of each other. This finding is consistent with complete heart block (a.k.a. 3rd degree AV block), which is not uncommon in inferior MI, especially with physical findings of nausea and increased vagal tone. The atrial rate is 75 bpm and ventricular rate is 40 bpm (this can be junctional escape rhythm). The QRS complex is > 100 ms and has a RBBB morphology (Rabbit ears in V1, slurred S waves in V6 and I), but it is not > 120 ms in duration. This supports the diagnosis of incomplete RBBB, which should raise concern for right ventricle involvement.

AMBULATORY ECG MONITORING

Ambulatory ECG monitoring devices (e.g., Holter monitor, event monitor) are useful for diagnosing and monitoring arrhythmias (e.g., A-fib, atrial flutter, SVT, VT), and can be used to assess for A-fib in a patient presenting with cryptogenic stroke (i.e., stroke of unknown etiology). Other indications for monitoring include episodic lightheadedness, dizziness, palpitations, or syncope.

All ambulatory ECG monitors are placed close to the heart. The main difference between the different types is the length of time they can record heart rhythms. Some are capable of recording for hours, others for years. Therefore, choose a device based on the patient's frequency of symptoms.

The ECGs recorded on these monitors allow for rhythm analysis, but waveform details may not render accurately; so, do not prescribe these monitors to assess for ischemia.

CONTINUOUS AMBULATORY ECG (HOLTER) MONITORS

Intermittent arrhythmias may not be captured during a 12-second ECG. A Holter monitor is attached to leads placed on the chest and continuously records the ECG over 24–48 hours. The monitor is returned and analyzed to detect arrhythmias. Holter monitors are useful in patients with frequent symptoms. Do not use this for symptoms that happen infrequently (e.g., once a week, once a month) because intermittent arrhythmias are unlikely to be detected during a 48-hour monitoring period.

The patient keeps a written diary of the symptoms experienced (including time) while wearing the Holter monitor. At the end of the monitoring period, the provider analyzes the entire recorded rhythm and assesses for correlation between symptoms and the patient's diary entries.

EVENT MONITORS

Similar to Holter monitors, event monitors are worn by patients at home to record their ECG over 2–4 weeks. Some devices come as a patch with adhesive that is attached to the left chest wall over the heart. These are used in patients whose symptoms occur infrequently (once or twice a month). A Holter monitor worn for 2 days is likely to miss such events; an event monitor, on the other hand, is likely to capture them.

When the patient experiences symptoms, a button on the monitor can be pushed to mark the ECG at that time. As with Holter monitors, the provider analyzes the entire recorded rhythm and correlates symptoms with the rhythms marked by the patient.

IMPLANTABLE LOOP RECORDERS

For symptoms that are even less frequent (e.g., once every 6 months, once a year) but severe, an implantable loop recorder may be a useful diagnostic tool. It is a chip that is inserted subcutaneously in the left upper chest over the heart. This can stay in place for 1–3 years and can be wirelessly accessed using a standard pacemaker programmer (a.k.a. interrogator). After 1–3 years, the device can be simply extracted from underneath the skin.

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Gastroenterology

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GASTROINTESTINAL (GI) PROCEDURES

PREVIEW | REVIEW

- What are the indications for an esophagogastroduodenoscopy?
- What is a potential severe complication of endoscopic retrograde cholangiopancreatography?

Esophagogastroduodenoscopy (EGD) is the procedure of choice for:

- Evaluation of difficulty swallowing in suspected esophageal dysphagia
- Evaluation of painful swallowing (odynophagia)
- Diagnosis of a peptic ulcer—instead of upper gastrointestinal (UGI) series or when the UGI is equivocal or negative—and always before peptic ulcer disease (PUD) surgery
- Workup of gastroesophageal reflux disease (GERD) if initial treatment fails, or if there are alarm signals (See [Gastroesophageal Reflux Disease \(GERD\)](#) on page 14-7.)
- UGI bleeding
- Evaluation and removal of an ingested foreign body
- Evaluation of small bowel disease (e.g., diarrhea, iron deficiency, bloating)
- Persistent dyspepsia despite treatment (Note: A normal EGD is a prerequisite for diagnosing nonulcer dyspepsia.)
- Placement of feeding or drainage tubes

Relative contraindications to EGD include recent myocardial infarction, a combative patient, and intestinal perforation.

Indications for **endoscopic retrograde cholangiopancreatography (ERCP)** include:

- Management of biliary obstruction (benign or malignant)
- Diagnosis and treatment of pancreatic duct obstruction
- Diagnosis of primary sclerosing cholangitis (PSC). Note: **Magnetic resonance cholangiopancreatography (MRCP)** is a noninvasive, safer alternative.
- Treatment of choledocholithiasis with or without cholangitis
- Evaluation of abnormal biliary or pancreatic duct imaging (after computed tomography [CT]/MRCP/EUS)

Asymptomatic elevations in amylase occur frequently following ERCP. However, acute pancreatitis develops

in only 2–5% (<0.2% severe) of patients. ERCP is contraindicated in acute pancreatitis, **except** in the following conditions:

- Impacted gallstones (gallstone-induced pancreatitis)
- Ascending cholangitis (bacterial infection causing cholangitis)

Use antibiotics before ERCP to treat patients with suspected bile duct obstruction.

MRCP can be used to:

- Diagnose bile duct obstruction
- Diagnose chronic pancreatitis
- Assess a lack of clinical improvement in acute pancreatitis
- Diagnose PSC—this is the test of choice!

Other tests of the pancreas and biliary system include:

- Retrograde cholangiography, which visualizes the bile tract
- Percutaneous transhepatic cholangiography (PTC)
- HIDA (hepatobiliary iminodiacetic acid) scan is sometimes used in the evaluation of acute cholecystitis.
- Retrograde pancreatography is used to visualize the pancreatic duct.

Endoscopic ultrasound (EUS) is a minimally invasive endoscopic procedure that uses ultrasound to evaluate the layers of the gastrointestinal tract and nearby organs such as the pancreas, biliary system, and regional lymph nodes.

Indications for EUS include:

- Staging of GI tract, biliary tree, and pancreatic malignancies
- Diagnosis of chronic pancreatitis
- Diagnosis and treatment of complications of pancreatitis
- Tissue sampling of regional lymph nodes and organs adjacent to the GI tract
- Providing access to pancreatic duct or biliary tree

Colonoscopy is the procedure of choice for:

- Evaluation and treatment of chronic diarrhea
- Evaluation and treatment of lower GI bleed
- Screening for colorectal cancer (See the [Oncology](#) section.)

ESOPHAGUS

PREVIEW | REVIEW

- What is the 1st test usually performed in the workup of dysphagia?
- What is the preferred treatment for achalasia?

- Esophageal neurologic dysfunction presents with which symptoms?
- Which is the most important part of therapy for diffuse esophageal spasm?
- What type of problem causes slowly progressive dysphagia for solids and then liquids?
- What is a likely cause of anatomic obstruction of the esophagus in younger patients? In older patients?
- Which anatomic problem causes slowly progressive constant dysphagia to solid food?
- What is the lower esophageal sphincter pressure in patients with dysphagia due to systemic sclerosis?
- Which drugs interact with proton pump inhibitors?
- What is the clinical presentation of gastroesophageal reflux disease (GERD)?
- What are the alarm signals in a patient with GERD symptoms? These indicate the need for what?
- Which diagnostic test may be helpful for GERD with atypical symptoms?
- What is used to treat severe GERD?
- For how long is severe GERD treated?
- In patients with GERD, which study must be done before antireflux surgery?
- What is the pathologic definition of Barrett esophagus?
- Which cancer is associated with Barrett esophagus?
- What follow-up is indicated in patients with non-dysplastic Barrett esophagus?
- What are the treatment options for Barrett esophagus with high-grade dysplasia?
- Discuss the differences between adeno and squamous cell cancer of the esophagus.
- Name the risk factors for esophageal cancer.

Know the indications for EGD, ERCP, pH monitor, and motility studies as they relate to the esophagus topics!

DYSPHAGIA

Normal swallowing (deglutition) is a voluntary action that leads to upper esophageal sphincter (UES) relaxation and epiglottis closure. The smooth muscle in the esophageal body then generates a peristaltic contraction, propelling the food bolus distally. The lower esophageal sphincter (LES) relaxes to allow the bolus to enter the gastric fundus.

Swallowing that does not proceed appropriately for any reason is termed **dysphagia**. The history often gives important clues as to the etiology of dysphagia. Distinguish dysphagia from **odynophagia**, where the patient experiences pain when the food bolus traverses the esophagus.

Dysphagia may be caused by (see Table 14-1):

- Transfer disorders (oropharyngeal)—neurologic/neuromuscular deficits lead to oropharyngeal muscle dysfunction, resulting in difficulty transferring food from the mouth to the esophagus. Symptoms include coughing, gagging, and nasal regurgitating immediately upon swallowing. Common causes include stroke, Parkinson disease, multiple sclerosis (MS), and amyotrophic lateral sclerosis (ALS).
- Anatomic or structural disorders—physical obstruction of the esophageal lumen, such as Schatzki ring or esophageal cancer.
- Motility disorders—trouble with transporting food from the upper esophagus to the stomach. Motility disorders have both endogenous and exogenous causes and often occur with failure of effective peristalsis and/or failure of LES relaxation.

Diagnosis:

- EGD is usually the 1st test performed in the workup of esophageal dysphagia. Esophageal dilation or biopsy can be done along with the EGD.
- Barium swallow (a.k.a. barium esophagram) follows a normal EGD if symptoms persist. A barium swallow can often detect subtle rings, which may be missed on EGD. It precedes endoscopy when:
 - there is a risk of perforation with EGD in a patient with diverticula or suspected high-grade obstruction (e.g., previous surgery for esophageal cancer, radiation therapy),
 - information from the barium swallow may preclude the need for endoscopy, or
 - patients are at high risk for sedation-related complications.

Table 14-1: Causes of Dysphagia

Disease	Etiology	Timing	Precipitated by
Schatzki ring	Anatomic	Intermittent	Solids
Stricture	Anatomic	Progressive	Solids, then liquids
Cancer	Anatomic	Progressive	Solids, then liquids
Achalasia	Motility/Neurologic	Long-standing	Solids and liquids
DES	Motility/Neurologic	Intermittent	Solids and liquids (esp. cold)
Systemic sclerosis	Various	Progressive	Solids and liquids

DES = diffuse esophageal spasm

- A video-fluoroscopic swallow study is the best 1st test when oropharyngeal dysphagia is suspect based on history (coughing, gagging, and difficulty initiating swallow). It is also used as the 1st test if symptoms are severe or if there is new-onset dysphagia with liquids. Nasopharyngeal laryngoscopy can be used if direct visualization is needed.
- High-resolution esophageal manometry (HREM), using multiple ports that can be combined with measurements of esophageal impedance, is generally done only if the patient has symptoms suspicious of motility disorders (e.g., dysphagia to solids and liquids) or if EGD and barium swallow are negative.

Always work up dysphagia. Do not treat empirically. See Figure 14-1.

Any type of dysphagia can cause aspiration. This aspiration is often well tolerated and does not need treatment unless pulmonary problems arise. These patients may complain of choking, gagging, and nasal regurgitation. You may need to address pulmonary complications separately.

If you suspect aspiration, perform a video-fluoroscopy swallow study to confirm the diagnosis. Tracheostomy does not prevent chronic aspiration. A percutaneous endoscopic gastrostomy (PEG) or percutaneous endoscopic jejunostomy (PEJ) tube may be required, although a PEG does not prevent aspiration of oral secretions or refluxed gastric material.

ACHALASIA

The pathogenesis of achalasia is unknown, but it has characteristic and diagnostic features. Neuronal denervation and ganglion cell degeneration of the myenteric plexus lead to the following findings:

- There is an absence of organized peristalsis in the esophageal body.
- The LES does not relax completely with swallowing.
- Often the LES has an elevated resting pressure.

The characteristic features of the history include:

- Dysphagia for **solids and liquids**
- Long-standing symptoms, usually years
- Regurgitation of food, especially at night
- Chest pain
- No age or gender predilection

The diagnosis of achalasia is made with:

- Barium swallow: The esophagus appears dilated and is often fluid-filled. The barium may take a long time to empty into the stomach, even if the patient is upright. There is a “bird-beak” narrowing distally, which represents the tight LES and is a classic finding (Figure 14-2).
- Esophageal manometry: This test is generally done to confirm the diagnosis before treatment is offered. Results clearly show the absence of normal peristalsis, often with a nonrelaxing LES. The use of high-resolution manometry with impedance has revealed 3 distinct subtypes of achalasia: traditional aperistalsis, esophageal compression, and generalized spasm. Each subtype may have a different long-term outcome and different responses to various treatments.
- EGD: The procedure is done mainly to confirm the diagnosis and to exclude a tumor at the esophago-gastric junction (“pseudoachalasia”). A popping sensation is often described as the endoscope passes through the nonrelaxing LES.



Figure 14-2: Achalasia
Source: James W. Smith, MD

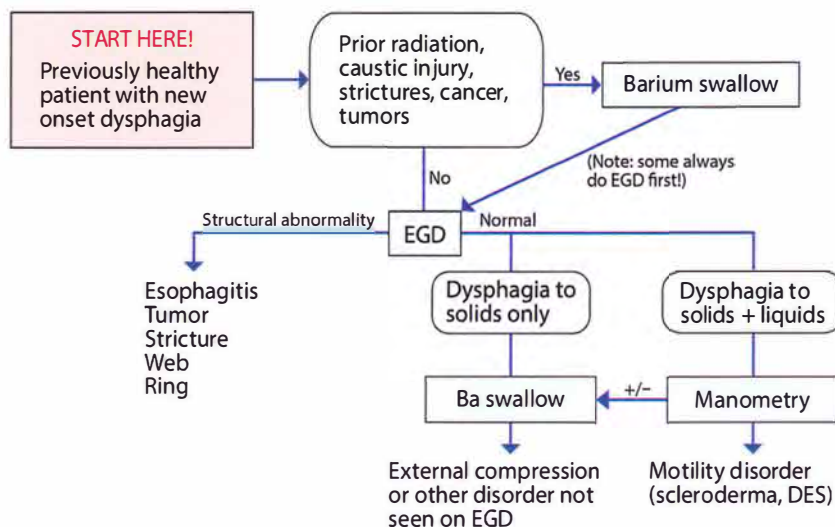


Figure 14-1: Dysphagia workup

Remember the 3 tests for achalasia: barium swallow, manometry, and endoscopy.

Also remember **pseudoachalasia**. A tumor (such as gastroesophageal carcinoma) at the esophagogastric junction can mimic the history and diagnostic findings of achalasia. Especially consider this diagnosis if onset of symptoms is rapid, patient is > 60 years of age, and symptoms are progressive and include profound weight loss.

Complications of achalasia include aspiration pneumonia and malnutrition.

Treatment: The focus of treatment for achalasia is on opening or relaxing the LES by pneumatic dilation. For good surgical candidates, pneumatic dilation and surgical myotomy are equivalent. With pneumatic dilation, a large 3- to 4-cm diameter balloon is inflated within the LES to tear the sphincter muscle fibers. This balloon is much larger and generates higher pressure than the balloons used to treat esophageal rings and strictures. There is a 2–4% risk of perforation. Surgical myotomy is also very effective and can be done via laparoscope. An alternative therapy is botulinum toxin. OnabotulinumtoxinA (Botox) is effective in 65% of cases but requires repeat therapy within 6–12 months. It is an alternative therapy in high-risk surgical patients or used to predict response to definitive therapy. A peroral endoscopic myotomy (POEM) provides a more definitive treatment for otherwise poor operative candidates.

DYSPHAGIA — NEUROLOGIC DYSFUNCTION

Neurologic problems involving the swallowing and/or esophageal peristaltic mechanisms cause dysphagia to both **solids and liquids** from time of onset. Neurologic causes of disordered swallowing always need to be considered after excluding anatomic abnormalities. Examples of neurologic causes include stroke, parkinsonism, ALS, and MS.

Video swallowing studies are useful in evaluating dysphagia related to neurologic dysfunction.

DIFFUSE ESOPHAGEAL SPASM (DES)

DES is a simultaneous, nonperistaltic contraction of the esophagus, often precipitated by cold or carbonated liquids. DES can cause dysphagia, chest pain, or both. Although the chest pain is usually atypical for angina, cardiac causes should be ruled out. Occult reflux can cause esophageal spasms even in the absence of typical reflux symptoms.

Barium swallow is commonly normal but may show the classic **corkscrew** pattern (Figure 14-3) if the study is done at the time of spasm. High-resolution manometry confirms the diagnosis by revealing excess, simultaneous (nonperistaltic) contractions in the distal esophagus with normal LES relaxation.

LES pressure may be low, normal, or high (i.e., nonspecific).

Endoscopy is used to rule out other structural disorders. Even in patients with spasm due to reflux, there is usually no obvious or gross reflux esophagitis.

If reflux is considered a possible cause of the DES, order a 24-hour esophageal pH recording or give 2× daily proton pump inhibitors (PPIs) for 3 months.

Treatment: Reassurance is the most important part of therapy.

However, if reassurance is not effective or the patient requests specific therapy, recommend treatment in this order:

- 1st line: diltiazem or imipramine
- 2nd line: isosorbide or sildenafil
- 3rd line: botulinum toxin injection at the mid and distal esophagus

Obviously, it is important to avoid any foods, such as cold beverages, which exacerbate symptoms. Treat with PPIs if you suspect GERD (half of pH studies are abnormal in DES). Some patients report benefit from empiric esophageal dilation, although the rationale for this is difficult to understand, and a benefit over placebo is hard to prove. There may be a role for the use of botulinum toxin for some types of DES, based on specific manometric patterns.

ANATOMIC OBSTRUCTION

Anatomic obstruction causes a slowly progressive dysphagia—**initially to solids**, then to liquids when severe. Depending on the cause, this slowly progressive dysphagia may be intermittent or constant.

In younger patients, slowly progressive solid-food dysphagia is typically caused by a Schatzki ring (see **Lower Esophageal (LE) Ring (Schatzki Ring)**), whereas in older patients, it is usually due to cancer (esophageal or extrinsic compression) or peptic stricture.

Lower Esophageal (LE) Ring (Schatzki Ring)

The LE ring (a.k.a. Schatzki ring; Figure 14-4) is a common cause of dysphagia, especially in younger patients. Patients often give a classic history of very slowly progressive, **intermittent** solid food dysphagia, especially for meat and bread. They may have to regurgitate the impacted bolus for relief. LE ring is always associated with a hiatal hernia, and, although reflux may have a role in pathogenesis, there is generally no obvious esophagitis on endoscopy.



Figure 14-3: Corkscrew esophagus
Source: James W. Smith, MD

Most symptomatic rings causing dysphagia are ≤ 13 mm in diameter. Treatment is dilation using either a bougie (soft, tapered) dilator or a through-the-scope hydrostatic balloon. Treat patients with PPIs after dilation.



Figure 14-4: Severe esophageal stricture on the left; Schatzki ring on the right

Source: James W. Smith, MD

Esophageal Stricture

Esophageal stricture presents with a history of slowly progressive, **constant** (not intermittent) dysphagia for **solid foods**. A long history of incompletely treated acid reflux commonly causes peptic stricture, and the use of PPIs has sharply reduced stricture incidence. Stricture can also result from prolonged nasogastric tube placement or lye ingestion (rare today, except in those who ingested lye decades ago; these have a chronic stricture and an increased risk of esophageal cancer). Esophageal strictures can also occur as a complication of treatment for dysplastic Barrett esophagus with radiofrequency ablation, photodynamic therapy, or endoscopic mucosal resection. Barium swallow shows narrowing, typically at the esophagogastric junction, and this narrowing may also be present on upper endoscopy. Severe esophageal stricture is seen in [Figure 14-4](#). Treatment is dilation and PPI therapy to prevent recurrence.

Malignant Obstruction

Malignant obstruction can be a result of esophageal cancer ([Figure 14-5](#); e.g., esophageal adenocarcinoma or squamous cell carcinoma) or extrinsic compression from nonesophageal primary cancers. Usually the history

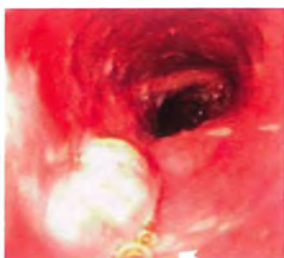


Figure 14-5: Esophageal cancer

is of **progression of symptoms**: solid food dysphagia to soft food difficulties and finally to problems with liquids. Dysphagia with weight loss represents esophageal malignancy until proven otherwise. For more information, see [Esophageal Cancer](#) on page 14-9.

Plummer-Vinson Syndrome

Plummer-Vinson syndrome, a rare disorder, causes dysphagia due to an **upper** esophageal web. An esophageal web is a thin fold of tissue covered with squamous epithelium that protrudes into the lumen. It is generally found in postmenopausal women in association with iron-deficiency anemia—the reason for this association is unknown. Patients with Plummer-Vinson syndrome have a slightly increased risk of squamous cell esophageal cancer.

ACUTE OBSTRUCTION

Acute obstruction is usually due to impacted food in the esophagus in a patient with an anatomic obstruction. In adults, foreign body obstruction is rare. Larger foreign bodies, foreign bodies with sharp edges, and button batteries are removed endoscopically. Button batteries stuck in the esophagus require immediate removal because the electrical current can result in esophageal liquefaction necrosis and rapid perforation.

SCLERODERMA AND SYSTEMIC SCLEROSIS (SSc)

Scleroderma is the term for shiny, hard, thickened skin. Scleroderma can occur in isolation, but when the sclerosis involves internal organs, it is called systemic sclerosis (SSc). SSc itself is further classified as diffuse or limited, based on the extent of cutaneous involvement. Esophageal involvement can be seen in both limited and diffuse SSc.

SSc is the most common connective tissue disease involving the esophagus. More than 80% of patients have involvement of the esophagus. When the esophagus is involved, the patient has very weak-to-absent esophageal peristalsis in the distal 2/3 of the esophagus. The LES is “wide open” with no tone or low pressure, resulting in severe acid reflux damage to the esophagus.

Dysphagia to solids and liquids can be due to any 1 or a combination of the following 3 problems:

- 1) Esophagitis
- 2) Stricture
- 3) Impaired motility

So, workup begins with an EGD to look for all 3 of these possibilities. Manometry can be helpful in detecting impaired motility. EGD can provide both diagnostic and therapeutic intervention at the same time. It offers the advantage of directly visualizing the esophagus, acquiring tissue biopsy, and even dilating the stricture to relieve the patient’s dysphagia.

If esophagitis is present, begin aggressive PPI therapy. Perform a follow-up endoscopy at 2–3 months to confirm healing and to ensure adequacy of the PPI dose. A stricture can be safely dilated using standard techniques.

Note: Polymyositis and dermatomyositis can have similar effects on the esophagus.

MALLORY-WEISS SYNDROME

Mallory-Weiss syndrome is characterized by longitudinal mucosal tears at the gastroesophageal junction, typically due to forceful vomiting or retching. However, any event that causes a sudden rise in intraabdominal pressure (e.g., coughing, straining) can result in this syndrome.

The prevalence of Mallory-Weiss tears is ~ 5% in patients presenting with upper GI bleeds. They occur most often in males 40–60 years of age. Predisposing factors include hiatal hernia and heavy alcohol use.

Patients present with hematemesis (often preceded by vomiting or retching). This can be accompanied by epigastric or back pain as well as melena. Although specific physical findings are often absent, tachycardia, hypotension, and even shock may be present if blood loss is severe.

Use endoscopy to both diagnose and treat Mallory-Weiss syndrome. Obtain complete blood count (CBC) to determine hemoglobin level.

Up to 70% of tears heal spontaneously. However, if bleeding persists, treatment options include endoscopic clip placement, heat cauterization, injection therapy, balloon tamponade, band ligation, and, in severe cases, surgery. PPIs are used to prevent rebleeding, though clinical efficacy is not well studied.

ESOPHAGEAL RUPTURE / PERFORATION

Esophageal rupture has a high morbidity/mortality rate. It is most commonly caused by medical instruments during diagnostic and therapeutic procedures, but rupture can also be spontaneous (a.k.a. Boerhaave syndrome) or from caustic or blunt trauma. Boerhaave syndrome results from a combination of increased intraesophageal pressure and negative intrathoracic pressure (e.g., vomiting, straining).

The majority of perforations occur in 3 areas of the esophagus (listed from most to least common): intrathoracic, cervical, and intraabdominal. Leakage of acidic gastric contents causes mediastinitis that can lead to sepsis and eventually death if not treated in a timely manner.

Clinical presentation includes pain (retrosternal chest, abdominal, or neck depending on the location of the tear) and subcutaneous emphysema. Within hours of the perforation, fever, dyspnea, tachypnea, and sepsis can occur.

CBC often reveals a leukocytosis. Diagnose by contrast esophagram (barium swallow) or CT scan.

Treatment includes patient stabilization, broad-spectrum intravenous (IV) antibiotics with coverage for both aerobes and anaerobes (e.g., ampicillin/sulbactam, carbapenem), and surgical repair. Delayed diagnosis and treatment increases mortality.

EOSINOPHILIC ESOPHAGITIS (EoE)

Primary EoE is an immune-mediated chronic eosinophil-predominant inflammatory disorder of the esophagus.

EoE typically affects men 20–40 years of age.

There is a strong association with allergies—environmental, food, asthma, and atopy. IgE is elevated in 2/3 of patients.

The leading symptom is recurrent attacks of dysphagia with food impaction. On average, patients have symptoms for 4–5 years before diagnosis. Symptoms are more pronounced in those with a peripheral eosinophilia, which is found in ~ 30% of patients.

The classic EGD finding is a scalloped appearance with ridges or “feline” rings (a.k.a. trachealization) in the esophagus (Figure 14-6), linear furrowing, and eosinophilic abscesses. Diagnosis is confirmed by esophageal biopsies showing a dense eosinophilic infiltration of the esophageal epithelium

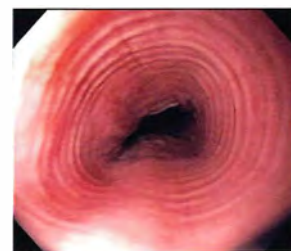


Figure 14-6: Trachealization of eosinophilic esophagitis

(> 15 eos/HPF) in the proximal and distal esophagus. Patients with only GERD can have lower levels of eosinophilic infiltration, usually < 5 eos/HPF.

Treatment can be difficult. A trial of PPI therapy should be attempted early, as EoE may coexist with GERD and a subset of patients respond well to this treatment. Most gastroenterologists refer for allergy testing with subsequent avoidance of potential allergens. Empiric elimination of common triggers (milk, eggs, soy, wheat, fish/shellfish, and peanuts/tree nuts) is often effective. Swallowed fluticasone (bid) or viscous budesonide usually results in a response within 1 week. Eosinophilic esophagitis typically requires long-term therapy, and relapses are common with the discontinuation of steroids. Esophageal dilatation is sometimes used in patients who fail to respond to medical therapy.

MISCELLANEOUS CAUSES OF ESOPHAGITIS

Odynophagia (painful swallowing) can be caused by pill-induced esophagitis or opportunistic infections.

Pill-induced esophagitis is most likely to occur when pills are taken with little or no water or before lying down. It is especially seen in patients taking doxycycline (e.g., teenagers with acne), potassium chloride, aspirin (ASA),

nonsteroidal antiinflammatory drugs (NSAIDs), iron, bisphosphonates (e.g., alendronate), and quinidine. The pain can be severe.

Diagnosis can be made based solely on history! If the history is typical, with abrupt onset of symptoms and an obvious offending medication, no EGD is needed.

Treatment: Stop the offending medicine and reassure the patient that the condition will improve. Educate your patients to take medications in the upright position with plenty of water.

Opportunistic infections (OIs) can occur in any immunocompromised patient, such as those with diabetes or HIV, but can also occur in otherwise immunocompetent patients who are taking corticosteroids. **Common OIs** are *Candida*, herpes simplex virus, and cytomegalovirus. If you see thrush in the mouth, you can assume that the esophagitis is due to *Candida*; treat the patient empirically with fluconazole. If there is no improvement, or you're unsure of the diagnosis, EGD with biopsy is the procedure of choice. Dilation is rarely needed or helpful.

PROTON PUMP INHIBITORS (PPIs)

PPIs are more commonly used today than H₂ receptor blockers because PPIs are more effective.

Efficacy of PPIs depends on plasma levels. PPIs are all metabolized via the cytochrome P450 pathway, primarily by the enzyme CYP2C19. There is a genetic mutation for CYP2C19 that results in a person being a "slow metabolizer." Heterozygotes are moderate metabolizers, and people without the mutation (i.e., wild type) are rapid metabolizers. The proportion of slow metabolizers varies by ethnicity. For instance, among Caucasians, it is 5%, 30%, 65% (slow to fast). Slow metabolizers of PPIs have much better symptom response at a given dose than fast metabolizers.

PPIs cause hypergastrinemia, achlorhydria, and possibly gastric atrophy. There are additional short-term and long-term effects of PPIs.

Short term: Studies suggest community-acquired pneumonia (CAP) is more likely to occur within 30 days of starting PPIs—and especially within 48 hours.

Long term, PPIs increase the risk of:

- Fractures
- Hypomagnesemia (symptoms include muscle spasms, arrhythmias, seizures)
- *Clostridioides difficile* (*C. difficile*; formerly known as *Clostridium difficile*) infection
- Chronic kidney disease

Although long-term PPI use leads to parietal cell hyperplasia, no dysplasia or neoplasia has been seen.

PPIs should be taken in the morning, 30 to 60 minutes before breakfast, for maximal efficacy. Rebound acid hypersecretion occurs when PPIs are stopped abruptly after several months—especially in *Helicobacter pylori*-negative patients.

Long-term use of PPIs is discouraged unless necessary (e.g., the prevention of GI bleeding with long-term antiplatelet therapy). When needed, maintain patients on the lowest tolerable dose. Attempt to control symptoms with H₂ blockers if possible.

Drug interactions with PPIs: PPIs interact with few drugs and are generally well tolerated. They **decrease** absorption and serum levels of thyroxine and itraconazole/ketoconazole and **increase** absorption of digoxin.

A controversy regarding the use of clopidogrel with omeprazole was addressed by the COGENT trial and a subsequent consensus statement in 2010 by the American College of Cardiology Foundation/American Heart Association (AHA)/American College of Gastroenterology (ACG):

- No significant cardiovascular harm was found with PPI use.
- PPIs are recommended to reduce GI bleeding among patients with a history of GI bleed and in patients with multiple risk factors for GI bleeding who require antiplatelet therapy.
- Further study is needed for the slow metabolizers of clopidogrel.

GASTROESOPHAGEAL REFLUX DISEASE (GERD)

GERD is generally a result of transient relaxation of the LES. The transient relaxation is a vagally mediated reflex and is the physiologic mechanism of belching. Transient relaxations occur at increased frequency with gastric distention and in the upright position. Hiatal hernia is a risk factor for GERD.

LES pressure is **increased** by motilin, acetylcholine, and possibly gastrin. Therefore, drugs that increase these mediators tend to decrease reflux. LES pressure is **decreased** by progesterone (pregnancy increases GE reflux; for more on GERD during pregnancy, see the [Women's and Men's Health](#) section), chocolate, smoking, and some medications, especially those with anticholinergic properties.

Suspect GERD in patients with classic symptoms of heartburn and regurgitation, as well as the atypical symptom of persistent, nonproductive cough—especially with hoarseness, continual clearing of the throat, and a feeling of fullness in the throat. This cough is commonly worse at night when the patient is supine.

Most noncardiac chest pain (70%) is caused by GERD! Most other GI-related chest pain is due to motility disorders. Note: These pains are not necessarily associated with pyrosis (heartburn) or dysphagia.

Extraesophageal manifestations of GERD:

- Nocturnal cough
- Frequent sore throat
- Hoarseness, laryngitis, clearing of the throat

- Loss of dental enamel
- Exacerbation of asthma
- Vocal cord dysfunction (VCD)

GERD is associated with 2 respiratory disorders: asthma and VCD.

Some asthma patients, even without symptoms of GERD, have improvement of their asthma symptoms with GERD treatment. In the workup of GERD, always ask about asthma symptoms—especially those occurring at night.

VCD is spasm of the vocal cords with associated **inspiratory** stridor. Patients may complain of nocturnal “wheezing,” not realizing it is inspiratory stridor.

Pulmonary function testing may help distinguish VCD from asthma. VCD is not always due to GERD; it is typically seen in young adults who engage in competitive sports and is thought to be a stress reaction. About 10% of exercise-induced asthma may be misdiagnosed VCD. Patients with suspected VCD or silent reflux benefit from ENT evaluation.

Obesity is associated with both GERD and asthma.

Complications of GERD include dysphagia, esophageal ulcers, stricture, bleeding, and Barrett esophagus (see **Barrett Esophagus**).

Diagnosis

If the patient has only the classic symptoms of heartburn without alarm signals, the diagnostic workup starts with a therapeutic trial of PPIs—EGD is indicated only if this trial fails (**Figure 14-7**).

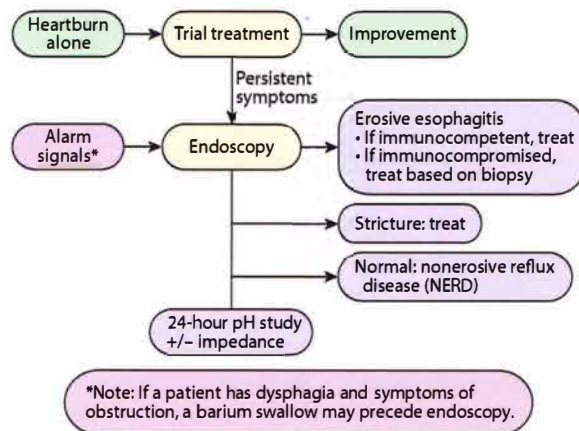


Figure 14-7: Workup of suspected GERD

Alarm signals in GERD indicating the need for EGD:

- Nausea/Emesis
- Blood in the stool or vomitus
- Family history of PUD
- Weight loss
- Anorexia
- Iron-deficiency anemia
- Abnormal physical exam (e.g., epigastric tenderness, cervical lymphadenopathy)

- Long duration of frequent symptoms, especially in Caucasian males > 50 years of age (high risk of Barrett esophagus)
- Failure to respond to full doses of a PPI
- Dysphagia
- Odynophagia

EGD is also done if you suspect Barrett esophagus. High risk factors for Barrett esophagus are being male, having a history of GERD for > 10 years, and being obese.

If the patient has obstructive symptoms, you can do a barium swallow before endoscopy.

Note: 62% of patients with GERD symptoms have a normal esophagus. This is termed **nonerosive reflux disease** or NERD!

Use ambulatory esophageal impedance pH monitoring to evaluate for GERD with atypical symptoms, such as:

- Refractory symptoms and a normal EGD
- Hoarseness, coughing, or atypical chest pain but no classic symptoms of GERD
- Failure to respond to PPIs

The pH monitor is similar to a Holter monitor in that the patient keeps a diary of symptoms. You then analyze the diary logs and pH monitor results for a correlation.

The combination of esophageal pH with ambulatory esophageal impedance monitoring has resulted in increased ability to identify types of GERD, including nonacid GERD.

Treatment

Mild-to-Moderate GERD

Initial treatment of mild-to-moderate GERD:

- Raise head of bed
- Encourage weight loss of >10 lb if overweight or if there has been recent weight gain.
- Small meals; no fatty meals in the evening; eat dinner at least 3 hours before bedtime; no sweets, especially chocolate, at bedtime.
- Stop smoking.
- Antacids as needed
- Avoid alcoholic and acidic beverages before bedtime (e.g., colas, orange juice, wine).

In clinical trials, only raising the head of the bed and weight loss have been shown to be effective. The remaining management options are mechanistically plausible but unproven.

If the treatment is unsuccessful, try antisecretory drugs.

Overall healing rates of patients with endoscopic evidence of esophagitis (not necessarily GERD!):

- Placebo: 25%
- H₂ blockers and prokinetic drugs: 50%
- PPIs: 80–95%

H₂ blockers may heal mild cases of GERD.

Severe GERD

Treatment of severe GERD (often described as Grade B or worse esophagitis in the gastroenterology literature) requires PPIs, such as omeprazole or lansoprazole. These PPIs are continued indefinitely* unless the patient has corrective surgery.

PPIs, in particular, are indicated for **long-term therapy*** in patients with EGD evidence of esophagitis.

*Note the concerns with the long-term use of PPIs in the earlier discussion of **Proton Pump Inhibitors (PPIs)** on page 14-7.

In patients with GERD symptoms who do not respond to PPIs, check for other medications that can delay gastric emptying and thus promote reflux—especially calcium channel blockers, antihistamines, narcotics, tricyclics, and anticholinergics.

Consider antireflux surgery (fundoplication, which is mostly laparoscopic) in patients with GERD refractory to medical treatment, in young patients with severe disease, and as an alternative to long-term PPIs. Antireflux surgery has the best outcomes in patients who respond to PPIs; however, even after reflux surgery, 60% still require PPI therapy. With Nissen fundoplication, the lower esophagus is wrapped in a sleeve of the stomach. Side effects of this surgery are bloating, dysphagia, and an inability to belch. You must do a motility study prior to antireflux surgery—because the results may influence the performance of the fundoplication. Patients with impaired peristalsis are at risk for postoperative dysphagia, and those with poor gastric motility are at risk for severe postoperative bloating. Endoscopic antireflux procedures are not ready for routine use.

Treat peptic strictures secondary to GERD with dilation and then PPIs. Note: Metoclopramide (too many side effects) and sucralfate (not very effective) have little role in the treatment of GE reflux.

Maintenance therapy consists of PPIs for moderate-to-severe cases. Long-term use of H₂ receptor blockers is typically ineffective.

Be aware that patients with GERD-related cough/hoarseness require longer treatment and higher doses (e.g., bid) for symptomatic improvement than those with run-of-the-mill heartburn.

BARRETT ESOPHAGUS

Barrett esophagus is a change in cell type—from esophageal squamous to specialized intestinal metaplasia (columnar epithelium with goblet cells)—caused by chronic GE reflux. Even though GERD is the cause, many patients with Barrett esophagus lack reflux symptoms. 10–20% of men and 2% of women who undergo endoscopy for chronic reflux have Barrett esophagus (**Figure 14-8**)!

Barrett esophagus can lead to **adenocarcinoma** (not squamous cell carcinoma). Those with Barrett esophagus have a **30×** higher incidence of esophageal adenocarcinoma

(~ 0.5% per year). The risk of adenocarcinoma increases with the length of Barrett esophagus, presence of a hiatal hernia, degree of dysplasia, and concurrent smoking. (For more information, see **Esophageal Cancer**.)



Figure 14-8: Barrett esophagus

Screening for Barrett esophagus is a controversial topic because of the absence of randomized clinical trials that prove a mortality benefit. The American Gastroenterological Association (AGA) 2016 guidelines recommend screening in high-risk patients (Caucasian males > 50 years of age, long-standing GERD, hiatal hernia, elevated body mass index). Screening of the general population is not recommended.

Treatment: Neither antireflux medication nor surgery reverses the epithelial changes of Barrett esophagus or eliminates the cancer risk.

If Barrett esophagus is found, conduct endoscopic surveillance as follows (2016 AGA guidelines):

- No dysplasia: 3–5 years
- Low-grade dysplasia in the absence of eradication therapy: 6–12 months
- High-grade dysplasia in the absence of eradication therapy: 3 months

Endoscopic surveillance includes EGD with 4-quadrant biopsies every 2 cm if there is no dysplasia and every 1 cm for known dysplasia.

For any high-grade dysplasia, eradication therapy is recommended over surveillance. This is done with radiofrequency ablation. Photodynamic therapy or cryotherapy is occasionally used as well. Esophageal stricture is a possible complication of these treatments (refer to **Esophageal Stricture** on page 14-5).

Esophagectomy is an alternative treatment for patients with refractory high-grade dysplasia, but it has higher morbidity. The procedure should be performed at centers that specialize in this type of surgery.

Patients with Barrett esophagus should generally be treated with a PPI, both to treat GERD symptoms (which are common in these patients) and because antireflux therapy may reduce risk of malignancy. High-dose PPI therapy is used for those with low-grade dysplasia.

ESOPHAGEAL CANCER

There are 2 types of esophageal cancer:

- 1) **Adenocarcinoma** occurs in the **distal 1/3** of the esophagus. Incidence is rising (mostly from Barrett esophagus); it is more common than squamous cell cancer in Western countries.

- 2) **Squamous cell** esophageal cancer generally occurs in the **proximal 2/3** of the esophagus and is caused by smoking and alcohol (hard liquor); it is a more common type of esophageal cancer in Asian countries. It is associated with other cancers of the head or neck and is rarely associated with achalasia, lye stricture, or Plummer-Vinson syndrome (refer to [Plummer-Vinson Syndrome on page 14-5](#)).

Smoking and alcohol have a **synergistic** (a multiplicative, not additive) carcinogenic effect on the esophagus. Incidence of squamous cell cancer has a marked geographic variation, and its occurrence appears to be strongly associated with diet and environment.

Diagnosis and evaluation of esophageal cancer involves many different tests. Dysphagia is the usual presenting symptom, so a barium swallow during the workup may suggest cancer. EGD is always done to allow confirmation via biopsy. Use PET/CT scan and endoscopic ultrasound for staging.

If small and localized, treat with endoscopic mucosal resection or surgical resection; individualize therapy. If large or metastasized, treat with combination chemotherapy.

Patients often require PEG placement to allow for nutrition in the setting of at least partial esophageal obstruction. Palliative endoscopic stent placements can also be used to ease dysphagia symptoms.

ZENKER DIVERTICULUM

Zenker diverticulum is an outpouching of the posterior pharynx. Patients have foul-smelling breath and may regurgitate food eaten several days earlier. Zenker diverticulum can be one cause of transfer or oropharyngeal dysphagia and may be demonstrated on barium swallow. These patients are often elderly. Treatment is surgery with cricopharyngeal myotomy.

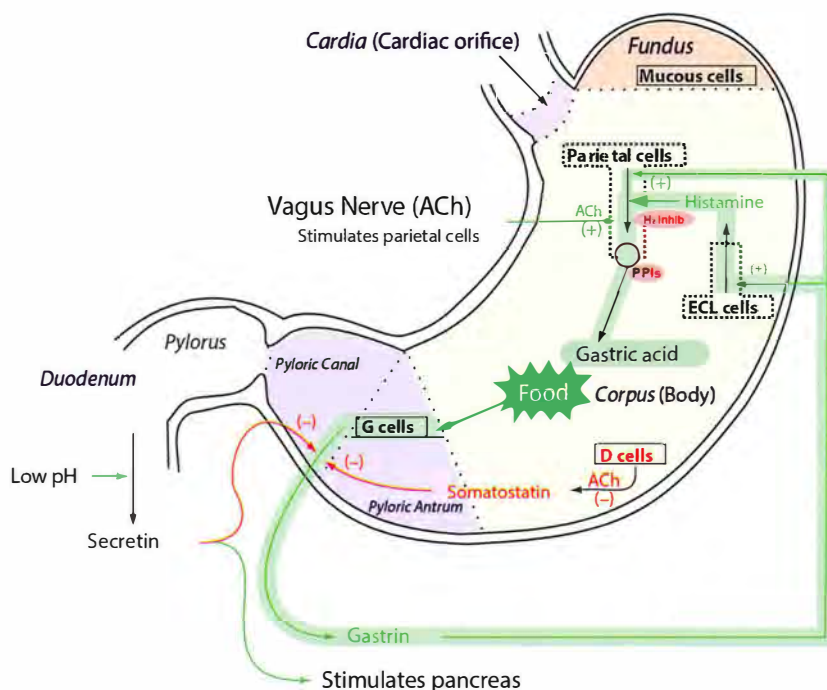
STOMACH

PREVIEW | REVIEW

- What is the clinical presentation of dyspepsia?
- What is the diagnostic/treatment approach to dyspepsia?
- When do you test for *H. pylori*?
- Is the rapid urease test accurate if a patient is taking a proton pump inhibitor (PPI)? Which other *H. pylori* tests are affected by PPIs?
- What is the 1st line treatment regimen for *H. pylori* infection?

NORMAL PHYSIOLOGY

First, a quick review of normal stomach physiology as it relates to gastritis and PUD. In [Figure 14-9](#), the light green highlight shows the main pathway used in the production of gastric acid.



Note: Low pH decreases gastrin by stimulating the D cells to produce somatostatin and the duodenum to produce secretin.

Figure 14-9: Stomach physiology

G cells are in the pyloric antrum. Parasympathetic vagal stimulation, amino acids (from food breakdown), and pyloric distention cause the G cells to release gastrin. Like acetylcholine (ACh) and histamine, gastrin stimulates fundal parietal cells to secrete hydrogen chloride (gastric acid) into the lumen, via the proton pump. Gastrin also stimulates enterochromaffin-like (ECL) cells to produce histamine.

The proton pump is the final common pathway for the action of these 3 receptors, which explains why proton pump inhibitors (PPIs) are the strongest antigastric acid drugs.

Gastrin is released into the circulation and is therefore an **endocrine** stimulus for gastric acid release. Gastrin is the dominant mediator of postprandial gastric acid production.

Histamine is released by the ECL cells in the corpus (due to gastrin stimulation), and it has a local **paracrine** effect via the H_2 receptors of the parietal cells.

Parasympathetic stimulation via the vagus nerve (a **neurocrine** effect) produces gastrin-releasing peptide, which directly stimulates G cells to (you guessed it!) release gastrin.

Therefore, endocrine, paracrine, and neurocrine stimuli affect parietal cells.

Somatostatin and **secretin** both decrease the production of gastrin (and therefore gastric acid). Low pH stimulates their production—hence, they are the negative feedback portions of the regulatory mechanism for maintaining stomach pH. A stomach pH < 3 causes production of somatostatin by corpus D cells. Secretin is produced in the duodenum in response to the acidified stomach output; it decreases gastrin production and stimulates output of HCO_3^- from the pancreas. Again, 2 inhibitors of gastrin (and therefore gastric acid) production are somatostatin (from low stomach pH) and secretin (from low duodenum pH).

Note: In patients with achlorhydria (as in autoimmune gastritis) or pernicious anemia, the serum gastrin level skyrockets because of the loss of this inhibitory effect. PPIs, in the setting of achlorhydria, can lead to a markedly elevated gastrin level (> 500 pg/mL).

Both gastric acid and pepsin (made from pepsinogen in the presence of acid) not only digest food but also attack the mucosal defenses.

Digested food needs to be < 2 mm to pass easily through the pylorus. This is accomplished in part by the mechanical actions of mixing and grinding.

The motor function of the stomach is controlled at 3 levels: the autonomic nervous system (sympathetic and parasympathetic), the enteric nervous system, and smooth muscle cells.

Gastric-emptying scans evaluate overall gastric function but do not provide information on mixing and grinding.

DYSPEPSIA

Dyspepsia is a nonspecific term that refers to recurrent upper abdominal pain or discomfort especially after meals. It includes epigastric fullness, belching, bloating, gnawing pain, and heartburn. It generally does not include severe pain. Dyspepsia is most often functional or caused by medications (e.g., iron, ASA, NSAIDs), but if onset is recent, there is no potentially causative medication, and the patient is ≥ 60 years of age, consider an organic cause; i.e., consider an EGD.

For patients < 60 years of age, test for *Helicobacter pylori* and treat if positive (see [More on *H. pylori* on page 14-12](#)).

Organic causes of dyspepsia include PUD, gastritis, GERD, biliary colic, gastroparesis, pancreatitis, and cancer. EGD is usually normal. Dyspepsia is typically classified by symptoms, and types can overlap:

- **GERD-like**
- **Ulcer-like** (improves on antiulcer therapy)
- **Dysmotility-type** (improves on promotility drugs, such as metoclopramide)

Recurrent upper abdominal pain with a normal EGD defines “**nonulcer dyspepsia**.”

So, how do we manage dyspepsia? Do the following:

- Discontinue NSAIDs.
- Test for *H. pylori*; if *H. pylori*+, treat based on local *H. pylori* prevalence.
- Conduct a PPI treatment trial.
- Order EGD for alarm symptoms (progressive dysphagia, unexplained weight loss, signs of GI bleeding, or failure of therapy).

GASTRITIS

Gastritis is generally classified by histology or etiology.

Classification by Histology

A neutrophil infiltrate is seen in acute gastritis, while a lymphocyte and plasma cell infiltrate occurs with chronic gastritis. Histologic classification reflects the findings throughout the possible life of the disease:

- Superficial gastritis (early, neutrophils)
- Atrophic gastritis (mid, lymphocytes)
- Gastric atrophy (late, gastropathy)—also called metaplastic atrophic gastritis

Biopsy of gastropathy shows atrophy of gastric glands with fibrosis but no inflammatory infiltrate.

Classification by Etiology

Type A: autoimmune, atrophic, pernicious anemia, achlorhydria. It affects the **proximal** stomach—fundus and body only. (Note: “Antrum” is not one of the “A” words!) Autoantibodies against both intrinsic factor and the parietal cells cause a progression to pernicious anemia and

to achlorhydria, with secondary hypergastrinemia (levels often > 1,000 pg/mL). **Metaplasia** is a universal feature of atrophic gastritis; it appears before, and is associated with, both pernicious anemia and gastric carcinoma. The 2015 American Society of Gastrointestinal Endoscopy (ASGE) guidelines recommend surveillance endoscopy in patients with gastric intestinal metaplasia. A baseline EGD is recommended for pernicious anemia. If normal, a subsequent EGD for surveillance is not recommended.

Type B is the most common form of chronic gastritis (80%). It is usually due to infection by *H. pylori*. Symptoms and findings can mimic Type A gastritis.

Note: Only 1/2 of patients who undergo successful treatment of *H. pylori* infection have resolution of gastritis symptoms!

Depending on chronicity and location of infection, gastric acid secretion can decrease with worsening *H. pylori* gastritis. Oral meds such as itraconazole, ketoconazole, and thyroxine **require gastric acid** for optimal absorption. 50% of AIDS patients have decreased stomach acid and are especially prone to itraconazole failure. Fluconazole does **not** require gastric acid for proper absorption.

EROSIVE GASTROPATHY

NSAIDs (Figure 14-10), alcohol, or severe physiologic stress can cause erosive gastropathy, frequently with sub-epithelial hemorrhage.



Figure 14-10: Acute erosive gastropathy due to NSAIDs

Note that gastritis, by definition, means there is an inflammatory response. In erosive gastropathy, there is **no** inflammation, so it is technically wrong to call this “gastritis,” as is commonly done.

Onset of erosive gastropathy in the ICU suggests stress-related mucosal damage (SRMD), which is due to severe physiologic stress, such as that induced by major surgery or burns. Ventilator dependence, coagulopathy, and severe CNS injuries or burns are also major risk factors. Several strategies can prevent SRMD: H_2 receptor antagonists, antacids, PPIs, sucralfate, and even early feedings.

Continuous infusion of PPI is the most effective treatment for SRMD. Potential side effects are nosocomial pneumonia (decreased stomach acidity leading to small intestinal bacterial overgrowth [SIBO]) and *C. difficile* infection.

MORE ON *H. PYLORI*

H. pylori infection can cause gastritis, PUD, gastric adenocarcinoma, and gastric B-cell (e.g., mucosa-associated lymphoid tissue [MALT]) lymphoma.

Chronic gastritis occurs in almost all adults infected with *H. pylori*, although only a minority have symptoms.

Virtually everyone in developing countries is infected with *H. pylori*. In the U.S., the incidence is ~ 50% in older patients and 30% overall. It is generally acquired in childhood. Incidence is decreasing in the U.S.

Testing

Know! Test for *H. pylori* when:

- there is any prior history of PUD (complicated or uncomplicated) and especially with history of duodenal ulcer;
- current findings on EGD show ulcer disease, erosive gastropathy, or duodenitis;
- MALT lymphoma is present; and/or
- patients are initiating chronic NSAIDs or low-dose ASA.

The strategy is “test and treat” in dyspeptic patients < 60 years of age even with no alarm symptoms/features.

Invasive tests include:

- The gold standard for *H. pylori* testing is histologic examination of biopsied antral and fundic body mucosa—obtained during EGD.
- A rapid urease test (RUT) is performed on biopsy samples and is based on *H. pylori* breakdown of urea into ammonia and CO_2 . Urease testing is good for checking for active disease and for response to therapy. These tests are sensitive (95%) and specific (95%). Urease tests are less sensitive if the patient is on a drug that may blunt the effect of *H. pylori* infection, such as PPIs and antibiotics. In such patients, it is appropriate to obtain biopsies for histologic evaluation with or without RUT or to plan noninvasive testing later after withholding the offending agents for 2–4 weeks.

Noninvasive evaluation includes:

- A urea breath test (UBT), which uses labeled urea, is the 1st choice for checking effectiveness of treatment.
- A fecal antigen test (FAT) is a good method for primary diagnosis, and if the patient is on PPIs, it is the best test for checking effectiveness of treatment (sensitivity and specificity = 94% and 98%). Confirm eradication with FAT 4–6 weeks after treatment completion; ideally discontinue PPIs for 2–4 weeks prior to testing, as PPI therapy can cause false negatives.

- Serologic tests are no longer recommended due to their low positive predictive value (PPV; < 50%) and low specificity. Also, serum tests are poor for checking effectiveness of treatment as they can stay positive for years after eradication.

Again:

PPIs interfere with any urease test (RUT and UBT) and FAT. Stop PPIs 2 weeks before these tests. Do not attempt to confirm eradication until at least 4 weeks after completion of antibiotic therapy.

Serologic tests are discouraged due to poor PPV for *H. pylori*.

PPIs and *H. pylori* pangastritis cause decreased gastric acid production, which, in turn, interferes with absorption of some medications (e.g., thyroxine, azole antifungals).

Treatment

Treat *H. pylori* only in symptomatic patients or in those with a history of gastric/duodenal ulcer, personal history of gastric cancer, or personal history of MALT lymphoma.

H. pylori treatment is the same whether the patient has gastritis or PUD. The 2017 ACG guidelines recommend the following.

Clarithromycin triple-drug therapy is reserved for patients with no previous macrolide use and only where macrolide resistance is low. This treatment is usually with OCLAM (omeprazole + clarithromycin + amoxicillin) for 10–14 days.

All others should receive:

- bismuth quadruple therapy with bismuth + metronidazole + tetracycline + PPI for 14 days or
- levofloxacin triple therapy with levofloxacin + amoxicillin + PPI for 14 days.

Know: The more drugs the better! Single- and dual-drug therapies are ineffective. Patient adherence to the regimen is an important predictor of successful treatment. With increasing antibiotic resistance, noninvasive post-treatment testing is recommended.

Perform testing no sooner than 4 weeks after the completion of therapy. In general, do noninvasive tests (not serology) for posttreatment testing unless there is a need for repeat EGD.

PEPTIC ULCER DISEASE (PUD)

PREVIEW | REVIEW

- What is the most common cause of peptic ulcer disease (PUD)?
- What is the relationship between nonsteroidal antiinflammatory drugs and PUD?
- How does smoking affect PUD?

- What is the relationship of alcohol to PUD?
- What is the relationship of steroids to PUD?
- How are peptic ulcers diagnosed?
- How are perforated peptic ulcers diagnosed?
- Name at least 3 indications for surgery in a patient with PUD.
- What is the main cause of bleeding ulcers in the U.S.?
- Name 3 esophagogastroduodenoscopy findings that indicate increased risk for rebleed of a peptic ulcer.
- What is the most common presentation of Zollinger-Ellison syndrome?

ETIOLOGY

PUD has 3 major causes:

- 1) *Helicobacter pylori* infection is still the most common cause of PUD—especially duodenal ulcer disease (50%, but incidence is decreasing in the U.S.). Lifetime ulcer risk for a person with *H. pylori* infection is 10–15% (higher for men). If *H. pylori* can be eradicated, ulcers virtually never recur, and the *H. pylori* recurrence rate is very small. The trouble is getting rid of it! If the ulcer does recur, suspect NSAIDs. Refer to [Testing](#).
- 2) In the U.S., NSAIDs cause the majority of peptic ulcers not caused by *H. pylori*. The prevalence of ulcers in patients on NSAIDs is ~ 25% (!) although many are < 5 mm and asymptomatic. Risk factors for NSAID-induced PUD include: first 3 months of use, high doses, elderly patient, history of ulcer disease or prior UGI bleed, cardiac disease, concurrent steroid or ASA use, and serious illness. NSAIDs cause both gastric and duodenal ulcers—but typically gastric. If NSAIDs must be used, and the patient is having or has had trouble with ulcer disease or dyspepsia, use any of the following:
 - Nonacetylated NSAIDs (e.g., salsalate)
 - NSAIDs that are nonacidic prodrugs (e.g., nabumetone [Relafen])
 - NSAIDs with a PPI—superior to H₂ blockers and sucralfate in the prevention of NSAID-induced ulcers
 - Cyclooxygenase (COX)-2 NSAIDs (See [Nonsteroidal Antiinflammatory Drugs \(NSAIDs\)](#) on [page 14-15](#).)
- 3) High acid-secreting states, such as Zollinger-Ellison syndrome (ZES; 1–3% of duodenal ulcers)

What about smoking? Smoking is a major risk factor for PUD. In gastric and duodenal ulcer disease, smoking exacerbates the ulcer. For non-*H. pylori* ulcers, smoking decreases the healing rate and increases recurrence and perforation rate. These recurrences are often asymptomatic.

Previously, the incidence of PUD was higher in men, but over the past 2–3 decades, the male-to-female ratio has been approaching 1. Diet, personality, and occupation are **not** significant risk factors for PUD! Low stress resilience may be a factor. Weight loss is uncommon in PUD.

Notes: Alcohol is not ulcerogenic! Corticosteroids alone are not ulcerogenic, but, when used with NSAIDs, they **double** the risk of serious NSAID-associated gastrointestinal complication and can increase the risk of bleeding 10-fold!

DIAGNOSIS

Diagnosis of PUD:

- For the young, healthy patient with classic symptoms, no diagnostic testing is required—empiric treatment with an H₂ blocker or PPI is acceptable.
- For this same young, healthy group, *H. pylori* “test and treat” is also acceptable.
- EGD is done for all other patients, particularly older patients or in patients of any age who present with melena, heme+ stools, early satiety, or iron-deficiency anemia.

EGD is always indicated in the workup of PUD in the following situations:

- If symptoms include dysphagia and odynophagia
- UGI bleeding
- Abnormal barium swallow or CT scan
- Family history of duodenal ulcer disease or gastric malignancy

If an ulcer is found and ZES is suspected, check serum gastrin levels (see **Zollinger-Ellison Syndrome (ZES)** on page 14-16). Test for *H. pylori* (refer to **Testing** on page 14-12).

Perforated gastric and duodenal ulcers often cause free air in the peritoneal space, which can be seen on an upright abdominal x-ray. If a perforated ulcer is suspected, **do the upright chest and abdominal x-ray first!** EGD and UGI are contraindicated until perforation is excluded.

Know: The pain of an ulcer tends to be gnawing, whereas that of a perforated ulcer is usually severe.

TREATMENT OF NONBLEEDING PUD

Treatment of PUD combines 3 main strategies:

- 1) Treat *H. pylori* infection (refer to **Treatment** on page 14-13).
- 2) Decrease acid secretion (i.e., H₂ receptor antagonists, PPIs).
- 3) Stop the exacerbating processes (e.g., smoking, NSAID use).

Mucosal protection (sucralfate) and acid neutralization (antacids) are less frequently used.

Sucralfate is effective in non-*H. pylori* PUD but requires qid dosing; so, PPIs are preferred. Sucralfate binds bile salts and forms a barrier at the ulcer site that prevents acid penetration. **Avoid sucralfate in patients with advanced chronic kidney disease** because it can cause aluminum toxicity (dementia and metabolic bone disease).

Stop smoking; smoking increases the risk of recurrence and perforation in ulcers not associated with *H. pylori* and in untreated *H. pylori* ulcers.

Indications for surgery in PUD:

- UGI bleed (most common)—an active bleed is not controlled with endoscopic therapy. Surgery is required in 5% of UGI bleeds.
- Gastric outlet obstruction—initial treatment is endoscopic balloon dilation. Surgery is required in ~ 25% of patients.
- Perforation—laparoscopic repair may be possible.
- Recurrent or refractory ulcers (rare)
- ZES—surgery is for underlying gastrinoma.

DUODENAL vs. GASTRIC ULCER

Duodenal ulcers (**Figure 14-11**): Again, the common causes are NSAIDs and *H. pylori*; only 1–3% are due to increased acid secretion (e.g., ZES).

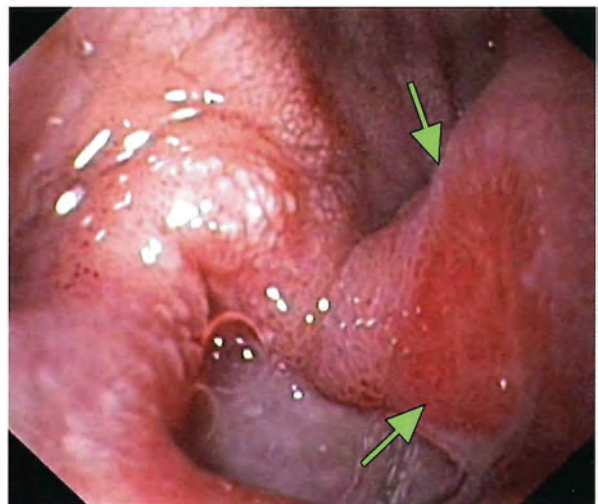


Figure 14-11: Duodenal ulcer

Gastric ulcers not associated with *H. pylori* are treated for 3 months. PPIs and misoprostol (a synthetic prostaglandin) are superior to H₂ blockers and sucralfate in the prevention of NSAID-induced ulcers.

Although gastric ulcers (**Figure 14-12**) were once thought to increase gastric cancer risk, studies have **not** demonstrated a higher rate of gastric carcinoma. However, all **nonhealing** gastric ulcers need to be examined via endoscopy and biopsied to rule out underlying cancer.

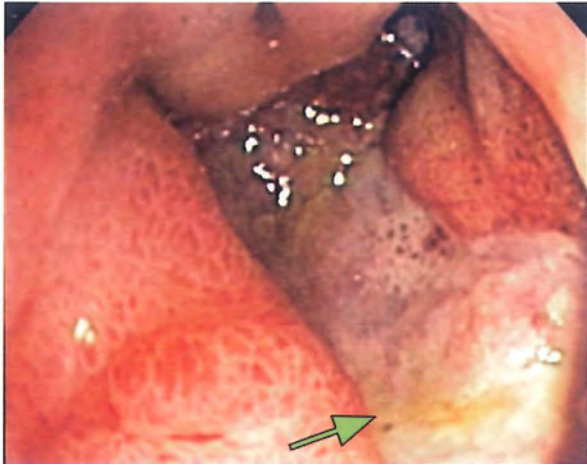


Figure 14-12: Deep gastric ulcer

BLEEDING PEPTIC ULCERS

Nonsteroidal Antiinflammatory Drugs (NSAIDs)

NSAIDs are the leading cause of **bleeding** ulcers in the U.S. Gastrointestinal bleeding may be the presenting symptom. The bleeding risk is related to both dose and duration of NSAID treatment. As mentioned previously, corticosteroids alone are **not** ulcerogenic, but they can increase the risk of NSAID-associated bleeding 10-fold!

Risk of bleeding with NSAIDs:

- General population: 1%
- In those using ASA concurrently as preventive medicine: 1.5%. Low-dose (81 mg) ASA carries about the same risk as standard prophylaxis dose (325 mg daily). Note that there is no perfectly safe dose of ASA.
- History of PUD/UGI bleed: 3%

NSAID-related ulcer risk is higher in females and in patients > 60 years of age.

If cardiac disease coexists with any of the previously listed factors, the risk increases.

Risk of bleeding with COX-2 NSAIDs:

- COX-2 used alone has minimally increased risk of GI bleeding (0.5%).
- COX-2 with low-dose (81 mg) ASA has the same risk as regular doses of NSAIDs (1%)!

COX-2 NSAIDs block the action of COX, an enzyme that converts arachidonic acid to prostaglandin. COX-1 is the constitutive enzyme, while COX-2 is inducible. COX-1 produces protective prostaglandins in the stomach, whereas the inducible COX-2 is involved in inflammatory response. COX-2 inhibitors (e.g., celecoxib [Celebrex]; meloxicam [Mobic]) appear to have decreased GI side effects (compared to conventional nonselective NSAIDs), while retaining the antiinflammatory and pain relief effects.

All NSAIDs (including COX-2 inhibitors) appear to have some dose-related cardiovascular risks (thrombosis and myocardial infarctions) and renal risks (acute kidney injury and hyperkalemia).

All NSAIDs have an FDA-mandated black box warning highlighting the potential for increased risk of death from cardiovascular events and GI bleeding.

Workup

EGD is the diagnostic and treatment procedure of choice for UGI bleeding. Do it emergently if the patient has any of the following findings suggestive of a severe bleed or high risk of rebleed:

- Hemodynamic instability
- Recurrent red-colored hematemesis or hematochezia

EGD is done for 2 reasons:

- 1) To treat the current bleed
- 2) To assess the risk for rebleed

EGD findings that indicate **increased** chance of rebleeding (based on the Forrest classification):

- Active bleeding at time of endoscopy (risk of rebleed 55%)
- Visible vessels on a nonbleeding ulcer (risk of rebleed 43%; [Figure 14-13](#))
- Visible clot (risk of rebleed 22%)

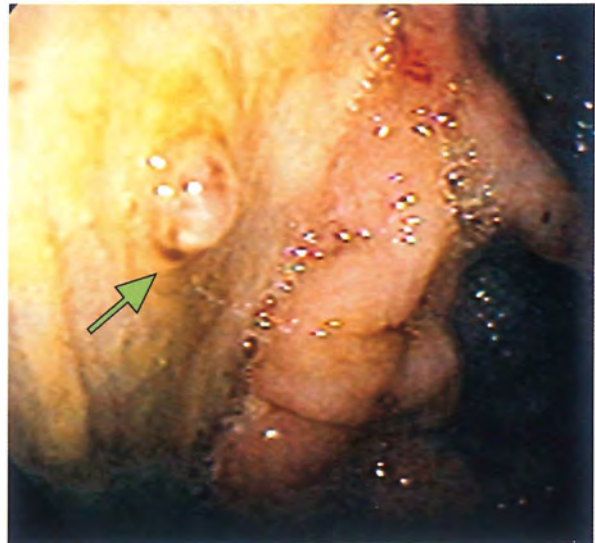


Figure 14-13: Ulcer with visible vessel
Source: James W. Smith, MD

Conversely, an ulcer with a clean base (no bleeding, no clot, and no visible vessels) has a very low chance of rebleed (< 10%). These patients are typically sent home the same or next day—unless they have other medical comorbidities that make them high risk for rebleeding.

Treatment

The best results are seen when endoscopic treatment of actively bleeding ulcers (or visible vessels) involves injection (epinephrine), followed by either thermal/laser coagulation or a hemoclip.

Increasing the gastric pH to > 6.0 reduces the risk of rebleeding—this is done with PPIs, given either IV or orally bid. Most patients with a bleeding ulcer get prompt IV PPI treatment before endoscopic therapy. They receive this treatment until they are able to switch to oral bid therapy.

What does not work: Gastric lavage does **not** stop bleeding or prevent rebleeding and is no longer recommended as a diagnostic tool. IV vasoconstrictors are also ineffective. Gastric lavage may be done to improve visualization of the stomach mucosa when large amounts of clot are found in the stomach on endoscopy.

NONULCER CAUSES OF UPPER GASTROINTESTINAL (UGI) BLEEDS

Osler-Weber-Rendu syndrome, or hereditary hemorrhagic telangiectasia (HHT), causes telangiectasias on the skin and buccal and nasal mucosa and throughout the GI tract, lungs, and brain. Occasionally, arteriovenous malformations (AVMs) occur and have the propensity to bleed. In the GI tract, these AVMs are generally in the stomach or duodenum. However, other causes of AVMs, such as aortic valvular disease, may be seen more frequently than hereditary illnesses.

Peutz-Jeghers syndrome (PJS) causes dark melanin spots on the lips, buccal mucosa, and the hands and feet. Most patients have hamartomatous polyps that can occur anywhere from the stomach to the rectum. These polyps may cause acute or chronic GI bleeds.

ZOLLINGER-ELLISON SYNDROME (ZES)

ZES occurs when a gastrinoma, which produces gastrin continuously, causes refractory (usually duodenal bulb) ulcers and diarrhea +/- steatorrhea. The most common presenting symptom of ZES is diarrhea. The diarrhea/steatorrhea is from the large volume of gastric juice causing acidification of duodenal contents, and the resulting pancreatic enzyme inactivation and intestinal villi damage (resulting in maldigestion/malabsorption).

Gastrinomas most frequently occur in the duodenum (~ 50%) or pancreas (~ 25%) and less frequently in the stomach, lymph nodes, and spleen. 90% are found in what is called the “ZE triangle”—which includes the porta hepatis, mid-duodenum, and the head of the pancreas. 80% are of the sporadic form; 20% are associated with multiple endocrine neoplasia Type 1 (MEN1), as discussed in the [Endocrinology](#) section.

Consider ZES in patients with:

- Severe esophagitis and chronic diarrhea
- Ulcer (especially duodenal ulcer) and chronic diarrhea

- Duodenal ulcer and big folds in the stomach (from parietal cell hyperplasia [a.k.a. Ménétrier disease])
- Recurrent ulcers and no other risk factors
- Recurrent complicated ulcers
- Postbulbar duodenal ulcers

To evaluate for ZES, first order a fasting serum gastrin while the patient is off PPI therapy. If the gastrin level is elevated (usually $> 1,000$ pg/mL) in a patient with gastric ulcer, perform a secretin stimulation test to differentiate gastrinoma from other causes of hypergastrinemia. If you see a marked rise in gastrin level, suggesting ZES, then localize the tumor with an abdominal CT or MRI scan and somatostatin receptor imaging (octreotide scan). If CT/MRI and somatostatin receptor imaging are negative and surgery is being considered, do endoscopic ultrasound (more sensitive for detecting small tumors).

Treatment: Surgical exploration is warranted in all newly diagnosed ZES patients who have no evidence of metastatic disease. 1/2 are cured by resection of the primary tumor. Even with metastatic disease, treat ZES aggressively with resection of the primary tumor because the mass effect of the tumor tissue can eventually cause problems (obstruction).

A PPI is the drug of choice for medical treatment of ZES, although the dose is higher than usual and often must be increased with long-term therapy.

Remember: Other conditions associated with an elevated gastrin level are vitiligo, renal failure, hyperthyroidism, and achlorhydria caused by PPI use or chronic Type A gastritis (refer to [Classification by Etiology](#) on page 14-11). Also remember that persistent high gastrin levels can cause gastric neuroendocrine tumors (NETs).

GASTRIC NEUROENDOCRINE TUMORS (NETs)

PREVIEW | REVIEW

- What is the usual cause of gastric neuroendocrine tumors (NETs)?
- What are the 3 types of gastric NETs?
- Gastric NETs can be associated with which skin condition?

Gastric NETs (previously described as gastric carcinoids) are rare (0.5% of gastric tumors) and typically caused by chronic hypergastrinemic states. The type of NET is based on the causes of hypergastrinemia:

- Type 1 (70–80%): Autoimmune gastritis/pernicious anemia
- Type 2 (5%): ZES, when it occurs as part of MEN1
- Type 3 (20%): Spontaneous (most aggressive)

Sometimes gastric NETs occur in patients with vitiligo.

Gastrin is trophic to the enterochromaffin-like (ECL) cells of the stomach, leading to hyperplasia and, occasionally, gastric NETs.

Note: The PPI omeprazole does **not** cause carcinoids in humans (based on > 10 years' worth of data), although it does increase the circulating gastrin level.

It is unusual for gastric NETs to metastasize or to be symptomatic. They are slow growing and **almost never** cause carcinoid syndrome. See [Carcinoid Syndrome on page 14-27](#) for more on carcinoids.

NETs are also discussed in the [Oncology](#) section.

GASTRIC CANCER

For information on gastric cancer, see the [Oncology](#) section.

OTHER GASTRIC SYNDROMES

PREVIEW | REVIEW

- What are the symptoms of dumping syndrome?
- What is the diagnostic workup for suspected gastroparesis?
- What are the recommended treatments of gastroparesis?

DUMPING SYNDROME

Dumping syndrome is a postgastrectomy syndrome that is infrequently seen because < 5% of peptic ulcer disease (PUD) cases warrant surgery. It consists of postprandial vasomotor symptoms: palpitations, sweating, diarrhea, nausea, abdominal pain, and lightheadedness. There are 2 types. The **early type** occurs 30 minutes after eating and is of uncertain etiology (but likely due to hyperosmolality of food and fluid shifts in the small bowel). The **late type** occurs ≥ 90 minutes after eating and is probably due to hypoglycemia. Treat both types identically: Restrict sweets and lactose-containing foods, separate liquid and solid intake by at least 30 minutes by avoiding liquids with meals, and encourage frequent small meals that are high in protein and complex carbohydrates.

GASTROPARESIS

Gastroparesis, or delayed gastric emptying, presents with symptoms of nausea, vomiting, early satiety, and abdominal pain. Normal gastric motor function requires the coordinated effort of the autonomic nervous system, enteric nervous system, and enteric smooth muscles. Any disturbance in this effort can result in gastric motility disorders.

Gastroparesis in Diabetics

Patients with diabetes have highly **variable** rates of gastric emptying, which can be slow, normal, or fast. However, diabetic neuropathy from long-standing diabetes can cause gastroparesis. This occurs much more commonly in Type 1 diabetes than in Type 2.

The clinical presentation of diabetic gastroparesis is nausea, vomiting, early satiety, and a predisposition for bezoars.

Blood glucose > 200 mg/dL has been shown to result in decreased antral motility and delayed gastric emptying. Hyperglycemia may also have a negative long-term direct effect on gastric motility.

Conversely, slowed gastric emptying itself tends to increase blood glucose because of the delay of insulinemic and glycemic responses to the carbohydrates, which leads to a vicious cycle. Treat by maintaining tight glucose control.

Other Causes of Gastroparesis

Aside from diabetic neuropathy, gastroparesis can be caused by other gastric motility disorders:

- Autonomic dysfunction—amyloid neuropathy
- Infiltrative processes of the smooth muscles—scleroderma, amyloidosis
- Antecedent viral infections—particularly norovirus and rotavirus
- CNS disorders—e.g., stress, MS, parkinsonism, tumor, spinal cord injury
- Postvagotomy syndrome/Postsurgical dysfunction
- Opioid analgesics

Diagnosis

Workup of suspected delayed gastric emptying requires that you rule out obstruction first, either with endoscopy or upper GI series. Then confirm the diagnosis with a radiolabeled solid meal (gastric emptying study). Abnormal gastric emptying of solids is consistent with traditional gastroparesis. Abnormal gastric emptying of liquids can suggest a motor disorder of the proximal stomach, which is involved in reflex relaxation after eating.

Treatment

Treat gastroparesis with:

- good hydration,
- dietary modification (low-fat, low-residue; multiple small meals),
- tight control of blood glucose,
- symptom management (antiemetics),
- metoclopramide (FDA warning for long-term use—extrapyramidal side effects—tardive dyskinesia may become permanent!), and
- domperidone (widely used outside the U.S.).

IV erythromycin, similar in structure to motilin, stimulates gastric motility but is not very useful as a long-term therapy. It can, however, be used in the acute setting when oral intake is inhibited by severe stasis.

Gastric electrical stimulation for drug-refractory gastroparesis may be a therapeutic option for select patients.

SMALL INTESTINE AND COLON

INFLAMMATORY BOWEL DISEASE (IBD)

PREVIEW | REVIEW

- When is colonoscopy contraindicated in inflammatory bowel disease (IBD)?
- Sulfasalazine is ineffective in which type of Crohn disease (CD)?
- What is the most concerning side effect of prolonged metronidazole therapy?
- When is budesonide used for CD? For ulcerative colitis (UC)?
- What are the indications for monoclonal antibodies in patients with IBD?
- What is the relationship of CD to cancer?
- Which screening should be done in patients with CD who have been treated with chronic steroids?
- What are the colonoscopy and biopsy findings in CD?
- What is the significance of an “apple core” lesion? How does it differ from the “string sign”?
- What genitourinary complication of the terminal ileum can arise in a patient with CD?
- What is the usual etiology of diarrhea in CD patients with < 100 cm of the distal ileum removed? With > 100 cm of the distal ileum removed? What is the treatment for each?
- What are the findings of UC on colonoscopy?
- Which serological marker may be found in 70–80% of patients with UC?

- Describe the extraintestinal manifestations of UC.
- What is the relationship of UC to cancer?
- What is the treatment for UC with high-grade dysplasia?
- What is the treatment for moderate-to-severe UC?
- Associate these “buzzwords” with UC or CD:
 - a) tenesmus, b) rectal bleeding, c) fecal soiling, and d) pneumaturia.

Common Factors

IBD comprises **Crohn disease** (CD) and **ulcerative colitis** (UC), as well as related disorders, such as microscopic colitis and collagenous colitis. In both CD and UC, family members are at increased risk of IBD, and the patient has an increased risk of GI cancer—but the risk of cancer is much higher in long-standing UC than in CD.

Toxic megacolon, an acute colitis characterized by systemic toxicity and colonic dilatation, is a complication in both Crohn disease (CD) and ulcerative colitis (UC). Avoid colonoscopy in patients with severe colitis due to the possibility of precipitating toxic megacolon.

Infectious colitis, early CD, and UC can appear identical on endoscopy. Stool examination for blood, WBCs, or lactoferrin, ova & parasites (O&P), culture & sensitivity (C&S), and *Clostridioides difficile* (*C. difficile*; formerly known as *Clostridium difficile*) toxin assay are included in the initial workup. Refer to [Table 14-2](#) as you review the diagnosis of CD and UC. See [Table 14-3 on page 14-22](#) for a comparison between treatments of CD and UC.

Smokers are more likely than nonsmokers to develop CD. For UC, however, smoking may be protective, and the risk of UC is highest in former smokers who have quit.

Colonoscopy is frequently used to assess IBD. Barium enema is no longer used, but CT scan or MR enterography can be helpful in diagnosing small bowel disease.

Drugs Used to Treat IBD

Many of the medications used to treat CD and UC are the same, but they are used with varying effectiveness within each disease. Here, we present the medications used in

Table 14-2: Clinical Features of Crohn Disease vs. Ulcerative Colitis

	Crohn Disease	Ulcerative Colitis
Lesions	Focal, skip, deep	Shallow, continuous
Clinical Course	Indolent	More acute
Prednisone*	Less responsive	Very responsive
Granulomas	Pathognomonic	None
Rectal Involvement	Rectal sparing in 50%	Rectum always involved
Perianal Disease	Abscesses, fistulae	None
Small Bowel Involvement	> 50%	Backwash ileitis in < 10%

* For flares; not for long-term maintenance therapy

both CD and UC. Later, when talking specifically about each disease, we'll discuss how these medications are applied to each disease.

The main drugs used to treat IBD include:

- Mesalamine (5-aminosalicylic acid [5-ASA] preparations)
- Sulfasalazine
- Metronidazole
- Budesonide
- Infliximab, adalimumab, golimumab, and certolizumab pegol (monoclonal antibodies to tumor necrosis factor- α [TNF- α])
- Vedolizumab (integrin inhibitors)
- Prednisone
- Azathioprine (off-label use) and its metabolite, 6-mercaptopurine (6-MP)
- Methotrexate (off-label use)

Mesalamine (5-aminosalicylic acid [5-ASA]) is rapidly absorbed from the upper digestive tract, but different oral formulations allow mesalamine release into the distal ileum and colon, making it more useful in IBD. For colonic inflammation, it is given either rectally—as an enema (for proctosigmoiditis) or suppository (for proctitis only)—or in a formulation designed to delay release of the drug until it gets to the colon. Mesalamine appears to be more effective for UC than CD.

Sulfasalazine is split, by bacterial action in the colon, into mesalamine (active component) and sulfapyridine. Because this takes place in the colon, sulfasalazine is **ineffective** for CD of the small bowel. The other breakdown product, sulfapyridine, is absorbed in the colon, acetylated in the liver, and excreted in the urine. Sulfapyridine is a highly reactive sulfa moiety, and it is responsible for most of the side effects of sulfasalazine—such as reversible infertility in men, leukopenia, and headache.

Metronidazole is beneficial for perianal abscesses and fistulae in CD. Long-term use is hampered by the side effect of peripheral sensory neuropathy (particularly if the dose is > 10 mg/kg).

Budesonide is an enteric-coated corticosteroid that is released mostly in the ileum and ascending colon. It is metabolized in the liver to inactive products. It has a 90% first-pass effect—thus, far fewer systemic side effects than prednisone. It was previously used specifically for small bowel CD. A preparation of extended-release budesonide, which targets the full length of the colon, was approved in 2013 for the treatment of mild-to-moderate UC but can be cost prohibitive. As with other corticosteroids, monitor bone mineral density yearly. At this point, it is uncertain whether budesonide has less effect than prednisone on bone density.

Infliximab (Remicade), **adalimumab** (Humira), **golimumab** (Simponi, SimponiAria), and **certolizumab pegol** (Cimzia) are monoclonal antibodies to TNF- α . They are given for moderate-to-severe CD, fistulous CD, and refractory UC. Know that tuberculosis (TB) can reactivate with their

usage, but the most common side effect is actually upper respiratory tract infection. Assess patients for latent TB and hepatitis B, and administer all recommended age-appropriate vaccinations before initiation of therapy. **Vedolizumab** (Entyvio) is an anti-integrin antibody, which can be used as an alternative to anti-tumor necrosis factor (anti-TNF- α) therapy in patients with moderate-to-severe disease.

Review: Monoclonal antibodies (mAb) are biologics that are identical antibodies derived from clones of a single parent cell. The standard recombinant DNA procedure produces mouse (i.e., murine) Ab. The human body reacts against these foreign Ab with an inflammatory response. To overcome this, a portion of mouse DNA that codes for the binding site is combined with human DNA. The result is a **chimeric** (i.e., human-murine) Ab or a **humanized** (mostly human) Ab. The more human, the less reaction. **Fully human** antibodies have been developed using transgenic mice. Monoclonal Ab generic names always end in “mab” (mAb, get it?) with the preceding letters further defining what type of antibody it is—chimeric (-ximab), humanized (-zumab), or human (-umab).

Prednisone is the most common corticosteroid used to treat IBD. Prednisone is often started initially to treat IBD and, in some cases, is administered parenterally, often in the hospital setting, and then changed to PO. Because all steroids have undesirable and well-known systemic side effects, the general rule is to use the lowest effective dose for the least amount of time to control a patient's IBD symptoms. Other, potentially less toxic medications (some of which take longer to act than corticosteroids) can be started along with steroids, and then the steroids can be tapered.

6-Mercaptopurine (6-MP) and **azathioprine** (off-label; metabolizes to 6-MP) are **prednisone-sparing** drugs useful in both CD and UC, but they usually take 3–4 months to show an effect. Because these 2 drugs have bone marrow suppressive effects, monitor CBC monthly. These steroid-sparing drugs also have the potential for hepatic toxicity. Measure thiopurine methyltransferase (TPMT) activity to determine the patient's ability to tolerate these drugs before starting them.

Methotrexate (MTX; off-label) is a chemotherapeutic agent that is a folic acid analogue and is used in maintenance of remission in CD. Long-term use can cause hepatotoxicity. It also is sometimes used in combination with anti-TNF therapy to minimize antibody formation.

Azathioprine, 6-MP, MTX, and infliximab have been proven to decrease the relapse rate in CD. (Infliximab reduces relapse only in infliximab-induced remission.) Note that **all** the standard drugs decrease the relapse rate in UC! Corticosteroids are good for inducing remission in CD but not for maintaining it, and mesalamine is no longer recommended for induction of remission in CD.

Smoking cessation decreases relapse rate in CD and **increases** it in UC!

Some drugs commonly prescribed to treat IBD have risks when used in pregnancy:

- No evidence of risk in humans: metronidazole (although, because of insufficient data, contraindicated in 1st trimester), prednisone, sulfasalazine, and mesalamine
- Risk cannot be ruled out: olsalazine
- Absolutely contraindicated: methotrexate

For more information on medications in pregnancy, see the [Women's and Men's Health](#) section.

Crohn Disease (CD)

Although most patients who present with CD (a.k.a. regional enteritis) are in their 20s or 30s, the disease can present at any age; there is a second, smaller peak of incidence in 70- to 80-year-olds. The overall incidence of CD is rising. CD can involve mouth to anus; however, most common locations are small bowel +/- colon. There is an increased risk of GI cancer with CD, especially with long-standing disease and Crohn colitis; screen long-term (> 8 years) CD patients every other year with colonoscopy.

CD tends to be **more indolent** than UC and **less responsive** to treatment. It is harder to get these patients off steroids. Patients with CD are more likely to have perianal fistulae and abscesses. They are also more likely to have strictures, inflammatory masses, and associated obstruction. One big problem with CD is the high rate of recurrence. It was once thought to be 50% at 10 years, but this is only the symptomatic recurrence rate. The radiologic/endoscopic recurrence rate is 75% at 3 years!

Diagnosis of CD

CD is diagnosed by endoscopic findings of patchy, focal, aphthous, and deep transmural ulcers, with occasional strictures and fistula formation. **Granulomas**, infrequently found on biopsy specimen of these ulcers, are pathognomonic. See [Figure 14-14](#) for early CD.

A tetrad to remember for Crohn colitis:

- 1) Rectal sparing
- 2) Skip lesions
- 3) Perianal disease
- 4) Ileocecal involvement

Patients with CD may present with fever, abdominal pain, and systemic symptoms. One classic but uncommon feature is the **string sign** ([Figure 14-15](#)), which may be seen in the **terminal ileum** during a small bowel follow-through. The terminal ileum is so edematous and/or fibrotic that the lumen is compressed and can be visualized only as a "string" of contrast. If you see this narrowing of the lumen elsewhere in the **colon**, with or without CD, it is likely an **"apple core"** lesion, which suggests **cancer**. Bowel involvement in CD: 30% colon only, 30% small bowel only, and 40% both.



Figure 14-14: Crohn proctitis
Source: Samir



Figure 14-15: Crohn colitis with "string sign"
Source: James W. Smith, MD

In up to 15% of IBD patients, a definitive diagnosis cannot be initially established. Serologic tests (perinuclear anti-neutrophil cytoplasmic antibody [p-ANCA] and anti-*Saccharomyces* antibody [ASCA]) can be useful in indeterminate cases. p-ANCA is associated with UC, and ASCA with CD. Panels containing additional serologic markers, which increase diagnostic capabilities, are commercially available.

Extraintestinal Manifestations of CD

Osteoporosis is common in patients with CD, and it is very important to regularly assess for bone loss. About 70% have abnormal bone density due to chronic disease, vitamin D deficiency, and/or steroids.

Extraintestinal manifestations occur primarily in CD that involves the colon and are identical to those of UC, which involves solely the colon. So, these manifestations are discussed under [Extraintestinal Manifestations of UC](#) on page 14-23.

Terminal Ileum Problems in CD

Problems related to disease/resection of the terminal ileum are found in CD—but ordinarily **not** in UC. These problems include:

- Calcium oxalate kidney stones
- Steatorrhea
- Gallstones
- B₁₂ deficiency
- Hypocalcemia (from vitamin D malabsorption)
- Bile acid-induced diarrhea
- Nutrient malabsorption

Pigment gallstones are the usual type of gallstones that occur, and the risk appears to correlate with the amount of ileal disease or resection.

Note that anytime > 60 cm of terminal ileum is resected, patients have B₁₂ malabsorption.

Bile acid-induced diarrhea occurs in CD when < 100 cm of the distal ileum is resected. Some of the bile acids escape absorption in the terminal ileum and go on to stimulate colonic salt and H₂O secretion by the colon. Treat with bile acid sequestrants (e.g., cholestyramine, colestipol), which bind and inactivate bile acids.

When > 100 cm of the distal ileum is resected, the patient gets steatorrhea from greatly decreased proximal gut concentration of bile salts. (Synthesis does not keep up with GI losses with the loss of distal ileum resorption.) Treat these patients with a low-fat diet. Sometimes, the low-fat diet does not allow them to get enough calories. In this case, give supplemental medium-chain triglycerides.

Treatment Overview for CD

Medical treatment of CD includes many of the same drugs as that for UC. See more details on these medications under [Drugs Used to Treat IBD on page 14-18](#).

Medical treatment of CD:

- 5-ASA (mesalamine—slow-release formulations)
- Corticosteroids (prednisone, budesonide)
- Infliximab, adalimumab, and certolizumab pegol
- Metronidazole
- Ciprofloxacin
- Azathioprine (and its metabolite, 6-MP)
- Methotrexate
- Vedolizumab

Know [Table 14-3 on page 14-22](#) and the following:

- Traditionally, initial treatment for mild disease was a slow-release oral 5-ASA, but meta-analyses suggest that 5-ASAs are minimally effective as compared with placebo. So, move quickly to other drugs if response is inadequate. 5-ASA analogs are more effective in CD with **colon** disease only vs. ileal or ileocolic disease.
- Prednisone is more effective in UC than CD—again, probably due to the indolent nature of CD. In CD, prednisone is more effective than sulfasalazine when

CD affects only the small intestine. Prednisone is best used only for flares; discourage long-term use (> 3 months) because of side effects.

- Budesonide is a 1st line drug for mild-to-moderate CD of the ileum or ileocecum.
- Infliximab is helpful in patients with fistulae, and it also facilitates successful withdrawal from corticosteroids. Before starting this agent (or any anti-TNF agent), screen for TB and hepatitis B. The most common adverse reactions are a positive ANA in 55% and upper respiratory infections in 32%. Severe fungal infections and TB can occur. Lymphoma, skin cancer, and MS have also been described.
- Metronidazole is effective, especially for fistulae and perianal CD (used for UC only when there is fulminant disease with peritonitis). Long-term use is hampered by neuropathy.
- Ciprofloxacin is also occasionally used for fistulous or perianal CD in conjunction with metronidazole.
- 6-MP and azathioprine are used in patients with Crohn's who cannot be weaned off prednisone. Long-term treatment with these drugs decreases recurrence rates in CD.
- Edematous stricture is treated with IV steroids or infliximab.
- Prednisone and metronidazole do not affect relapse rate.

Surgery and Recurrence in CD

Surgery is only for intractable disease and specific serious complications. Previously, 60% of patients with Crohn's required surgery in the first 5 years and then again after ~ 8 years. These numbers are decreasing with improved medical therapy options (especially 6-MP and infliximab). Fibrotic stenosis is treated with surgery or endoscopic balloon dilation (if ≤ 5 cm in length).

The incidence of recurrence after surgery depends on:

- Site—ileocolic is highest.
- Nature of the complication—obstruction, perforation, and abscesses have a higher rate of recurrence.

Essentially, the worse the disease is at the resection site, the more likely the recurrence of disease at that site. Colectomy and ileostomy provide the best results for Crohn colitis when there is no ileal inflammation (> 60% have no recurrence).

Treatment Scenarios for CD

A summary of IBD treatment is listed in [Table 14-3 on page 14-22](#). Treatment for CD varies, depending on the extent of disease and presence or absence of complicating factors:

- **Colon only:** aminosalicylate (sulfasalazine or mesalamine) tablets/enemas. Sulfasalazine is much less expensive than mesalamine and other 5-ASA drugs. Therefore, sulfasalazine is the 1st choice—then mesalamine if required because of intolerance to the side effects of sulfasalazine.

Table 14-3: Comparison of Treatments Used for Crohn Disease and Ulcerative Colitis

Severity and Status	Stools / Day	KUB	Physical Exam	Treatment for Ulcerative Colitis	Treatment for Crohn Disease
Mild	< 4	Normal	Normal; but history of intermittent fecal blood	Distal disease: rectal corticosteroids; oral or rectal aminosalicylates Extensive colon involvement: oral aminosalicylates	Oral aminosalicylates; sulfasalazine +/- antibiotics
Moderate	4–6	Between mild and severe		Same treatment as mild severity	Oral corticosteroids (short term, < 3 months); budesonide, azathioprine, 6-MP, or methotrexate if steroid dependent or refractory
Severe	> 6	Air, edema, thumbprinting	Fever, abdominal tenderness, frequent fecal blood	Distal disease: oral or rectal corticosteroids Extensive colon involvement: oral corticosteroids, anti-TNF	IV corticosteroids; IV infliximab; IV vedolizumab; elemental diet or TPN = transient benefit
Fulminant	> 10	Bowel dilation	Fever, abdominal tenderness, and distention	IV corticosteroids or infliximab if resistant to corticosteroids	N/A
Post-op			N/A		Metronidazole +/- ciprofloxacin (delays anastomotic recurrence—danger of neuropathy), azathioprine, anti-TNF
Remission		Normal		Sulfasalazine, mesalamine, azathioprine; 6-MP +/- anti-TNF Colonic release budesonide; infliximab and adalimumab (or other anti-TNF agents) as maintenance therapy	Oral aminosalicylate; azathioprine or 6-MP especially if steroid dependent or refractory; 6-MP or azathioprine is standard maintenance therapy. Infliximab and adalimumab are frequently used to maintain remission. Vedolizumab is also an option.

Note the differences and similarities in these treatments! Metronidazole and diet (bowel rest) are ineffective in UC. Rectal preparations are used only in UC of the distal colon.

6-MP = 6-mercaptopurine
IV = intravenous
KUB = abdominal radiograph (kidney-ureter-bladder)
TNF = tumor necrosis factor
TPN = total parenteral nutrition

- Any ileum or small bowel involvement: slow-release mesalamine
- Only ileum or small bowel involvement: slow-release mesalamine or budesonide
- Fistula or perianal: infliximab (or other immunomodulators), metronidazole, or ciprofloxacin. 6-MP is also used.
- Steroid-dependent: 6-MP, azathioprine, or a mAb

Corticosteroids are 1st line for incomplete acute small bowel obstruction. Otherwise, they are used for flares and only if there is inadequate response to the 5-ASA drugs. Ironically, during an acute flare it is recommended to hold mesalamine/5-ASA, because up to 10% of patients may have a reaction to the medication that looks like a flare.

Ulcerative Colitis (UC)

In UC, colonoscopy shows uniform, contiguous mucosal inflammation with shallow ulcers. The inflammation always starts in the rectum, extends proximally, and is always confined to the colon (Figure 14-16). There is typically a sharp margin between the area of involvement and the normal mucosa. The area of involvement tends to remain the same from the time of diagnosis, but in 10% of patients it does extend more proximally.

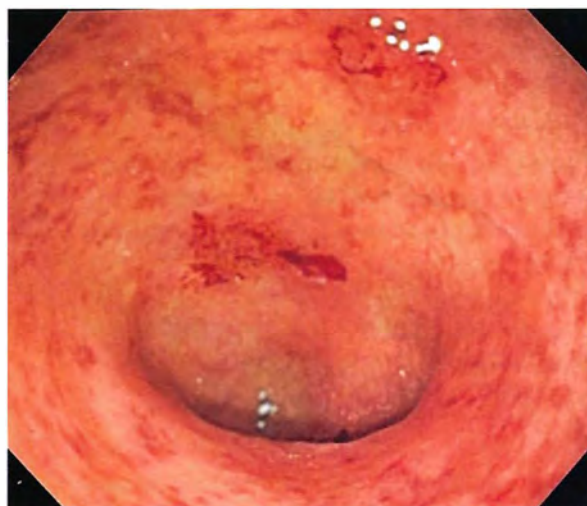


Figure 14-16: Ulcerative colitis

70–80% of UC patients are p-ANCA positive, although this test is of little use clinically (low sensitivity and specificity). ESR and C-reactive protein (CRP) are often elevated.

The main symptoms of UC are abdominal pain and bloody diarrhea. Clinical course and degree of involvement are variable—from mild ulcerative proctitis (rectal

area only) with minimal symptoms to severe colitis of the entire colon with bad cramps, liquid stools containing blood and pus, anemia, extraintestinal manifestations, and constitutional symptoms. Occasionally, tenesmus (painful anal sphincter spasm with no bowel movement) and constipation may be the major clinical presentation.

You must rule out infectious causes of colitis:

- *C. difficile*—most important to rule out
- *Campylobacter*
- *Escherichia coli* O157:H7 (EHEC)
- *Shigella*
- *Salmonella*
- *Yersinia*
- *Entameba histolytica* (amebiasis)

Consider *C. difficile* infection in a flare-up—it is generally thought of as an acute disease, but it can manifest as diarrhea 1–3 months after antibiotic use! Remember that *C. difficile* can occur even without preceding antibiotic use. Diagnose with nucleic acid amplification tests (NAATs) for *C. difficile* toxin genes.

It is **especially** important to rule out *Campylobacter*, because it can have a chronic, relapsing course that mimics UC.

Diagnose with colonoscopy or sigmoidoscopy with biopsies. Endoscopic visualization is not sufficient to establish the diagnosis.

Extraintestinal Manifestations of UC

Extraintestinal manifestations of IBD usually occur with colitis (so they are typically associated with UC, although they can be seen in CD involving the colon).

These extraintestinal manifestations include:

- RF-negative peripheral polyarthritis (Types 1 and 2)
- Ankylosing spondylitis (also HLA-B27+)
- Skin lesions—erythema nodosum and pyoderma gangrenosum—which correlate with disease activity
- Iritis/episcleritis/uveitis (HLA-B27+)
- Venous thrombosis
- Pericholangitis
- Primary sclerosing cholangitis (PSC; HLA-B8+; see [Primary Sclerosing Cholangitis \(PSC\) on page 14-49](#))
- Aphthous ulcers of the mouth

The complications associated with human leukocyte antigens (HLAs) tend **not** to improve with improvement of colitis, whereas the other problems usually get better as colitis improves.

Ulcerative colitis is associated with 2 types of **peripheral arthritis**:

- **Type 1** (pauciarticular)—parallels disease activity
- **Type 2** (polyarticular)—predominantly metacarpophalangeal; independent of disease activity

So, what disease do you think of if a patient with UC develops jaundice, itching, and cholestatic liver function tests (LFTs)?

Note that the commonly used **JSEM** (joint, skin, eyes, mouth) mnemonic leaves out **primary sclerosing cholangitis**, the answer to this question! PSC occurs in 5% of UC patients. The workup: First, as with any initial evaluation of elevated LFTs, get an ultrasound, and then magnetic resonance cholangiopancreatography (MRCP). PSC causes multifocal strictures of intrahepatic bile ducts, which show up as a “string of beads” on MRCP.

So, in patients with UC, check LFTs, especially alkaline phosphatase, initially and periodically. If the alkaline phosphatase becomes 2× normal and persists, work up for PSC.

Cancer in UC

Risk of cancer in patients with UC is **high**. Risk starts increasing about 8 years after onset of symptoms in patients with pancolitis. It is up to 5–10% at 20 years and up to 12–20% at 50 years. Risk increases with:

- Duration of UC
- Extent of UC—pancolitis has the highest risk, whereas ulcerative proctitis has no increased risk.
- Concurrent PSC
- Persistent mucosal inflammation (disease activity)
- Dysplasia

Any patient who has had pancolitis for 8 years or left-sided colitis for 15 years should have a colonoscopy with multiple biopsy samples to check for dysplasia. Once started, continue routine colonoscopy screening for cancer every 1–2 years.

Treatment of UC

UC is **cured** with surgery! Offer colectomy to UC patients not responding to optimal medical therapy, patients with contraindication to medical therapy, and those with **fulminant** colitis or toxic megacolon. Colectomy is also recommended for UC patients with dysplasia in a mass lesion and for high-grade dysplasia in flat mucosa. Repeat colonoscopy in 6 months if there is low-grade dysplasia without inflammation. Some authorities recommend colectomy if low-grade dysplasia without inflammation is confirmed on 2 biopsies within 6 months. Repeat colonoscopy in 6–12 months for dysplasia with inflammation (usually not precancerous).

In UC, other noncancerous indications for surgery are:

- Intractable disease
- Perforation
- Growth restriction in children
- Toxic megacolon
- Stricture
- Steroid dependence
- Exsanguinating hemorrhage
- Complication from therapy

Know all the treatments for UC! Therapy for UC is changing due to the advent of 5-ASA compounds without sulfa, immunomodulators, anti-TNF agents, and integrin inhibitors. UC, a more acute inflammatory process, responds to steroids much better than CD. Steroids are used for acute flare and not for maintenance therapy. Chronic steroid use has many side effects, including cataracts, weight gain, insomnia, and avascular necrosis of the hip. (See [Table 14-3 on page 14-22.](#))

For **mild disease**, there are several options:

- Oral sulfasalazine
- Oral mesalamine
- Topical rectal mesalamine (suppository for proctitis; enema for proctosigmoiditis) helps with tenesmus (rectal urgency).
- Hydrocortisone (HC) enemas

All have similar efficacy—75% response and 30% remission after 2 months. HC enemas have few side effects and lead to quicker symptom relief compared with mesalamine.

For **moderate-to-severe UC**, initial therapy is oral prednisone. Hospitalize patients with fulminant UC and treat with IV corticosteroids or infliximab; the patient may need a colectomy if fulminant symptoms persist for > 48 hours.

Maintenance therapy after remission:

- Sulfasalazine or mesalamine daily
- Azathioprine or 6-MP for frequent recurrences/steroid dependence; treatment can take 3–4 months to show an effect.
- Immunomodulators (e.g., infliximab, adalimumab, vedolizumab)

A few buzzwords:

- Tenesmus (= UC)
- Rectal bleeding (= UC)
- Fecal soiling (think fistula = CD)
- Hydronephrosis without stones (obstruction from inflammatory mass = CD)
- Pneumaturia (think fistula to the bladder = CD)

DIARRHEA

PREVIEW | REVIEW

- What are the 2 main types of acute diarrhea?
- Which tests are initially done for the workup of acute diarrhea?
- Which antibiotic is generally used for invasive diarrhea? Name 2 important exceptions.
- Which cause of invasive diarrhea should not be treated with antibiotics?
- What is the osmotic gap in patients with osmotic diarrhea?

- How does a 24-hour fast affect osmotic diarrhea?
- In an AIDS patient with fever and diarrhea, which organisms are on your differential list?
- Which neuroendocrine tumor sites are most frequently associated with carcinoid syndrome?
- What is the clinical presentation of carcinoid syndrome?
- How do you diagnose carcinoid syndrome?
- Explain each of the 3 stages used in the workup of chronic diarrhea.
- Which lab tests are done in the workup of malabsorption?
- What are the extraintestinal manifestations of celiac disease?
- How do you diagnose celiac disease?
- What is the clinical presentation of Whipple disease?
- What must be ruled out in a patient > 55 years of age with pancreatic insufficiency?
- Steatorrhea is the best indicator of ____.
- What is the “gold standard” test for determining steatorrhea?
- What is the best screening test for steatorrhea?
- What is the significance of a normal D-xylose absorption test in a patient with steatorrhea? Low D-xylose?
- What are some important causes of small intestinal bacterial overgrowth (SIBO)?
- SIBO is associated with which dermatologic condition?
- How do you diagnose SIBO as a cause of diarrhea?

Diarrhea is defined variably as > 200–250 g/day of stool. Normal average daily output is 150–180 g. Note: Small-volume, loose stools are not considered diarrhea. Normal bowel frequency varies from 3 to 21 stools/week.

Diarrhea is typically categorized by duration of symptoms. Acute is < 2 weeks, persistent is 2–4 weeks, and chronic is > 1 month.

Acute Diarrhea

Note: The infectious causes of acute diarrhea are covered in the [Infectious Disease](#) section.

Acute diarrhea commonly has an **infectious** etiology, but it may also be caused by drug side effects. Infectious diarrhea can be invasive or noninvasive. Invasive diarrhea is characterized by bloody or mucoid stools and is usually caused by bacterial infections such as *Salmonella*, *Shigella*, *Campylobacter*, EHEC, and *C. difficile*. Noninvasive diarrhea consists of watery, nonbloody stool and is often viral in etiology.

Diagnosis of Acute Diarrhea

Do the simple things first! Check diet and travel history.

Lab: First, check stool for stool calprotectin (or lactoferrin or WBC if calprotectin test is not available).

If calprotectin (or lactoferrin or WBC count) is elevated, do:

- C&S
- O&P, especially with positive travel history
- +/- Sigmoidoscopy with biopsy

If you suspect EHEC, specifically ask for MacConkey agar with sorbitol for the stool culture medium. If you suspect *C. difficile*, also add *C. difficile* NAAT assay.

Colonoscopy/sigmoidoscopy with biopsies can be useful in differentiating infectious colitis from IBD. Crypt abscesses may be found in both, but crypt distortions are found **only** in IBD.

Treatment of Acute Diarrhea

Generally, invasive diarrhea is treated with quinolones (especially ciprofloxacin), but use macrolides for *Campylobacter* (high quinolone resistance) and metronidazole for amebiasis. Antibiotics may prolong *Salmonella* infections and, therefore, are typically **not** used.

Another big exception is EHEC infection, which is treated only symptomatically; antibiotics are **contraindicated** as they may increase risk of thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS)!

See the **Infectious Disease** section for more details on specific organisms and treatments.

Chronic Diarrhea

Mechanisms of Chronic Diarrhea

Chronic diarrhea is defined as loose stools > 200–250 g/day for > 1 month.

Chronic diarrhea can be classified according to 3 mechanisms: secretory, osmotic, and increased motility. First, let's compare and contrast osmotic and secretory mechanisms. When discussing ion concentrations, note that [x] indicates "concentration of x."

In normal bowel contents, the total cations are equal to the total anions:

$$[\text{Na}^+] + [\text{K}^+] = [\text{Cl}^-] + [\text{HCO}_3^-] + \text{other anions}$$

(The "other anions" are mostly short-chained fatty acids that are usually absorbed early in bowel transit.)

You can estimate stool osmolality using only the Na^+ and K^+ concentrations:

$$\text{Stool osmolality}_{\text{est}} = 2([\text{Na}^+] + [\text{K}^+])$$

For normal stool and for diarrhea of any cause:

$$\text{Stool osmolality} = \text{serum osmolality}$$

But! ... Depending on the cause of the diarrhea, the concentration of **unmeasured** anions can vary from normal to high.

Note: Serum osmolality is typically 280–300 mOsm/kg. Extremely low stool osmolality raises suspicion of dilution of stool sample with fluid/urine (factitious diarrhea).

Because the fluid in **secretory** diarrhea is, in essence, an ultrafiltrate of the serum, the osmolality of secretory diarrhea is similar to normal stool:

$$2([\text{Na}^+] + [\text{K}^+]) = \sim 290 \text{ mOsm/kg}$$

With **osmotic** diarrhea, excess unmeasured, nonabsorbable, osmotically active molecules are pulling water into the stool (osmosis), diluting the normal electrolytes—so $2([\text{Na}^+] + [\text{K}^+])$ is much less than 290 mOsm/kg. This difference is usually > 100 mOsm/kg.

Summary: Here are the pertinent equations again. Learn them, and you should be able to handle this topic:

$$\text{Stool Osm}_{\text{est}} = 2(\text{stool } [\text{Na}^+] + \text{stool } [\text{K}^+])$$

$$\text{Stool osmotic gap (SOG)} = 290 \text{ mOsm/kg} - \text{Stool Osm}_{\text{est}}$$

If the **SOG** is > 100 mOsm/kg, the gap is increased, suggesting **osmotic** diarrhea.

When the **SOG** is < 50 mOsm/kg, either the stool is normal or the diarrhea is **secretory**.

These calculations work in straightforward situations, but **many** causes of diarrhea have **both** secretory and osmotic components. At the bedside, the calculations are less useful.

Make sure this makes sense to you before you move on!

Secretory Diarrhea

In secretory diarrhea, $2([\text{Na}^+] + [\text{K}^+])$ of the stool is $\sim 290 \text{ mOsm/kg}$, which equals serum osmolality (SOG is < 50 mOsm/kg). There is more stool volume in secretory diarrhea than in osmotic diarrhea, often > 1 L/day, so there is obviously an increased secretion of electrolytes; thus, the patient is at risk for an electrolyte deficiency.

There are many causes of secretory diarrhea:

- Enterotoxins from *E. coli*, cholera, and *Staphylococcus aureus*
- Gastrinomas
- Microscopic colitis
- Collagenous colitis
- Bile acids
- VIPomas that produce vasoactive intestinal peptide (VIP)
- Villous adenomas (rare cause)

A 24- to 48-hour fast does not decrease secretory diarrhea (see **Table 14-4 on page 14-26**), **except** in diarrheas related to fatty acid and bile acid.

Table 14-4: Osmotic vs. Secretory Diarrhea

	Osmotic	Secretory
Volume	< 1 L/day	> 1 L/day
Effect of Fasting on Volume of Diarrhea	Decreases > 50%	Decreases < 20%
Serum Osmolality*	~ 290 mOsm/kg	~ 290 mOsm/kg
Stool $\text{Osm}_{\text{est}} = 2([\text{Na}^+] + [\text{K}^+])$	< 290 mOsm/kg	~ 290 mOsm/kg
$\text{SOG} = 290 \text{ mOsm/kg} - 2([\text{Na}^+] + [\text{K}^+])$	> 100 mOsm/kg	< 50 mOsm/kg

* Serum osmolality = total stool osmolality
SOG = stool osmotic gap

Osmotic Diarrhea

In osmotic diarrhea, $290 \text{ mOsm/kg} - 2([\text{Na}^+] + [\text{K}^+])$ is $> 100 \text{ mOsm/kg}$. So, there is at least a 100 mOsm/kg osmotic gap that is due to a nonabsorbable osmotic agent.

A 24-hour fast does resolve or greatly improve the diarrhea (refer to Table 14-4). Lactase deficiency is one of the most common causes of osmotic diarrhea. Other common causes are magnesium-containing laxatives and antacids, non- or poorly absorbable carbohydrates (e.g., xylitol, lactulose, sorbitol—typically found in sugar-free candies), and nutrient malabsorption (i.e., pancreatic insufficiency, celiac disease, small intestinal bacterial overgrowth [SIBO]).

If an osmotic diarrhea persists despite a 24-hour fast, suspect surreptitious ingestion of a magnesium-containing antacid. Most laxatives, including castor oil, cause an osmotic diarrhea.

Increased Motility Diarrhea

The 3rd mechanism of diarrhea is increased motility. The dysmotility syndromes include antibiotic-associated diarrhea, hyperthyroidism, diabetes, irritable bowel syndrome, and carcinoid syndrome. See [Carcinoid Syndrome](#).

Different mechanisms of diarrhea may occur together in certain diseases. In celiac disease, for example, osmotic and secretory mechanisms coexist, because there is malabsorption of carbohydrates (osmotic) and fat (secretory). Exudative diarrhea (i.e., high fecal WBCs; includes invasive bacteria and IBD) contains all 3 mechanisms: Inflammation causes altered motility, and malabsorption can cause both osmotic and secretory components.

Treatment for most antibiotic-associated diarrhea is simply to stop the drug. Note: *C. difficile* diarrhea does not fall into this category!

Causes of Chronic Diarrhea

Human Immunodeficiency Virus (HIV) / Acquired Immunodeficiency Syndrome (AIDS)

Know: With the advent of highly active antiretroviral therapy (HAART), infectious causes of diarrhea in patients with AIDS has decreased dramatically from $> 50\%$ to 13% .

Despite HAART, diarrhea still occurs frequently. If the patient has diarrhea and weight loss **without fever** but has a low CD4 count, suspect one of these noninvasive organisms: *Cryptosporidium* (usual cause), *E. histolytica*, *Giardia*, *Isospora*, *Strongyloides*, or AIDS enteropathy.

With fever, think *Mycobacterium*, *Campylobacter*, *Salmonella*, *Cryptococcus*, *Histoplasma*, and CMV. (These are covered in the [Infectious Disease](#) section.)

Volume is a big clue in AIDS-associated diarrhea; $> 1 \text{ L/day}$ suggests a small bowel cause.

A CD4 count $< 200 \text{ cells}/\mu\text{L}$ ($0.20 \times 10^9/\text{L}$), especially if accompanied by weight loss, points to an infectious etiology rather than AIDS enteropathy.

Inflammatory Bowel Disease (IBD)

Know: Chronic inflammatory diseases of the colon (UC and Crohn colitis) cause loose stools with many WBCs and histologic damage. Volume can be $>$ or $< 200 \text{ g/day}$. Chronic bloody stools suggest UC. Chronic loose stools associated with chronic RLQ abdominal cramping, especially with palpation of thickened bowel in the RLQ, suggest CD.

Note: Fecal WBCs and blood are found in **both** invasive diarrhea and UC. See [Inflammatory Bowel Disease \(IBD\)](#) on page 14-18.

Diabetes

Diabetic diarrhea may be caused by:

- Foods rich in sorbitol (e.g., sugar-free candy and gum)—it can cause an osmotic diarrhea.
- Visceral autonomic neuropathy—especially suspect this in the incontinent diabetic patient.
- Malabsorption due to:
 - Celiac disease (present in 5% of diabetics)
 - Pancreatic insufficiency
 - Gastroparesis
 - SIBO (Treat with metronidazole and amoxicillin/clavulanate.)
- Pancreatic exocrine insufficiency (more common in diabetes mellitus due to pancreatic disease)

Carbohydrate Intolerance

Consider carbohydrate intolerance in all patients with chronic diarrhea who excessively ingest beverages rich in sorbitol and fructose—consider especially caffeinated soft drink intake.

Carcinoid Syndrome

Carcinoid is an uncommon cause of chronic diarrhea.

Neuroendocrine tumors (NETs) mainly form in the GI tract and lungs but occasionally may arise in kidneys and ovaries. The carcinoid syndrome typically occurs with disseminated disease, particularly liver metastases. NETs can present with symptoms caused by tumor growth, such as pain or obstruction.

Carcinoid syndrome results from the release of vasoactive mediators, including 5-hydroxytryptophan, 5-hydroxytryptamine, histamine, kallikrein, and prostaglandins.

Most carcinoids are asymptomatic, are found in the GI tract outside of the midgut, and do not metastasize. Carcinoid syndrome occurs **only** when the primary tumor, usually in the midgut (ileum and proximal colon), has metastasized to the liver. In other tumors, the liver deactivates the vasoactive mediators, so symptoms do not occur. But, with hepatic metastases, the liver does **not** deactivate and **directly** releases vasoactive mediators into the circulation. Some bronchial carcinoids can present with carcinoid syndrome, but it's extremely rare.

So, when you see carcinoid **syndrome**, think (midgut) GI primary with **hepatic metastases**.

Gastric NETs (previously known as gastric carcinoids) are related to hypergastrinemic states. See [Gastric Neuroendocrine Tumors \(NETs\) on page 14-16](#).

Carcinoid syndrome presents as paroxysmal flushing; crampy, explosive diarrhea; and hypotension or tachycardia. The flushing is often bright red to violaceous, with well-defined borders, and can be on the whole body—including palms and soles.

In carcinoid syndrome, increased metabolism of tryptophan, a precursor of niacin, may cause **niacin deficiency** (pellagra; scaly rash, thickened tongue, angular cheilitis, and mental status changes).

Diagnosis of carcinoid syndrome: Check 24-hour urine for 5-hydroxyindoleacetic acid (5-HIAA)—a breakdown product of 5-hydroxytryptamine. Normal is < 10 mg/day; with carcinoid, the patient has > 25 mg/day and serum chromogranin level. Approximately 60–80% of NETs in the pancreas and the GI tract have an elevated chromogranin. In patients with carcinoid syndrome from a primary GI tumor, CT of the liver usually shows metastatic lesions. Radionuclear scanning, via iodine-123-metaiodobenzylguanidine (¹²³I-MIBG) or octreotide scanning, may assist with management of carcinoids.

Visceral Autonomic Neuropathy (Diabetes, Amyloidosis)

Visceral autonomic neuropathy is characterized by:

- Delayed gastric emptying (i.e., gastroparesis)
- Postural decrease in blood pressure
- Anhidrosis (inability to tolerate heat, lack of functioning sweat glands)—especially in lower extremities
- Fecal incontinence
- Impotence (men)
- Urinary overflow incontinence

Patients may exhibit any one or all of the above!

Microscopic Colitis

Microscopic colitis consists of **collagenous colitis** and **lymphocytic colitis**. These patients have grossly normal-looking mucosa but abnormal findings on mucosa biopsy (hence the name microscopic colitis). Patients have a chronic secretory, watery diarrhea. Consider in patients with sudden-onset severe watery diarrhea on NSAIDs or PPI therapy.

Colonoscopy is normal, but mucosal biopsy of the normal-looking mucosa shows a lymphocytic infiltrate or a collagenous band in the submucosa. **Know:** Microscopic colitis does **not** progress to either UC or CD.

First-line treatment is an antidiarrheal medication, such as loperamide; use budesonide if diarrhea persists. High-dose bismuth therapy is also an option.

Radiation Enteritis

Radiation enteritis is the inflammation of the intestines that develops weeks to years after receiving radiation therapy for abdominal or pelvic malignancy. Half of the 200,000 cases per year of new abdominal and pelvic malignancies require radiation therapy. While almost all of these have some degree of acute radiation enteritis, most symptoms subside several weeks after treatment ends. Only about 10% develop chronic enteritis/colitis.

Acute radiation damage causes polymorphonuclear neutrophil (a.k.a. neutrophil) and plasma cell infiltration of the lamina propria, submucosal edema, and transient mucosal atrophy. If the radiation damage is chronic, obliterative arteritis of the intestinal wall small vessels occurs along with lymphoid atrophy and submucosal fibrosis.

Symptoms of acute disease include:

- Diarrhea
- Abdominal pain
- Nausea/Vomiting (N/V)
- Anorexia
- Hematochezia

In addition to the above symptoms, chronic cases can present with malabsorption and anemia.

Suspect radiation enteritis in any patient with chronic diarrhea and a history of radiation therapy. CBC may reveal anemia (i.e., blood loss) or elevated WBC count (i.e., intraabdominal sepsis, bowel obstruction). Typically, reserve aggressive investigation (including CT, MRI, and endoscopy) for chronic cases.

Management focuses on treating the symptoms until the inflammation heals. This includes low-residue diet, anti-diarrheal medication, and antibiotics if SIBO is suspected. Bile acid sequestrants can be helpful for persistent diarrhea in chronic cases. Surgery is reserved for refractory cases involving fistulae, obstruction, perforations, and/or hemorrhages.

Other

Other causes of chronic diarrhea include:

- Steatorrhea (discussed further under [Malabsorption](#))
- Endocrinopathies (hyper- and hypothyroidism, adrenal insufficiency)
- Colon cancer
- Fecal incontinence (radiation, diabetes, rectal surgery, and childbirth injury to anal sphincter—especially forceps delivery)

Patients may not want to mention that they have fecal incontinence. They frequently tiptoe around the issue by asking for “medication to control the diarrhea.” Ask patients with diarrhea if they experience fecal incontinence > 1×/week.

Chronic Loose Stools

The following may cause loose stools < 200 g/day, so they do **not** meet the criteria of diarrhea:

- Lactase deficiency (lactose intolerance) is a common cause of loose stools, although the volume is generally < 200 g/day.
- Irritable bowel syndrome (IBS) has loose stools with normal daily volume. See [Irritable Bowel Syndrome \(IBS\) on page 14-34](#).

Diagnosis of Chronic Diarrhea

Know the following 3 stages of diagnosis.

Stage 1:

- Stool O&P; rule out GI infection with broad “GI PCR test” if available
- Rule out inflammation with stool calprotectin
- Serum chemistry and thyroid profile
- *C. difficile* toxin assay
- Stool pH
- Weight of stool/day
- Qualitative stool for fat or a quantitative 3-day fecal fat (If steatorrhea is definitely being considered, a 3-day fecal fat collection is usually ordered.)
- Lactose-free diet if lactase deficiency is at all suggested by history

Stage 2:

- Immunosorbent assay for giardiasis
- If steatorrhea is confirmed, order endoscopic ultrasound or CT scan to rule out chronic pancreatitis as a cause of pancreatic exocrine insufficiency. (Further tests for steatorrhea are discussed in detail under [Malabsorption Due to Decreased Digestion on page 14-31](#).)
- If patient is diabetic, do either a lactulose (or glucose) breath test for SIBO or (more often) just treat empirically. Note: Do not confuse the lactulose breath test (used to diagnose SIBO) with the lactose hydrogen breath test used to diagnose lactose intolerance!
- If > 1,000 mL/day of stool, check vasoactive intestinal polypeptide (VIP).
- Check for laxative abuse by:
 - Urine tests for bisacodyl, anthraquinones, and phenolphthalein
 - Stool osmotic gap > 100 mOsm/kg (magnesium-containing agents)
 - Stool measurement of phosphate and sulfate
- If the stool osmolality is < 290 mOsm/kg, the patient could be adding water or urine to the stool.

Stage 3:

- EGD and colonoscopy

A significant number of patients have no discernible cause of the diarrhea, no abdominal pain, and have a normal EGD and colonoscopy. These patients have **idiopathic chronic diarrhea**.

An inpatient hospital stay may be required after Stage 3 to redo the previous tests with better controls. Suspect occult bile acid diarrhea if the patient has loose watery stool but no abdominal pain.

Loose Stools and Fecal Impaction

Watery stool may leak around a fecal impaction, causing small-volume watery effluent. See [Fecal Impaction on page 14-34](#).

Malabsorption

Patients with malabsorption often present with chronic diarrhea and nutritional deficiencies, typically reflected as abnormalities in the “Big 6” blood tests: albumin, Ca²⁺, cholesterol, carotene, serum iron (all low), and prothrombin time (PT; prolonged).

The causes of malabsorption can be divided into **decreased mucosal transport** (something wrong with intestinal uptake) and **decreased digestion** (not enough digestive enzymes). The latter is sometimes called maldigestion.

Malabsorption Due to Decreased Mucosal Transport

Decreased mucosal transport can be caused by celiac disease, tropical sprue, common variable immune deficiency with hypogammaglobulinemia, Whipple disease, intestinal lymphoma, eosinophilic gastroenteritis, SIBO, and other small bowel disease.

Celiac Disease

Celiac disease (gluten-sensitive enteropathy; previously celiac sprue, nontropical sprue) is one of the most commonly undiagnosed disorders. It occurs in up to 1% of the population in most countries. It is more common in Caucasians.

Celiac disease is an autoimmune intestinal disorder in which there is an altered gut mucosal response to dietary gluten, which is in wheat, barley, malt, and rye. This results in small bowel villous atrophy and crypt hypertrophy with resulting malabsorption. It can cause growth restriction in children and is associated with HLA-DQ2 and HLA-DQ8. Remission may occur during adolescence, and then recur. If detected early, the patient may have only mild symptoms, such as bloating and loose stools.

Extraintestinal manifestations of celiac disease:

- Iron-deficiency anemia (the most common presentation; iron is absorbed mostly in the duodenum): low hemoglobin (Hgb), mean corpuscular volume (MCV), and ferritin
- Abnormal serum aminotransferases
- Dermatitis herpetiformis
- Osteoporosis
- Osteomalacia
- Neuropsychiatric symptoms
- Dental enamel defects

Primary intestinal lymphoma is a rare, late complication of celiac disease. Patients with celiac disease are also at increased risk of developing Type 1 DM and Addison disease.

Deficiencies caused by celiac disease:

- Iron
- Folic acid
- Ca^{2+}
- Vitamin D
- Vitamin K
- Vitamin B₁₂ (rarely)

There is a wide spectrum of presentations. Patients often have few to no GI symptoms and may present with only a psychiatric disorder, osteomalacia, or a purulent pustular rash.

Dermatitis herpetiformis is a manifestation of celiac disease. It is characterized by intensely itchy vesiculopapular eruptions on the face, trunk (Figure 14-17), buttocks, sacrum, and extensor surfaces of elbows and knees.

Most patients with dermatitis herpetiformis do not have abdominal symptoms, although 85% have the characteristic findings on intestinal wall biopsy.

Diagnosis of celiac disease includes these 4 criteria:

- 1) Evidence of malabsorption (e.g., steatorrhea, weight loss, iron-deficiency anemia)
- 2) Positive IgA anti-tissue transglutaminase (anti-tTG) antibody test ($\geq 90\%$ sensitivity)

- 3) Abnormal small bowel biopsy to clinch the diagnosis
- 4) A positive response to a gluten-free diet (clinical, chemical, histological, and immunologic)



Figure 14-17: Dermatitis herpetiformis

The best antibody tests are:

- Anti-tTG IgA and total IgA level
- Anti-deamidated gliadin peptide (anti-DGP)—in case of IgA deficiency

Because IgA deficiency occurs in 1–2% of the U.S. population, if IgA tTG antibody is negative in the setting of a strong suspicion of celiac disease, check serum IgA levels. Check anti-DGP. These antibody tests can also be useful for identifying latent celiac disease or as a measure of compliance with the gluten-free diet.

If there is a high suspicion for celiac disease, diagnose using serology in conjunction with early EGD with small bowel biopsy. HLA typing may also have utility; a patient who is negative for DQ2 and/or DQ8 does not have celiac disease.

Note: The small bowel biopsy results are characteristic but not pathognomonic, since you may see similar villous atrophy with hypogammaglobulinemia (a.k.a. hypogammaglobulinemic sprue), SIBO, lactose intolerance, giardiasis, peptic duodenitis, and tropical sprue. Many small bowel disease processes can cause villous atrophy.

Treat celiac disease with a gluten-free diet.

80% of patients eventually respond. For those who do **not**, consider:

- Dietary noncompliance (most common)
- Intestinal lymphoma
- Microscopic colitis
- T-cell enteropathy
- Lactose intolerance secondary to lactase deficiency (damaged mucosa)
- Pancreatic insufficiency
- Collagenous sprue
- Ulcerative jejunoileitis

Emphasize to the patient the need for **lifetime** gluten avoidance.

Test for compliance by doing repeat tests for tTG antibody. Anti-tTG antibody titers should fall to normal within 3–12 months on a gluten-free diet.

Now that you know about celiac disease, what test will you remember to order in the following patients?

- A 16-year-old presents with a diagnosis of bipolar disorder.
- A 33-year-old presents with bone pain in his spine and legs.
- A 28-year-old presents with a pruritic papulovesicular eruption on her extensor elbows and knees.
- A 30-year-old presents with heme-negative stool and low Hgb, MCV, and ferritin.

Good! tTG IgA or anti-DGP IgG for celiac disease. Celiac disease is a commonly missed diagnosis.

Collagenous Sprue

Refractory or collagenous sprue is a variant of celiac disease in which the small bowel biopsy shows flattened mucosa with large masses of subepithelial eosinophilic hyaline material (collagen) in the lamina propria. Suspect it in patients who do not respond to a gluten-free diet.

Treat with corticosteroids and other immunosuppressive agents.

Tropical Sprue

Tropical sprue causes malabsorption with partial villous atrophy and is probably caused by a still-unknown infectious organism. It is endemic in areas of the Caribbean, South Africa, Venezuela, India, and Southeast Asia (i.e., the equatorial areas). Patients often have megaloblastic anemia.

Treat with tetracycline or doxycycline for 3–6 months. Folic acid replacement can also be effective either alone or as adjunctive treatment.

Olmесartan-Associated Enteropathy

The angiotensin receptor blocker olmesartan can cause a spruelike enteropathy and carries a warning from the FDA.

Whipple Disease

Whipple disease is rare (< 1,000 cases total reported worldwide, although it is probably underreported). It is caused by *Tropheryma whipplei*, a gram-positive actinomycete.

The tetrad of symptoms:

- 1) Arthralgias—the most common symptom preceding diagnosis (much more so than abdominal problems)
- 2) Abdominal pain
- 3) Weight loss
- 4) Diarrhea

Patients may have severe malabsorption—often with marked hypoalbuminemia and neurologic symptoms (e.g., depression, paranoia, dementia). Some of these symptoms are the result of lymphatic obstruction.

Upper endoscopy with small intestine biopsy is the diagnostic procedure of choice. Small bowel biopsy shows specific foamy macrophages containing periodic acid-Schiff (PAS)-positive bacterial remnants. You can also check cerebrospinal fluid for *T. whipplei* by polymerase chain reaction (PCR), which is diagnostic if positive.

Differential diagnosis: Lymphatic blockage from primary intestinal (or other) lymphoma may cause similar symptoms.

Treat with ceftriaxone or IV penicillin for 14 days, then trimethoprim/sulfamethoxazole (TMP/SMX) for 1 year. Relapse often manifests with CNS symptoms.

See more on Whipple disease in the [Rheumatology](#) section.

Eosinophilic Gastroenteritis

Eosinophilic gastroenteritis can mimic intestinal lymphoma and regional enteritis. Patients have N/V, diarrhea, abdominal pain, weight loss, albumin wasting, and iron deficiency anemia. They often have a peripheral eosinophilia; and even though it is thought to be due to food allergies, which are IgE mediated, only 20% have specific food allergies with an increased IgE.

Treat with corticosteroids for 2–6 weeks and avoidance of the causative foods (7-food elimination diet: soy, milk, seafood, wheat, corn, egg, and peanut). *Strongyloides* can also cause a peripheral eosinophilia (*Giardia* does not), so be sure to rule this out before you start the steroids.

Short Bowel Syndrome

Short bowel syndrome occurs after massive resection of the small bowel, generally due to:

- severe ischemic injury,
- surgery for small bowel volvulus,
- jejunioileal bypass for morbid obesity, or
- multiple surgeries for CD.

Short bowel syndrome is likely when there is (roughly) < 2 feet (60 cm) of remaining small bowel, especially when the proximal jejunum and/or distal ileum are removed. Lifelong total parenteral nutrition (TPN) is likely to be required if the remaining small bowel is < 100 cm and there is loss of the ileocecal valve.

These patients are susceptible to calcium oxalate kidney stones (secondary to steatorrhea) and gastric acid hypersecretion.

Treat short bowel syndrome with a low-fat diet, small frequent meals, and vitamin supplements. Octreotide, growth factors, H₂ blocker, and loperamide may also

be useful. Teduglutide is an FDA-approved, glucagon-like peptide analog that can promote intestinal mucosal growth in short bowel syndrome. TPN may be needed after large resection and/or while waiting for bowel adaptation after surgery.

Malabsorption Due to Decreased Digestion

There are 2 main causes:

- 1) **Pancreatic insufficiency** can be seen in chronic pancreatitis, pancreatic cancer, and cystic fibrosis. Diagnose pancreatic insufficiency by qualitative stool exam that reveals undigested muscle fibers, neural fat, split fat, and low levels of fecal elastase:
 - The undigested muscle fibers indicate impaired digestion.
 - Low fecal elastase is characteristic of pancreatic insufficiency steatorrhea.
 - Further confirm impaired digestion by a positive response to treatment with pancreatic enzymes. The D-xylose absorption test may also be done during the workup and is normal.
 - You must rule out pancreatic cancer if there is evidence of pancreatic insufficiency in patients > 55 years of age. CT scan frequently shows pancreatic abnormalities, but MRI or endoscopic ultrasound (EUS) may be better than CT scan for detecting lesions.
- 2) **Bile acid deficiency:**
 - Ileal resection > 100 cm (see [Bowel Resection and Diarrhea on page 14-32](#)) or disease that decreases bile acid uptake
 - Severe liver disease, which decreases production of bile acids
 - ZES, in which the patient has increased acidity in the small bowel, with precipitation of bile acids
 - SIBO, resulting in the breakdown of bile acids, making them useless for fat digestion (See [Small Intestinal Bacterial Overgrowth \(SIBO\)](#).)

Steatorrhea is the best indicator of malabsorption, because it is often the most prominent problem:

- The 3-day, quantitative fecal fat measurement is the “gold standard” for determining steatorrhea. Steatorrhea is defined as > 7 g/day of fecal fat.
- Sudan stain of the stool tests for fat, which is the best **screening** test.
- Serum carotene levels are a less specific indicator of malabsorption (See [Diagnosis — Transport vs. Digestion](#).)

Steatorrhea from pancreatic insufficiency causes the most fecal fat (can be > 50 g/day). Any patient having > 40 g/day of fecal fat almost certainly has pancreatic insufficiency—barring history of a massive intestinal resection, which can also increase fecal fat to these levels.

Diagnosis — Transport vs. Digestion

First, determine whether it is a small bowel **mucosal** problem or a **digestive** problem by testing directly for celiac disease and chronic pancreatitis. Other common causes of malabsorption are Crohn disease and SIBO. A small bowel biopsy may be needed.

The xylose (D-xylose) absorption test is not used much. Still, it is frequently an exam topic and is useful for differentiating disorders in carbohydrate absorption.

D-xylose requires normal transmucosal transport; but absorption is not dependent on pancreatic enzyme digestion. Therefore, a **normal** test result in a patient with steatorrhea tells you that mucosal transport is normal. Diffuse small bowel disease can be excluded (i.e., CD, short bowel syndrome) and pancreatic insufficiency is more likely. These patients are often empirically treated with pancreatic enzymes. Resolution of the symptoms with treatment confirms the diagnosis.

On the other hand, **low** D-xylose absorption is not specific. It can be caused not only by small bowel disease but also by many other conditions, including poor gastric emptying, SIBO, ascites, chronic kidney disease, and old age. But, if the patient definitely has steatorrhea, the diagnosis is probably small bowel disease, since most of the other causes of an abnormal xylose test do not cause steatorrhea. So, if the xylose test is low, do a small bowel biopsy.

Again, normal D-xylose = normal small bowel. In which case, pancreatic insufficiency is probably the cause of steatorrhea.

The absorption of carotene, vitamin K, vitamin D, folate, and iron are also independent of pancreatic enzyme digestion. So, low serum carotene, hypocalcemia, hypoprothrombinemia, and/or iron- deficiency anemia in the patient with steatorrhea suggests a small bowel malabsorption problem rather than a pancreatic disorder. This is true only if steatorrhea is chronic and the patient has a normal dietary intake. Conversely, chronic diarrhea and normal levels of the above indicate pancreatic insufficiency.

An alcoholic who has an elevated PT easily corrected by vitamin K more likely has malabsorption as the cause of the high PT—not liver disease!

Again, when malabsorption occurs with steatorrhea:

- Low levels of any micronutrient suggest a small bowel mucosal problem or SIBO.
- Normal xylose absorption test with normal carotene, Ca^{2+} , and prothrombin suggests pancreatic insufficiency—especially if there is very high fecal fat.

Small Intestinal Bacterial Overgrowth (SIBO)

There can be combined causes of malabsorption, as in SIBO, which results in bile acid deconjugation and patchy destruction of intestinal villi.

Patients with SIBO usually have moderate steatorrhea, but their presenting complaint is often abdominal distention. The overgrowth of bacteria makes more folate but decreases absorption of B₁₂, so you can get the odd finding of macrocytosis with high folate and low B₁₂ levels.

SIBO occurs in a variety of conditions:

- **Structural abnormalities**—diverticula, fistulae, strictures, after ileocecal resection
- **Motility disorders**—peristalsis is a major mechanism for clearing the small intestine of bacteria. (Peristalsis can be defective in diabetes, scleroderma, and a number of other conditions.)
- **Achlorhydria**—acid in the stomach kills bacteria before it enters the small bowel.
- **Immune disorders**—immunoglobulins secreted in the small bowel can decrease bacterial growth.

Clinical data suggests a causative relationship between SIBO and rosacea. In one study, almost 50% of patients with rosacea had SIBO and 100% of these patients had long-term resolution when their SIBO was resolved with a 10-day course of rifaximin—a nonabsorbable antibiotic. Further investigations are ongoing to confirm this association.

Diagnose SIBO with the lactulose hydrogen breath test, although there are several other types of breath tests available, including a glucose breath test. It can also be diagnosed by quantitative culture from small bowel aspirate during EGD. Also remember the high folate levels, low B₁₂, and macrocytosis. Patients may also present with vitamin D deficiency and osteoporosis. CT or UGI may show small bowel diverticula (typically from scleroderma) and dilated small bowel.

The specific overgrowth tests are generally available only at large medical centers. After suggestive history and lab findings, SIBO is often treated empirically with 1 of the following:

- Rifaximin (a nonabsorbable antibiotic that stays in the digestive tract)
- Amoxicillin/clavulanate
- TMP/SMX
- Metronidazole
- Ciprofloxacin or norfloxacin
- Doxycycline or tetracycline

Antibiotic treatment regimens for recurrent SIBO: on antibiotics for 2 weeks, off antibiotics for 1 week, repeating indefinitely. If symptoms recur while on a given antibiotic, switch to a different one.

Bowel Resection and Diarrhea

Massive resection of small bowel can cause malabsorption (short bowel syndrome), especially with resection of

the terminal ileum and ileocecal valve. The ileum absorbs specific nutrients, especially B₁₂ and bile acids. Know the following:

- > 60 cm of terminal ileum resected: B₁₂ deficiency
- < 100 cm of terminal ileum resected: Bile acid uptake capacity decreases, causing bile acid to make it to the colon, leading to a bile acid-induced diarrhea—treat with bile acid sequestrants.
- > 100 cm of terminal ileum resected: Bile acid uptake capacity is lost. Synthesis cannot keep up with loss, resulting in bile acid deficiency and subsequent fat malabsorption. Treat with low-fat diet +/- medium-chain triglycerides. See [Terminal Ileum Problems in CD on page 14-21](#).

CONSTIPATION

PREVIEW | REVIEW

- Most cases of constipation are due to what?
- Which common gynecologic surgery leads to constipation in 5% of patients?
- Which demographic groups are more likely to experience fecal incontinence?
- What is the clinical presentation of fecal impaction?

Causes

There are many causes of chronic constipation, usually resulting from:

- generalized or regional colonic inertia and
- pelvic floor muscle dysfunction.

The large majority of cases are **idiopathic**. Lifestyle habits, such as a change to low-fiber diet; sudden, prolonged inactivity; and high stress, may result in constipation.

Recent onset of constipation without change in lifestyle habits (e.g., no changes to diet, no new medications) suggests an **obstructing lesion** (e.g., neoplasm, stricture, foreign body). Pelvic floor dysfunction acts like an outlet obstruction. Hysterectomy leads to refractory constipation in 5% of patients.

Injury or disease involving the parasympathetic innervation of the distal colon and rectum causes **acquired megacolon**; e.g., traumatic sacral nerve damage, MS, Chagas disease, aganglionic megacolon (Hirschsprung disease). Chagas disease is endemic in Central and South America. It is caused by infection with *Trypanosoma cruzi*, resulting in achalasia, cardiomyopathy, and acquired megacolon. Aganglionic megacolon is typically diagnosed within the first 6 months of life, but a milder variant may present in adults.

Anticholinergic drugs are common causes of constipation. These include antipsychotics, antidepressants, 1st generation antihistamines, and anticholinergic cold medications. **Opioids** are another common cause of constipation. Refer to the [General Internal Medicine](#) section for a discussion of opioid-induced constipation. Other causes include iron preparations, calcium supplements, calcium channel blockers, and antacids containing aluminum or Ca^{2+} . **Dehydration** is one of the most common causes of constipation, especially in the elderly.

Endocrine disorders, such as DM and hypothyroidism, often cause mild constipation. Myxedema may result in acquired megacolon. Altered progesterone and estrogen levels are the probable cause of constipation in **pregnancy**. (For more on constipation in pregnancy, see the [Women's and Men's Health](#) section.)

Collagen vascular diseases, especially progressive systemic sclerosis, also cause constipation.

A careful history can determine many of these causes of constipation.

Diagnosis

Do the following work up for patients with constipation with weight loss, rectal bleeding, or anemia:

- A colonoscopy (to exclude structural disease; e.g., cancer, strictures)
- Serum Ca^{2+} and TSH (to exclude hyper/hypocalcemia and hypothyroidism)—check calcium and TSH in all patients with chronic constipation.

Other tests for chronic constipation include evaluation of pelvic floor function, often by anorectal manometry with or without anal electromyography (EMG), and defecogram. Pelvic floor retraining may help many patients with refractory constipation.

A defecogram is a functional x-ray test that visualizes pelvic floor muscles and the rectum during defecation. It can be helpful in evaluating chronic constipation and can indicate the presence of prolapse, rectoceles, or occult intussusception—all of which may need surgical evaluation.

For intractable constipation, test for colonic transit function. 24 radio-opaque markers (a.k.a. Sitz markers) are taken by capsule, and a flat plate of the abdomen is done 5 days later. Normally, most markers are gone. It is abnormal for ≥ 5 to be retained. If the markers are spread throughout the colon, the cause is generalized colonic inertia. Clustering of markers in the rectosigmoid colon indicates pelvic floor dysfunction. A wireless motility capsule provides similar data (available at tertiary centers).

Treatment

Treat constipation by correcting any reversible causes. If idiopathic or irreversible, treat by increasing dietary fiber to > 20 g/day and encouraging adequate fluid intake (to avoid dehydration).

Note: Fiber or bulking agents often help with colonic inertia but **not** with pelvic floor dysfunction, which often responds to pelvic floor retraining (+/- biofeedback). Fiber can also cause bloating and abdominal cramping (especially in female patients).

Increase exercise.

Short-term use of an osmotic laxative and/or stool softener is okay. Avoid chronic use of stimulant laxatives.

Pelvic floor retraining, using modified Kegel exercise, can be quite helpful in refractory cases of constipation.

Difficult cases generally respond well to daily use of polyethylene glycol powder with water or the prescription agents lubiprostone (Amitiza), linaclotide (Linzess) and plecanatide (Trulance). Surgical treatment is indicated for Hirschsprung disease. In patients with constipation related to narcotic use, μ -opioid antagonists (e.g., naloxegol) can be used to counteract peripheral effects of narcotics on the bowel without affecting pain-killing properties.

Osmotic laxatives (e.g., polyethylene glycol, sorbitol, glycerin) cause increased fluid movement into the lumen, increasing fecal bulk.

Stimulant laxatives (senna or bisacodyl) cause colonic muscles to contract. They are indicated only for short-term use.

Prophylaxis: When you initiate narcotic treatment, also start a stool softener + fiber supplement “bowel regimen” to reduce the risk of iatrogenic constipation.

Hemorrhoids

Patients with constipation often develop hemorrhoids. Hemorrhoids are dilated submucosal arteriovenous sinuoids within the anal canal. Patients may present with rectal pain, bright red blood per rectum, or itching. They may also notice a lump protruding from the rectum that can be painful or painless.

Most often hemorrhoids can be treated with topical over-the-counter agents and treatment of the constipation. (See [Treatment](#).) Resistant internal (proximal to the dentate line) hemorrhoids often respond to banding but can require more intense therapy. Previously, the only option was surgery, but newer techniques, such as radio-frequency ablation and sclerosing therapy with aluminum potassium sulfate and tannic acid (ALTA), are less invasive but effective alternatives.

Anal Fissures

An anal fissure is a tear in the anal mucosa distal to the dentate line that can result from constipation or straining during bowel movements. Symptoms occur during or following bowel movements and include:

- Pain
- Bleeding
- Itching

Diagnose by visual inspection.

Conservative treatment is usually effective and consists of:

- Increasing fiber in diet
- Increasing fluids
- Bulk-forming laxatives
- Sitz baths
- Stool softeners

If symptoms persist, then further treatment options include externally applied nitroglycerin to increase blood flow and promote healing, botulinum toxin (Botox, Myobloc) injection to relax anal sphincter spasms, and topical calcium channel blockers to relax the anal sphincter. Surgery is reserved for chronic anal fissures that are resistant to other treatments and consists of making a small cut in the anal sphincter to reduce spasm (lateral sphincterotomy).

Fecal Incontinence

Fecal incontinence is a major health problem, especially in the elderly and women who have had childbirth-related pelvic floor injuries. The diagnostic evaluation uses the same tests as those used for chronic constipation: anorectal manometry, transit studies, and defecography.

The goal of traditional therapies is to increase stool bulk and/or decrease diarrhea (which can contribute to fecal incontinence). Several newer therapies for refractory cases have become available, including injection of a submucosal bulking agent (e.g., dextranomer microspheres, sodium hyaluronate) to increase anal tone, and sacral nerve stimulation to improve function of the anal sphincter and pelvic floor muscles.

Fecal Impaction

Fecal impaction is a large mass of dry, hard stool in the rectum causing constipation. Those at greatest risk are elderly persons with inadequate fluid intake, those with decreased mobility, or those who use narcotics or anticholinergic medications.

Often, more proximal watery stool leaks around the impaction causing a watery fecal incontinence. Presentation is sudden onset of watery stools/incontinence in a person with chronic constipation.

Treat by removing the impaction. Try a mineral oil enema first, but often the impaction must be removed by manually breaking off small pieces until the obstruction is cleared. Longer-term treatment focuses on remedying the constipation: docusate stool softeners and bulk-forming agents used along with a bowel-training program (daily/regular bowel movements).

IRRITABLE BOWEL SYNDROME (IBS)

PREVIEW | REVIEW

- Which other diagnoses do you exclude prior to diagnosing a patient with irritable bowel syndrome (IBS)?
- What are the Rome IV criteria for IBS?
- What are the available treatment options for IBS?

A large part of a gastroenterologist's practice consists of **functional** complaints. Around 15% of the population has signs/symptoms of IBS, and women are diagnosed with it more often than men (2:1). IBS has characteristic symptoms of abdominal pain or discomfort associated with disturbed defecation. Abdominal pain improves with defecation. Symptoms can be either continuous or intermittent. There are no nocturnal or organic symptoms. Patients generally have an increased bowel motor response to emotional and physical stimuli, but these motor patterns are not specific to IBS.

Diagnosis of IBS

Establish diagnosis of IBS by:

- excluding other diseases and
- looking for characteristic symptoms.

Rarely, diagnosis of IBS requires invasive evaluation with colonoscopy or sigmoidoscopy.

These patients are more likely to have psychosocial dysfunction that does not meet criteria for major disorders. They may have neuroses, anxiety, or depression. They are also more likely to have a history of physical or psychological trauma.

Consider a workup to look for an alternative, organic cause in patients > 50 years of age with new-onset IBS-like symptoms.

Exclude Other Diseases

Celiac disease: 2–4% of patients with a diagnosis of IBS, especially those referred to a secondary center, actually have celiac disease. (See [Celiac Disease on page 14-29](#).) In this population, screening with anti-tTG antibody testing is helpful.

Lactose intolerance: Rule out lactose intolerance with a lactose hydrogen breath test. Also, consider that 33% of patients with lactose intolerance do not improve on a lactose-restricted diet, because they have concurrent IBS.

SIBO has been implicated in some cases.

Sorbitol: Rule out excessive sorbitol intake from excess ingestion of “sugarless” candies, mints, and gums.

Look for Characteristic Symptoms

The characteristic symptom pattern of abdominal pain and altered bowel habits is defined by the International Classification for Irritable Bowel Syndrome—commonly called the Rome IV criteria.

Rome IV criteria—at least 3 months of recurrent abdominal pain (at least 1 day/week) with ≥ 2 of the following:

- Related to defecation
- Associated with a change in frequency of stool
- Associated with a change in appearance, form, or consistency of stool

Additional symptoms patients can have that are not part of the Rome IV criteria include:

- Abnormal frequency not meeting the above criteria
- Defecation straining, urgency, feeling of incomplete emptying
- Bloating and belching from aerophagia
- Passing mucous
- No constitutional signs or symptoms, such as fever, weight loss, anorexia, and anemia; specifically, no nocturnal symptoms!

Treatment of IBS

Know the following:

Reassurance is paramount, as evidenced by the very impressive 60–70% (!) response to placebo in these patients—although only 30% have adequate relief with placebo. It is critical to form a therapeutic physician-patient relationship.

Diet: Take a diet history. Have the patient keep a diet log to identify foods that worsen symptoms. Patients should avoid:

- “Sugar-free” or “sugarless” foods that contain sorbitol
- Gas-producing foods (e.g., beans, onions, celery)
- Lactose-containing foods (trial); if symptoms improve on a lactose-free diet, the patient may have lactose intolerance.

If avoidance of the above foods is not effective, consider a low-FODMAP diet (see below).

Behavioral and cognitive therapies help the psychosocial issues.

Fiber supplementation is a traditional standard of care, although it is more helpful in constipation-predominant IBS and can actually worsen bloating.

Probiotics: Try probiotics such as *Lactobacillus acidophilus* and *Bifidobacterium longum*.

Antispasmodic agents used for IBS (e.g., dicyclomine, hyoscyamine) are anticholinergics. Long term, these have more side effects than benefits. They are, however, acceptable for **short-term** or intermittent use.

Tricyclic antidepressants (TCAs) in low doses work well for IBS, especially if patients have loose stools, because TCAs slow bowel motility and may improve neuropathic pain.

Antimotility drugs: Loperamide decreases motility, increases sphincter tone, and is good for loose stools.

Lubiprostone is effective for constipation-predominant IBS.

Linaclotide is used for constipation-predominant IBS. It is a guanylate cyclase agonist that stimulates intestinal fluid secretion and transit.

Low-FODMAP diet: Limited data suggests symptomatic benefit from avoiding fermentable oligo-, di-, and monosaccharides and polyols. This includes a variety of foods including wheat, dairy, legumes, and many fruits. Information about a low-FODMAP diet is available from a number of online sources.

Alternating diarrhea and constipation may be due to patients' use of “stoppers,” such as antidiarrheal medications, and “starters,” such as laxatives.

COLON CANCER

For information on colon cancer, see the [Oncology](#) section.

DIVERTICULAR DISEASE AND LOWER GI BLEED

PREVIEW | REVIEW

- What may be seen on abdominal computed tomography scan in a patient with diverticulitis?
- What is the treatment of moderate-to-severe diverticulitis?
- Which hereditary condition is associated with arteriovenous malformations?

Diverticular Disease

There are 4 types of diverticular disease:

- 1) Asymptomatic diverticulosis (most common)
- 2) Symptomatic uncomplicated diverticulosis (persistent pain without overt colitis or diverticulitis)
- 3) Diverticular bleeding
- 4) Diverticulitis

Asymptomatic Diverticulosis

Diverticulosis (Figure 14-18) is the presence of ≥ 1 diverticulum in the colon. Incidence increases with age. About 80–85% are asymptomatic.

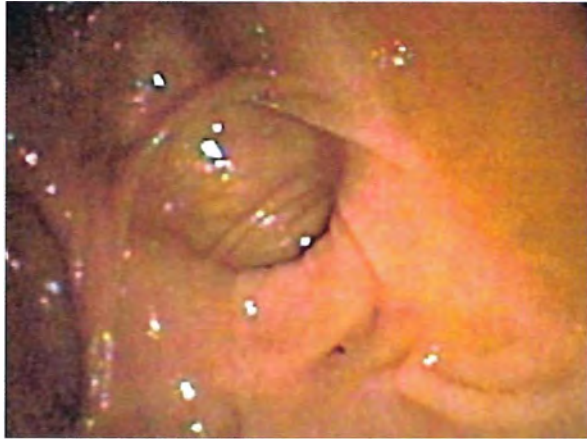


Figure 14-18: Diverticulosis

There is an assumption that diverticulosis is caused by a low-fiber diet and can be warded off by a high-fiber diet. A 2011 study casts doubt on this theory. Still, a high-fiber diet is commonly recommended for those with diverticulosis.

Symptomatic Uncomplicated Diverticulosis

Symptomatic uncomplicated diverticular disease (a.k.a. painful diverticulosis) is due to hypertrophy of both circular and longitudinal colonic musculature myochosis, which leads to luminal narrowing, pencil-thin stools, and bouts of colicky pain often relieved by passing flatus or having a bowel movement. This occurs in a minority of diverticulosis patients. Another helpful clue in establishing a diagnosis of colonic myochosis is a palpable and thickened sigmoid and left colon.

Treat with psyllium- or methylcellulose-containing bulking agents. Probiotics may be beneficial as well.

Diverticular Bleeding

Even though diverticular bleeding occurs in only a small percentage of patients with diverticulosis, it is still the most common cause of colonic bleeding in the elderly. Angiodysplasia is the 2nd most common and often results in more severe bleeds. Diverticular bleeding usually originates in the right colon and typically stops spontaneously.

Patients classically present with “painless, maroon stool,” but the color can actually vary from red to black.

Treatment for diverticular bleeding: Stabilize the patient with IV crystalloid and give packed red blood cell transfusion if needed. Rule out UGI bleed. Correct any coagulopathies and discontinue any medications that worsen bleeding. Colonoscopy is indicated only if bleeding does not stop.

Note: Suspect a UGI bleed when the BUN/Cr ratio is $> 30:1$; this suggests digestion of blood with absorption of breakdown products.

Diverticulitis

Diverticulitis, as the word suggests, is caused by inflamed diverticula. It is typically due to microperforations. It occurs in $< 5\%$ of patients with diverticulosis. Signs and symptoms include:

- LLQ pain and tenderness
- Fever
- High WBC
- No bleeding!

The LLQ tenderness, and sometimes rebound tenderness, is usually localized. Look for a sigmoid mass (i.e., palpable, tender sigmoid) on physical exam, ultrasound, or CT. CT is most useful in assessing diverticulitis; it may show areas of thickened sigmoid colon or pericolic fluid accumulation. Avoid colonoscopy on any patient with diverticulitis (due to risk of perforation).

Include coverage of both aerobic and anaerobic gram-negative organisms in the treatment of diverticulitis.

Treat mild diverticulitis in a patient able to drink and without peritoneal signs with outpatient metronidazole (for gram-negative anaerobic coverage) plus either ciprofloxacin or TMP/SMX (for gram-negative aerobic coverage) and follow up closely.

Treat those with moderate-to-severe diverticulitis, or those who have peritoneal signs, with inpatient parenteral dual- or single-drug therapy:

- 1) Dual-drug therapy (best!), such as:
 - Aminoglycoside or ciprofloxacin (gram-negative aerobic) **plus**
 - Clindamycin or metronidazole (gram-negative anaerobic)
- 2) Single-drug therapy, such as:
 - Ticarcillin/clavulanate
 - Piperacillin/tazobactam
 - Imipenem/cilastatin
 - Ampicillin/sulbactam
 - Cefotetan

Note that all of these single-drug therapies cover both aerobic and anaerobic gram-negative organisms.

Drain abscesses percutaneously.

Perforation from sigmoid colon cancer can present similarly to diverticulitis, so the follow up for patients > 50 years of age is a flex-sig/colonoscopy 6 weeks after the acute condition resolves if colonoscopy has not been performed in the last 2 years.

Meckel diverticulum is the most common congenital GI anomaly. Although $< 1/2$ of these diverticula have gastric mucosa, these are the only ones that ulcerate and bleed. Meckel diverticula cause $1/2$ of all GI bleeds in children; they can also cause obstruction and intussusception. They may be seen with the technetium scan (a.k.a. Meckel scan). Technetium is taken up by gastric mucosa.

Angiodysplasia and Lower GI Bleed

Angiodysplasia (which includes vascular ectasia and arteriovenous malformation [AVM]) is the 2nd most common cause of lower GI bleeding in the elderly (diverticular bleeding is the 1st). Think of these as spider nevi of the GI tract.

Bleeding in angiodysplasia can be occult to severe. The usual bleeding site is the **right colon** (cecum, ascending).

AVMs are typically not cauterized unless they are bleeding significantly.

Hereditary hemorrhagic telangiectasia (HHT); a.k.a. Rendu-Osler-Weber syndrome) is a hereditary condition in which there are multiple AVMs affecting all the organs, including the brain, lungs, and skin, as well as the mucous membranes and the GI tract—especially in the **upper** GI tract (in contrast to AVMs that are located in the lower GI tract). Patients with HHT frequently have a history of epistaxis.

Angiography may be used in the workup of severe disease. Indications for angiography in GI disease:

- Chronic and acute mesenteric ischemia
- Severe lower GI bleed
- UGI bleed (rarely) for some duodenal ulcers/lesions not amenable/refractory to endoscopic therapy
- TIPS (transjugular intrahepatic portosystemic shunt) in variceal bleeding
- Therapeutic uses: embolization, vasopressin infusion

Endoscopic treatment can help, although there are often many lesions and not all can be treated.

Video Capsule Endoscopy (VCE)

With EGD you can see the upper GI tract, and there is colonoscopy for the lower GI tract. VCE can visualize the previously unvisualizable small bowel. It is especially useful in working up small bowel bleeds or occult blood loss without an obvious cause.

Know: Use wireless VCE for a patient presenting with suspected GI bleed, with negative EGD and colonoscopy.

The VCE is also useful for assessing other small bowel problems; e.g., tumors, Crohn disease, celiac disease.

A wireless motility capsule, similar to VCE, is also available. It measures pressure, temperature, and pH and may have a role in the evaluation of transit disorders.

Balloon-Assisted Enteroscopy

Single- and double-balloon-assisted enteroscopy allows for evaluation and treatment of small bowel lesions that were previously out of reach of standard endoscopes.

BOWEL OBSTRUCTION

PREVIEW | REVIEW

- What are the symptoms of bowel obstruction?
- What is the initial treatment for bowel obstruction?

The most common cause of small intestine obstruction is postoperative adhesions. The most common causes of colonic obstruction are (in decreasing frequency): carcinoma, diverticulitis, and volvulus.

Persistent vomiting, obstipation, and abdominal pain suggest the diagnosis of obstruction. Confirm the diagnosis radiographically with a flat and upright abdominal film showing excessive amounts of air in the small bowel with no air in the colon. The presence of air fluid levels is especially helpful when there are “J-loops,” in which the air fluid levels are at different heights on either side of the same loop of bowel. This signifies a **dynamic obstruction**. If the fluid levels are the same height on either side of the loop, **paralytic ileus** is the more likely diagnosis.

Treat initially with IV fluids and nasogastric suction. Further workup is indicated if the symptoms do not resolve in 1–2 days. Nonresolving bowel obstruction (after decompression, correction of electrolytes, and minimization of narcotics) may require surgical intervention. Contrast enema can be helpful if the obstruction is thought to be of colonic origin.

Sigmoid volvulus has a characteristic finding, showing the twisting of the sigmoid on imaging, such as a contrast enema. Sigmoid volvulus can be decompressed by sigmoidoscopy but may also require definitive surgical correction.

INTESTINAL ISCHEMIA

PREVIEW | REVIEW

- What is the clinical presentation of acute mesenteric ischemia?
- What is thumbprinting, and when is it seen?
- What is the clinical presentation of chronic mesenteric ischemia?

There are 4 types of intestinal ischemia:

- 1) Acute mesenteric ischemia (70% mortality!)
- 2) Ischemic colitis (most common)
- 3) Chronic mesenteric ischemia
- 4) Mesenteric venous thrombosis

Acute Mesenteric Ischemia

Acute mesenteric ischemia is the **most severe** and life-threatening form of intestinal ischemia, with a mortality rate of 70%—even with treatment! It is caused by the lodging of a thromboembolus in a mesenteric artery, leading to acute loss of blood flow to the corresponding small intestine and/or ascending colon.

Acute mesenteric ischemia is seen in older patients with a history of heart failure (HF), recent myocardial infarction, or hypotensive episodes. Patients are especially likely to have concomitant valvular heart disease or cardiac arrhythmias, such as atrial fibrillation, because this condition is usually due to emboli.

These patients are **acutely ill** with vomiting, diarrhea, and rectal blood. Intestinal angina may present with intermittent milder symptoms starting months before the acute event.

Bowel infarction leads to lactic acidosis. In the early stages, excruciating abdominal pain (from ischemia) can be disproportionate to the abdominal exam, which can be relatively benign.

Do CT or MRA (magnetic resonance angiography) of abdomen and pelvis unless there is evidence of perforation (e.g., rigid abdomen, lactic acidosis, intraperitoneal air). If there is perforation, the patient goes directly to surgery for dead-bowel resection (and possibly embolectomy). If there is no perforation, management consists of supportive care, empiric broad-spectrum antibiotics, and anticoagulation with consideration of embolectomy (if caused by mesenteric venous thrombosis or a thromboembolic event).

Ischemic Colitis

Ischemic colitis is the most common form of intestinal ischemia. It is due to a **nonocclusive** ischemia involving portions of the splenic flexure, descending colon, and/or sigmoid colon (i.e., inferior mesenteric circulation). Most often, no specific cause for the ischemia is found. Hypotension is a risk factor. It is a disease primarily of the elderly and may be seen post-op (e.g., colonic surgery, aortic aneurysm repair). It is occasionally associated with low-flow conditions (e.g., HF) and medications (e.g. cocaine). Because ischemic colitis is virtually never embolic, patients are **not** likely to have valvular heart disease or cardiac arrhythmia.

A typical history for ischemic colitis is acute LLQ pain with an urge to defecate, followed by passage of red-to-maroon stool within 1 day. Also think of this in extreme athletes; e.g., marathon runner with abdominal pain and hematochezia after a long race.

The mildest injuries—mucosal and submucosal hemorrhage and edema—are completely reversible. More severe injury ranges from replacement of mucosa and submucosa with granulation tissue to transmural infarction and fulminant colitis.

Submucosal hemorrhage and edema (mildest injury) are seen on abdominal x-ray or barium enema as **thumbprinting** (Figure 14-19)—thickening of the large bowel wall in a segmental pattern. This thumbprinting lasts only a few days and is not specific for the type of ischemia, just for submucosal hemorrhage or edema. CT scan is generally the 1st diagnostic test. Portal venous gas on CT of the abdomen and pelvis with oral and IV contrast indicates transmural necrosis/injury and may require urgent surgery consultation.



Figure 14-19: Ischemic colitis—thumbprinting

If there are no peritoneal signs, diagnose with colonoscopy (which is generally done without bowel prep to reduce risk of decreasing blood flow due to use of dehydrating agents). Sigmoidoscopy is also acceptable. Angiography is **not** typically done.

The usual treatment for colonic ischemia is bowel rest, fluids, and antibiotics. Most cases resolve with conservative measures. Rarely, strictures or acute abdomen develop.

Chronic Mesenteric Ischemia

Chronic mesenteric ischemia is also called **intestinal angina**. Patients may require further evaluation if they have the classic triad:

- 1) Abdominal pain after meals
- 2) Abdominal bruit
- 3) Weight loss (from tolerating only smaller meals)

The pain is due to episodes of inadequate blood flow brought on by digestion.

Suspect mesenteric vascular ischemia in the above setting, especially if abdominal pain is out of proportion to any physical findings.

Symptoms are 1–3 hours of dull, gnawing abdominal pain ~ 30 minutes after eating. Patients often describe a fear of eating, leading to weight loss due to pain following meals. The etiology is atherosclerosis of the mesenteric arteries, with the symptoms caused by gastric “steal” after eating. Patients often have signs of other types of peripheral vascular disease (PVD) and often have a history of smoking (no clear association).

Base diagnosis mainly on symptoms. The next step is commonly an MRA or CT angiogram. These have good sensitivity for proximal lesions, such as superior mesenteric or celiac arteries, but are much less sensitive for more distal lesions. Two major vessels need to be involved, such as celiac and superior mesenteric artery (SMA). Dilated collateral vessels further support the diagnosis. Do splanchnic angiography if these are abnormal.

Treat with angioplasty or surgical bypass.

Mesenteric Venous Thrombosis (MVT)

MVT is associated with hypercoagulable states, such as deficiencies of antithrombin III, prothrombin 20210A (a gene variant), protein S, protein C, and Factor 5 Leiden mutation.

MVT is also linked to the following:

- Pancreatitis
- Liver disease (cirrhosis)
- Intraabdominal sepsis
- Sickle cell disease
- Paroxysmal nocturnal hemoglobinuria (PNH)

MVT can be acute, subacute, or chronic. Like mesenteric infarction, the pain of MVT is often out of proportion to the abdominal exam. Be sure to rule out other possible causes of abdominal pain, such as appendicitis. If the portal or splenic veins are involved in chronic MVT, there may be bleeding from gastroesophageal varices. Cirrhosis patients with coagulopathy can still develop MVT.

Diagnose with CT (the procedure of choice), because it has > 90% sensitivity.

Treat acute MVT with thrombolytics and long-term anticoagulants; patients with peritoneal signs may require surgery. Treat chronic MVT with supportive care, and manage variceal bleeding with sclerotherapy, portosystemic shunts, or similar devices.

ACUTE APPENDICITIS

Acute appendicitis is often diagnosed based on history, physical exam, and lab findings. Typical symptoms are RLQ pain and anorexia. Typical findings are a low-grade fever and mild leukocytosis. In > 50% of cases, pain starts in the periumbilical area and migrates to the RLQ.

Imaging studies tend to be better at confirming the diagnosis than excluding it. An abdominal CT scan or ultrasound can be helpful diagnostic tools, especially in elderly patients and in women (to help differentiate from a gynecologic problem).

PERIRECTAL ABSCESS

Perirectal abscesses are most often caused by obstruction of anal glands. Although most patients have no specific risk factors, certain conditions increase the risk, including Crohn disease, immunodeficiency, and prior radiation therapy. Both aerobes and anaerobes have been implicated in abscess formation.

The primary symptom is rectal pain that is constant in nature. Other clinical manifestations are swelling around the rectum, rectal drainage, constipation, and fever. In most patients, a fluctuant, indurated mass is palpated on digital rectal examination.

Diagnosis is made by history and physical findings. CT or MRI is helpful if the perirectal abscess is not palpated on exam. Usually, laboratory evaluation is not indicated in these patients unless the patient has diabetes or is immunocompromised and bacteremia is a concern, in which case CBC and blood culture are needed.

Perianal infections present similarly to perirectal abscess (rectal pain), but treatment differs. Perianal abscesses are more superficial and lack systemic findings. With adequate analgesia, a perianal lesion can be treated with incision and drainage. On the other hand, a perirectal abscess is more extensive and usually demonstrates fever, leukocytosis, and (sometimes) fistula formation.

The definitive intervention for a perirectal abscess is surgical exploration and debridement of necrotic tissue. Antibiotics alone are inadequate due to poor tissue penetration; however, they are used in addition to surgery in certain circumstances—if the patient has diabetes, immunosuppression, or valvular heart disease.

PANCREAS

PREVIEW | REVIEW

- What is the 1st test in evaluating the etiology of acute pancreatitis?
- What happens to serum amylase and lipase levels over time with acute pancreatitis?
- Describe 2 relationships that high triglyceride levels have with acute pancreatitis.
- Know the Atlanta classification of acute pancreatitis.
- Which physical findings are seen with severe pancreatic necrosis with multiple organ failure?
- What is Cullen sign?

- What is Grey Turner sign?
- How is pancreatic necrosis best confirmed?
- Which masses may develop due to acute pancreatitis? What is their timeline, and what is their treatment?
- Symptomatic pseudocysts persisting for > 3–6 months generally require which intervention(s)?
- What is the clinical presentation of chronic pancreatitis?
- What is the classic diagnostic triad for chronic pancreatitis?
- What is the preferred initial test used in the workup of chronic pancreatitis?
- When is endoscopic retrograde cholangiopancreatography (ERCP) preferred over magnetic resonance cholangiopancreatography (MRCP) as a 2nd line test in the workup of chronic pancreatitis?
- What are the classic symptoms of pancreatic carcinoma?
- How is pancreatic cancer treated if there are no metastases? With metastases?
- When is ERCP indicated in pancreatic cancer?

ACUTE PANCREATITIS

Gallstones, alcohol abuse, and nonalcoholic fatty liver disease (NAFLD; see [Nonalcoholic Fatty Liver Disease \(NAFLD\) on page 14-60](#)) are the main causes of acute pancreatitis in the U.S.—with regional variations in the prevalences. In working up the causes of acute pancreatitis, the 1st test is gallbladder ultrasonography to rule out gallstones.

Endoscopic retrograde cholangiopancreatography (ERCP) causes acute pancreatitis in 2–5% of patients (see [Gastrointestinal \(GI\) Procedures on page 14-1](#)). Other causes of acute pancreatitis are diabetic ketoacidosis, hypertriglyceridemia, hypercalcemia, trauma, and other problems that result in obstruction of the ampulla of Vater (e.g., pancreatic cancer).

Always check medications. Quite a few drugs can cause acute pancreatitis:

- Diuretics: furosemide and thiazides
- Estrogens
- Azathioprine
- 5-Aminosalicylic acid (5-ASA) derivatives
- Antibiotics: tetracycline and sulfonamides
- Anti-HIV drugs; i.e., pentamidine, didanosine
- Oral hypoglycemics
- 6-Mercaptopurine, L-asparaginase, and valproic acid

Many cases of “idiopathic” pancreatitis are actually secondary to biliary microlithiasis, cystic fibrosis, hereditary pancreatitis, or hypertriglyceridemia.

With acute pancreatitis, amylase and lipase levels are generally elevated. The serum amylase level is almost always elevated early on (> 3× the upper limit of normal [ULN] is almost always due to pancreatitis) but decreases within 2–3 days after disease onset. The lipase level increases later and stays elevated longer than the amylase (beyond day 7). Remember, lipase is more specific than amylase and, therefore, is used more often. (See [Pearls of Acute Pancreatitis on page 14-42](#).)

High triglyceride levels in the setting of acute pancreatitis can cause a spuriously **normal** amylase level!

Additionally, triglyceride levels > 1,000 mg/dL (11.3 mmol/L) can cause pancreatitis.

The 2012 revision of the Atlanta classification for acute pancreatitis identifies that at least 2 of the following must be present for diagnosis:

- 1) Acute, persistent, severe epigastric pain, often radiating through to the back
- 2) Serum amylase or lipase 3× ULN
- 3) Characteristic findings of acute pancreatitis on imaging (contrast-enhanced CT, MRI, or U/S)

Severity of Pancreatitis

Factors and Results

The severity of acute pancreatitis is directly related to the degree of pancreatic necrosis (10–25% have necrosis) and whether this necrotic tissue is infected (mortality ~ 30%) or not (mortality ~ 10%). Overall, mortality rate for acute pancreatitis is 5–10%!

Severe pancreatitis with pancreatic necrosis causes shock and multiorgan failure. Indicators of organ dysfunction include:

- Hemoconcentration
- Heart: systolic BP < 90 mmHg; tachycardia > 130 bpm
- Lungs: oxygen < 60 mmHg
- Renal: progressive azotemia or oliguria to < 50 mL/hour
- CNS: altered sensorium
- Metabolic: low Ca²⁺ (< 8 mg/dL [2 mmol/L]) and albumin < 3.2 g/dL (32 g/L)

Assessing Severity

Okay, so we know severity of pancreatitis is linked to the degree of necrosis and signs of organ failure. How do we determine severity on admission?

Bedside Index of Severity in Acute Pancreatitis (BISAP) Score

One method for assessing severity is by using the BISAP score (Table 14-5). It is a good score to predict mortality in acute pancreatitis and has fewer variables than Ranson's criteria. (For more information on SIRS, see Organ Failure.)

Table 14-5: Predicting Severity of Acute Pancreatitis Using BISAP Scores

Indicator	Points
BUN > 25 mg/dL (8.9 mmol/L)	1
Abnormal mental status with a Glasgow coma score < 15	1
Evidence of systemic inflammatory response syndrome (SIRS)*	1
Patient > 60 years old	1
Pleural effusion on imaging study	1
Total Score	0-2: mortality < 2% 3-4: mortality > 15%
* SIRS is present if patient has ≥ 2 of the following:	
1) Temperature < 96.8°F (36.0°C) or > 100.4°F (38.0°C)	
2) Tachycardia (HR > 90 bpm)	
3) Tachypnea (RR > 20 breaths/minute or P _a CO ₂ < 32 mmHg)	
4) Abnormal WBC (< 4,000/mm ³ or WBC > 12,000/mm ³ or > 10% bands found on blood smear)	

Skin Signs

Skin signs can be good clues to assessing severity. Severe acute pancreatitis may be accompanied by these:

- **Cullen sign**, a faint blue discoloration around the umbilicus, indicates hemoperitoneum.
- **Grey Turner sign**, a bluish-reddish-purple or greenish-brown discoloration of the flanks seen when the patient is turned to the side, results from tissue catabolism of hemoglobin from retroperitoneal blood dissecting along tissue planes.

Cullen sign and Grey Turner sign are unusual but, when seen, are indicative of severe necrotizing pancreatitis. They are characteristic, but **not** pathognomonic, for acute pancreatitis. Cullen sign is also seen with intraperitoneal bleeding (especially ruptured ectopic pregnancy), and Grey Turner sign is seen with other causes of retroperitoneal bleeding.

Organ Failure

Severe acute pancreatitis is defined by the presence of persistent organ failure (failure to resolve within 48 hours) and/or death. Organ failure can manifest as shock, respiratory failure, renal failure, and/or GI bleeding.

The systemic inflammatory response syndrome (SIRS) score is also useful for assessing severity.

SIRS is a measurement of the body's physiologic response to an undefined insult (infectious or not) and does not necessarily imply multiple organ failure.

SIRS requires ≥ 2 of the following:

- 1) Temperature < 96.8°F (36.0°C) **or** > 100.4°F (38.0°C)
- 2) Tachycardia (HR > 90 bpm)
- 3) Tachypnea (RR > 20 breaths/minute **or** P_aCO₂ < 32 mmHg)
- 4) WBC abnormal (> 12,000/μL [12 × 10⁹/L] **or** < 4,000/μL [4 × 10⁹/L] or > 10% bands)

American Gastroenterology Association (AGA) Recommendations

According to the 2018 AGA Guideline on Initial Management of Acute Pancreatitis, the following are important components of a successful management strategy:

- Early goal-directed therapy for fluid management
- Avoidance of hydroxyethyl starch fluids
- Avoidance of prophylactic antibiotics in patients with predicted severe and necrotizing pancreatitis
- Avoidance of early ERCP in patients with acute biliary pancreatitis and no cholangitis
- Initiation of early (within 24 hours) oral feeding, as tolerated
- Initiation of enteral rather than parenteral feeding in patients who are unable to feed orally
- Cholecystectomy before discharge in patients with acute biliary pancreatitis
- Brief alcohol intervention in patients admitted with acute alcoholic pancreatitis

Pancreatic necrosis is best confirmed by dynamic CT scan or MRI (at some centers). It is considered severe if ≥ 30% of the pancreas is necrotic.

After admission, check the BISAP score, monitor with a daily SIRS evaluation, and look for signs of organ failure. Worsening indicators suggest worsening severity.

Fluid / Masses in Acute Pancreatitis

Know the types of fluid collections used and masses found in acute pancreatitis.

Acute fluid collections with high amylase levels appear in up to 50% of patients within 48 hours of pain onset (Figure 14-20 on page 14-42). They usually resolve spontaneously. A sympathetic transudative left pleural effusion frequently occurs. Rarely, a diaphragmatic defect into the pleural space causes an effusion high in amylase.

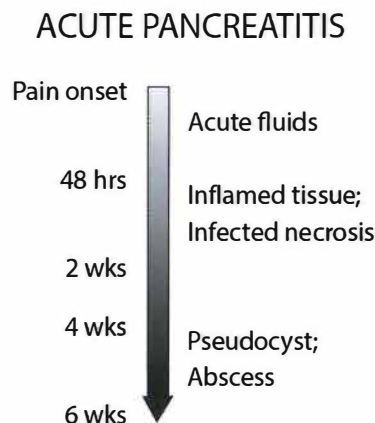


Figure 14-20: Timeline of acute pancreatitis complications

Necrotic tissue: Inflamed, edematous, necrotic pancreas occurs in the first 1–2 weeks and may simulate a pseudocyst (which typically occurs later; discussed below). Necrotic tissue can be differentiated from a pseudocyst by ultrasonography. Pancreatic necrosis is serious and may require drainage.

Infected necrosis: Suspect in patients with pancreatic or extrapancreatic necrosis who fail to improve after 7–10 days of hospitalization. Treat empirically with antibiotics or diagnose definitively by CT-guided aspiration of necrotic pancreas with Gram stain and culture. Infected pancreatic necrosis generally requires either drainage (endoscopic or CT-guided) or surgery (infrequent nowadays) within 2 weeks of the episode.

Pseudocyst: A pancreatic pseudocyst develops in < 10% of patients with acute pancreatitis. It requires a minimum of 4 weeks to develop after the acute attack. Walled-off necrosis can mimic a pseudocyst. Basically, a pseudocyst is a collection of pancreatic fluid, which, if small enough, resolves spontaneously. Pseudocysts > 5 cm may not resolve on their own. If clinically stable, use expectant management with imaging every 3–6 months to document resolution. Remember, an asymptomatic pseudocyst does not require drainage, no matter its size.

If the pseudocyst persists > 3–6 months and causes symptoms, it may require surgical, radiologic, or endoscopic drainage. Remove enlarging or symptomatic pseudocysts because they can cause serious complications—fistula, pseudoaneurysm, rupture, and hemorrhage. Rupture without hemorrhage = 15% mortality, while rupture with hemorrhage = 60% mortality! Consider this in a patient who is recovering normally and then suddenly gets worse.

Abscess: A pancreatic abscess can occur 4–6 weeks after acute severe pancreatitis with pancreatic necrosis. It may be seen as a “soap bubble” sign on upright abdominal x-ray. This is a very serious condition that can present with fever and septic shock.

Diagnose pancreatic abscess with Gram stain and culture of a CT-guided percutaneous aspirate, which is 90% accurate. This allows for immediate surgical or radiologic debridement and drainage. Empiric antibiotics may be added when pancreatic infection is suspected, but they may have poor abscess penetration.

Treatment

With supportive care, ~ 90% resolve spontaneously within a few days. Patients require NPO for a variable period of time, but typically not nasogastric suction. Provide vigorous IV crystalloid fluid hydration plus colloids as needed, especially for the first 24 hours. Lactated Ringer's is better than normal saline. One protocol is to give 20 mL/kg bolus of lactated Ringer's followed by continuous infusion at a rate of 3 mL/kg/hour for the next 6–8 hours. At 8 hours, if the patient is fluid responsive, continue 1.5 mL/kg/hour; if patient is fluid refractory, give another 20 mL/kg bolus followed by a continuous infusion at a rate of 3 mL/kg/hour. Recheck at 16 hours. Monitor for signs of adequate hydration (e.g., declines in creatinine) and, more importantly, the hematocrit. When the patient is ready to start eating, a low-fat diet is as good as starting with a clear liquid diet.

Early enteral feeds are superior to TPN in maintaining nutritional status in patients with protracted acute pancreatitis. High-protein, low-fat, semielemental formulas via nasojejunal tube are usually recommended. A 2014 meta-analysis concluded nasogastric (instead of nasojejunal) is effective and well tolerated in 90% of patients.

Give systemic antibiotics only if there is established infection or concomitant cholangitis. Watch for antibiotic-associated fungal infections.

Antibiotics are indicated for infected necrosis, which may develop 7–10 days after necrotizing pancreatitis. CT-guided fine needle aspiration (FNA) of the pancreatic fluid can be done prior to initiation of antibiotics to help guide therapy. Effective antibiotics include carbapenem, quinolones, or metronidazole. Endoscopic step-up approach with percutaneous drainage of infected necrosis is superior to using antibiotics alone in preventing complications.

Pearls of Acute Pancreatitis

If pancreatic enzymes are still abnormal after 10 days, consider other diagnoses, such as a leaking pseudocyst. With large fluid collections, consider a disrupted pancreatic duct leaking fluid. Treat with ERCP and stenting of the duct or with surgery. Recurrent acute pancreatitis with no evidence of gallstones or alcohol abuse may be due to microlithiasis, so consider an elective cholecystectomy.

In the absence of esophageal varices, gastric varices occur only in the setting of splenic vein thrombosis, which is a complication of both severe acute pancreatitis and chronic pancreatitis.

ERCP is not done acutely unless a patient has biliary sepsis. Use magnetic resonance cholangiopancreatography (MRCP) after the acute period to diagnose suspected common bile duct (CBD) stones; e.g., the bilirubin is > 2.5 mg/dL (42.76 μ mol/L) and rising, or the U/S shows a dilated common duct. Do therapeutic ERCP to treat ductal obstructions found on MRCP. For gallstone pancreatitis, perform cholecystectomy as soon as possible after the inflammation has resolved during the index admission.

In necrotizing pancreatitis, delay the cholecystectomy until fluid collection resolves.

The primary criteria for resumption of oral feeds in acute pancreatitis is that the patient is hungry and wants to eat!

Question: What conditions can cause abdominal pain with an elevated amylase? Answer: Acute pancreatitis, acute cholecystitis, intestinal infarction, diabetic ketoacidosis, perforated ulcer, salpingitis, and ectopic pregnancy. Other causes of hyperamylasemia are increased salivary amylase and macroamylasemia (a benign condition due to a low urinary excretion of amylase).

CHRONIC PANCREATITIS

In developed countries, chronic pancreatitis is commonly (60–70%) a result of chronic (typically > 10 years) alcohol ingestion. The next most frequent cause is idiopathic (30%). About 10% of cases are caused by cystic fibrosis, pancreas divisum, pancreatic tumor, hyperparathyroidism, and rare hereditary disorders (e.g., *SPINK-1* abnormality—lack of cationic trypsinogen activator inhibitor). Autoimmune pancreatitis is a more recently described, rare disorder, accounting for 1–5% of cases. (For more information, see [Autoimmune Pancreatitis \(AIP\) on page 14-44.](#))

Chronic pancreatitis has an initial, asymptomatic phase, followed by recurrent bouts of abdominal pain associated with nausea and vomiting. Late in the disease, when > 80 – 90% of the endocrine and exocrine pancreatic function is lost, patients develop **steatorrhea** and **diabetes mellitus** (DM). The fecal fat in late-stage patients is elevated—it can be > 100 g/day. More than 40 g/day is highly suggestive of chronic pancreatitis. Ultimately, 40–80% of patients with chronic pancreatitis develop diabetes, and 50–80% develop exocrine insufficiency. Chronic pancreatitis also increases the risk of pancreatic cancer 26-fold (4% lifetime risk)—but it is not enough to recommend screening.

Diagnosis

The classic diagnostic triad for chronic pancreatitis is:

- 1) Pancreatic calcification
- 2) Diabetes
- 3) Steatorrhea

But this triad is present in $< 20\%$ of cases and is usually found only during late-stage disease.

Diagnosis can be difficult, so begin evaluation with simple, noninvasive tests that detect advanced forms of chronic pancreatitis. First, get a CT of the abdomen. Any one of these is diagnostic of chronic pancreatitis:

- Pancreas is calcified.
- Pancreatic duct is dilated.
- Pancreas is atrophic.
- Pancreas is fibrotic.

Other tests useful in the diagnosis of chronic pancreatitis:

- Abdominal CT has 80–85% sensitivity and specificity and is the initial procedure of choice in most centers.
- Endoscopic ultrasound (EUS) is very sensitive and may be the best test yet, but it requires a very skilled gastroenterologist. It is the procedure of choice in some centers.
- Plain radiograph of the abdomen showing pancreatic calcification has only 30% sensitivity but is very specific.
- Abdominal U/S—although this may be lower yield due to overlying gas
- Secretin stimulation test (see below)

If results from the above tests are negative, and you still have suspicions, do either MRCP (preferred) or ERCP:

- **MRCP** uses MRI to view the bile ducts and the pancreatic duct. It is accurate in diagnosing chronic pancreatitis without the risk of causing acute pancreatitis (unlike ERCP). Since MRCP allows for visualization of the biliary tree, it can diagnose bile duct stones or other biliary diseases like primary sclerosing cholangitis (PSC). MRCP is the preferred 2nd line test, and some centers advocate secretin-stimulated MRCP.
- **ERCP** is a procedure that requires an endoscope to look at the bile ducts. It may induce acute pancreatitis (2–5%) due to a number of mechanisms. The main advantage ERCP has over MRCP is the potential for immediate endoscopic removal of calcific stones, which may be located within the duct and, hence, can be reached with the endoscope.

Both MRCP and ERCP can show large duct disease and small duct disease. With large duct disease, the pancreatic duct has stenoses and dilations, which visualize as an irregular “**chain of lakes**” (see [Figure 14-23 on page 14-49](#)).

Dilation of the CBD can be caused by chronic pancreatitis but also by pancreatic cancer (see [Pancreatic Cancer on page 14-45](#)). Either can compress the CBD as it passes through the head of the pancreas. A **double duct sign**, referring to the dilation of the CBD and pancreatic duct, is associated with a pancreatic head mass.

The secretin stimulation test is the most sensitive test for pancreatic exocrine function; however, because it is complicated, it is generally performed only in major medical centers and only when there is still a high index of suspicion after conventional testing is negative. (This does

vary—in some places with ready access, it is done before ERCP.) IV infusion of secretin (+/- cholecystokinin [CCK]) directly stimulates the pancreas. Duodenal pancreatic secretions, particularly HCO_3^- , are then measured via a duodenal catheter. CCK stimulates lipase, amylase, trypsin, and chymotrypsin, all of which can be measured. An endoscopic secretin test is also available. Fecal elastase and a fecal fat test can also be used to evaluate for malabsorption. A low fecal elastase ($< 100\text{--}200\ \mu\text{g/g}$ of stool) is consistent with exocrine dysfunction.

Complications

If there is persistent and severe abdominal pain:

- Rule out continued ethanol use.
- Rule out pseudocyst.
- Do MRCP, EUS, or MRCP with secretin to define duct anatomy.

Complications of chronic pancreatitis include gastric varices (from splenic vein thrombosis), B_{12} malabsorption, jaundice, pleural effusion, and brittle DM.

Pancreatic cancer develops in 4% of patients with chronic pancreatitis (> 20 years).

The **only** skin involvement is tender red nodules from fat necrosis; this is unusual but can simulate erythema nodosum.

The diabetes associated with chronic pancreatitis is **different** from the usual DM.

- DM occurs when $> 80\%$ of the pancreas is destroyed, and there is a decrease in production of insulin and glucagon.
- Because the pancreas produces so little glucagon, the patient is very prone to hypoglycemia. Therefore, less stringent control of hyperglycemia is recommended to decrease the chance of life-threatening hypoglycemia.
- These patients typically do **not** develop diabetic retinopathy and nephropathy. If they do get neuropathy, it is more likely secondary to alcoholism and/or malnutrition.

Treatment

Treatment includes:

- Alcohol and tobacco cessation
- Pancreatic enzyme supplementation (50,000–75,000 units of lipase/meal and 20,000–35,000 units of lipase/snack)
- Low-fat diet
- Antioxidants

Pancreatic enzymes must either have an enteric coating or be given with antacids/ H_2 blockers because gastric acid destroys enzymes. Avoid alcohol consumption. Smoking cessation is very important because smoking accelerates the development of pancreatic calcification and makes pain management more difficult.

Constant low-grade pain is worse than no pain with intermittent pain spikes. Patients sometimes require analgesia. Try to control pain with an opioid-sparing regimen to avoid dependence, but if absolutely needed, prescribe a trial of a short-term opioid with amitriptyline. No therapy yet shows proven benefit if the pain persists. Other therapeutic options include pancreatic sphincterotomy, pancreatic duct stenting, pancreatic duct stone extraction, nerve blocks, surgical duct drainage (e.g., lateral pancreaticojejunostomy, lateral pancreaticojejunostomy with localized pancreatic head resection), pylorus-preserving pancreaticoduodenectomy, and lastly total pancreatectomy.

AUTOIMMUNE PANCREATITIS (AIP)

Know AIP, even though it occurs in $< 5\%$ of cases of chronic pancreatitis. There are 2 types. **Type 1 AIP** occurs as part of a systemic IgG4-related disease. **Type 2 AIP** is usually IgG4 negative and does not have any systemic features.

What to know about AIP:

- 50% present with obstructive jaundice (simulating cancer of the pancreas).
- CT can show a mass in the head of the pancreas (again simulating cancer) or diffuse enlargement (sausage-shaped pancreas).
- There may be bile duct and pancreatic duct strictures.
- Serum IgG4 level is usually $\geq 2\times$ normal (mostly for Type 1).

Histology shows a dense lymphoplasmacytic infiltrate. Treat with prednisone at an initial dose of 40 mg/day with a taper of 5 mg/week. Add immunomodulators (e.g., azathioprine, rituximab) for patients who relapse on corticosteroids. Type 1 AIP is recognized as an IgG4 systemic disease, which, in addition to autoimmune pancreatitis, can include any or all of the following:

- Mediastinal fibrosis and adenopathy
- Retroperitoneal fibrosis
- Chronic periaortitis
- Tubulointerstitial nephritis
- IgG4-associated cholangitis

PANCREATIC CYSTS

Most pancreatic cystic lesions are asymptomatic and found incidentally with imaging studies done for other indications. These cysts can be divided into:

- Inflammatory fluid collections
- Nonneoplastic cysts
- Neoplastic cysts

Inflammatory fluid collections are not true epithelial cysts and result from complications of acute pancreatitis. This category includes acute fluid collections, necrotic collections, pseudocysts, and abscesses. (See [Fluid / Masses in Acute Pancreatitis on page 14-41](#) for further information.)

Nonneoplastic pancreatic cysts are very rare and typically asymptomatic. Although they do not require resection,

they are difficult to distinguish from pancreatic cystic neoplasms; therefore, the diagnosis is often made after surgical resection for presumed neoplasm.

The AGA suggests that pancreatic cysts with at least 2 high-risk features—such as size ≥ 3 cm, a dilated main pancreatic duct, or the presence of an associated solid component—should be examined by endoscopic ultrasound with fine needle aspiration (EUS-FNA).

It is important to classify the pancreatic cystic neoplasms because they have differing malignant potential. The types include:

- **Serous cystic tumors** (e.g., serous cystadenomas)—benign neoplasms of the pancreas that can grow large enough to cause localized obstruction. The morphologic features of microcysts and a central scar are pathognomonic for a serous cystadenoma. Follow conservatively because this type has a low rate of malignant transformation.
- **Mucinous cystic neoplasms** (i.e., mucinous cystadenoma, cystadenocarcinoma)—typically located in the body and tail of the pancreas and are defined histologically by the presence of ovarian stroma. This type has malignant potential, so surgical resection is recommended.
- **Intraductal papillary mucinous neoplasms (IPMN)**—mucin-producing intraductal epithelial neoplasms that have malignant potential, especially if the main pancreatic duct is involved. In most cases, resection is indicated.
- **Solid pseudopapillary neoplasms**—mixed solid and cystic tumors that have malignant potential. Surgically resect these lesions unless the patient's general health or advanced age make surgery inadvisable.

PANCREATIC CANCER

Pancreatic cancer is astonishingly aggressive. 80% of patients present with advanced disease. Heavy smokers have 2 $\times$ the baseline risk. Other risk factors include DM Type 2, pancreatic cancer in two 1st degree relatives, hereditary pancreatitis, and chronic pancreatitis.

Patients frequently present with some combination of jaundice, unexplained upper abdominal pain, nausea, vomiting, and/or weight loss.

Tumor location affects presenting signs and stage:

- **Head:** **Painless** jaundice tends to be the presenting sign with early-stage cancers of the head of the pancreas, due to the compression of the CBD.
- **Body and tail:** These patients are more likely to present with pain and weight loss (jaundice in only ~ 30%) and with the cancer at a much more advanced stage.

Pain and weight loss indicate advanced disease. The pain typically has a gnawing quality, is not relieved by eating, and occasionally radiates to the back.

Make the diagnosis with a multitiered approach. First, look at clinical presentation of patient. Then check serum

transaminases, alkaline phosphatase, and bilirubin. Then check abdominal U/S if the patient is jaundiced, or contrasted CT (triple-phase pancreas protocol) if the patient is not jaundiced, + ERCP/MRCP + EUS + FNA biopsy. Endoscopic ultrasound with fine needle aspiration (EUS-FNA) biopsy is preferable to CT-directed needle aspiration biopsy because EUS-FNA provides better imaging and tissue acquisition for pancreatic lesions.

CA 19-9 is the most commonly used serum marker for pancreatic adenocarcinoma. It can be checked any time a diagnosis of pancreatic adenocarcinoma is under consideration.

Treatment of pancreatic cancer: Resection is the only hope for cure.

The most common reasons for tumor unresectability:

- Distant metastases
- Local invasion of major vessel (portal vessel or superior mesenteric vein or artery)

If the patient is a surgical candidate, the mass is in the **head** of the pancreas, and the cancer appears resectable, do a pancreaticoduodenectomy (Whipple resection). Evaluate lymph nodes for evidence of metastasis.

There is a modest survival benefit (survival increased 3+ months) with chemoradiotherapy (especially with 5FU or gemcitabine).

If noninvasive workup shows that the cancer has already metastasized, **avoid** surgery—provide supportive care and consider chemotherapy. Place a stent using ERCP to palliate biliary obstruction. This is the **only** time you use ERCP for pancreatic cancer.

Postsurgical prognosis: 5-year survival is 30% if node negative and 10% if node positive.

PANCREATIC NEUROENDOCRINE TUMORS

Refer to the discussion on MEN1 (multiple endocrine neoplasia Type 1) in the **Endocrinology** section. The following are pancreatic neuroendocrine tumors.

Glucagonoma

A glucagonoma is a glucagon-secreting α -cell tumor of the pancreas that causes a unique set of clinical findings:

- Scaly, migratory necrolytic erythema
- Weight loss
- Anemia
- Diarrhea
- Persistent **hyperglycemia**
- Plasma glucagon usually $> 1,000$ pg/dL (10 ng/L)

Insulinoma

Insulinoma is a very rare, insulin-secreting β -cell tumor of the pancreas. This is covered in the **Endocrinology** section.

Gastrinoma

Gastrinomas are discussed under **Zollinger-Ellison Syndrome (ZES)** on page 14-16. 50% of gastrinomas are found in the duodenum, 24% in the pancreas. This diagnosis is likely when the serum gastrin is > 500 pg/mL (240.5 pmol/L) in a patient who is able to secrete gastric acid (e.g., not on proton pump inhibitors, no prior peptic ulcer surgery).

VIPoma

VIPomas are tumors that secrete vasoactive intestinal peptide (VIP); 2/3 occur in the pancreas, and $> 1/2$ of these are malignant. They cause a **profuse secretory diarrhea** ("pancreatic cholera"). Diagnosis: increased serum VIP level and hypokalemia. Treatment: Replace fluids and electrolytes, give somatostatin analogs (e.g., octreotide) to inhibit VIP secretion, and surgical resection.

BILIARY SYSTEM

PREVIEW | REVIEW

- What are the 3 causative factors of cholelithiasis?
- What should you investigate in the patient who has persistent right upper quadrant pain after cholecystectomy or with symptoms of cholangitis?
- What is the hallmark test for primary biliary cholangitis (PBC)? How do you confirm the diagnosis?
- What is the best proven treatment for early PBC disease? For late disease?
- A patient presents with cholestatic jaundice and a history of inflammatory bowel disease (or a history of chronic diarrhea). Which of the following do you include in your differential—PBC or primary sclerosing cholangitis (PSC)? Why?
- List the similarities and differences between PBC and PSC. These are commonly confused diseases.
- What are the alkaline phosphatase, bilirubin, hepatic copper, and anti-mitochondrial antibody test values in PBC and PSC?

CHOLELITHIASIS

Cholelithiasis (a.k.a. gallstones) is widespread (8–12% of women and 4–6% of men) and typically asymptomatic. It is **not** associated with hypercholesterolemia.

The pathophysiology of cholelithiasis involves ≥ 1 of the following 3 factors:

- 1) Abnormal bile secreted by the liver (lithogenic—supersaturated with cholesterol)
- 2) Accelerated nucleation of microcrystals to macrocrystals
- 3) Defective gallbladder emptying

Cholelithiasis is associated with obesity, oral contraceptive use, clofibrate treatment, and ileal disease or resection. 75% of gallstones are composed of radiolucent cholesterol (pure or mixed); the rest are (bile) pigment gallstones.

Clinical features of **cholesterol stones**: rapid weight loss in an obese patient, Native American, or octreotide use. These stones are prevented by ASA or ursodeoxycholic acid.

Clinical features of **pigment stones**: history of ileal resection (as in Crohn disease), sickle cell disease, or anything else that causes hemolysis (e.g., *Clonorchis sinensis*, a biliary dwelling trematode).

Symptoms: RUQ pain lasting 20–60 minutes (especially after a fatty meal). But fatty food intolerance is a very non-specific finding.

Diagnosis

To detect the presence of stones, do an U/S (90% sensitive). A normal U/S in the presence of normal bilirubin and liver enzymes is sensitive for excluding common bile duct stones. If the U/S is technically inadequate, consider MRCP or oral cholecystogram. MRCP, ERCP, and transhepatic cholangiography are the procedures typically used for diagnosing CBD obstruction.

The hepatobiliary iminodiacetic acid (HIDA) scan (cholescintigraphy) is the best test for confirming acute **cystic** duct obstruction (i.e., acute cholecystitis) by imaging of the bile duct but not the gallbladder. HIDA scan is used less often than U/S because U/S has characteristic findings for acute cholecystitis.

About 1/2 of pigment stones are radiolucent, whereas all cholesterol stones are radiolucent. Therefore, a plain abdominal x-ray is insensitive for gallstones as it is likely to miss cholesterol stones and some pigment stones.

Treatment

If the patient has gallstones and is symptomatic, do an elective cholecystectomy because 70% of these patients have recurrent symptoms if not treated.

Do **not** treat asymptomatic cholelithiasis because only 20% of patients develop symptoms within 10–20 years. Do not mistake symptoms of reflux for those of cholelithiasis, even if you incidentally find stones in the gallbladder.

Supplemental oral bile acid (ursodeoxycholic acid) can treat gallstones for those who are too ill to have surgery or refuse surgery. Lithotripsy can be effective, but few centers have the expertise necessary to perform this procedure.

Acalculous cholecystitis occurs only in seriously ill patients; e.g., major trauma, burns, after major surgeries. Make the diagnosis with U/S or CT scans showing no stones but a large, tense, often thickened gallbladder with pericholecystic fluid (or no stones on CT or U/S imaging and a HIDA scan showing cystic duct obstruction). Obtain

blood cultures. Treatment is cholecystectomy, but cholecystostomy (percutaneous drainage) or placement of a nasobiliary drain can be done if the patient is too sick for surgery. Start empiric broad spectrum antibiotics upfront.

Common Duct Stones

Alkaline phosphatase and bilirubin are generally **not** elevated in most cases of cholelithiasis because the gallstones block only the exit to the gallbladder. Consider CBD stones (a.k.a. choledocholithiasis) in a patient with increased alkaline phosphatase (> 120 U/L) and bilirubin (bilirubin > 4 mg/dL [68.42 μ mol/L]) or the postcholecystectomy patient with persistent pain. Cholelithiasis can cause **Mirizzi syndrome** (common hepatic duct obstruction due to extrinsic compression from a gallstone in the cystic duct) and gallstone ileus. CBD stones can cause gallstone pancreatitis, cholangitis, and biliary obstruction. Common duct blockage can also cause acute cholangitis.

CBD stones are removed by ERCP with possible endoscopic sphincterotomy.

CHOLESTASIS

Cholestasis (failure of bile to flow from the liver to the duodenum) can be extrahepatic/obstructive (as with CBD stones) **or** intrahepatic/hepatocellular. In both cases, substances that normally are released into bile are retained, and there is a cholestatic pattern of jaundice, with increased alkaline phosphatase and conjugated bilirubin with bilirubinuria (see [Jaundice on page 14-50](#) and [Table 14-8 on page 14-51](#)).

CHOLANGITIS

Acute cholangitis is a biliary bacterial infection occurring along with CBD blockage—usually from bile duct stone or cancer.

The triad of biliary colic (RUQ pain), fever, and jaundice (i.e., **Charcot triad**) suggests acute cholangitis. In addition to these 3 symptoms, suppurative cholangitis has mental confusion and shock (**Reynolds pentad**).

Treatment is with parenteral antibiotics, IV hydration, and urgent biliary drainage; antibiotics alone are **not** sufficient. Whenever you suspect acute cholangitis—e.g., in a postcholecystectomy patient who has a stone in the CBD—the best procedure for both diagnosis and treatment is ERCP with endoscopic sphincterotomy. Consider surgery or percutaneous transhepatic cholangiography with drain placement if ERCP is unavailable.

Emphysematous cholecystitis requires antibiotics and emergent laparotomy with cholecystectomy. In both suppurative cholangitis and emphysematous cholecystitis, the antibiotics must be effective against both gram-negative and anaerobic organisms. Do **not** use ceftriaxone—it can cause biliary sludge and has no (zero!) anaerobic coverage.

PORCELAIN GALLBLADDER

An x-ray showing a gallbladder with a calcified outline (“porcelain gallbladder”) suggests the possibility of cancer and is an indication for laparoscopic cholecystectomy.

SPHINCTER OF ODDI DYSFUNCTION (SOD)

The sphincter of Oddi is a muscular structure present at the junction of the distal CBD and pancreatic duct as they open into the second part of the duodenum. The dysfunction related to this sphincter comprises the following two syndromes:

- **Sphincter of Oddi stenosis**—The orifice is narrowed by inflammation or scarring due to processes such as infection, passage of a gallstone through the papilla, or intraoperative trauma.
- **Sphincter of Oddi dyskinesia**—functional disorder caused by periodic spasmodic contractions of the sphincter. Spasms may be influenced by local hormonal or neurologic disturbances.

For both disorders, patients may present with biliary type pain without apparent causes or recurrent episodes of acute pancreatitis. Ultimately, both conditions cause biliary or pancreatic obstruction.

Diagnosis may be suspected in the appropriate clinical setting in the presence of elevated liver function tests (LFTs) or amylase/lipase. Do a U/S of the RUQ first, focusing on the CBD diameter. This can be followed if needed by CT scan, MRCP, HIDA scan, and endoscopic U/S. In cases of sphincter of Oddi dyskinesia, manometry of the sphincter is considered the gold standard test.

Treatment is usually directed at underlying etiologies. Medical treatments aimed at reducing the tone of the sphincter by using calcium channel blockers or nitrates can be used for sphincter of Oddi dyskinesia. In some cases, a botulinum toxin injection may be used. In cases of mechanical obstruction, endoscopic or surgical sphincterotomy has proven to be successful.

PRIMARY BILIARY CHOLANGITIS (PBC)

PBC (previously known as primary biliary cirrhosis) has a **slow** onset. 95% are women, and typically they are middle aged. PBC is characterized by a nonsuppurative, progressive, destructive cholangitis. Florid duct lesions on liver biopsy are pathognomonic. However, these lesions are often absent in percutaneous liver biopsy samples, especially in early stage disease.

The bile ducts become chronically inflamed and eventually cause obstructive jaundice and liver cirrhosis.

The cause of PBC is unknown, but 70% of PBC patients have associated autoimmune diseases (e.g., Sjögren's, scleroderma, autoimmune thyroiditis, limited scleroderma). The disease **does** tend to run in families. 90% have a positive anti-mitochondrial antibody (AMA) test

(> 1:40), but degree of elevation does **not** correlate with severity of disease.

PBC patients who present with symptoms have advanced disease. Most patients present asymptotically or with fatigue and are worked up because of a high alkaline phosphatase noted on a liver enzyme screening. High levels of alkaline phosphatase occur in up to 95% of patients with PBC. If they have symptoms, patients initially complain of **itching**—first in the palms and soles and later throughout the body.

Later, patients develop jaundice (Figure 14-21), hyperpigmentation, inflammatory arthropathy, keratoconjunctivitis and/or xerostomia, and accelerated osteoporosis. Patients can develop xanthomas and xanthelasmata (Figure 14-22) from associated hypercholesterolemia, but this does **not** convey increased risk of coronary artery disease (i.e., it is not an atherosclerogenic lipid pattern). Rarely, PBC patients can develop hepatocellular carcinoma.



Figure 14-21: Jaundice in primary biliary cholangitis
Source: CDC



Figure 14-22: Xanthelasmata
Source: Klaus D. Peter

PBC is indolent but relentlessly progressive. Symptomatic patients previously had a median survival of 7 years, and asymptomatic patients 10–16 years. Survival has improved significantly in recent years, as patients are diagnosed earlier and there is more widespread use of ursodiol (ursodeoxycholate—a synthetic bile acid).

When the bilirubin increases to > 2 mg/dL (34.21 $\mu\text{mol/L}$), the disease accelerates. Most die within 2 years after the bilirubin reaches 10 mg/dL (171.04 $\mu\text{mol/L}$) unless the patient undergoes liver transplantation.

Diagnosis

The AMA test is the hallmark test for PBC. Even so, it is **not** a good indicator of the severity of PBC. The AMA test is **occasionally** positive in both autoimmune hepatitis and drug-induced chronic hepatitis; a high titer in a patient with autoimmune hepatitis suggests an overlap syndrome (Table 14-6).

Table 14-6: Serologic Markers in Primary Biliary Cholangitis (PBC) and Chronic Hepatitis

	PBC	Drug-Induced Chronic Hepatitis	Autoimmune Chronic Hepatitis
Anti-Mitochondrial Ab (AMA)	90–95% positive	Negative	Occasionally positive*
Anti-Smooth Muscle Ab (anti-SMA)	Negative	Negative	Positive
Anti-Nuclear Ab (ANA)	Usually negative	Positive	Positive

* In low titers; high titer suggests overlap syndrome.

Confirm the diagnosis with a liver biopsy, which may show granulomas (florid duct lesions); often findings are nonspecific. PBC patients also have a high hepatic copper level (as do patients with primary sclerosing cholangitis and Wilson disease).

Treatment

Ursodiol (ursodeoxycholate) 13–15 mg/kg/day is the best proven treatment available for early PBC. It improves LFTs, decreases symptoms, and slows progression of the disease. Patients who have a biochemical response to ursodiol (defined as a decrease in alkaline phosphatase, AST, and/or bilirubin) at 1 year have dramatic slowing of the progression.

Additionally, symptomatic treatment includes:

- Pruritus: cholestyramine
- Osteomalacia: vitamin D and Ca^{2+}
- Malabsorption: decreased dietary fat

Treatment has no effect in late disease. For late disease, liver transplantation improves survival. PBC is one of the most common indications for liver transplantation (hepatitis C is the most common). The **AAAABCs** of PBC are: **anti**mitochondrial **antibody** **a**ttack **i**ncreases **a**lkaline **p**hosphatase and causes **o**bststructive **b**iliary lesions and **l**iver **c**irrhosis.

PRIMARY SCLEROSING CHOLANGITIS (PSC)

Like primary biliary cholangitis (PBC), primary sclerosing cholangitis (PSC) is also indolent. It primarily occurs in males (70%) with a median age of 45 years.

PSC is strongly associated with colitis. It is mainly seen in ulcerative colitis (UC)—up to 75% of PSC patients have UC—but can occur in patients with Crohn colitis as well. Incidence of PSC has no relationship to the severity of colitis.

PSC occurs in 5% of UC patients and ~ 2% of Crohn disease (CD) patients. Inflammatory bowel disease (IBD) may precede the diagnosis of PSC, but not necessarily; so, order a colonoscopy for all PSC patients to check for UC/CD. Conversely, screen UC patients who have a persistent, $\geq 2\times$ increase in alkaline phosphatase for PSC.

The cause of PSC is unknown. Patients develop inflammation and sclerosis of the entire biliary tract (intra- and extrahepatic), leading to obstructive jaundice and, eventually, cirrhosis.

Patients are initially asymptomatic but, with advanced disease, develop weakness and fatigue, abdominal pain, itching, and jaundice.

Bilirubin and alkaline phosphatase levels are usually elevated (cholestatic pattern). Bilirubin can fluctuate depending on the degree of bile duct blockage. There is an elevated hepatic copper level (as in primary biliary cholangitis and Wilson disease), but AMA is **negative**. The total protein level gives an idea of how much the disease has affected liver function.

Of patients with PSC, 8–15% develop cholangiocarcinoma. Cholangiocarcinoma in PSC can be seen on MRCP or ERCP as a dominant stricture at its early stage. 1/3 of patients with PSC have cholangiocarcinoma at the time of PSC diagnosis! Suspect cholangiocarcinoma if symptoms of PSC abruptly worsen. CA 19-9 is elevated in 80% of patients with cholangiocarcinoma. This is diagnosed with biliary cytology brushings or biopsies during ERCP. Treatment options include chemotherapy, radiation, and liver transplant.

Diagnosis

Diagnosis of PSC is made with MRCP, ERCP, or transhepatic cholangiography. These reveal irregularly narrowed bile ducts with small bile duct ballooning just prior to obstructions, producing the typical “beaded” appearance (Figure 14-23). With ERCP, if a dominant stricture exists, it can be dilated. Liver biopsy shows “onion skin” fibrosis in portal triads. Patients with PSC are also often perinuclear antineutrophil cytoplasmic antibody (p-ANCA) positive.

In small duct PSC, the extra- and intrahepatic biliary system may be nondiagnostic, but liver biopsy abnormalities establish the diagnosis.

You must rule out secondary causes of sclerosing cholangitis. These include bacterial cholangitis (from stones or bile duct stricture), atypical anatomy (congenital or

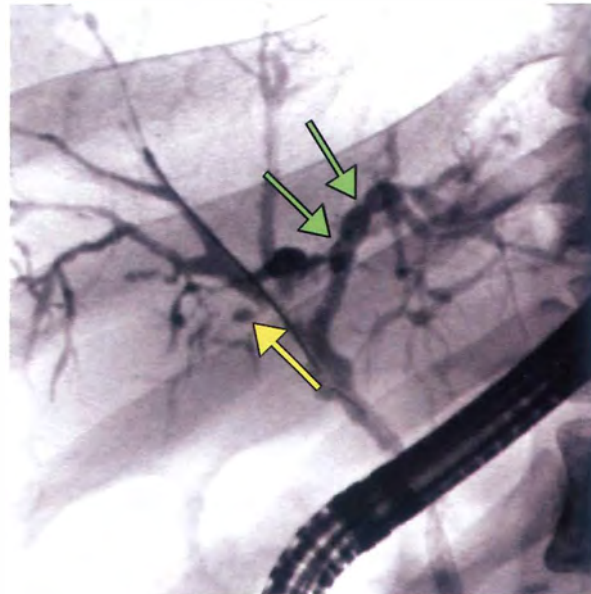


Figure 14-23: Primary sclerosing cholangitis. Green arrows show strictures of biliary tree and the yellow arrow shows the outpouchings of dilated bile ducts.

previous surgery), bile duct neoplasms, IgG4-related disease (exclude with an IgG4 antibody test), and AIDS-associated cholangiopathy.

Treatment

The only sure treatment for PSC is liver transplantation. Colectomy cures comorbid ulcerative colitis but does not alter the course of PSC. Unlike in PBC, ursodeoxycholic acid is ineffective in PSC.

Remember: When a patient presents with jaundice and increased alkaline phosphatase and has a history of chronic diarrhea or IBD, **especially UC**, rule out PSC with MRCP or ERCP! (Look for PSC because PBC has no correlation with diarrhea or IBD.)

Again, for PSC, remember these: sclerosing cholangitis, colitis, high cholestatic bilirubin and alkaline phosphatase levels, negative AMA, cirrhosis, and liver failure. Look for abnormal magnetic or endoscopic retrograde cholangiopancreatography (MRCP, ERCP).

PBC vs. PSC

PBC and PSC are often confused because they have similar names, affect the bile tracts, and have high alkaline phosphatase. Both eventually cause obstructive jaundice and cirrhosis.

To help remember the differences, drop the abbreviations and think:

- Biliary cholangitis: 55-year-old woman with fatigue and pruritus; AMA+
- Sclerosing cholangitis: 45-year-old man with IBD (especially UC)

Also review Table 14-7 on page 14-50. Note the similarities in some lab results.

Table 14-7: Primary Biliary Cholangitis (PBC) vs. Primary Sclerosing Cholangitis (PSC)

	PBC	PSC
Sex	Female	Male
Age	Middle age	Any age
IBD	No	Yes
Cancer	Rare (hepatocellular carcinoma)	8–15% lifetime risk of cholangiocarcinoma
Treatment	Ursodiol (early stage) Liver transplantation (late stage)	Liver transplantation
Alkaline Phosphatase	High	High
Bilirubin	Elevates with disease progression	Elevates with disease progression
Hepatic Copper	High	High
Anti-mitochondrial Antibody (AMA)	High	Usually negative
Hyperlipidemia	Present	Variable

LIVER

EVALUATION OF ABNORMAL LIVER BIOCHEMICAL TESTS

Increased Transaminases

Confirm an abnormal laboratory value before ordering follow-up tests. To confirm, order a full set of liver biochemical tests including alkaline phosphatase, total and direct bilirubin, albumin, PT, and CBC. If the transaminases are still elevated, order more specific tests for hepatitis A, B, and C—and tests for hemochromatosis with iron studies and ferritin level. Transaminase levels in the 1,000s U/L range may be from liver ischemia, HSV or CMV hepatitis, or acetaminophen/drug toxicity. Remember autoimmune hepatitis (AIH) when there are concurrent elevations in anti-nuclear antibody (ANA), anti-smooth muscle antibody (anti-SMA), and IgG levels.

Increased Alkaline Phosphatase

Remember that alkaline phosphatase comes from **liver** and **bones**. γ -glutamyl transferase (GGT) typically rises in parallel with alkaline phosphatase from the liver; check in cases of increased alkaline phosphatase with normal bilirubin and transaminases. Generally, the next test is abdominal U/S to look for dilated biliary ducts or metastatic liver lesions. In appropriate patients, also order AMA test to screen for PBC.

Cholestasis and Hyperbilirubinemia

Cholestasis refers to any condition where the bile cannot flow from the liver to the duodenum and can be due to either a **mechanical** disorder, such as blockage of a bile duct, or a number of **metabolic** disorders. Hyperbilirubinemia can be due to conditions involving the production, handling, or excretion of bilirubin. Investigation of the specific etiology of hyperbilirubinemia is necessary. The liver conditions that result in cholestasis or hyperbilirubinemia are discussed as part of those diagnoses (see [Cholestasis on page 14-47](#) and [Hereditary Liver Disease on page 14-65](#)). Hyperbilirubinemia can lead to the physical manifestation of jaundice, which is discussed next.

JAUNDICE

PREVIEW | REVIEW

- Which causes of hyperbilirubinemia also lead to bilirubinuria?
- What is the usual cause of jaundice in persons < 30 years of age? 40–60? 60–80?
- Know [Table 14-8](#).

Jaundice (a.k.a. icterus) is a yellowish pigmentation of the skin, the conjunctival membranes over the sclerae (whites of the eyes), and other mucous membranes caused by hyperbilirubinemia (increased levels of bilirubin in the blood).

Unconjugated bilirubin is conjugated in the liver and enters the biliary system. Overproduction (from heme breakdown) or defects in uptake or conjugation causes unconjugated hyperbilirubinemia. Problems with the hepatobiliary system (e.g., cholestasis) result in conjugated hyperbilirubinemia.

Unconjugated bilirubin is tightly bound to albumin, and this complex is too large to pass through the glomerulus. Conjugated bilirubin is less tightly bound to albumin, and the unbound portion easily passes into the urine. So, **bilirubinuria** is seen only with **conjugated** hyperbilirubinemia. Because bilirubin is conjugated in the liver, bilirubinuria is an indication of cholestasis.

The differential diagnosis of jaundice includes:

- With unconjugated hyperbilirubinemia:
 - Viral hepatitis
 - Drug-induced jaundice
 - Alcoholic liver disease
 - Chronic hepatitis
 - Sickle cell disease
 - Gilbert syndrome
- With conjugated hyperbilirubinemia:
 - Gallstones and complications
 - Pancreatic cancer, causing CBD blockage

- Primary biliary cholangitis (PBC)
- Primary sclerosing cholangitis (PSC)
- Ascariasis (roundworm infection)

The majority of jaundice cases are caused by acute viral hepatitis, chronic cirrhosis, or obstruction by a CBD stone or pancreatic cancer. These 3 causes are strongly associated with certain age groups:

- Acute viral hepatitis is the most common cause (85–90%) in those < 30 years of age.
- Chronic cirrhosis is the usual cause (50–70%) in those 40–60 years of age.
- Obstructive jaundice (common duct stone or pancreatic cancer) is the usual cause (80%) in those 60–80 years of age without other risk factors. (See also [Pancreatic Cancer on page 14-45](#).)

If the patient recently arrived from outside the United States, consider ascariasis—especially in a patient with eosinophilia. (See the [Infectious Disease](#) section for more on ascariasis.)

For more on hyperbilirubinemia, see [Hereditary Liver Disease on page 14-65](#).

Jaundice workup consists of:

- a careful history,
- detailed physical exam,
- U/S, and
- liver function tests (LFTs; [Table 14-8](#)).

U/S findings determine the next step in evaluation:

- Dilated CBD and stones: ERCP
- Dilated CBD and no stones: CT (think pancreatic cancer) or EUS
- Dilated intrahepatic ducts: CT
- Dilated ducts and testing to exclude PSC: MRCP
- If no dilated ducts: liver biopsy

HEPATITIS NOTES

Know the following regarding AST (aspartate aminotransferase) and ALT (alanine aminotransferase):

- ALT is more liver specific than AST, think of “L-L” (ALT-Liver).
- With alcoholic hepatitis, the AST:ALT ratio is about 3:1 because the alcohol damages mitochondria, which release AST. Mitochondrial damage is less liver specific. In alcoholic hepatitis or any alcoholic liver disease, AST and ALT do not exceed 200–300 U/L (3.34–5.01 μ kat/L); if they do, there is another cause for elevation.
- With viral hepatitis, generally ALT > AST because its toxicity is more liver specific.
- Nonalcoholic fatty liver disease (NAFLD) is also more liver specific and has an AST:ALT ratio < 1.
- Acute viral hepatitis has histologic characteristics of diffuse liver cell injury and swelling, increased macrophages, accelerated apoptosis (the normal programmed cell death is accelerated by viral hepatitis), and inflammatory periportal infiltrates (mostly lymphocytic). (LFT results for acute viral hepatitis are in [Table 14-8](#).)

[Table 14-9 on page 14-52](#) is a review of serologic testing for viral hepatitis. **Know these!**

Chronic viral hepatitis has histologic characteristics of interface hepatitis (formerly known as piecemeal necrosis) and fibrosis.

HEPATITIS A

PREVIEW | REVIEW

- With which coinfections can hepatitis A become fulminant?

Table 14-8: Workup of Jaundice

	Acute Viral Hepatitis	Chronic Cirrhosis	Obstructive: Common Duct Stone or Pancreatic Cancer
Bilirubin (mg/dL [μ mol/L])	< 20 (342.08)	< 20 (342.08) unless impaired renal function	< 20 (342.08)
AST and ALT (U/L [μ kat/L])	> 400 (6.68); generally ALT > AST	< 400 (6.68)	< 400 (6.68) usually
Alkaline Phosphatase	NI to 2 $\times$ ULN	NI to 4 $\times$ ULN	4–10 $\times$ ULN
Albumin/Globulin	NI/NI	Low/High	Usually NI/NI
PT/aPTT	NI/NI usually	High/High	Usually NI/NI
Cholesterol	NI	NI to low	NI to high
Serologies (Hepatitis A, B, C; EBV; CMV)	May be diagnostic	Excludes acute viral etiology if needed	Excludes acute viral etiology if needed
Abdominal U/S	NI	May be helpful	93/95 sensitivity and specificity if bilirubin > 10 mg/dL (171.04 μ mol/L) $\times$ 10 days
ALT = alanine transferase AST = aspartate aminotransferase PT = prothrombin time aPTT = activated partial thromboplastin time NI = normal ULN = upper limit of normal			

Table 14-9: Viral Hepatitis — Serological Tests

		Anti-HAV IgM	Anti-HAV IgG	HBsAg	Anti-HBs	Anti-HBc Total	Anti-HBc IgM	HBeAg	HBV DNA	HBeAb	Anti-HDV
Hepatitis A (HAV)	Acute HAV	+	–	–	–	–	–	–	–	–	–
	Previous HAV	–	+	–	–	–	–	–	–	–	–
Hepatitis B (HBV)*	Acute HBV	–	–	+ Early	–	–	+	+	+	–	–
	Acute HBV—Window	–	–	–	–	–	+	–	–	–	–
	Chronic Active HBV	–	–	+	–	+	–	Usually +	+	–	–
	Remote HBV (Immune)	–	–	–	+	+	–	–	–	+	–
	Vaccinated (Immune)	–	–	–	+	–	–	–	–	–	–
Hepatitis D (HDV)	Acute HDV (w/ Acute HBV)	–	–	+ Early	–	–	+	+	+	–	+
	Acute HDV (w/ chronic active hepatitis [CAH])	–	–	+	Rarely +	+	–	Usually +	+	–	+

* See Table 14-10 for additional possible test results for hepatitis B.

Hepatitis A is an RNA virus. It is easily transmitted by the fecal-oral route—commonly via food or water. It can also be sexually transmitted. There is **no** transplacental transmission! There are **no** carrier or persistent states, although, occasionally patients get prolonged cholestasis (with increased bilirubin and alkaline phosphatase) for up to 4 months. Incubation period is 15–50 days (Figure 14-24).

Symptoms are unusual in children and very common in adults (70%). Complications are rare; there is ~ 1% chance of fulminant hepatitis. Immunoglobulin (IG) is good prophylaxis **only** against hepatitis A virus (HAV); use hepatitis B immunoglobulin [HBIG] for hepatitis B virus (HBV).

Diagnosis of acute infection: high titers of anti-HAV IgM in serum. (IgG indicates only a previous infection.)

The incidence of hepatitis A has fallen dramatically due to immunization. Inactivated hepatitis A (HepA) vaccine (Havrix and Vaxta) is recommended in children > 1 year of age and is given as 2 doses, 6+ months apart. Virtually all of those completing the series develop protective antibodies (anti-HAV IgG), which persist for at least 20 years after

vaccination. If completion of the 2-dose series is delayed, there is **no** need to start the series over again.

Indications for HepA vaccine:

- Men who have sex with men
- IV drug use
- Chronic liver disease
- Chronic hepatitis B or hepatitis C; if these patients get hepatitis A, it can be fulminant.
- Clotting factor disorders
- Travel to high-risk countries
- All children, starting at 1 year of age
- Close personal contact with international adoptee from an endemic country during the first 60 days of arrival in the U.S.
- Postexposure prophylaxis (for healthy individuals > 12 months of age; given along with IG in certain other circumstances) should be given to close contacts up to 2 weeks after exposure.

Note: Onset of jaundice after exposure is 3 weeks with hepatitis A and 3 months with hepatitis B—an important diagnostic clue!

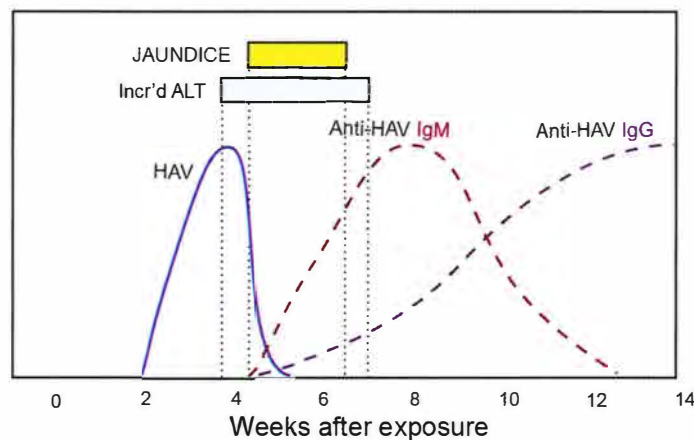


Figure 14-24: Hepatitis A serology timeline

HEPATITIS B

PREVIEW | REVIEW

- Know Figure 14-25 on page 14-54 and Table 14-10.
- Regarding the various hepatitis B antigens (HBsAg, HBcAg, and HBeAg) and associated antibodies: What is the best marker for past infection? What is the best marker for infectivity?

- What antibody test is positive during the “window” period of hepatitis B virus infection?
- Polyarteritis nodosa is associated with which hepatitis virus?
- Are hepatitis B (HepB) vaccines safe for pregnant patients?
- How do you confirm that a HepB vaccine was immunogenic?

HBV is the only hepatitis virus composed of DNA. The incubation period is 1–6 months. It is transmitted by contaminated blood products and infected body fluids.

The 5 main serologic markers in hepatitis B are listed below (see also Table 14-9 and Table 14-10):

- 1) HBsAg (hepatitis B surface antigen)
- 2) HBsAb (hepatitis B surface antibodies; anti-hepatitis B surface antigen). One test measuring total antibody
- 3) HBcAb (hepatitis B core antibodies; anti-hepatitis B core antigen). Two tests available, IgM and total antibody
- 4) HBeAg (hepatitis B e-antigen; a small polypeptide that exists in a free form in the serum of individuals during the early phase of hepatitis B infection)
- 5) HBeAb (hepatitis B e antibodies; anti-hepatitis B e-antigen) One test measuring total antibody

In this section, as you’ll find in the “real world,” we use the “anti-” and “Ab” terminology interchangeably; e.g., anti-HBc = HBcAb.

HBsAg: There are 3 HBsAg+ proteins seen in the serum of patients with hepatitis B: 1 large, double-shelled 42-nm particle that is the intact virion and two smaller 22-nm spherical or rod-shaped protein particles that outnumber the large particle by up to 1,000:1! These 22-nm HBsAg+ particles are thought to be excess viral coat protein. HBsAg+ means you are producing hepatitis B virus (HBV).

HBsAb: Finding HBsAb in the serum indicates past exposure to either hepatitis B virions or to the vaccine. Usually

it indicates **immunity**. This test measures total antibody, not a specific type.

HBcAg is the inner shell protein of the 42-nm virion. HBcAg is expressed in hepatocytes but is not detectable in serum. Because antibody to HBcAg appears early in the disease (initially IgM, then IgG) and the HBcAb IgG persists for life, HBcAb IgG is the best marker for previous exposure to HBV. However, it does **not** distinguish between active and resolved infection. Note: there are 2 tests available, one for IgM and the other for **total** HBcAb; once IgM has disappeared, all the remaining antibody is IgG.

HBeAg is a soluble protein made from the same gene as HBcAg, but, unlike HBcAg, HBeAg **is** secreted from the hepatocytes and circulated in the serum. HBeAg correlates with the quantity of intact virus and, therefore, with **infectivity** and liver inflammation.

HBeAb appears several weeks after the illness. Detecting HBsAg **and** HBeAg indicates active virions and high infectivity (more so than HBsAg+ and HBeAg–). This test measures total antibody, not a specific type.

Confused? Reread the highlighted text and remember:

- **HBsAg+** means a patient is making HBV. Levels may be low or very high. It can be acute or chronic.
- **HBsAb+** almost always means the patient has resolved previous hepatitis B infection, or if this is the only marker (specifically no IgG HBcAb), then the patient was vaccinated. The patient is usually **immune** to reinfection.
- **HBeAg+** means the patient is **highly infectious** and actively making HBV.

Once infected, the 1st marker detectable in the serum is the antigen HBsAg. This is followed by the appearance of antibody to the core antigen (anti-HBc IgM). After HBsAg becomes undetectable, there is a period of weeks to months (typically from 24th to 32nd week) before the HBsAb antibody becomes detectable. This is called the **window**, and you must perform an HBcAb IgM test during this period to detect acute hepatitis B (Figure 14-25 on page 14-54 and Table 14-10).

Table 14-10: Interpretation of Hepatitis B Tests

HBsAg	HBcAb	HBsAb	Interpretation
+	–	–	Acute infection
+	+	–	3 possibilities: • Acute infection (HBcAb IgM) • Chronic hepatitis B (high ALT, HBcAb IgG) • Inactive carrier (normal enzymes, HBcAb IgG)
–	–	+	Immunized
–	+	+	Remote infection
–	+	–	3 possibilities: • Window disease • Remote infection • False positive
+	+	+	> 1 infection; e.g., IV drug user with HBV and HDV or renal dialysis patient with both acute and chronic hepatitis B (infected with different strains of HBV)

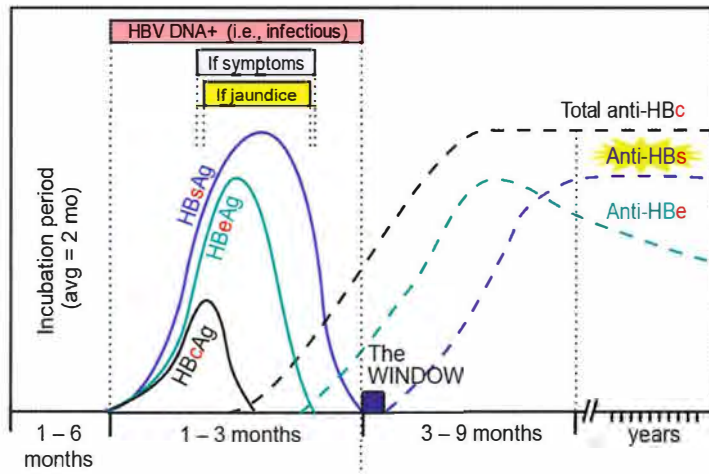


Figure 14-25: Acute hepatitis B serology timeline

Hepatitis B is associated with polyarteritis nodosa (PAN). The surface antigen is found in 20–30% of these patients. It appears that the hepatitis B infection precipitates an autoimmune reaction resulting in PAN.

Acute Hepatitis B

There are about 20,000 estimated new cases of hepatitis B each year in the U.S.

Clinical: First, there are prodromal constitutional symptoms, which typically resolve at the time jaundice becomes apparent. Occasionally (10–15%), the prodromal symptoms resemble serum sickness: fever, arthritis, urticaria, and angioedema. This seems to be caused by circulating immune complexes (especially HBsAg-HBsAb immune complex), which activate the complement system. With the onset of jaundice, the patient generally feels much better but can have liver swelling and tenderness as well as cholestatic symptoms.

Removal of HBV is T-cell mediated, and the only purpose of HBsAb is to prevent reinfection.

HBIG provides partial protection against hepatitis B when given to patients who have had exposure to hepatitis B and do not have immunity to it.

HBIG is partially effective both as short-term prophylaxis and when given in early infection.

Hepatitis B (HepB) Vaccines

The 2 HepB vaccines are composed of HBsAg. They are equally effective and are safe for pregnant patients. (For more on vaccines during pregnancy, see the [Women's and Men's Health](#) section.) It is best if the HepB vaccine

is given **before** the patient is exposed to HBV. 95% of immunocompetent patients develop antibodies, whereas only about 50% of dialysis patients do (even though dialysis patients also are given a much higher dose of the vaccine).

To ensure effectiveness after the course of vaccine is given, check for HBsAb, which is produced in response to the vaccine. There is **no** HBcAb produced in response to the HepB vaccine.

Indications for HepB vaccine in adults include persons engaging in high-risk sexual behavior, those with chronic liver disease, persons with HIV infection, health care personnel, and dialysis patients. There is universal preschool vaccination in the U.S.

Hepatitis B Treatment Scenarios

Scenarios:

- If an asymptomatic patient has HBsAg in the serum, it means either the patient is a carrier or the patient has early hepatitis B—so initial action is only to follow closely. (Once the patient is infected, neither vaccine nor HBIG helps.)
- Give both HBIG and a HepB vaccine to a newborn of a mother with hepatitis B. There is a 5–10% transplacental transmission of HBV.
- Give HBIG followed by a HepB vaccine to sexual contacts of, and infants cared for by, an individual with acute hepatitis B infection.

Several months after an episode of HBV infection, check for disappearance of HBsAg and HBV DNA to ensure that chronic infection has not developed.

Chronic Hepatitis B

There are ~ 2 million estimated cases of chronic hepatitis B in the U.S. The likelihood of developing chronic hepatitis B is **inversely** related to age. Chronic hepatitis B

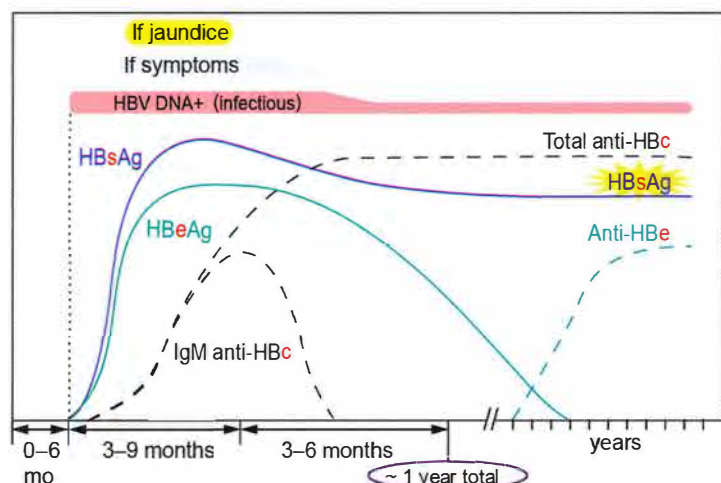


Figure 14-26: Chronic hepatitis B serology timeline

(when virus remains > 6 months) occurs in 90% of infants infected at birth, 25–50% of children infected at 1–5 years of age, and 5% of those infected as older children and adults. Note that comorbid conditions (e.g., hemochromatosis, AIDS/HIV, alcoholism) worsen the course and response to treatment. Less than 1% of patients with hepatitis B develop fulminant hepatitis, but 5–7% develop chronic carrier states. Figure 14-26 illustrates the timeline for chronic hepatitis B.

There are 2 types of hepatitis B carrier states:

- 1) Inactive carrier state (asymptomatic with normal liver enzymes)
- 2) Chronic active hepatitis B (abnormal enzymes)

A liver biopsy is usually required to confirm the diagnosis of chronic hepatitis B.

Patients with inactive carrier states can develop severe exacerbations of hepatitis B if they become immunocompromised. For example, what drug is given in addition to her chemotherapy if a woman with breast cancer is also a hepatitis B inactive carrier? Antiviral therapy with tenofovir or entecavir should be given to blunt viral replication.

Chronic hepatitis B is a serious illness. It often progresses to cirrhosis and is strongly associated with hepatocellular carcinoma (HCC; 2% conversion per year). Lifetime risk for HCC is 20%.

Screen for HCC every 6 months with abdominal U/S irrespective of cirrhosis. Helical CT or MRI can also be used (more sensitive but much more expensive).

α -Fetoprotein (AFP) is sometimes used in conjunction with liver U/S for HCC surveillance (guidelines are equivocal). AFP alone has limited sensitivity. Liver U/S is the primary screening modality; however, combining it with AFP testing increases the sensitivity from 78 to 97%.

Treatment of Chronic Active Hepatitis B

Use HBV DNA, ALT, HBeAg, and degree of cirrhosis to determine when to treat.

Treatment is generally recommended for those with HBV DNA > 20,000 U/mL and ALT > 2 $\times$ ULN. Specifically:

- Treatment is started immediately for HBeAg-negative patients with ALT > 2 $\times$ ULN and with HBV DNA > 2,000 U/mL.
- Treatment is also started immediately for HBeAg-positive patients if ALT > 2 $\times$ ULN and with HBV DNA > 20,000 U/mL.
- Delay treatment for 3–6 months in newly diagnosed HBeAg-positive patients with compensated liver disease to see if seroconversion takes place.

If cirrhosis is present, initiate treatment at lower levels of HBV DNA:

- Treat compensated cirrhosis when HBV DNA > 2,000 U/mL
- Treat decompensated cirrhosis when HBV DNA > 200 U/mL

Table 14-11 shows the treatment options for chronic active hepatitis B. Lamivudine used to be a main treatment option, but it is less desirable now because the other drugs shown in the table have a lower rate of drug resistance.

The current primary treatment is tenofovir or entecavir for most patients, or pegylated interferon- α (IFN- α) for younger patients who do not wish to be on long-term treatment. Pegylated IFN- α is given at a dose of 180 mcg once weekly for 48 weeks.

Liver transplantation is the only treatment for end-stage liver disease. HBV recurs in the transplanted liver, but an antiviral treatment program can help.

HEPATITIS C

PREVIEW | REVIEW

- Which test confirms that a previous hepatitis C infection did not become chronic?
- Mixed cryoglobulinemia is strongly associated with which infection? How does it present?

Table 14-11: Treatment of Chronic Active Hepatitis B

Treatment	Benefits	Disadvantages	Used for
Tenofovir	Resistance is rare Drug of choice for lamivudine-resistant HBV	Limited data about use in adefovir-resistant disease	Primary treatment
Entecavir	Low drug resistance Potent antiviral	Not for lamivudine-resistant HBV	Primary treatment
Telbivudine	Slightly more potent than adefovir and entecavir	Same resistance profile as lamivudine	Not used much
Adefovir	Active against lamivudine-resistant HBV	Low viral suppression	Lamivudine-resistant HBV
Pegylated interferon- α (IFN- α)	Limited duration of therapy 35% complete remission Potent No resistance	Side effects may be severe Contraindicated in decompensated liver disease	Primary treatment for young patients who do not wish to be on long-term treatment
Lamivudine	Lower cost Extensive clinical experience	High rate of drug resistance	Patients coinfecting with HIV

Know this topic well! Hepatitis C is a single-strand RNA virus. It is one of the most common liver diseases in the U.S., with an estimated 30,000 new cases each year. It is 2nd in prevalence only to NAFLD (see [Nonalcoholic Fatty Liver Disease \(NAFLD\)](#) on page 14-60). Hepatitis C has bloodborne transmission and was the cause of 90% of transfusion-associated hepatitis prior to the early 1990s. Since then, especially with the 2nd generation hepatitis C virus (HCV) Ab assays, the incidence of transfusion-related hepatitis has become very rare.

Hepatitis C genotypes are 1a, 1b, 2, 3, 4, 5, and 6. The genotype influences response to treatment. Most HCV infections in the U.S. (> 70%) are genotype 1, which happens to be **less** responsive to treatment than the other genotypes. Screening for HCV is recommended in the following high-risk populations:

- Patients born between 1945 and 1965 and living in the U.S.
- Immigration from a high-prevalence region
- Illicit IV drug and intranasal cocaine users
- Past or present incarceration
- Blood transfusion/transplant recipients before 1992
- Men who have sex with men
- Sexual partners of HCV-positive individuals
- HIV-infected persons
- Needlestick injuries or mucosal exposure to HCV-infected blood
- Percutaneous exposure in an unregulated setting (including unregulated tattoos)
- Past or present chronic hemodialysis
- Children born to HCV-infected mothers

The hepatitis C “rule of 2s”:

- 2% of U.S. population
- 2% risk of needlestick transmission (though some say ≥ 5%)
- 2% risk of neonatal transmission
- 2% risk of spousal transmission
- 2% of cirrhotic patients with hepatitis C develop HCC each year

Serology and Hepatitis C

In a person positive for HCV Ab, check for active virus with HCV RNA. This is necessary because the HCV Ab does **not** confer immunity (unlike the HBV Ab, which does confer immunity to hepatitis B).

Within 2–4 months after infection with or diagnosis of hepatitis C, recheck for loss of HCV RNA (using polymerase chain reaction [PCR]) to ensure the disease has not become chronic.

Chronic Hepatitis C

Whereas < 5% of adults with hepatitis B develop chronic disease, 70–80% of acute HCV infections become chronic! There are about 3 million cases of chronic hepatitis C in the U.S.

Hepatitis B has high virus counts, whereas hepatitis C has lower virus counts, measured by hepatitis C viral RNA level (U/mL). These low virus counts are consistent with the more insidious nature of hepatitis C:

- Only 25% of acute infections are symptomatic.
- HCV infection has a high likelihood of becoming chronic.
- The chronic form is relatively benign. (25% are only carriers; 50% have no symptoms but have abnormal LFTs; 25% have chronic active disease with symptoms.)
- Low rates of sexual transmission are seen in monogamous couples—2% after 10–20 years. This is low, but it does occur, so safe sex **is** required! Sexual transmission increases with multiple sexual partners.
- Needlestick transmission from a known infected patient is 2–6%.
- Transplacental infection can occur (~ 2%), although this is less of a risk than for hepatitis B (5–10%).

About 25% of those with chronic hepatitis C get end-stage cirrhosis after 20–25 years. 1–4% of patients with cirrhosis develop **hepatocellular cancer** (HCC) each year (similar to chronic active hepatitis B).

Per the 2017 American Association for the Study of Liver Diseases (AASLD) HCC guidelines: Screen patients with chronic hepatitis C for HCC every 6 months with abdominal U/S (as with chronic hepatitis B and alcoholic cirrhosis). Helical CT or MRI can also be used (more sensitive but much more expensive).

Chronic HCV infection has become the #1 reason for liver transplantation in the U.S.

Vaccinate all patients with chronic hepatitis C against hepatitis A and B.

Mixed cryoglobulinemia is **strongly** associated with chronic HCV infection (55% of those with chronic hepatitis C). It presents as a small vessel (leukocytoclastic) vasculitis with a rash consisting of palpable purpura or “crops of purple papules.” Mixed cryoglobulinemia is far less common in patients with chronic hepatitis B (15%), other chronic liver diseases (30%), HIV, and connective tissue diseases.

Treatment of Chronic Hepatitis C

Treatment for hepatitis C is constantly evolving. For the most recent recommendations, go to [hcvguidelines.com](#). These guidelines were released jointly by the AASLD and the Infectious Diseases Society of America (IDSA) in 2014.

The cornerstone of treatment is antiviral therapy. The goal is to eradicate HCV RNA, which is defined as undetectable RNA levels 12 weeks after completing the treatment. There are several direct-acting antiviral (DAA) agents on the market, all of which are well-tolerated all-oral regimens. These are now considered the treatment of choice. The correct regimen selection is different for different HCV genotypes. Some common regimens include ledipasvir/sofosbuvir, sofosbuvir/velpatasvir, and glecaprevir/pibrentasvir.

Extrahepatic Disease with Hepatitis C

Extrahepatic disease includes:

- Small vessel vasculitis with glomerulonephritis and neuropathy
- Mixed cryoglobulinemia (discussed under [Chronic Hepatitis C](#))
- Porphyria cutanea tarda (PCT)

PCT is associated **only** with hepatitis C—it is not associated with hepatitis B!

HIV and Hepatitis C

In the U.S., 25% of patients with HIV are coinfecting with HCV. These patients progress more rapidly to cirrhosis than those with HCV alone. The traditional HCV treatment for HIV/HCV coinfecting patients was a combination pegylated IFN- α and ribavirin (with the addition of HCV-specific protease inhibitors in genotype 1). Direct-acting antivirals have largely supplanted the use of IFN- α . Aside from paying careful attention to drug-drug interactions with HIV medications, the treatment for HCV in HIV-infected individuals is similar to treating non-HIV-infected individuals. Refer to a specialist for treatment, as new regimens for dual HIV/HCV-infected patients are being developed.

HEPATITIS D

PREVIEW | REVIEW

- In order for hepatitis D virus replication to occur, coinfection with which other virus is necessary?

Hepatitis D is an RNA virus that requires a **coexistent** HBV infection as a helper virus for virion assembly and replication. It is typically found in IV drug abusers and high-risk HBsAg carriers (HBV DNA levels > 10 million U/mL).

Hepatitis D infection can occur acutely with hepatitis B, or it can occur as a superinfection in those with previously established chronic hepatitis B.

Acute coinfection can present with acute hepatitis (ranging from mild to fulminant in severity) but there is generally a low risk of chronic infection. In hepatitis D virus (HDV) superinfection, acute hepatitis may develop, as well as an exacerbation chronic underlying hepatitis B disease.

Immunity to hepatitis B implies immunity to hepatitis D. Suspect hepatitis D if sudden decompensation occurs in a patient with chronic hepatitis B.

Diagnosis: anti-HDV IgM (early in course of hepatitis D infection).

HEPATITIS E

PREVIEW | REVIEW

- Hepatitis E is associated with which risk factor(s)?

Hepatitis E is a single-strand RNA virus with fecal/oral spread (like HAV). It is found in the Far East, Africa, and Central America, commonly due to contamination of water supplies after monsoon flooding. Like hepatitis A, no chronic form is known.

Unlike hepatitis A, hepatitis E carries a very high risk for fulminant hepatitis in the 3rd trimester of pregnancy, with a 20% fatality rate. Think of hepatitis E in a traveler with acute hepatitis and negative standard serology (hepatitis A, B).

HEPATITIS G

Hepatitis G is bloodborne, like hepatitis B and C. The mode of transmission is not well defined but is likely similar to HCV. There is evidence of infection in 1.5% of blood donors. It causes < 0.5% of community-acquired hepatitis. There is no evidence that HGV causes chronic liver disease.

CHRONIC HEPATITIS

PREVIEW | REVIEW

- Which test is positive in ~ 80% of those with chronic autoimmune hepatitis (AIH)?
- What is the treatment for chronic AIH?
- Which drugs are commonly associated with chronic drug-induced hepatitis?
- How does alcohol intake affect liver toxicity from acetaminophen?

There are quite a few causes of chronic hepatitis, as shown in [Table 14-12](#). We have already discussed chronic hepatitis B and C. We'll cover the other causes here.

Table 14-12: Differential Diagnosis of Chronic Hepatitis

Use the Alphabet Mnemonic for Recall (but skip E)	Diagnosis
A	Autoimmune results may include these: • ANA +/- anti-dsDNA • Anti-SMA • Anti-SLA antibody • Anti-actin antibody • p-ANCA
B	Hepatitis B
C	Hepatitis C
D ₁	Hepatitis D (only with hepatitis B)
D ₂	Drugs
D ₃	Diseases: • Wilson disease • α_1-Antitrypsin deficiency • Hemochromatosis
F	NAFLD

ANA = anti-nuclear antibody
 anti-SLA = anti-soluble liver antigen
 anti-SMA = anti-smooth muscle antibody
 NAFLD = nonalcoholic fatty liver disease
 p-ANCA = perinuclear anti-neutrophil cytoplasmic antibody

Autoimmune Chronic Hepatitis (AIH)

Type 1 AIH generally has an insidious onset and is most often found in young women. **Type 2** is a childhood disease and is not discussed here. The following concerns Type 1 only.

Among adult patients with AIH, 50% also have other disorders of altered immunity; e.g., thyroiditis, Coombs+ anemia, and immune thrombocytopenia (ITP; formerly known as immune thrombocytopenic purpura).

Autoantibodies are common; affected patients may have a positive ANA (+/- anti-double-stranded DNA [anti-dsDNA]), anti-SMA, anti-actin antibodies, p-ANCA, and anti-soluble liver antigen (anti-SLA).

Consider the following tests:

- **ANA** is the **most sensitive** but the **least specific** serological marker.
- **Anti-SMA** is **more specific** than ANA, and it is positive in ~ 80% of patients with Type 1 AIH. It is occasionally seen as an overlap syndrome with PBC or PSC. Refer to [Table 14-6 on page 14-48](#).
- **Anti-actin antibody** is also available in some labs and has replaced the anti-SMA test because it is even more specific and sensitive.
- **Anti-SLA** is the most specific but not sensitive.
- IgG levels are often elevated.
- You can also check for AMA—it is only occasionally slightly positive, but high titer occurs in PBC and indicates an overlap syndrome.

Remember, as a rule of thumb, PBC occurs in middle-aged women, AIH occurs in **young** women, and PSC occurs in middle-aged men.

Diagnosis: Early diagnosis is essential because this form of chronic hepatitis responds well to treatment. Exclude other forms of hepatitis, and order and review the results for the above antibody tests. See [Table 14-13](#) for diagnostic scoring.

Confirm diagnosis by characteristic changes (piecemeal necrosis with plasma cell infiltrate) found on histologic examination of a liver biopsy. These changes are characteristic but not specific, so drug history and serologic tests are required to rule out other types of hepatitis.

Treatment: Unlike other types of hepatitis, patients with chronic autoimmune hepatitis typically have a rapid reversal of symptoms and increased survival with prednisone/budesonide +/- azathioprine (AZA). Vaccination against Hepatitis A and B should also be considered.

AZA is used as a steroid-sparing drug. Initially, AZA has no effect as a sole agent; however, if used in combination with steroids over years, some patients can be tapered off steroids and remain on AZA.

IFN- α **exacerbates** AIH and is therefore contraindicated (although effective in chronic hepatitis B and C). So, it is vital to make the correct diagnosis.

Table 14-13: Scoring System for Autoimmune Hepatitis (AIH)

Tests	Lab Results	Score
ANA or anti-SMA	> 1:40	1
ANA or anti-SMA	> 1:80	2
IgG	> ULN	1
	> 1.1× ULN	2
Liver histology	Compatible with AIH	1
	Typical AIH	2
Absence of viral hepatitis		2
Total Score		6: Probable AIH ≥ 7: Definite AIH
ANA = anti-nuclear antibody anti-SMA = smooth muscle antibody ULN = upper limit of normal		

Despite the usual response to treatment (above), there is no cure for AIH, and it frequently progresses to cirrhosis and sometimes hepatocellular carcinoma (less often than with chronic viral hepatitis).

Liver transplant is indicated for end-stage disease, although the disease process slowly recurs.

Drug-Induced Hepatitis

Drug-induced hepatitis can be either chronic or acute. **Chronic** drug-induced hepatitis can be caused by methyldopa, nitrofurantoin, acetaminophen, trazodone, phenytoin, methotrexate, oral contraceptives, and isoniazid (a.k.a. isonicotinic acid hydrazide [INH]; although INH far more commonly causes **acute** hepatitis). Histologic changes are similar to those seen in AIH, and the patients are often ANA+. Hypergammaglobulinemia is also often present. ([Table 14-6 on page 14-48](#) gives a comparison of test results for drug-induced chronic hepatitis, PBC, and AIH.) The best treatment is to stop the offending drug.

Acute drug-induced hepatitis results from the direct toxic, allergic, and/or idiosyncratic effects of drugs. Acetaminophen causes a direct toxic effect. Drugs causing an idiosyncratic effect are halothane, phenytoin, chlorpromazine, and erythromycin. Drugs causing **both** toxic and idiosyncratic effects are methyldopa, INH, and sodium valproate.

Anabolic steroids, chlorpromazine, amoxicillin/clavulanate, and erythromycin are associated with cholestasis but **not** hepatitis.

Now let's talk a little more about acetaminophen, alcohol, methotrexate, INH, oral contraceptives, and ASA.

Acetaminophen

Acute acetaminophen poisoning is discussed in the [General Internal Medicine](#) section. Briefly, when

acetaminophen is ingested, 90% of it is processed via the glucuronidation pathway, 5% is excreted unchanged in the urine, and 5% is oxidized by the cytochrome P-450 system. The P-450 system produces a toxic, intermediate compound (*N*-acetyl-*p*-benzoquinone imine [NAPQI]), which is quickly reduced by glutathione. When there is an acetaminophen overdose, glutathione is rapidly depleted, and the resulting unreduced toxin causes direct liver damage.

In alcohol-acetaminophen syndrome, chronic, moderate-to-heavy use of alcohol has a 2-fold effect—the cytochrome P-450 system is cranked up (i.e., more NAPQI is produced) and the amount of glutathione is decreased (so less is available for detoxifying the NAPQI). Therefore, long-term users of moderate-to-heavy amounts of alcohol who take acetaminophen in normal or higher doses are at risk for severe hepatic toxicity or liver failure.

Glutathione levels are depressed in malnutrition. Acetaminophen liver toxicity can develop by not eating for 3–4 days (e.g., with an acute viral illness) and then taking therapeutic doses of acetaminophen; i.e., at ≤ 4 g/day.

30% of healthy people taking the maximum recommended dosage (4 g/day) for 2 weeks develop an ALT > 100 U/L (1.67 μ kat/L).

Again, know: Acetaminophen liver damage is potentiated with chronic alcohol use, one-time heavy alcohol use, malnutrition, chronic use, and even dieting.

Acetaminophen toxicity is the most common cause of fulminant hepatitis in the U.S. If suspected, draw acetaminophen blood levels and treat early with intravenous or oral *N*-acetylcysteine (NAC; e.g., Mucomyst and Mucosil). The specifics of treatment are discussed in the General Internal Medicine section. There is also potential value to NAC treatment even with late diagnosis (> 48 hours after ingestion and/or toxicity). Liver failure in this setting can be fatal without life-saving liver transplant.

Alcohol

Alcoholic liver disease results in a macrovesicular fat accumulation. There is also neutrophil infiltration in the liver. Women are more susceptible than men to alcoholic liver disease.

Alcohol induces γ -glutamyl transferase (GGT), so this enzyme is disproportionately high in alcoholic liver disease. Also, there is discordance between AST and ALT with an AST:ALT ratio of 2:1. The AST is virtually always < 300 U/L (5.01 μ kat/L)—even with severe alcoholic liver injury.

Other factors, including nutrition and other drugs, modify alcohol's direct toxic effect. Alcoholics are very susceptible to acetaminophen liver damage because alcohol induces the cytochrome P-450 system.

The combination can cause fulminant hepatitis. Acetaminophen may not be on the patient's medication list; patients may know only that they have been taking a "nonprescription pain reliever."

Corticosteroids and pentoxifylline are of transient benefit in severe alcoholic hepatitis.

NAFLD is very similar to alcoholic liver disease; see [Nonalcoholic Fatty Liver Disease \(NAFLD\)](#) on page 14-60.

Methotrexate (MTX)

MTX can cause an indolent, asymptomatic liver disease that progresses to cirrhosis. Liver enzyme monitoring is recommended routinely in patients taking even intermittent doses of MTX. Liver injury is believed to be related to cumulative lifetime dose.

Isoniazid

Isoniazid (a.k.a. INH [isonicotinic acid hydrazide]) causes an occasional, mild, transient increase in liver enzymes. Medication does not usually have to be discontinued. The risk of isoniazid hepatitis is $< 1\%$ but increases with advancing age, underlying liver disease, or concomitant alcohol use.

Oral Contraceptive Pills (OCPs)

OCPs are associated with benign hepatic adenoma, peliosis hepatis (blood-filled sinusoids), and focal nodular hyperplasia of the liver. So, a young woman on OCPs who has a mass in her liver? Probably an adenoma. Hepatocellular cancer can occur in the setting of cirrhosis.

Aspirin and Reye Syndrome

Reye syndrome occurs exclusively in children < 15 years of age. Although rare, it tends to develop after a viral illness—especially influenza A or B or chickenpox—and especially when there has been concurrent aspirin (ASA) use. These patients get a fatty liver (microvesicular—as in acute fatty liver of pregnancy; for more on liver disease during pregnancy, see the [Women's and Men's Health](#) section) and progressive encephalopathy. ALT, AST, ammonia (NH_3), and prothrombin time (PT) are elevated. Hypoglycemia, as a result of severe liver failure, is common. Mortality is 50%.

Other Diseases that Cause Chronic Hepatitis

These hereditary liver diseases also cause chronic hepatitis:

- Wilson disease
- α_1 -Antitrypsin deficiency
- Hemochromatosis

More information on hereditary liver diseases is found under [Hereditary Liver Disease](#) on page 14-65.

NONALCOHOLIC FATTY LIVER DISEASE (NAFLD)

PREVIEW | REVIEW

- What is nonalcoholic fatty liver disease (NAFLD), and what are the risk factors?
- What are the treatment recommendations for NAFLD?

NAFLD is an increasingly important cause of liver disease. It looks just like alcoholic liver disease on liver pathology, but there is **no** history of alcohol abuse. NAFLD includes a spectrum of disease, from steatosis (fat accumulation) to steatohepatitis, fibrosis, and cirrhosis. 75–80% of “cryptogenic” cirrhosis is due to NAFLD.

The pattern of liver enzyme elevation is **opposite** that of alcoholic liver disease, with **ALT > AST**.

NAFLD is associated with the following:

- Obesity
- Type 2 DM
- Protein malnutrition
- Hyperlipidemia
- Amiodarone
- Corticosteroids
- “DROP” (see below)
- Prolonged total parenteral nutrition (TPN)

DROP is a metabolic syndrome with dyslipidemia, insulin resistance, obesity, and increased blood pressure. Patients with NAFLD and DROP have a higher incidence of fibrosis.

Treatment of NAFLD is **not** standardized. In general, treat with weight loss and control of any DM or hyperlipidemia. For patients with NAFLD and none of the common risk factors, recommend a low-fat diet. 2012 Guidelines from the AGA and AASLD recommend vitamin E 800 U/day as 1st line therapy for biopsy-proven NAFLD in nondiabetics. All patients with NAFLD should avoid alcohol and be immunized against hepatitis A and B.

Screen patients with cirrhosis due to NAFLD for hepatocellular carcinoma (see next topic).

HEPATOCELLULAR CARCINOMA (HCC)

PREVIEW | REVIEW

- What is the most likely diagnosis in a patient with tender hepatomegaly, a right upper quadrant bruit, bloody ascites, a high alkaline phosphatase, and a very elevated α -fetoprotein level?

Cirrhosis precedes HCC in 75% of HCC patients (see [Cirrhosis](#)). HCC is associated with chronic liver disease of **any** type: chronic hepatitis B and C, hemochromatosis, α_1 -antitrypsin deficiency, alcoholic liver disease, and

autoimmune hepatitis. In addition, HCC is associated with aflatoxin exposure (can be found in raw peanuts or raw peanut butter, especially in Asia).

Alcoholic liver disease, frequently with concurrent hepatitis C, is the most common cause of HCC in the U.S. Chronic hepatitis B infection, acquired at birth, is the most common cause of HCC in developing countries.

HCC can cause tender hepatomegaly, a bruit in RUQ, bloody ascites, and high alkaline phosphatase. 70–80% of patients have a very elevated α -fetoprotein (AFP) level.

HCC-associated paraneoplastic syndromes are common and are clues to the diagnosis:

- Hypercalcemia (due to parathyroid-like hormone produced by the tumor)
- Hypoglycemia (due to the tumor’s high metabolic needs or, more rarely, insulin-like growth factor 2 [IGF-2])
- Watery diarrhea
- Fever of unknown origin (FUO)

Consider HCC in any cirrhotic patient who decompensates without an obvious reason. Achieving a sustained virologic response with antiviral treatment in chronic hepatitis C reduces the risk of HCC.

For all patients with cirrhosis, screen every 6 months for HCC with abdominal U/S with or without AFP as per AASLD HCC guidelines 2018. Alternately, some centers use helical CT or MRI, which are more expensive but have better sensitivity than U/S.

Know some basics about the treatment of liver cancer:

- 1) Resect a solitary tumor without vascular invasion (best if ≤ 5 cm in diameter).
- 2) If unresectable or underlying liver disease is severe (typically due to cirrhosis), consider liver transplant (single lesion < 5 cm, ≤ 3 lesions all < 3 cm, no extrahepatic disease or vascular invasion).
- 3) Even with advanced disease, there are many treatment options, including radiofrequency ablation, transarterial chemoembolization, and oral targeted therapies.

CIRRHOSIS

PREVIEW | REVIEW

- Name the causes of cirrhosis.
- Bleeding risk of esophageal varices correlates with which feature of the varices?
- Which drug class is used for prophylaxis against bleeding with large esophageal varices?
- Which drug and which endoscopic therapies are used for active variceal hemorrhages?
- Why are antibiotics given to cirrhotic patients with gastrointestinal bleed? Which antibiotics are used?
- What do you do with small esophageal varices?

- Which drug is given to a cirrhotic patient with a history of variceal hemorrhage to decrease the chance of rebleeds?
- If the prolonged prothrombin time in an alcoholic is easily corrected with vitamin K, what does this indicate?

Causes

Anything that causes chronic liver disease can lead to cirrhosis:

- Alcohol (most common cause in the U.S.)
- Hepatitis (B or C)
- Steatohepatitis, postnecrotic (drugs and toxins)
- NAFLD (a.k.a. NASH)
- Biliary disease
- α_1 -Antitrypsin deficiency
- Hemochromatosis
- Wilson disease
- Schistosomiasis
- Cardiac causes—primarily severe, prolonged right-sided heart failure, which is rare

LFT results for chronic cirrhosis are listed in [Table 14-8 on page 14-51](#). Chronic cirrhosis is generally associated with milder elevations in AST and ALT, compared to acute viral hepatitis.

Stigmata

The physical exam findings of cirrhosis may include any of the following alone or in combination:

- Hepatosplenomegaly
- Jaundice
- Ascites (see [Ascites on page 14-63](#))
- Caput medusae (periumbilical varices)
- Spider angiomas/telangiectasias ([Figure 14-27](#))
- Gynecomastia and testicular atrophy
- Palmar erythema
- Fetor hepaticus
- Asterixis (in hepatic encephalopathy)
- Clubbing (usually in biliary causes)



Figure 14-27: Spider telangiectasias

Complications of Cirrhosis

Portal Hypertension

Portal hypertension is a progressive complication of cirrhosis. Portal pressure increases because of resistance to blood flow through the liver, mainly due to structural distortion from fibrosis and nodule formation. Resistance also increases due to intrahepatic vasoconstriction. This occurs as a result of increased production of vasoconstrictors and decreased production of vasodilators. Portal hypertension results in portosystemic collateral formation, which can lead to hemorrhage (see [Esophageal / Gastroesophageal Variceal Hemorrhage](#)).

Diagnosis is based on cirrhosis and clinical manifestations of portal hypertension, including splenomegaly, collateral vessels on abdominal wall (i.e., caput medusae), and thrombocytopenia. However, if the diagnosis is in doubt, perform a hepatic venous pressure gradient (HVPG; i.e., wedged free hepatic venous pressure). A positive result for portal hypertension is an HVPG ≥ 6 mmHg (normal is between 1 and 5 mmHg).

Treatment consists of preventing and treating complications of portal hypertension (i.e., gastroesophageal varices, ascites). See [Esophageal / Gastroesophageal Variceal Hemorrhage](#) and [Ascites on page 14-63](#) for these treatments.

Esophageal / Gastroesophageal Variceal Hemorrhage

Gastroesophageal varices are present in 50% of patients with cirrhosis and are a result of portal hypertension pushing blood into surrounding blood vessels. Because their rupture results in hemorrhage, you must screen for these portosystemic collaterals at diagnosis of cirrhosis and then periodically afterward, depending on size and risk of bleeding. 1/3 of patients with esophageal varices ([Figure 14-28](#)) bleed, and bleeding has a 30% mortality rate. With a bleed, the HVPG is usually > 12 mmHg (normal range 1–5 mmHg). **Size** of varices correlates with risk of bleeding. Diagnose with esophagogastroduodenoscopy (EGD).

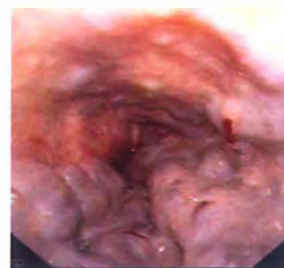


Figure 14-28: Esophageal varices

Prophylaxis

Nonselective β -blockers, such as propranolol and nadolol, decrease rebleeds and may delay or prevent the occurrence of the 1st variceal bleed. Therefore, prescribe these agents to **all** patients with medium-to-large varices—whether or not they have had bleeding. The second option is endoscopic variceal ligation.

Endoscopic ligation can be used for primary prophylaxis in patients with large varices or in those who cannot tolerate β -blockers or in whom they are contraindicated. For instance, β -blockers have been shown to increase mortality in patients with refractory ascites.

Sclerotherapy does **not** prevent a 1st hemorrhage—it actually appears to make things worse.

Active Bleeds

The risk of bleeding is increased in cirrhosis due to a number of factors. The most widely recognized cause is elevated pressure in the portal circulation, which then results in rupture of the most susceptible vessels (e.g., esophageal and/or gastric varices). While some aspects of blood clotting may be maintained, cirrhosis can result in coagulation factor defects that cause both impaired hemostasis and an increased risk of thrombosis. Vitamin K deficiency is also often present, leading to further coagulation abnormalities via the vitamin K-dependent factors of proteins C and S, prothrombin, and Factors 7, 9, and 10. Patients with severe liver disease may develop disseminated intravascular coagulation as well.

Primary therapy of actively bleeding varices is HBV is the only hepatitis virus composed of **DNA**. The incubation period is 1–6 months. It is transmitted by contaminated blood products and infected body fluids. Endoscopic banding +/- somatostatin (such as octreotide) or sclerotherapy. Note, however, that endoscopic injection of a sclerosant (sodium morrhuate or ethanolamine) into bleeding varices stops bleeding but causes necrosis of the esophageal tissue, which can lead to esophageal ulcers and eventual stricture formation.

Octreotide is a splanchnic vasoconstrictor. It is frequently given parenterally in conjunction with endoscopic therapy and has a proven benefit over endoscopic therapy alone.

Balloon tamponade is rarely used because it has a high rate of complications.

Any cirrhotic patient with GI bleeding should be carefully managed in the ICU. Consider elective endotracheal intubation if there is active hematemesis because aspiration pneumonia is common. **Always do endoscopy**. Remember: Cirrhotic patients can bleed from sources other than varices; e.g., peptic ulcer disease (PUD).

Give prophylactic oral or IV antibiotics to all cirrhotic patients with bleeding and ascites to prevent primary peritonitis (a.k.a. spontaneous bacterial peritonitis) and to decrease mortality. The preferred antibiotics are 3rd generation cephalosporin or quinolones or—if patient is not allergic—penicillin/cephalosporin.

Again, if bleeding is due to varices, do endoscopic therapy +/- somatostatin such as octreotide with either banding or sclerotherapy.

Preventing Rebleeds

Refer to the discussion about prophylaxis of variceal hemorrhage ([Prophylaxis on page 14-61](#)).

TIPS (transjugular intrahepatic portosystemic shunt; i.e., portal vein to hepatic vein) is used only for rebleeding or failed endoscopic therapy. TIPS decompresses the portal vein, effectively acting as a portacaval shunt without the major surgery. The other main use for TIPS is for intractable ascites due to cirrhosis. TIPS procedures may **worsen** hepatic encephalopathy.

Summary of treatment for esophageal varices:

- Nonselective β -blockers are the only treatment recommended for small esophageal varices.
- Propranolol or nadolol are used for all sizes of varices or any history of bleeding varices. They are especially given to cirrhotic patients with a history of variceal hemorrhage to decrease the chance of rebleeds.
- Endoscopic banding or sclerotherapy for active bleeds or to prevent rebleeds—preferably with somatostatin (e.g., octreotide)
- TIPS for rebleeds or failed endoscopic therapy

Hepatic Encephalopathy

Hepatic encephalopathy has a complex pathophysiology and may be precipitated by:

- GI bleed
- Hypovolemia
- Hypoxia
- Hypokalemia
- Sedatives
- Tranquilizers
- Portal venous obstruction
- Infections (pneumonia, bacteremia, urosepsis, and primary peritonitis)
- Alkalosis

Alkalosis worsens hepatic encephalopathy because it increases the ammonia:ammonium ratio ($\text{NH}_3:\text{NH}_4^+$)—and only NH_3 crosses the blood-brain barrier. Acidosis has the opposite effect.

Signs of hepatic encephalopathy include fetor hepaticus (unique musty odor to breath and urine), hyperreflexia, asterixis, and altered mental status. Serum ammonia levels are far **less** important than physical exam.

Treat with lactulose with the goal of ~ 3 bowel movements/day. This disaccharide, more commonly used as an osmotic laxative, passes through the upper GI tract and is broken down by colonic bacteria into organic acids. The excess H^+ in the proximal colon:

- inhibits coliform bacterial growth, thereby decreasing NH_3 production, and
- traps NH_3 as inactive NH_4^+ .

Supplemental/alternative treatments:

- Oral antibiotics (also to decrease NH_3 production) may be given if the patient does not respond to lactulose. Neomycin was previously used but has nephro-/ototoxicity. Rifaximin, metronidazole, rifampin, and vancomycin are used instead.
- Acarbose (used for DM) inhibits breakdown of carbohydrates into monosaccharides. Monosaccharides promote the growth of bacteria that produce NH_3 .
- Probiotics alter gut flora and similarly decrease NH_3 levels.

Hepatorenal Syndrome

Hepatorenal syndrome (a.k.a. oliguric hepatic failure) is a diagnosis of exclusion, so other causes of renal failure such as prerenal azotemia, obstruction, and drugs must be excluded before a diagnosis can be made. More information on hepatorenal syndrome is in the [Nephrology](#) section.

Know: Urine Na^+ is very low (commonly $< 10 \text{ mEq/day}$ [10 mmol/day]) in hepatorenal syndrome.

Current treatment: Careful volume management (IV albumin infusions) and midodrine (an α_1 -agonist) + octreotide (stimulates fluid absorption from GI tract).

Prothrombin Time (PT) in an Alcoholic Patient

Alcohol causes malabsorption of some vitamins, including vitamin K. Alcoholic liver disease decreases synthesis of clotting factors in the liver, which include vitamin K-dependent clotting factors (Factors 2, 7, 9, and 10). This leads to a prolonged prothrombin time. If prolonged prothrombin time in an alcoholic is easily corrected by IV or oral vitamin K, malabsorption is the probable cause.

If the PT is **not** corrected by vitamin K, but corrected by a 1:1 mix, the disorder is due to decreased coagulation factors. If it does not correct with the 1:1 mix either, there is likely a circulating inhibitor.

ASCITES

PREVIEW | REVIEW

- What causes chylous ascites?
- How does primary peritonitis (a.k.a. spontaneous bacterial peritonitis) differ from neutrocytic ascites?
- How does primary peritonitis differ from secondary bacterial peritonitis?
- Why is albumin given in the treatment of primary peritonitis?

Ascites is defined as the accumulation of fluid in the peritoneal cavity.

Causes

The following are causes of ascites:

- Cirrhosis
- Alcoholic hepatitis
- HF (especially right-sided)
- Constrictive pericarditis
- Peritoneal diseases
- Myxedema
- End-stage renal disease
- Fluid with a high triglyceride content (chylous ascites)
- Malignancy
- Fluid that is milky in appearance due to the presence of pus (pseudochylous ascites)
- Fulminant and subfulminant hepatitis
- Hepatic venoocclusive disease (including Budd-Chiari syndrome)
- Hypoalbuminemia (usually nephritic syndrome, protein-losing enteropathy, severe malnutrition)
- Pancreatogenous (usually pseudocyst, disrupted duct)

In cirrhosis-induced ascites, the ascitic fluid is resorbed via the peritoneal surface. Maximum capacity is $\sim 900 \text{ mL/day}$. So, if you try to diurese off $> 1 \text{ L/day}$, it is at the expense of intravascular volume. This disease causes the most avid sodium-retention state known.

Chylous ascites is due to lymphatic blockage (trauma, tumors—especially primary lymphoma, tuberculosis [TB], and filariasis), **not** cirrhosis or HF.

Diagnosis

Determining the cause of ascites often requires analyzing a peritoneal fluid specimen for appearance, cell count with differential, cytology, total protein, and albumin.

Know the following:

Appearance:

- Bloody fluid suggests a tumor.
- Cloudy fluid suggests infection.
- Milky fluid suggests lymphatic obstruction.

Cell count: If the neutrophil count is elevated ($> 250 \text{ cells}/\mu\text{L}$ [$0.25 \times 10^9/\text{L}$]), do a C&S and start antibiotics.

Chemistry: A serum-to-ascites albumin gradient (SAAG) $> 1.1 \text{ g/dL}$ (11 g/L) suggests portal hypertension. This occurs in ascites due to any of the following conditions, where the albumin level in the ascites is low (generally $< 1.0 \text{ g/dL}$ [10 g/L]):

- Cirrhosis (most common)
- Right-sided heart failure

- Liver failure
- Budd-Chiari syndrome
- Myxedema

SAAG < 1.1 g/dL (i.e., high level of albumin in the ascites and no portal hypertension [HTN]) is seen with ascites due to tuberculous peritonitis, bacterial/fungal peritonitis, nephrotic syndrome, pancreatitis, and peritoneal carcinomatosis. Note: SAAG is a difference, not a ratio! It is defined as:

$$\text{SAAG} = \text{albumin}_{\text{Serum}} - \text{albumin}_{\text{Ascites}}$$

An elevated ascites protein level (≥ 2.5 g/dL [25 g/L]) is seen in all cases that cause increased levels of albumin (Table 14-14). It is also seen in cardiac ascites.

Table 14-14: Causes of Ascites and Associated Albumin and Protein Findings

Causes	SAAG	Ascites Protein (g/dL)
Cirrhosis, liver failure, Budd-Chiari syndrome, myxedema	> 1.1	< 2.5
Right-sided heart failure	> 1.1	≥ 2.5
Tuberculous peritonitis, bacterial/fungal peritonitis, nephrotic syndrome, pancreatitis, and peritoneal carcinomatosis	< 1.1	> 2.5

SAAG = serum-to-ascites albumin gradient

Primary Peritonitis

Primary peritonitis is an ascitic fluid infection without an obvious intraabdominal source. It is diagnosed by performing paracentesis and obtaining peritoneal fluid for evaluation. A peritoneal fluid with a neutrophil (PMN) concentration > 250 cells/ μL [$0.25 \times 10^9/\text{L}$] is consistent with primary peritonitis. Usual bacterial causes are *E. coli*, *Streptococcus pneumoniae*, and *Klebsiella*.

Because primary peritonitis patients may not have abdominal pain or tenderness, you **must** consider it if there is deterioration in the status of any patient with ascites (e.g., new-onset confusion, fever, signs of hepatic encephalopathy, renal failure).

Risk factors for primary peritonitis:

- Ascites protein < 1 g/dL (10 g/L)
- History of variceal bleed
- Prior episode of primary peritonitis
- Bilirubin > 2.5 mg/dL

Give patients with these risk factors either intermittent (preferred) or continuous prophylactic oral antibiotic therapy. Typically, use oral therapy with a quinolone (e.g., norfloxacin 400 mg daily).

You must rule out 2 other possible causes of high WBC in ascitic fluid before you can assume it is primary peritonitis:

- 1) Neutrocytic ascites: Basically, this is neutrophils > 250 cells/ μL [$0.25 \times 10^9/\text{L}$] with **no** evidence of primary peritonitis and negative cultures.
- 2) Secondary bacterial peritonitis is due to perforated viscus. In cirrhotics, it can be confused with primary peritonitis.

Secondary bacterial peritonitis has markedly different ascitic fluid lab findings than the primary peritonitis findings below:

- Total protein > 1 g/dL (10 g/L), frequently > 3 g/dL (30 g/L)
- Glucose < 50 mg/dL (2.77 mmol/L)
- WBC very elevated, often > 5,000 cells/ μL ($5 \times 10^9/\text{L}$)
- Ascites fluid LDH > serum LDH
- High amylase in ascites fluid

It is critical to differentiate primary peritonitis from secondary bacterial peritonitis because:

- Mortality is ~ 100% in patients with secondary bacterial peritonitis who do **not** go to surgery.
- Mortality is 80% in patients with primary peritonitis who **get** an exploratory laparotomy.

Treatment: Primary peritonitis is typically treated with a broad-spectrum 3rd generation cephalosporin. Milder cases can be treated with oral antibiotics.

IV albumin is also given in the treatment of primary peritonitis (1.5 g/kg on day 1 and 1 g/kg on day 3). Albumin maintains blood volume and thereby decreases the incidence of irreversible renal impairment and mortality.

Thus, the cardinal paracentesis fluid findings for infected ascites are neutrophils > 250 cells/ μL , high SAAG, few RBCs, culture+ (culture and Gram stain often negative due to organism/fluid volume ratio), and negative cytology.

Treatment of Ascites

Treatment: mainly dietary sodium restriction. Water restriction is needed only if serum Na^+ < 125 mEq/L (125 mmol/L; normal range 135–145 mEq/L [135–145 mmol/L]). Then, if needed, start spironolactone, then a loop diuretic. Stop all antiprostaglandin medications (e.g., ASA) because these decrease urinary sodium excretion. Also, do not give aminoglycosides in this setting because they can precipitate renal failure. Target is a random urine $\text{Na}^+:\text{K}^+ > 1$.

Again, do **not** diurese > 1 L/day. It is okay to do daily paracenteses during the initial treatment of

recent-onset ascites or with severe refractory ascites if the patient's renal function is normal and there is:

- No GI bleeding
- No sepsis
- No portosystemic encephalopathy (PSE)

With large-volume paracentesis (≥ 5 L), replace 6–8 g of albumin for each liter of fluid removed.

TIPS (transjugular intrahepatic portosystemic shunt) is used to treat refractory ascites caused by cirrhosis. TIPS allows for decompression of the portal vein. Effectively, it is a portacaval shunt without the major surgery. A common complication of TIPS is encephalopathy, so it is generally not recommended for elderly patients (who are most susceptible). As discussed under [Preventing Rebleeds on page 14-62](#), TIPS is also used in the treatment of rebleeding esophageal and gastric varices.

HEREDITARY LIVER DISEASE

PREVIEW | REVIEW

- Which hereditary liver disease has increased unconjugated bilirubin?
- When does jaundice in Gilbert syndrome typically occur?
- What is the risk of hepatocellular cancer in a patient with cirrhosis caused by hemochromatosis?
- What is a pathognomonic finding in Wilson disease?

Hyperbilirubinemia is the main finding in hereditary liver diseases. More on hyperbilirubinemia is located under [Jaundice on page 14-50](#).

Gilbert Syndrome

Gilbert syndrome (a.k.a. familial nonhemolytic jaundice) is the hereditary liver disease that has increased unconjugated bilirubin. It is a very common, benign, chronic disorder resulting in a mild, unconjugated hyperbilirubinemia. Remember: Unconjugated = indirect = without bilirubinuria. Jaundice may come and go and is typically brought on by physical stress (especially surgery, exertion, and infection), fasting, and alcohol ingestion. Around 7% of the population has Gilbert syndrome. Depending on the location of the mutation on the *UGT1A1* gene, Gilbert syndrome can be inherited either in an autosomal dominant (AD) or autosomal recessive (AR) pattern.

Gilbert syndrome is due to decreased or absent glucuronyl transferase in the liver cells or decreased liver cell uptake of unconjugated bilirubin. 50% of patients have a very low-grade, chronic hemolysis. Phenobarbital stimulates glucuronyl transferase and decreases the bilirubin level.

Diagnosis is by an increase in unconjugated bilirubin after prolonged fasting. No treatment is needed.

Benign Postoperative Cholestasis

If a patient is noted to have increased conjugated bilirubin after a major surgery, it is **not** Gilbert syndrome (which is unconjugated). It is most likely an entity called benign postoperative cholestasis. This is most often seen if the patient became hypotensive or required many transfusions during the operation.

Dubin-Johnson syndrome and Rotor syndrome are rare benign AR disorders that cause conjugated hyperbilirubinemia.

α_1 -Antitrypsin (AAT) Deficiency

AAT deficiency is AR. It mainly affects the liver and lungs and causes chronic hepatitis, eventually leading to cirrhosis and emphysema. For diagnosis, check a serum AAT level and phenotype. Accumulation of intrahepatocytic AAT molecules causes liver disease.

Treatment: Other than liver transplant or liver + lung transplant, the only (minimally effective) treatment is augmentation therapy with weekly infusions of pooled human α_1 -antitrypsin. Augmentation therapy has no effect on liver disease associated with AAT deficiency.

Hemochromatosis

Know this topic very well. Consider all of the following as highlighted; this relatively common disease is quite treatable if detected early!

There are 2 types of hemochromatosis: genetic and acquired.

The **genetic** form is an AR disorder that involves the *HFE* gene.

The **acquired** form is generally secondary to blood transfusions used to treat underlying anemia, such as sickle cell disease. Less frequently, acquired hemochromatosis can occur secondary to an iron-related chronic anemia with secondary erythropoiesis, such as sideroblastic anemia or thalassemia. This form usually develops in men between 40 and 60 years of age.

In both genetic and acquired types, there is abnormally increased intestinal iron absorption, which leads to iron deposition in the tissues. This iron deposition causes fibrosis and damage to organs—especially the liver, heart, pancreas, and pituitary gland.

Symptomatic hemochromatosis of both types is 10× more frequent in men—this is probably because menstruation lowers iron stores in women.

Clinical findings:

- Hepatomegaly (95%)
- Gray hyperpigmentation (90%)
- Secondary diabetes, “bronze diabetes” (65%), so suspect this in a thin 50-year-old with new-onset DM
- Dark skin and arthropathy (40%—especially pain at 2nd and 3rd MCP joints and the wrist)
- Cardiac involvement, typically a cardiomyopathy (15%)

Secondary hypogonadism and infertility also occur and are caused by depression of the hypothalamic-pituitary axis. There is a 25–30% risk for hepatocellular carcinoma in patients with cirrhosis caused by hemochromatosis—higher than any other type of cirrhosis!

High levels of serum iron, ferritin, and transferrin suggest the diagnosis of hemochromatosis. The most helpful screening and best initial test is transferrin saturation > 45%. (You can read up on these lab tests in the [Hematology](#) section.) Liver biopsy confirms the diagnosis and allows for staging of fibrosis. Imaging of hemochromatosis can show reduced signal intensity on MRI and increased organ density on CT.

Liver biopsy is indicated when serum ferritin is > 1,000 ng/mL (2,247 pmol/L).

Confirm the diagnosis for the hereditary type with genetic testing for mutations in the *HFE* gene.

If this disease is successfully treated early enough, especially if prior to development of cirrhosis, patients have a normal life span with negligible risk of cancer. Initial treatment is weekly phlebotomy. Ultimately, the patient may require phlebotomy 4×/year with the goal of a ferritin level between 50 and 100 ng/mL (112.35 and 224.70 pmol/L). This treatment results in decreased skin pigmentation, improved cardiac function, and prolonged life expectancy. But, if already lost, secondary sex characteristics and fertility do not return; the damage is done.

Wilson Disease

Wilson disease (a.k.a. hepatolenticular degeneration) is an AR genetic disorder that typically presents as liver disease or neurologic/psychiatric dysfunction. Usually the liver disease component manifests itself in children and adolescents, whereas the neurologic/psychiatric manifestations arise in older adults. Other symptoms include arthritis from chondrocalcinosis. Wilson disease is caused by impaired excretion of copper into bile, which results in excess copper in body tissues—especially the liver.

Hemolysis is common. Serum ceruloplasmin is low (in most liver diseases, it is high) and urinary copper level is high. Kayser-Fleischer rings are pathognomonic; if suspected, a slitlamp exam is required. Look for a single brownish corneal ring in each eye, formed by copper deposition along the outer edge of the cornea ([Figure 14-29](#)). Liver biopsy confirms the diagnosis; it shows a high liver copper level—but remember, so do PBC and PSC!

Screen with the following tests for Wilson disease in all adults who have chronic liver disease without obvious cause, especially if < 40 years of age:

- Serum ceruloplasmin
- Slitlamp exam
- Urine copper

All 3 of the above are positive in < 50% of patients with Wilson disease.

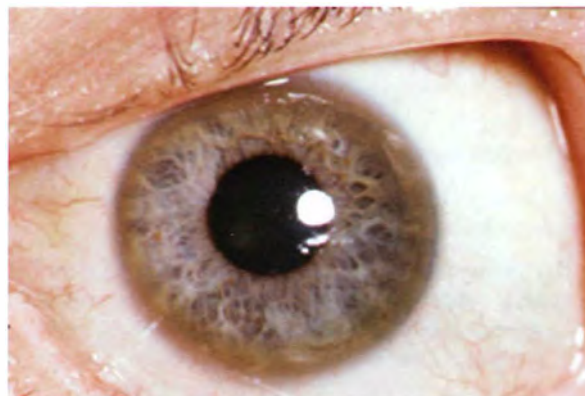


Figure 14-29: Kayser-Fleischer ring
Source: Herbert L. Fred, MD

Treatment of Wilson disease is a 2-phase process:

- **Phase 1:** Decrease copper levels, generally with chelation using D-penicillamine (must give supplemental pyridoxine with this drug). If the patient cannot tolerate D-penicillamine or has progressive neurologic manifestations, use trientine. Zinc is a 3rd option.
- **Phase 2:** For maintenance therapy to prevent its reaccumulation, use low-dose penicillamine or trientine, or use oral zinc to block the absorption of copper. Avoid foods high in copper (e.g., nuts, peas, chocolate, mushrooms, shellfish, liver).

A liver transplant cures Wilson disease.

In fulminant Wilson disease, there is severe hemolytic anemia and a high serum copper level due to the release of copper from the liver. Penicillamine therapy is not effective; the only treatment is liver transplant.

LIVER DISEASE DURING PREGNANCY

For more information on liver disease during pregnancy, see the [Women's and Men's Health](#) section.

1st Trimester

Hyperemesis gravidarum can cause N/V, volume depletion, and mild increase in AST and ALT.

2nd Trimester

2nd trimester is the best time for surgery for severely symptomatic gallstone patients.

3rd Trimester

Remember that hepatitis E can cause fulminant hepatitis in the 3rd trimester of pregnancy—with a 20% fatality rate.

Acute fatty liver of pregnancy is a very serious condition in which there is only modest elevation of AST/ALT/bilirubin along with **microvesicular** fat deposition in the liver (as in Reye syndrome). (Alcoholic liver disease has **macrovesicular** fat.) Acute fatty liver of pregnancy

occurs in the 3rd trimester and is associated with encephalopathy, hypoglycemia (e.g., Reye syndrome), preeclampsia, pancreatitis, disseminated intravascular coagulation, and renal failure. Early delivery is required.

HELLP syndrome: hemolysis, elevated liver enzymes, low platelets. Most patients also have hypertension and proteinuria. This is a severe variant of preeclampsia. It tends to occur before 36 weeks of pregnancy. Delivery of the infant is the only treatment.

Intrahepatic cholestasis of pregnancy causes itching and increased alkaline phosphatase, bilirubin, AST, and ALT. The condition tends to recur in subsequent pregnancies.

ACUTE LIVER FAILURE (ALF)

ALF is characterized by acute liver injury resulting in coagulopathy, typically INR (international normalized ratio) > 1.5 and encephalopathy in a previously healthy individual. To classify as ALF, the duration of liver disease must be < 26 weeks. There are a variety of causes, but the 2 main etiologies of ALF are drug-induced and viral hepatitis. Other causes include metabolic disorders, acute fatty liver of pregnancy, HELLP syndrome, and hypoperfusion of the liver (e.g., shock, hepatic vein thrombosis). Acetaminophen is the most common cause of ALF in the U.S.

In addition to the abnormal INR and encephalopathy (ranging from behavioral changes to coma), other clinical manifestations can include:

- Hepatomegaly
- Jaundice
- RUQ tenderness
- Pruritus
- Anorexia
- Fatigue
- Ascites

The typical abnormal laboratory findings include:

- Prolonged PT and INR > 1.5
- Elevated aminotransferase levels
- Low platelet count ($\leq 150,000$ cells/ μ L [150×10^9 /L])
- Elevated bilirubin level

It is important to determine the cause of ALF (which can be established in up to 80% of patients) because that influences therapy. Other laboratory tests that can help determine the cause include:

- Acetaminophen level
- Viral hepatitis serologies
- Toxicology screen
- Autoimmune markers
- Ceruloplasmin level (if Wilson disease is suspected)

Doppler U/S is the initial imaging study obtained. If further information is needed, order a CT or MRI/MRV (magnetic resonance venography). If these imaging

studies and laboratory testing fail to reveal the etiology, liver biopsy is performed and may aid in the diagnosis of malignancy, Wilson disease, atypical hepatitis, and acute fatty liver of pregnancy.

Management includes treatment of the underlying cause, managing complications, and providing nutritional support. Consult gastroenterology. If present, correct hypokalemia, hyponatremia, and hypoglycemia. Monitor for cerebral edema and treat with mannitol if needed. This condition can deteriorate rapidly, and it is imperative to contact a transplant center as soon as possible to initiate transport because the only definitive treatment is liver transplant. There are prognostic models that help determine probability of recovery, but the main predictive factors are degree of encephalopathy, age of patient, and etiology of ALF.

LIVER TRANSPLANTATION

PREVIEW | REVIEW

- Know which patients should be considered for a liver transplant.
- Which Model for End-Stage Liver Disease with Sodium score indicates that the patient is a candidate for liver transplantation?

Consider liver transplant for all patients with irreversible end-stage acute and chronic liver disease. The selection process excludes many of these patients. Patient selection is commonly made by a liver transplant committee at the liver transplant center. The process is inexact, and the waiting period for a liver is often > 1 year. So, evaluate patients with chronic, progressive liver disease early in the course of the disease.

The Model for End-Stage Liver Disease (MELD) scale gives a fairly accurate, short-term (3- to 6-month) prediction of mortality risk, and it is used to prioritize organ allocation for liver transplant. It uses bilirubin, creatinine levels, and INR (normalized prothrombin time).

$$\text{MELD score} = 3.78 \log_e (\text{bilirubin [mg/dL]}) + 11.2 \log_e (\text{INR}) + 9.57 \log_e (\text{creatinine [mg/dL]}) + 6.43$$

In 2016, serum Na⁺ was added to the MELD score (now called MELDNa), as hyponatremia is strongly associated with mortality in cirrhosis.

Know this about the MELDNa score:

- < 10 = won't be on the transplant list unless patient has a liver tumor
- > 20 = candidate for transplant

Common indications for liver transplant: most types of chronic end-stage liver disease, metabolic liver disease, primary and secondary biliary cholangitis, primary sclerosing cholangitis, and fulminant hepatitis. Cirrhosis with a small, early-stage hepatocellular cancer (HCC) is another indication.

Biochemical indications for transplant in end-stage chronic liver disease: bilirubin 10–15 mg/dL (171.04–256.56 $\mu\text{mol/L}$), albumin < 2.5 g/dL (25 g/L), and a PT > 3–5 seconds above normal (10–12 seconds). Other signs/symptoms suggesting it is time to transplant: intractable pruritus, hepatic encephalopathy, bacterial peritonitis, intractable ascites, and the development of HCC.

Controversial: liver transplant to treat alcoholic cirrhosis.

Absolute contraindications: preexisting advanced or uncontrolled nonhepatic disease (e.g., malignancy, cardiopulmonary disease, HIV), active alcohol or drug abuse, life-threatening systemic disease, and metastatic cancer. There are many relative contraindications, including advanced age.

A prior TIPS (see [Preventing Rebleeds on page 14-62](#)) is **not** a contraindication to transplant. In fact, it is often a lifesaving “bridge” to transplantation.

- **Months:** copper (hypochromic microcytic anemia) and vitamin K (bleeding, high PT/INR)
- **Year:** vitamin A (night blindness), vitamin D (osteomalacia, osteoporosis), selenium (myalgias, cardiomyopathy, and hemolytic anemia), and chromium (glucose intolerance and peripheral neuropathy)
- **Several years:** iron, cobalt (anemia)
- **Many years:** B₁₂ (megaloblastic anemia, neurologic abnormalities like ataxia)

These deficiencies are important. Know them cold! A good way to review this topic is to fill in the following sentence, using the appropriate times, symptoms, and mineral deficiencies described above.

If, after 1–2 (___), a patient on TPN develops (___); suspect (___).

SPECIFIC VITAMINS AND DISEASE

Disease may be due to vitamin deficiencies or overdose.

NUTRITION

PREVIEW | REVIEW

- What is the timeframe for development of vitamin deficiency for each of these: a) water-soluble vitamins, b) vitamin A and D, c) iron and cobalt, and d) vitamin B₁₂?
- What are the symptoms of wet beriberi? Dry beriberi?
- What is the classic presentation of a patient with Wernicke encephalopathy?
- What are the findings associated with excessive continuous ingestion of vitamin B₆?
- Petechiae are associated with which vitamin deficiency?
- Explain how vitamin D is produced and then converted to the active form in the body.
- What does vitamin D deficiency cause in the adult?

SYMPTOM ONSET FOR VITAMIN AND MINERAL DEFICIENCIES

The time until onset of symptoms in vitamin or mineral deficiency varies with respect to factors such as solubility; e.g., recall that vitamins B and C are water soluble, while vitamins A, D, E, and K are lipid soluble. Be alert to the timing of deficiency onset, especially for patients on TPN without vitamin supplementation (and barring other problems):

- **Weeks:** water-soluble vitamins, Mg²⁺ (muscle stiffness and cramps—often causes tetany in patients with Crohn disease), zinc (acrodermatitis and poor wound healing), and essential fatty acids (e.g., scaly skin, hair loss, thrombocytopenia)

Vitamin A Deficiency

Vitamin A deficiency is a major cause of blindness in developing countries. Night blindness is the earliest symptom.

Vitamin A Overdose

Hypervitaminosis A can be caused by eating polar bear liver, but it is much more commonly a result of over-ingestion of vitamin supplements. Symptoms include headache and flaky skin. A single massive overdose causes abdominal pain, sluggishness, papilledema, and a bulging fontanel in infants. In a few days, this is followed by desquamation of the skin and recovery. Chronic overingestion (25,000 U/day) can cause arthralgias, anorexia, dry skin, hair loss, low-grade fever, and hepatosplenomegaly.

Vitamin B₁ Deficiency

Vitamin B₁ is thiamine. Thiamine deficiency causes beriberi. It commonly develops in people who are alcoholic or in patients on chronic hemodialysis.

There are 2 major manifestations of thiamine deficiency:

- 1) **Wet beriberi** symptoms include heart failure, ascites, and often an accompanying peripheral edema.
- 2) **Dry beriberi** is confined to the nervous system:
 - Peripheral neuropathy (symmetrical sensory, motor, and reflex loss)
 - Wernicke encephalopathy (vomiting and nystagmus, ophthalmoplegia, ataxia, and mental deterioration)
 - Korsakoff syndrome (confabulation and poor recent memory and learning)

Thiamine replacement usually cures Wernicke encephalopathy, but it reverses symptoms in only 1/2 of patients with Korsakoff syndrome—and fully cures only 25%.

Glucose infusions can precipitate Wernicke encephalopathy. The classic presentation of Wernicke's is a closet drinker who develops ophthalmoplegia or nystagmus postsurgery. Always give thiamine to an alcoholic patient before starting an IV dextrose solution.

Wernicke encephalopathy is a medical emergency. Immediately give thiamine 500 mg IM or IV. Repeat daily for 3-5 days, then transition to oral dosing.

Vitamin B₂ Deficiency

Vitamin B₂ is riboflavin. B₂ deficiency almost invariably occurs in association with other vitamin deficiencies. Phenothiazines and tricyclic antidepressants increase the tendency to develop riboflavin deficiency. Patients present with a normochromic normocytic anemia, sore throat with hyperemic mucosa and glossitis, cheilosis, angular stomatitis, and a seborrheic dermatitis, especially involving the perineal/scrotal area. Symptoms are reversed with riboflavin.

Vitamin B₃ Deficiency

Vitamin B₃ (niacin, a.k.a. nicotinic acid) deficiency causes pellagra. Niacin is made from tryptophan in the body (so it is not technically a "vitamin"). Niacin deficiency is rare in the U.S. because niacin is now added to grains. It is still seen in carcinoid syndrome, in which tryptophan is depleted, and when isoniazid is used in treating tuberculosis. Presenting signs of niacin deficiency are dermatitis (especially on sun-exposed surfaces), glossitis ("bald tongue"), stomatitis, proctitis, diarrhea, and changing mental status ranging from depression to dementia to psychosis. (Remember these by the **3 Ds**: mucosal dermatitis, diarrhea, and dementia.) Patients may be hyperpigmented.

Vitamin B₃ Overdose

High pharmacologic doses of niacin can cause acanthosis nigricans and cholestatic jaundice. Prevent the flushing and pruritus that often occur at the start of treatment by advising the patient to take ASA 30 minutes before the niacin, and/or in divided doses, or after meals.

Vitamin B₆ Deficiency

Vitamin B₆ is pyridoxine. Deficiency is rare and frequently caused by drugs, but it can also be seen with malabsorption syndromes and chronic alcoholism. The main drug culprits are isoniazid, cycloserine, and penicillamine. Presenting symptoms include glossitis, cheilosis, vomiting, and seizures.

Vitamin B₆ Overdose

Vitamin B₆ excess can cause a peripheral neuropathy with normal motor and sensory function but absent positional and vibratory sensation.

Vitamin B₁₂ Deficiency

Vitamin B₁₂ (cobalamin) deficiency is discussed in the [Hematology](#) and [Neurology](#) sections. It results in macrocytic anemia, smooth tongue, and peripheral neuropathy. Subacute combined degeneration of the spinal cord is rather specific for B₁₂ deficiency; patients initially experience pins-and-needles sensation, followed by loss of vibration and proprioception (position) sensation. Dementia is a rare manifestation of B₁₂ deficiency.

Vitamin C Deficiency

Vitamin C (ascorbic acid) deficiency causes scurvy. Ascorbic acid is vital in connective tissue formation. Scurvy generally occurs in poverty-stricken urban areas. First symptoms of vitamin C deficiency are petechial hemorrhages and ecchymoses; then the patient develops hyperkeratotic papules around hair follicles, hemorrhage into muscles and joints, purpura, and splinter hemorrhages in the nail beds. **Perifollicular hemorrhage** is a rather specific finding. In children, it affects bone formation and can cause intracerebral hemorrhage. Symptoms improve when the normal pool is replenished.

Vitamin C Overdose

Megadose vitamin C intake increases the incidence of oxalate renal stones and can interfere with the absorption of vitamin B₁₂.

Vitamin D Deficiency

Vitamin D deficiency causes rickets in children and osteomalacia in adults. Most vitamin D is synthesized in the skin (from provitamin D + sunlight), but some is absorbed from the gut. In the liver, this vitamin D is then converted to 25-OH-D, and then the kidney further converts it to 1,25-(OH)₂-D, the active form.

25-OH-D is the form typically measured on blood tests. 1,25-(OH)₂-D levels are quite labile and are not routinely measured due to poor reproducibility.

Vitamin D deficiency causes decreased absorption of calcium from the gut and decreased calcium reabsorption by the kidneys. Vitamin D deficiency also stimulates the release of parathyroid hormone (PTH). Early in the course of the disease, the hypocalcemia is blunted by the increase in PTH, which increases absorption of calcium from the gut and leaches calcium from the bones. Therefore, despite a normal or slightly low serum calcium level, patients still develop bone problems.

Symptoms in adults are often solely musculoskeletal pain and weakness.

Main causes of decreased 25-OH-D:

- Decreased production in skin
- Elderly: decreased skin synthesis at > 70 years of age
- Winter: decreased sun exposure (roughly 40% in northern climes deficient by end of winter)
- Decreased intestinal absorption: steatorrhea, insufficient dietary intake
- Patients with kidney disease can develop deficiency of active vitamin D (i.e., 1,25-(OH)₂-D) with normal 25-OH-D levels (see the [Nephrology](#) section).

Consider vitamin D deficiency especially in an older patient who has musculoskeletal pain/weakness and especially if there is a history of fat malabsorption or vegetarianism. After any osteopenia or osteoporosis diagnosis, check 25-OH-D levels.

Vitamin D Overdose

Hypervitaminosis D results in increased calcium absorption from the bowel, hypercalcemia, and hypercalciuria. It probably increases the tendency for calcium renal stones. The hypercalcemia and hypercalciuria seen in chronic granulomatous diseases (such as sarcoidosis and lymphomas) are due to a hypervitaminosis D state, in which there is increased 1,25-(OH)₂-D production.

Vitamin E Deficiency

Vitamin E is an antioxidant. Deficiency is rare and is usually seen in the setting of malabsorption and codeficiency of the other fat-soluble vitamins. Vitamin E-deficient patients can have areflexia and decreased vibration and position sense.

Vitamin E Overdose

Acutely, vitamin E is relatively nontoxic. The main trouble with vitamin E is that large doses can cause a marked potentiation of oral anticoagulants. Long-term vitamin E supplementation is associated with increased all-cause mortality.

ENTERIC FEEDING vs. TOTAL PARENTERAL NUTRITION (TPN)

Given a choice between enteric feeding and TPN, enteric feeding is the better option. Fatty acids are synthesized in the small intestine. The short-chain fatty acid substrates in enteric feedings help maintain the integrity of the small intestinal wall—the loss of which is associated with the onset of multisystem failure. Percutaneous endoscopic gastrostomy (PEG) is often used in patients who cannot swallow. It is a better alternative than the nasogastric tube, and general anesthesia is not required. Contraindications to PEG are delayed gastric emptying and gastric outlet obstruction. In these instances, various types of jejunostomy tubes can be used for feeding.

MALNUTRITION

Simple clues to malnutrition:

- Weight/Ideal weight < 70%
- Lymphocyte count < 1,000/ μ L (1×10^9 /L)
- Low albumin or prealbumin
- Low triceps skin-fold thickness
- Low urine creatinine-to-height ratio: (24-hour urine excretion of creatinine in μ g) $\div$ (height in centimeters) is < 10 in men and < 6 in women.

Greater than 10% weight loss over 6 months indicates a possibility of malnutrition. Albumin is an indicator of nutritional status, but it can also be lower after major trauma or during an infection (due to vascular leakage) or secondary to liver disease (low production) or the nephrotic syndrome. Malnourished patients may be anergic (unable to mount a normal immune response). Triceps skin-fold measurement is good only for long-term assessment of nutritional status. Short-term changes may not be meaningful because of fluctuations in hydration and edema.

Indirect calorimetry units that measure oxygen consumption and CO₂ production are more precise and usually better for determining needed calories for in-hospital, critically ill patients.

Refeeding Syndrome

Refeeding syndrome is a potentially fatal group of complications—resulting from fluid and electrolyte shifts—that can occur with nutritional therapy in malnourished patients. Carbohydrate intake releases insulin and results in cellular uptake of K⁺, phosphate, and Mg²⁺; this causes reduced serum concentrations of these electrolytes.

Chronically malnourished patients (e.g., anorexia nervosa, cancer, short gut)—especially those with resting bradycardia, hypotension, or body weight < 80% of ideal—are at risk for cardiac failure with rapid refeeding. Monitor electrolytes frequently, replace phosphate and K⁺, and use telemetry during the initial days of refeeding to minimize the risk of cardiac failure.

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General Internal Medicine

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PHARMACOLOGY

PREVIEW | REVIEW

- The first-pass effect causes what difference in dosage between oral and parenteral drugs?
- How is volume of distribution related to plasma concentration of a drug?
- What is first-order kinetics?
- Approximately how many half-lives does it take for a first-order drug to reach steady state if no loading dose is given?
- What is zero-order kinetics?
- What is an adverse drug reaction?
- Which drugs are most likely to cause hyperkalemia?
- Which mechanisms are known to cause drug-drug interactions?
- Combining warfarin with which drugs elevates INR?
- What is the most common statin side effect?

OVERVIEW

Pharmacokinetics refers to “how the body affects the drug” (i.e., drug absorption, distribution, metabolism, and elimination). Pharmacodynamics refers to “how the drug affects the body” (i.e., the relationship between the concentration of the drug and the biochemical and physiologic effects). Pharmacokinetics, in concert with pharmacodynamics, determines dose and dosing schedule of a particular drug.

PHARMACOKINETICS

There are 4 main components of pharmacokinetics:

- 1) **Absorption**—the process by which the drug gains access to the bloodstream from the site of drug administration
- 2) **Distribution**—the process by which the absorbed drug moves around the body and is distributed throughout the body tissues
- 3) **Metabolism**—the process by which the drug’s chemical structure changes in order to increase the ease of its excretion
- 4) **Excretion**—the process by which the drug is removed from the body

Absorption

Absorption can be enteral (via gastrointestinal [GI] tract), aerosol (via lungs), dermal (via skin) or parenteral (via IM or IV).

First-pass effect: Oral drugs are absorbed from the GI tract, pass through the portal vein, and then enter the liver. Some drugs are rapidly metabolized by the liver and undergo “first-pass” metabolism, which means the concentration of the drug is greatly reduced before it reaches the systemic circulation. These drugs require a much higher oral dose to reach similar serum concentrations as a parenteral dose of the same medicine. Common drugs that are subject to the first-pass effect include:

- Opioids: meperidine, morphine, and naloxone
- Ca^{2+} channel antagonists: nifedipine, verapamil, and diltiazem
- Some β -blockers: labetalol, metoprolol, and propranolol
- Tricyclic antidepressants (TCAs)
- Some benzodiazepines (BDZs): e.g., midazolam
- Others: e.g., lidocaine, terbutaline

Some drugs—especially the azole antifungals (except fluconazole and voriconazole), iron, and thyroid hormone—require an acidic environment for absorption. Patients taking H_2 blockers or proton pump inhibitors (PPIs) may require a dose adjustment; giving the medication with acid (e.g., vitamin C or orange juice) can help. PPIs can also decrease Ca^{2+} and Mg^{2+} absorption.

Important! The ingestion of cations (e.g., calcium and iron supplements, antacids containing magnesium and aluminum) can interfere with the absorption of thyroid hormone or quinolones.

Distribution

Volume of distribution describes the relationship between the amount of drug in the body and the concentration of the drug (i.e., the amount of space a drug must occupy in order to achieve a certain plasma concentration). The plasma concentration of a drug is inversely related to the volume of distribution, while the half-life is parallel. With increasing age, a decrease in muscle mass and decrease in total body water occurs; this changes the volume of distribution, with a reduction for hydrophilic medications and an increase for hydrophobic medications. As the volume of distribution increases, there is a parallel increase in plasma half-life.

Know: The volume of distribution is the effective volume for determining the total amount of drug in the body and for determining the loading dose. The total amount of drug in the body (D_T) is equal to the apparent volume into which the drug is dispersed (V_D) $\times$ concentration of the drug in the plasma (C_P):

$$D_T = V_D \times C_P$$

So, the volume of distribution is:

$$V_D = D_T / C_P$$

If the tissues hold more drug than the plasma at equilibrium, V_D is large.

Factors that affect the V_D include:

- Plasma proteins—drug bound to protein is inactive and only unbound drug has a biological effect
- Blood flow
- Lipid solubility
- Size of drug

Note that the loading dose does not depend on excretion capability! The loading dose in a patient with renal failure is the **same** as that in a healthy patient, **but** if the drug is cleared by the kidney, the subsequent maintenance dose is very different.

Metabolism

Drug metabolism refers to the biotransformation of a drug to facilitate its elimination from the body. The main site for drug metabolism is the liver.

Know: Most medications given at normal doses are metabolized in linear fashion (the rate of drug metabolism increases in proportion to drug plasma concentration; i.e., by **first-order kinetics**) because drug plasma concentration is well below available enzyme active sites. Metabolism shows **zero-order kinetics** when the drug concentration exceeds the therapeutic range and saturates all enzyme systems, so that the rate of drug clearance remains the same no matter any further increase in the drug's plasma concentration.

Michaelis-Menten pharmacokinetics equation generates the entire spectrum of this occurring with a single drug. It shows first-order kinetics at the beginning, zero-order at the end, and a large nonlinear area in between (Figure 15-1). As a drug's plasma concentration increases, the rate of drug elimination assumes a hyperbolic curve which reaches a plateau when all enzyme systems are saturated.

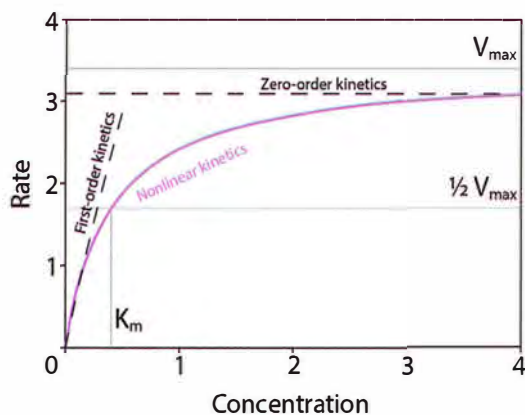


Figure 15-1: Michaelis-Menten saturation curve of an enzyme reaction

First-Order Kinetics

First-order clearance kinetics: The rate at which a drug is cleared is dependent on, and proportional to, the drug

concentration. The rate of drug clearance increases as the plasma concentration of the drug increases—in a linear progression when you plot metabolism vs. concentration. First-order clearance can only be maintained as long as the available enzymatic sites far exceed the substrate molecule. After 1 half-life, the drug concentration in the serum is 1/2 of the initial concentration. It is possible to determine the half-life by checking 2 blood levels at a consistent interval (between doses).

As seen in Table 15-1, 5 half-lives after a patient is started on a first-order drug **without** a loading dose, the drug concentration is 97% of steady state. So, when starting patients on a medication with no loading dose, wait 4–5 half-lives before checking the blood concentration or before reassessing drug effectiveness.

Table 15-1: Half-Lives of First-Order Drugs

Number of Half-Lives	Percent of Steady State
1	50
2	75
3	87.5
4	93.75
5	96.875

Because steady-state serum concentration is often well below the saturability of enzyme systems, linear pharmacokinetics are the norm for most medications.

Zero-Order (Saturable) Pharmacokinetics

Zero-order clearance processes are nonlinear and occur when all the metabolizing enzyme system sites are saturated and the maximum rate of metabolism is achieved (V_{max}). At this point, the rate of drug clearance is a **constant value** despite any increase in drug plasma concentration; that is, it is nonlinear. The drug concentration builds up and can cause toxic effects because the rate of drug metabolism is constant. Steady-state drug serum concentrations increase disproportionately to dose changes.

Excretion

Primary routes of drug excretion include the kidneys (e.g., aminoglycosides, levetiracetam) and the liver (where the drug is metabolized and converted, usually into inactive or less active products after the first-pass effect, and then excreted into the bile).

In a person with cirrhosis, the decreased first-pass effect increases the bioavailability of the drugs that are metabolized in the liver. Clearance is also decreased, so the effective dose of a drug can be very small.

PHARMACODYNAMICS

Pharmacodynamics refers to the relationship between the concentration of the drug and the body's response to the drug. The response can be either desirable (therapeutic effect) or undesirable (adverse effect).

Adverse Drug Reactions

Mechanisms

Adverse drug reaction refers to any unwanted or dangerous effect caused by a drug. Most adverse drug reactions are dose-related exaggerations of the therapeutic effect of the drug. This can be caused by excessive dosing or decreased drug clearance in a patient with hepatic or renal dysfunction. **Idiosyncratic adverse drug reactions** are rare and refer to effects that are **not** dose dependent or related to the known pharmacologic actions of the drug, such as primaquine-causing nonimmune hemolytic anemia in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Idiosyncratic drug reactions are hard to predict, can result from genetic alterations

in the patient, and have variable presentations. Adverse drug reaction reporting is voluntary in the U.S. and can either be submitted to the FDA or to the manufacturer of the product. Adverse psychiatric effects may occur in response to some major drug groups commonly prescribed in clinical practice (Table 15-2).

Drugs That Cause Hyperkalemia

Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) cause hyperkalemia by causing decreased aldosterone synthesis. Spironolactone and eplerenone cause hyperkalemia by interfering with aldosterone binding to its receptor. Potassium-sparing diuretics (amiloride, triamterene)

Table 15-2: Important Psychiatric Adverse Effects of Major Drug Groups Prescribed in Clinical Practice

Drug Group	Major Implicated Drugs	Important Adverse Side Effects
Anticancer/Chemotherapy	5-fluorouracil, asparaginase, bortezomib, ifosfamide, vincristine	More common: cognitive impairment, delirium, psychosis Less common: depression, anxiety, suicidal ideation
Immunomodulators	Cyclosporine, corticosteroids, interferon- α , interleukins, isotretinoin, tacrolimus	More common: anxiety, insomnia, depression Less common: mania, psychosis, agitation, delirium Corticosteroids can also cause dependence.
Cardiovascular drugs	ACE inhibitors, α - and β -adrenergic blockers, antiarrhythmics, statins	More common: fatigue, sleep disorders Less common: depression, anxiety Antiarrhythmics can also cause delirium.
Antiseizure medications	Carbamazepine, levetiracetam, phenytoin, topiramate	More common: sedation, cognitive impairment, agitation Less common: depression, suicidal ideation, delirium
Antiparkinsonians	Anticholinergics, dopamine agonists, entacapone	Agitation, sleep disorders, psychosis, delirium Dopamine agonists can also cause dopamine dysregulation syndrome.
Antiretrovirals	Efavirenz, ritonavir, zidovudine	More common: anxiety, fatigue, sleep disorders, depression Less common: euphoria, agitation, psychosis, delirium
Antitubercular antibiotics	Cycloserine, isoniazid, rifampicin	Sleep disorders, depression, psychosis, delirium
Other antimicrobials	Mefloquine, metronidazole, quinolones	Anxiety, insomnia, psychosis, delirium
Hypoglycemics	Glimepiride, metformin	Anxiety, depression, irritability, cognitive impairment
Anabolic and androgenic steroids	Testosterone and its derivatives	Irritability, mania, psychosis, dependence
Antihistaminics	Cimetidine, promethazine	Sedation, agitation, psychosis, delirium
Analgesics	Aspirin, ibuprofen, indomethacin	Sleep disorders, fatigue, agitation, anxiety, mood changes
Surgery and critical care	Anaesthetics, propofol, suxamethonium	Cognitive impairment, delirium
Respiratory system drugs	β -adrenergic agonists, decongestants	Agitation, insomnia, euphoria, delirium
Muscle relaxants	Baclofen, dantrolene	Anxiety, agitation, mood changes, delirium

Adapted from: Gupta, A. and R.K. Chadda. 2016. Adverse Psychiatric Effects of Non-Psychotropic Medications. *BJPsych Advances* 22(5):325–334.

and trimethoprim/sulfamethoxazole cause hyperkalemia by blocking epithelial Na⁺ channels in the cortical collecting duct. In elderly patients, even normal doses of trimethoprim/sulfamethoxazole can cause hyperkalemia, whereas in the younger patients, it takes higher IV doses, such as those used to treat pneumocystis pneumonia. Any combination of the mentioned medications can multiply the risk of hyperkalemia.

Other Adverse Drug Reactions to Know

Know the frequently tested side effects in Table 15-3.

Table 15-3: Well-Known Drug Side Effects	
Drug	Side Effects
Thiazolidinediones or glitazones (rosiglitazone and pioglitazone)	Edema; worsening heart failure (HF); weight gain
Dihydropyridines	Peripheral edema
Nondihydropyridines (e.g., verapamil)	Constipation
SSRIs	Hyponatremia (by causing SIADH); sexual dysfunction; platelet dysfunction
Topiramate	Blocks carbonic anhydrase in the proximal tubules, causing normal anion gap metabolic acidosis (NAGMA; a.k.a. non-anion gap metabolic acidosis); kidney stones; weight loss
Hydrochlorothiazide	Low Na ⁺ , K ⁺ , and Mg ²⁺ ; high Ca ²⁺ and uric acid
NSAIDs	Increase risk of symptomatic HF in patients at risk for coronary artery disease; gastric ulcers; acute kidney injury (AKI); hyponatremia (from fluid retention)
Bisphosphonates	Myalgias; arthralgias; nephrotoxicity; osteonecrosis of the jaw
Oral contraceptives	Increase risk of deep vein thrombosis/pulmonary embolism (DVT/PE) and hypertension (HTN)
Proton pump inhibitors	Hyponatremia; hypomagnesemia; Vitamin B ₁₂ deficiency; nephrotoxicity by causing interstitial nephritis; <i>Clostridioides difficile</i> -associated diarrhea
Allopurinol	Increases serum concentrations of azathioprine in chronic kidney disease (CKD) Stage III; increases levels of mercaptopurines

Drug Interactions

Mechanisms

Drug interactions occur when a drug’s effect is altered because of another drug, food, or supplement. Certain foods or supplements can alter the absorption of

medications. One such example is grapefruit juice which increases the absorption of certain statin drugs (e.g., simvastatin), resulting in an increased likelihood of side effects. Drug-drug interactions can take place when > 1 drug is taken concurrently. Possible mechanisms for such interactions include:

- Absorption—e.g., PPIs can impair the absorption of iron supplements, magnesium, calcium, and vitamin B₁₂.
- Distribution and protein binding—e.g., administration of diclofenac in a patient on warfarin can increase free warfarin levels and hemorrhagic complications.
- Metabolism—use of enzyme-inducing agents (e.g., phenytoin, phenobarbital) can decrease efficacy of birth control pills. St. John’s wort increases metabolism of statins, cyclosporine, some HIV/AIDS drugs, and oral contraceptives (causing treatment failure). Clarithromycin inhibits cytochrome P450 (which metabolizes colchicine), causing elevated colchicine levels and possibly death. Colchicine can potentially cause death by multiple mechanisms, including rhabdomyolysis, blood cytopenias, myopathy, peripheral neuropathy, liver failure, or severe cutaneous eruption.
- Excretion—use of NSAIDs can potentiate complications of methotrexate by blocking its renal clearance.
- Competition for the same receptor—use of aminoglycosides enhances the effects of neuromuscular blocking agents.
- Same clinical effect—the synergistic effect of aminoglycosides and loop diuretics causes ototoxicity. Aminoglycosides given in combination with cephalosporins increase nephrotoxicity. ACE inhibitors, ARBs, spironolactone and other potassium-sparing diuretics, trimethoprim, and heparin can cause severe hyperkalemia. Combining antiseizure medications and psychiatric medications increases the risk of sedation.

A clinician must take a careful drug history, including over-the-counter medications and supplements. When prescribing medications, carefully consider drug interactions and remember that the fewest drugs for the shortest amount of time is best.

Patients do not always include complementary medications when they provide drug lists, so always inquire about them when taking a thorough history. For example, coadministration of indinavir and St. John’s wort must be avoided because both induce the hepatic cytochrome P450 system, resulting in the decreased bioavailability and effectiveness of indinavir. Always caution patients about complementary therapies that could interfere with their medications.

Warfarin Interactions

Know: Table 15-4 outlines the most important warfarin interactions that result in increased INR (international normalized ratio). Especially know that TMP/SMX can markedly raise the INR within the first few days of therapy.

TMP/SMX displaces warfarin from protein-binding sites and decreases warfarin metabolism. However, **any** antibiotic can affect the INR without affecting warfarin metabolism by decreasing vitamin K-producing bacteria in the intestine.

Table 15-4: Warfarin Interactions (Increased INR)

Most Severe Interactions	Possible Interactions
TMP/SMX	Omeprazole
Erythromycin, clarithromycin, azithromycin	Methotrexate
Amiodarone	Propafenone
Androgens	Prednisone
Azole antifungals	Acetaminophen
Fluoroquinolones	
Vitamin E	
Metronidazole	

Natural products with the potential to enhance the anticoagulant effect of warfarin include glucosamine, ginkgo, ginseng, garlic, feverfew, gulinggao, and dong quai.

Statin Interactions

The most common statin side effect is myalgias. The most life-threatening reaction is **rhabdomyolysis**. Combining statins with drugs that slow their metabolism increases the risk of drug toxicity.

Except for pravastatin, which is metabolized by the kidneys, statins are metabolized by the liver's cytochrome P450 system. Fibrates, clarithromycin, erythromycin, cyclosporine, azole antifungals, protease inhibitors, verapamil, diltiazem, and amiodarone affect statin hepatic metabolism and increase the potential for rhabdomyolysis.

Grapefruit juice also markedly raises the blood levels of some statins by inhibiting initial hepatic metabolism. Lovastatin and simvastatin are most affected; pravastatin is least affected (because it is metabolized by the kidneys).

Fluvastatin and pravastatin have the lowest risk of myopathy. The incidence of serum creatine kinase (CK) elevation with pravastatin was similar to a placebo in a large, double-blind, randomized controlled trial in Scotland.

BIOSTATISTICS

PREVIEW | REVIEW

- Define sensitivity, specificity, positive predictive value, and negative predictive value.
- What does the positive predictive value (PPV) help determine?
- Know how to solve questions for screening tests using the foursquare grid (Table 15-5 through Table 15-8 on page 15-7).
- What happens with sensitivity and specificity if you increase the threshold for what is considered a positive result of a test?
- Define positive and negative likelihood ratios in terms of sensitivity and specificity.
- What is the advantage of a randomized trial?
- What p value is considered statistically significant?

DIAGNOSTIC TESTING AND SCREENING

The Bayesian Foursquare Model

The foursquare is very useful in understanding sensitivity, specificity, and positive and negative predictive values. Let's review the diagram in Figure 15-2 to understand how to use this tool. Assume we are testing a group

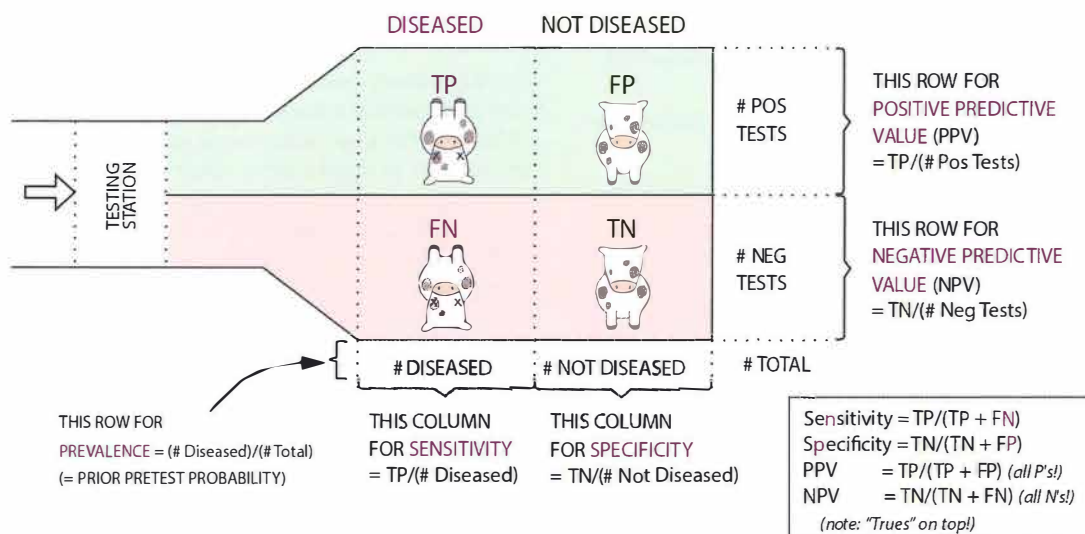


Figure 15-2: The Bayesian foursquare

of cattle for a deadly disease. These cattle go through the testing station on the left, and you direct them either to the upper corral if their test is positive or to the lower corral if their test is negative. You then drive them all the way across the corral to the right—but this disease is so deadly, all the diseased cattle die before they get to the far right of the corral. So, we are left with the 4 sets of cattle in the chart. The upper corral contains those that have the disease and tested positive (true positives = TP) and those that do not have the disease but tested positive (false positives = FP). The lower corral contains those that have the disease and tested negative (false negatives = FN) and those that do not have the disease and tested negative (true negatives = TN). As you read the following text, keep referring to [Figure 15-2 on page 15-5](#).

Sensitivity and Specificity

The **sensitivity** of a test refers to how often a positive result correctly identifies those that **have** the disease. The higher the sensitivity, the lower the number of results that are falsely negative. Sensitivity = true positives (# of patients with the disease who test positive) divided by the total number of patients with the disease (those who test positive plus the false negatives). Thus,

$$\text{Sensitivity} = \frac{\text{TP}}{\text{TP} + \text{FN}} = \frac{\text{TP}}{\# \text{ Diseased}}$$

The **specificity** of a test identifies how often a negative result correctly identifies those who do **not** have the disease. The higher the specificity, the lower the number of patients without disease that are testing falsely positive; i.e., the more certain you are that, given a negative result, the patient does not have the disease. Specificity = true negatives (# of patients without disease who test negative) divided by the total # of patients without the disease (true negatives plus the false positives). Thus,

$$\text{Specificity} = \frac{\text{TN}}{\text{TN} + \text{FP}} = \frac{\text{TN}}{\# \text{ Not Diseased}}$$

The mnemonics **SPIN** and **SNOUT** may be helpful in remembering this distinction.

- **SPIN:** **SP**ecific tests help rule **IN** disease because the false-**P**ositive rate is low.
- **SNOUT:** **Se**Nsitive tests help rule **OUT** disease because the false-**N**egative rate is low.

A test with 100% sensitivity means that there are no false negatives. If your patient has a negative result, he/she does **not** have the disease.

A test with 100% specificity means there are no false positives. If your patient has a positive result, he/she **does** have the disease. It's as simple as that.

Note that sensitivity and specificity reflect how well a test performs. The values remain the same regardless of group size and are unaffected by **prevalence** (i.e., what percent of the population has the disease).

Positive and Negative Predictive Values

The **positive predictive value** (PPV) of a diagnostic test is the probability of disease in a patient with a positive test. The formula is:

$$\text{PPV} = \frac{\text{TP}}{\text{TP} + \text{FP}}$$

(Refer to [Figure 15-2 on page 15-5](#).)

Divide true positives by the total of all those who test positive. The PPV takes into account both the number of true positives and the number of false positives. Unlike sensitivity and specificity, PPV is affected by disease prevalence. If a disease has a low prevalence in a population, the PPV of a diagnostic test will be low. This essentially means that a positive result is more likely to be a false positive than a true positive. Conversely, if the disease prevalence is high, a high PPV indicates a higher chance of a positive result being true positive than false positive. The PPV helps determine the usefulness of a screening program.

The **negative predictive value** (NPV) of a diagnostic test is the probability of not having a disease if the test is negative. The formula is:

$$\text{NPV} = \frac{\text{TN}}{\text{TN} + \text{FN}}$$

(Refer to [Figure 15-2 on page 15-5](#).)

Divide true negatives by the total of all those who test negative. The NPV takes into account both the number of true negatives and the number of false negatives and is affected by disease prevalence. If a disease has a low prevalence in a population, the NPV will be high. This essentially means that a negative result is more likely to be a true negative than a false negative. Conversely, if the disease prevalence is high, a low NPV indicates a higher chance of a negative result being false negative than true negative.

Another way to determine PPV and NPV is described in [Pretest and Posttest Probability on page 15-8](#).

Prevalence and Incidence

We mentioned prevalence above. Let's go over it a bit more. The **prevalence** of a disease is the **percent** of those **with** the disease in the **population being studied**. The concept of prevalence is important in understanding sensitivity/specificity, predictive values, and likelihood ratios (see [Likelihood Ratios on page 15-8](#)), but you usually hear the term itself used with long-term medical conditions (e.g., prevalence of Type 2 diabetes is the percent of people with Type 2 diabetes in the population). The formula is:

$$\frac{\# \text{ Diseased}}{\text{Total \# in studied population}} \quad \text{or} \quad \frac{\text{TP} + \text{FN} \text{ (Everybody who has the disease)}}{(\text{TP} + \text{FN}) + (\text{TN} + \text{FP}) \text{ (The whole population)}}$$

The **incidence** of a disease is the occurrence of **new cases** of a disease within a **specified period of time**; it can also be seen as the probability that a person develops that disease during that period of time. The formula is:

$$\frac{\text{Total \# of new cases of disease}}{\text{Total \# tested during specific time period (The population tested)}}$$

Note that although the Bayesian formula is the same for prevalence and incidence, the determination and use of the terms is different.

Special note on number of columns involved (see [Figure 15-2 on page 15-5](#)): Sensitivity involves only those **with** disease and is determined using the left column of the foursquare; specificity involves only those **without** disease and is determined using the right column. Neither takes into account the **prevalence** of the disease, which is determined using **both columns** of the foursquare. PPV and NPV account for prevalence because each one uses information from both columns.

Working the Foursquare

When an exam question asks you to find sensitivity, specificity, PPV, or NPV, but does not provide all the data, it is very useful to quickly sketch a foursquare grid based on the one shown in [Table 15-5](#). After reading through the problem, we fill in the “givens” first, and then simply add or subtract to fill in the other cells of the table. When all the spaces are complete, we can easily answer just about any statistics question that might be asked.

Table 15-5			
	Disease	No Disease	Total
Abnormal test results	TP	FP	TP + FP
Normal test results	FN	TN	TN + FN
Total	TP + FN	TN + FP	

Scenario: Prevalence of asthma is 1/200 in a population. A test has been developed that screens infants at birth for asthma. For this test, if sensitivity = 99% and the frequency of abnormal tests in the population is 1.3%, what is the ratio of false positives to true positives, and is this a good screening test? To solve, first fill in the foursquare grid with all the known information.

Step 1: Sketch the basic table ([Table 15-6](#)).

Table 15-6			
	Disease	No Disease	Total
Abnormal test results			
Normal test results			
Total			

Step 2: Based on the given information, complete the table in the sequence shown. If the population is not given, assume 1 million.

$$1/200 \text{ prevalence} = 5,000 \text{ total persons with asthma}$$

$$0.013 \times 1 \text{ million} = 13,000 \text{ total abnormal tests}$$

Use subtraction to find the next 2 totals:

$$1,000,000 - 5,000 = 995,000 \text{ persons without asthma}$$

$$1,000,000 - 13,000 = 987,000 \text{ persons with normal tests}$$

Then figure out the other variables in the order shown in [Table 15-7](#): blanks (1), (2), (3), and (4).

Table 15-7			
	Disease	No Disease	Total
Abnormal test results	(1)	(3)	13,000
Normal test results	(2)	(4)	987,000
Total	5,000	995,000	1,000,000

Step 3: Complete the table. Blank (1) is the only blank requiring thought (the rest will easily follow). We are told that the sensitivity is 99%. Using the formula:

$$\text{Sensitivity} = \text{TP} / (\# \text{ Diseased})$$

$$0.99 = \text{TP} / 5,000$$

$$0.99 \times 5,000 = \text{TP}$$

$$4,950 = \text{TP}$$

Note that the 5,000 and 995,000 are the **denominators** in the sensitivity and specificity equations. The others—(2), (3), and (4)—are found by subtraction ([Table 15-8](#)).

Table 15-8			
	Disease	No Disease	Total
Abnormal test results	4,950	8,050	13,000
Normal test results	50	986,950	987,000
Total	5,000	995,000	1,000,000

Once you fill in the entire matrix, you can solve any problem! In this example, $\text{PPV} = \text{TP} / (\text{TP} + \text{FP}) = 38\%$ —**not** a good percentage for a screening test! The ratio of false positives to true positives is high, indicating most positive results are false positives rather than true positives, which also is bad for a screening test. Remember, you will not be able to fill in all the blanks if you are provided insufficient data to solve the problem.

Changing the Threshold for a Positive Result

For deeper understanding: Given a disease and a test for that disease, know what happens if you change the

threshold for what is considered a positive test result. If you **increase** this threshold (i.e., a higher test result is needed for a positive test), you will get **more** negative test results—both true negatives and false negatives. This decreases the sensitivity and increases the specificity. Why is this?

Assume we did this for the previous example. Because the number of people with and without the disease remains the same, the denominators in the sensitivity and specificity equations remain the same. In the sensitivity equation, the numerator **decreases** (decreased TP due to increased FN), so **sensitivity** decreases; i.e., fewer of those with the disease are found by the test. In the specificity equation, the numerator **increases**, so **specificity** increases; i.e., those testing negative are less likely to have the disease.

As a quick trick to remember the above concepts, think of the **threshold** for a positive result as the **horizontal line** in the foursquare that divides the top from the bottom (refer to [Figure 15-2 on page 15-5](#)). As the threshold increases, this line rises, causing fewer positive results and more negative results. As the threshold decreases, the horizontal line moves lower, causing the opposite (i.e., more positive results and fewer negative results).

Look at the sensitivity and specificity formulas at the base of each column. Again, the total number of diseased doesn't change nor do the total number of those not diseased. As the number of TP results increases (when the horizontal line moves down), **sensitivity** increases. Conversely, as the number of TN results increases (when the horizontal line moves up), **specificity** increases. Play around with the horizontal line and you will confirm that whenever any previously negative results are redefined as "positive," sensitivity increases at the expense of specificity, and vice versa.

To see how changes in disease **prevalence** affect FP and FN, use a similar quick trick with a **vertical line** separating Diseased from Not Diseased. As disease prevalence/incidence decreases, the vertical line moves left, and the number of TP and FN decreases while the number of TN and FP increase, and vice versa. Remember that this is solely due to the change in prevalence of the disease, not because of any change in the sensitivity or specificity of the diagnostic test.

Likelihood Ratios

The last derivative from the foursquare that we'll deal with is positive and negative likelihood ratios (LR+; LR-). LR+ ratios deal **only** with those who have tested **positive**. LR- ratios deal **only** with those who have tested **negative**. Because the LR is derived from sensitivity and specificity, it has no association with prevalence of the disease.

A **positive likelihood ratio** tells us how much to increase the probability of having a disease given a positive test result. It is determined using sensitivity and specificity:

$$LR+ = \text{Sensitivity} / (1 - \text{Specificity})$$

Regarding "(1 - Specificity)," think about how this works in this formula. Specificity is the probability that a person who does not have a disease tests negative. So (1 - Specificity) describes the rest—i.e., all those without the disease who **test positive**.

For example, if the presence of peripheral edema has a sensitivity of 80% and a specificity of 40% for the presence of cirrhosis, what is the LR+? Plugging in the numbers:

$$0.8 / (1 - 0.4) = 0.8 / 0.6 = 1.33$$

This is an odds ratio, so it is 1.33:1. It captures how likely it is for a patient with edema to have cirrhosis compared to patients with edema not having cirrhosis. The higher the number, the greater chance of having the disease. In this case, since LR+ is only 1.33, it means that the likelihood of a patient with edema to have cirrhosis is not great (bad test!). An LR+ of 1 means the test is useless.

A **negative likelihood ratio** tells us how much to decrease the probability of having a disease given a negative test result.

$$LR- = (1 - \text{Sensitivity}) / (\text{Specificity})$$

For example: If the presence of expiratory wheezing has a sensitivity of 98% and a specificity of 95% for COPD exacerbation, what is the LR-? Plugging in the numbers:

$$(1 - 0.98) / 0.95 = 0.02 / 0.95 = 0.021$$

Or, expressed as odds, 0.021:1. It captures how unlikely it is for a patient with no expiratory wheezing to have COPD exacerbation compared to patients with no expiratory wheezing who do not have COPD exacerbation. The lower the number, the less chance of having the disease. In this case, since LR- is 0.021 and very close to zero, it means that the likelihood of having COPD exacerbation in a patient with no wheezing is extremely low (good test!). An LR- of 1 means the test is useless. Next we'll see how LR is used to determine posttest probability of disease.

Pretest and Posttest Probability

Pretest probability and posttest probability of disease are the probability of disease before and after a diagnostic test.

Pretest probability is simply the prevalence of the disease in the study population.

Posttest probability is the proportion of patients testing positive who truly have the disease. It is similar to the PPV but also includes a patient-based probability of having disease. With increasing prevalence of disease, the pretest probability of disease increases whether you test positive or negative.

PPV increases with increased pretest probability (prevalence) of disease, but the NPV goes down. This is simply due to the definitions of PPV and NPV. This explains why a negative HIV test in a high-prevalence setting can have a vastly different NPV than in a low-prevalence setting. It also helps explain why a negative stress test is not helpful in the setting of a patient with a high pretest probability

of coronary disease. So, pretest probability, posttest probability, PPV, and NPV are all influenced by prevalence of the disease.

Sensitivity and specificity, however, are independent of disease prevalence. Likelihood ratios, being a function of sensitivity and specificity, are also independent of prevalence.

STUDY DESIGNS

There are 2 primary categories of study design: observational and experimental.

Observational studies attempt to correlate exposures (such as smoking) with outcomes (such as lung cancer) but do not assign patients to one group or another. Most observational studies are either:

- **cohort** studies, in which a group of individuals is followed prospectively over time to see which exposures cause disease (e.g., to determine if there is a causal association between thimerosal exposure in infants and developmental disorders) or
- **case-control** studies, in which people with the disease are compared to those without the disease to identify relevant risk factors (e.g., to see if there is a causal relationship between aspirin and Reye syndrome).

Experimental studies include **randomized controlled trials (RCTs)** where the researcher assigns a single group of patients **randomly** into different study groups, usually an intervention (e.g., a drug or new treatment) vs. a control (e.g., a placebo or an established treatment). The objective is to determine which treatment is better. RCTs are the gold standard of testing for new medical interventions. The strength of random assignment is that it reduces the risk of confounding variables and biases that frequently arise when patients choose treatments themselves. For example, women who choose to take estrogen after menopause may also make other healthy lifestyle choices, leading to an apparent benefit in prevention of cardiovascular disease. However, randomized trials reduce the impact of these other healthy lifestyle variables and show that there is no benefit to estrogen for prevention of heart disease.

Although the randomized trials are less susceptible to bias and are considered the gold standard, observational trials have advantages. They are less expensive than randomized trials and make it possible to study interventions to which we cannot ethically randomize subjects (e.g., smoking, carcinogens).

Type 1 and Type 2 Errors

The **null hypothesis** is the default hypothesis being tested in all studies. It says there will be **no difference** in outcomes of study and control groups. On the other hand, the **alternate hypothesis** is accepted if the null hypothesis is proven wrong (is “rejected”); i.e., there **is** a statistically significant difference in outcomes. If you’re testing a new drug, you certainly hope the study results will indicate the

null hypothesis should be rejected! Get used to hearing phrases such as “accepted null hypothesis,” meaning the study shows no statistically significant difference in outcomes, and “rejected null hypothesis,” meaning it does show a statistically significant difference in outcomes. And “failing to reject the null hypothesis” means there is no difference in outcomes. A little nerdy, but this **is** statistics!

Statistical analyses attempt to prevent 2 common errors:

- **Type 1 error** = concluding there **is** a difference in outcomes when there is not (i.e., rejecting the null hypothesis incorrectly). Type 1 errors are exposed by investigating the **p value** (statistical significance) of the results.
- **Type 2 error** = concluding there is **no** difference when there actually is (i.e., failing to reject the null hypothesis). Type 2 errors are exposed by investigating the **power of a study**.

p Value

The *p* value is a way of expressing a study’s **statistical significance**. The *p* value represents the probability of finding an association (by chance) when one genuinely does not exist. Suppose a randomized trial compares 2 drugs and concludes that drug A is better than drug B. The smaller the *p* value, the more confident we can be that drug A really is better than drug B—and that this is not simply a chance occurrence. Thus, if a study has a *p* value of 0.05, the likelihood that the results are due to chance is only 1 in 20 (= 5% or 0.05). A *p* value of < 0.05 (such as 0.01 or 0.001) implies even **greater** statistical significance, and the null hypothesis must be rejected. A *p* value ≤ 0.05 is considered statistically significant—this is probably all you need to know on an exam!

The Power of a Study

The power of a study is the probability that it can detect a treatment effect if it is present (i.e., that the test can correctly reject the null hypothesis). Suppose a study shows no difference between experimental groups. If the power is 80%, the chance of a Type 2 error is 20%. In other words, you’ll be wrong 1 out of every 5 times in which the study shows no difference. If you increase the power of the study to 95%, the false-negative probability is now 5%, giving you much more confidence in the negative result because it is much less likely to be falsely negative. The only way to increase the power of a study is to use more subjects, to continue for a longer duration, or both.

It is important to note that we restrict this discussion to superiority study design (i.e., a trial designed to demonstrate that one treatment is superior to another).

Meta-Analysis

Meta-analysis is the retrospective analysis of **multiple** studies concerned with the same topic. It generally involves the aggregation of data to try to find a statistically

significant answer from multiple studies that have conflicting or nonsignificant results. By combining the conclusions from multiple studies, we can use the amplified statistical power to better understand the collective effects of an intervention.

Challenges to meta-analysis include identifying study biases and study errors (Type 1 and Type 2), as well as addressing the great deal of heterogeneity that exists between research studies.

Confidence Interval Charts

Confidence interval (CI) charts are used to evaluate most study data.

A CI of 95% is essentially the same as $p = 0.05$. A CI of 99% is similar to $p = 0.01$. In the first case, it reflects the spread of 95% of the data points measured. In the second case, it reflects the spread of 99% of the data points. A consistent result that falls outside the CI of 95% is statistically significant. A CI of 99% is even more significant.

Look at charts A–D in Figure 15-3. Results of a meta-analysis are given in a “forest plot” that shows a solid horizontal line representing the 95% CI of each study being reviewed, with the size of the square on each line showing the weight of that study in the meta-analysis. The results of the meta-analysis are typically shown as a diamond shape at the bottom, with the diamond’s horizontal range being the 95% CI.

Pay attention to the vertical dotted line, which always means **no effect**. In charts A and B, the vertical dotted line represents no response to treatment. In C and D, the vertical dotted line is equal to an odds ratio of 1 (again, no effect). In other representations, the vertical line can be given a specific number that represents the mean from the entire population or from controls.

Let’s see why both 0 and 1 mean no difference in outcomes on the two types of charts. Remember that the null hypothesis is what is being tested in every study, and the outcomes vs. the null hypothesis are being represented in each chart.

If the difference between treatment x and treatment y is assumed to be 0, but 95% of the time the difference is $<$ (or $>$) 0, then there must be a **difference** in treatment outcomes that cannot be ignored—that is, it is statistically significant. This type of chart has a vertical dotted line through 0 (as in charts A and B) representing the null hypothesis.

The null hypothesis can also be expressed as an odds ratio. An **odds ratio** is a way of comparing whether the probability of an event is the same for 2 groups; it commonly compares a control group and the study group (1 = same odds). In such a comparison, the null hypothesis is that treatment outcomes will be the same, and therefore the ratio between treatment group x and treatment group y is 1 (i.e., no difference). In charts C and D, the vertical dotted line is shown with a value of 1.

So, if the 95% CI does not cross the vertical line (representing no effect), then the results are considered **significant** and the null hypothesis is rejected. For example, if you are reviewing a trial looking at response to treatment (i.e., vertical line = 0) and see that the 95% CI is 0.5 to 1.9, you know the study shows a significant response. However, if the 95% CI is -0.7 to 1.6 , then it is a **nonsignificant** result!

Let’s go over these charts so you know how to quickly interpret them:

- Chart A is a meta-analysis with each study showing a significant response to treatment. The diamond shape of the meta-analysis result also does not cross 0.
- Chart B shows a similar meta-analysis in which no study shows a significant response to treatment. The diamond shape of the meta-analysis result also crosses 0.
- Chart C shows a significantly different odds ratio in all studies reviewed; none of the results cross 1 (again, 1 = same odds). The diamond shape of the meta-analysis result also does not cross 1.
- Chart D shows 2 studies with nonsignificant results but 3 others with significant results. The diamond shape of the meta-analysis result does not cross 1, so it shows an overall significantly different outcome with rejection of the null hypothesis. Look at how the weight of the studies elongates the CI in the meta-analysis result!

Effectiveness of Treatment

The **number needed to treat (NNT)** is the number of people who need to be treated to prevent 1 event. NNT is calculated by taking the inverse of the absolute risk reduction (ARR).

First calculate ARR. (ARR is presented as a percentage.)

$$\text{ARR} = \begin{array}{c} \text{control event rate} \\ \text{[i.e., placebo arm]} \end{array} - \begin{array}{c} \text{experimental} \\ \text{event rate} \\ \text{[i.e., treatment arm]} \end{array}$$

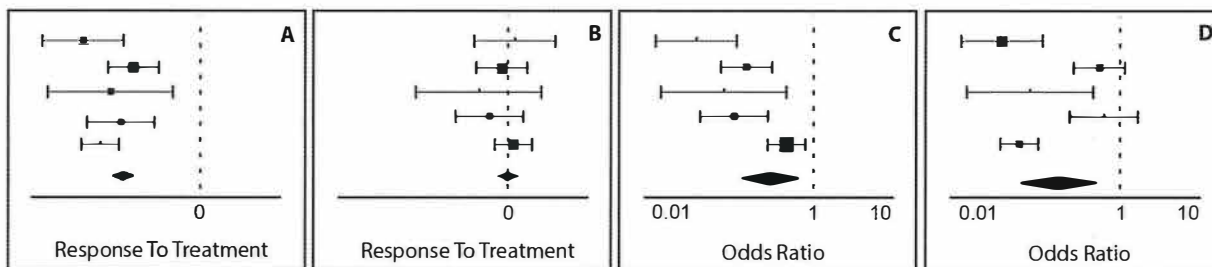


Figure 15-3: Confidence interval charts

Now calculate the NNT:

$$\text{NNT} = 1/\text{ARR}$$

Example: A new drug is studied to see if it can reduce HF mortality. With a p value of < 0.001 , mortality in the treatment arm (active drug) was 10%, whereas mortality in the placebo arm was 30%. This is statistically significant. The NNT helps to determine the impact of the results.

First calculate the ARR:

$$\text{ARR} = 30\% - 10\% = 20\%$$

Remember, you must convert to the decimal form:

$$20/100 = 0.2$$

Now calculate the NNT by:

$$\text{NNT} = 1/0.2 = 5$$

This means 5 patients must be treated with the new drug to prevent 1 HF death.

Alternatively, **NNH** means **number needed to harm**. It is the number of patients who get a drug or intervention for each patient harmed.

Analyzing a treatment requires knowing **both** NNT and NNH. You certainly don't want to treat pancreatic cancer with a drug that has an NNT of 10 of curing pancreatic cancer if the drug has an NNH of 2 with a harm endpoint of death (although it is usually more subtle than this!).

There are a few problems with NNT and NNH, including not having CIs and not being tied to a time span. Often these are added; e.g., NNT is 12 $\pm$ 3 for treatment over 2 years.

Also, note the difference between **relative** risk reduction and **absolute** risk reduction. Relative risk compares the risk of a particular outcome in 2 different groups of people.

$$\text{Relative risk reduction} = \text{ARR} / (\text{control event rate})$$

Recall, in our example, the ARR is 20% and the control event rate (i.e., mortality in the placebo arm) is 30%. Therefore, this drug has a relative risk reduction of 66.7% (20/30) and an absolute risk reduction of 20% (30% [placebo] – 10% [active]). Both reflect clinical importance, but relative risk is sometimes used preferentially. For NNT and NNH, always use **absolute** risk reduction.

Using the above example, if the treatment and mortality numbers were to be changed to 1/100 and 3/100, respectively, the NNT would change from 5 to 50 because the absolute risk reduction is now 2% instead of 20%. But the relative risk reduction is still 66.7%! Again, always use **absolute** risk reduction for NNT and NNH.

Now let's try to calculate NNH with an example.

Drug Y is a new drug for the control of hypertension (HTN). It was found to be as effective as an existing drug Z. However, drug Y causes acute kidney injury (AKI) in 8% of the population compared with 6% caused by drug Z. What is the NNH for drug Y as compared to drug Z?

Just like ARR is calculated for NNT, absolute risk increase (ARI) is calculated for NNH:

$$\text{ARI} = 8\% - 6\% = 2\%$$

Remember, you must convert to the decimal form.

$$2/100 = 0.02$$

Now calculate the NNH by:

$$\text{NNH} = 1/\text{ARI} = 1/0.02 = 50$$

Therefore, for every 50 patients treated with drug Y compared to drug Z, 1 additional patient will develop AKI.

ETHICS

PREVIEW | REVIEW

- Name a scenario in which a physician can ethically have a sexual relationship with a current or former patient.
- You see a colleague drinking shots in a bar shortly before his 12-hour shift in the emergency department. Are you obligated to inform anyone?
- What is an advance directive?
- What are the types of written advance directives?
- What purpose does a durable power of attorney for health care serve?
- What is a living will?
- About 6 months ago, a man with terminal cancer decided to invoke a living will that states he refuses all life support in case of cardiopulmonary arrest. Today, he presents to the emergency department in severe distress and says he wants everything done, including intubation. His family does not want anything done; you have the signed living will at the bedside. What should you do?
- Know all the scenarios at the end of the Ethics topic!

OVERVIEW

The "American College of Physicians Ethics Manual: 7th Edition" (2019) provides a detailed review on medical and professional ethics.

PHYSICIAN'S DUTY AND PATIENT'S RIGHTS

The physician's duty to the patient is based on 4 principles that are the basis for all ethical physician-patient interaction:

- 1) **Beneficence:** the duty to act in the best interests and welfare of the patient and the health of society
- 2) **Nonmaleficence:** the duty to do no harm to the patient

- 3) **Autonomy:** helping the patient make free, uncoerced choices
- 4) **Justice:** the duty to provide fair and impartial opportunities for enhancing life

Let's look at specifics.

The patient's right to accept or refuse health care is based on 2 principles:

- 1) The philosophical concept of personal autonomy—a value held close to the heart in our culture
- 2) Common law right of self-determination

Patients should be able to choose and follow their own ideas and plans for their lives. Constraint of a person's free choices is permissible only when these choices infringe on another person's rights and welfare. Paternalism—the practice of overriding or ignoring preferences of patients in order to benefit them—used to be the standard of interaction between the physician and patient. Today, except for certain cases (mental illness and some emergencies), paternalism is considered ethically improper. Patients should be active participants in the decision-making process. Doctors must obtain their patients' informed consent, which is defined as the willing acceptance of medical intervention after adequate disclosure by the physician of the nature of the intervention and all its risks and benefits.

Patients are entitled to the disclosure of the following:

- The patient's current medical status with the probable course, whether medical intervention is used or not
- The medical interventions that may help and the risks associated with them
- The physician's opinion about other alternatives
- The physician's own recommendations based on best clinical judgment

Physicians are responsible for caring for patients with contagious infectious diseases. It is deemed unethical by the American College of Physicians (ACP) for physicians to refuse care for patients with HIV/AIDS, hepatitis viruses, multidrug-resistant tuberculosis (TB), and influenza because of a physician's own fear of becoming infected. It is assumed that the physician takes appropriate infection control precautions.

Physicians are responsible for providing honest information on disability claim forms and should not attempt to assist a patient in fraudulently obtaining disability benefits.

Generally, physicians should avoid caring for close family members and friends.

It is **unethical** for physicians to have any sexual relationship with a current or former patient, regardless of who initiates the relationship. Quite a few former patients continue to feel dependency toward the physician even after the culmination of their professional association.

Moreover, a physician may exploit the knowledge gained from previous encounters with the patient. Because of these factors, a physician should consult with a colleague or other professional before becoming sexually involved with a former patient. Every situation is unique, and the ACP manual does not go into deeper details. The ethics document from the Federation of State Medical Boards says that physicians cannot even have sexual relationships with the relatives of existing patients.

With the increasing use of the internet, **telemedicine** has flourished rapidly. However, its ethical side has to be kept in mind. In cases in which a physician is providing care to a new telemedicine patient, the physician must use technically appropriate audiovisual technology to establish a relationship before rendering care.

A physician may use e-mail to communicate with the patient; however, the consent of the patient must be obtained prior to any e-mail communications. Using e-communications has other benefits too, such as being environmentally friendly.

Also gaining significant traction lately is **precision medicine**, which uses patient-specific profiles, genetic and genomic data, and clinical and environmental factors to assess individual risks and tailor prevention and disease-management strategies. Genomic testing, which is at the heart of precision medicine, can not only show increased risk of disease in a patient but also in relatives, who may not even be aware of the testing. Therefore, consider the analytical and clinical validity of the test as well as its clinical and personal utility before ordering it.

CULTURAL DIFFERENCES

A patient from another country or culture can present some ethical dilemmas. If family members of your elderly patient express the wish that their grandmother not be told about a terminal illness such as cancer, you can explain to your patient in front of her family that she is very sick and ask whether she wishes to know her diagnosis. It is up to her to express whether she wishes to direct her own care or designate her family members to make decisions regarding her care. This can then be considered an **authorized delegation** of decision-making authority. If the patient says she wants to know everything and make her own decisions, you must abide by the patient's wishes.

DISCONTINUING PATIENT RELATIONSHIPS

Physicians can sever relationships with patients so long as care is available elsewhere by another physician and the patient's health is not placed at risk. The physician must give the patient written notice of intent (usually 30 days) and must request approval from the patient for transfer of medical records to the accepting physician. If this process is not followed, legal action can be taken for physician "abandonment."

MEDICAL RECORDS

The physical chart belongs to the hospital or physician, but the information in the chart belongs to the patient. If requested, you must release the entire chart to the patient, and you cannot hold the chart “hostage” to compel payment for services. However, it is legal to charge a reasonable fee for copies.

Electronic health records (EHRs) and computer use facilitate patient care and should align with physician’s ethical duties in supporting the patient–physician relationship. Physicians must observe due diligence in using the copy-and-paste feature in EHRs to ensure it reflects their own thought processes regarding the patient encounter. EHRs provide remote access, allowing physicians to participate in the care of their patients off-site, but also present challenges such as unauthorized disclosure and use of protected health information.

CONFIDENTIALITY AND PUBLIC WELFARE

The personal and medical information that a physician obtains from a patient is ethically and legally confidential. **But!** In general, if the condition or disease of a patient can endanger other persons, the physician is legally and ethically obligated to report the situation to the appropriate parties.

Many specifics are straightforward and are addressed with legal statutes. Common examples are certain conditions that could affect the operator of a motor vehicle (e.g., seizures and severe cardiac arrhythmias) and sexually transmitted infections (STIs). Other diagnoses are more difficult. A patient with a serious, highly infectious disease (e.g., TB, meningococemia) should not be allowed to infect others. These patients can be held against their will if their behavior is a threat to others. Some infectious diseases may necessitate informing the patient’s employer (e.g., health care worker, food worker).

In some states, adolescents can consent for some services without parental involvement. **Know the laws of your own state in this regard.** Adolescent consent for contraception is protected under federal law by language in the federal budget that restricts individual states from passing teen contraceptive laws if that state receives federal subsidies for health care. Therefore, adolescent consent for birth control is acceptable in all states. Consent for abortion services, however, is state dependent.

PHYSICIAN–PHYSICIAN vs. PUBLIC WELFARE OBLIGATIONS

The physician should **not** allow **any** incompetent or unethical conduct by other physicians. If you **know** of such conduct, present the evidence to the appropriate authority, such as the Inspector General for the Department of Health and Human Services (HHS),

the U.S. Attorney for the region, or the division chief or ethics committee of the hospital. Most state and many county medical societies offer confidential treatment of impaired physicians. Physicians who strongly suspect another physician is chemically impaired are obligated to urge the physician to seek treatment. If this impairment may affect medical competence, the obligation is to report the “credible evidence” to the local licensing board. **Note:** A physician must **not** act only based on hearsay—there must be credible evidence before reporting it.

PHYSICIAN ERROR

Physicians must disclose to the patient **any** errors in judgment and procedure when the information is deemed “material to the patient’s well-being.” In general, one must always disclose errors—disclosure is **not** equivalent to admitting negligence.

DRUG RESEARCH

It is unethical to use socioeconomic differences in choosing patients for a drug study unless the socioeconomic status is considered a variable. For example, one cannot ethically test a drug only on those who can pay for it. Conversely, one cannot ethically offer a free drug for research only to those in a lower socioeconomic status.

FINANCIAL CONFLICTS

The ACP ethics document is very clear that certain financial relationships are unethical:

- Physicians **must** disclose to patients if they intend to refer patients to a facility or research study in which the physician has a financial stake.
- A physician should not refer patients to a care facility where the physician holds a financial interest but is not employed.
- A physician may not pay another physician for referrals.
- A physician may not receive payment or gifts (even “small ones”) from device manufacturers or pharmaceutical companies in exchange for recommending or using their products.
- Physicians should not sell products out of their offices **unless** they are meeting an unmet need of the community (e.g., selling crutches or walkers in a small town). Physicians should not sell supplements or cosmetics out of their offices.
- Physicians should not use unsubstantiated or false statements in advertising nor should they omit necessary information.
- Physicians can and should act as expert witnesses to benefit society, but they cannot accept payment in exchange for biased testimony. Fees charged should be for “reasonable time and expenses.”

ADVANCE DIRECTIVE

An advance directive is a set of instructions that a competent person with decision-making ability develops to dictate his/her care if he/she is incapacitated. There are 2 types of written advance directives: a durable power of attorney and living will. A durable power of attorney for health care enables a patient to nominate a surrogate to dictate his/her care if the patient is unable to do so. The patient can also specify how much authority they are delegating to their surrogates. A living will enables a patient to outline the treatments he/she would like to have if he/she loses decision-making capacity.

Remember that the patient has a right to change his/her mind! For example, “Joe” has a living will stating no life support. If he comes into the emergency department and requires intubation to survive—and states that he has changed his mind and wants all possible treatments available—then you honor his current decision.

Know that fluids and nutrition are ethically regarded as the same as other forms of treatment, and patients can address the desire for discontinuation of fluids and nutrition in their advance directives.

CPR AND DNR

Cardiopulmonary resuscitation (CPR) is usually a standing order in a hospital; i.e., it is to be carried out, without specific order, on any patient who suffers cardiac or respiratory arrest. The only time CPR is not done is when there is an **order** stating as such—a “do not resuscitate” (DNR), “do not attempt resuscitation” (DNAR), or “no code” order. The decision about nonresuscitation has 3 considerations that must be assessed:

- 1) Whether CPR would be futile (i.e., that the resuscitation would be unlikely to succeed or, if it did, another cardiac or respiratory arrest would soon follow)
- 2) The preferences of the patient
- 3) Expected quality of life of the patient if resuscitation succeeds

It is the responsibility of the physician to initiate code status discussions with the patient who is terminally ill or has an incurable disease or, if the patient is incompetent, with family members or a surrogate. The attending physician should clearly enter the “do not resuscitate” order in the patient’s chart if that is the final decision after discussion with the patient (and/or the family or surrogate). The progress notes should detail the facts and opinions leading to that decision.

MEDICAL CARE DECISIONS

Decision-Making Capacity and Competency

The **decision-making capacity** refers to the ability of the patient to comprehend, evaluate, and choose among realistic options. Decision-making capacity

is determined by the physician and at times can be difficult to determine. In general, patients with decision-making capacity should be able to understand the indications for the intervention, the benefits and adverse effects, and the consequences of using other less effective interventions or of not acting. In cases in which a patient lacks decision-making capacity, care must be delivered based upon the patient’s advance care wishes. If the patient does not have any advance care wishes specified, a physician must try to find out what the patient would have wanted in these circumstances based upon the patient’s belief systems (substituted judgment).

Competency refers to the legal determination of one’s decision-making capacity. Most decisions on patient care are carried out without need for competency hearings in a court of law.

There are many transitory or reversible conditions that can interfere with decision-making capacity. Examples are anxiety, depression, drug-induced confusion, infection, and abnormal metabolic states. The waxing and waning symptoms of certain conditions, such as organic brain syndrome, is a manifestation of pathology, and the patient should be considered to have impaired capacity.

Surrogacy

A “surrogate” or “proxy” is a person who is authorized to make decisions on behalf of an incapacitated person. Traditionally, the next of kin is considered the default surrogate. In some states, there is a well-defined list of the priority for next of kin to assume surrogacy, while others have no list at all. Know your state laws regarding proxy decision makers! The most definitive option is for the subject to give someone **durable medical power of attorney**. This gives a particular person legal authority to make all medical decisions for the subject.

The surrogate’s decisions must promote the patient’s wishes and welfare. If the patient has expressed certain wishes on a topic regarding medical intervention in the past, the surrogate **must** use that knowledge in the decision-making process. This is known as **substituted judgment**. To help the surrogate use substituted judgment, ask this question, “If the patient could understand the current medical situation, what decision do you think he/she would make?”

If the surrogate has no knowledge of the patient’s wishes, then the surrogate should make decisions based on the patient’s welfare. Welfare considerations include suffering, preservation of life, restoration of function, and quality of life. This is also stated another way. When the patient’s specific wishes are unknown, decisions should be based on what a reasonable person would want in similar circumstances.

The surrogate's authority ends when the patient dies (e.g., a surrogate is not able to give consent for autopsy). Organ donation decisions are best made in advance of illness. However, to avoid conflicts of interest or a perception of conflicts of interest, organ donation should be broached with the surrogate at the appropriate time by organ procurement specialists who are separate from prospective donors' health care providers. Health care providers of prospective recipients should not be providing care to prospective donors for similar reasons.

Remember: The "contract for health care" is between the physician and the **patient**, not the patient's family or other surrogate. The physician always acts in the best interest of the patient, which may or may not be the same as the interest of the family or surrogate.

Emergency Situations

For patients unable to express their preferences, the physician may perform life- or limb-sustaining emergency interventions under the presumption that the alternative would be death or severe disability. All states have statutes empowering health care professionals to hold certain patients with psychiatric conditions against their will for medical and/or psychiatric treatment, although the specific logistics vary from state to state.

Suicide Attempts

Suicide attempts should always be treated despite the wishes of the patient. These patients are "crying for help." They are also often in a pathological mental state that may be transitory or treatable. For example, a patient may have intermittent suicidal ideations but no weapon and no plan. Take this in contrast to a patient who has purchased a gun and wants to shoot himself. Clearly, the latter is at much higher risk and should be placed in an inpatient psychiatric facility. This could be voluntary if he agrees, but if he does not agree, he should be warranted. These situations are different from the patient who refuses life-sustaining treatment. The difference is that with refusal of care, the patients are not killing themselves—rather, they are refusing help that will keep them alive.

Brain Death

Physicians can stop treatment if a person is "brain dead" (i.e., has loss of entire brain function, including the brain stem). An EEG is **not** required for diagnosis. Organs can then be donated **without** patient's prior consent if the next of kin (or surrogate) gives permission, knowing that the patient would want that.

ETHICS SCENARIOS

Some scenarios:

- 1) A patient is brought to the hospital unconscious and near death with a terminal disease. What should the physician do in these instances?
 - The patient has a properly executed living will that states no intubation, CPR, etc.
 - The patient has no living will, but family members say they strongly prefer the patient be allowed to die with dignity and without heroics.
 - The patient has a properly executed living will that states no intubation, CPR, etc., **but** family members (many of whom are lawyers) say they want all possible heroic measures to be taken—and threaten dire consequences if their wishes are not followed!
- 2) A patient comes to the emergency department with an extensive, acute MI, has decision-making capacity, and refuses to be admitted despite being fully informed of the possible consequences. What do you do?
- 3) A ventilator-dependent patient requests in writing to be extubated. What do you do?
- 4) A female health care worker who is found to have hepatitis B antigen positivity requests that you not tell her supervisor at the hospital where she works.
- 5) A man is diagnosed with inoperable metastatic cancer. He states to his physician that he does not want his wife to know.
- 6) A newly married man just finds out that he has a serious autosomal dominant genetic disease (e.g., Huntington disease). He requests that the physician not tell his wife.
- 7) A man finds out he is HIV-positive and requests that you not tell his spouse. They are sexually active and do not use a barrier contraception.
- 8) A woman with suspected meningococcal meningitis refuses to be admitted to the hospital and wants to go back to work.

Answers:

- 1) The physician should:
 - Follow instructions in the living will.
 - Try to obtain more information and define the wishes of the patient, **not** the family.
 - Follow instructions in the living will because the contract is between the physician and the patient. (Besides, so far, all living wills have upheld in court.)
- 2) You must show empathy for the patient's situation yet attempt to dissuade the patient from leaving. If the patient still decides to leave, it is prudent

to have the patient sign out “AMA” (i.e., against medical advice), although the patient is not legally required to do this. You cannot stop patients from leaving unless you think they are mentally incompetent or a danger to others (e.g., they intend to drive home).

- 3) You need more information (e.g., Is the patient mentally competent and fully informed?). This is a problem with probable far-reaching consequences—not just for you, but for the patient’s other doctors, the hospital, and the patient’s family. The 1st step is to contact the hospital’s palliative care team and/or ethics committee. You may also need assistance from the patient’s other doctors, family, and psychiatric and social services.
- 4) This health care worker has a direct obligation not to cause harm to the patients with whom she interacts. If she refuses to inform the hospital infection control team, then you are obligated to do so.
- 5) Although the physician can strongly encourage the man to inform his wife of the situation, communicating this to the spouse is ultimately the patient’s obligation and not the physician’s.
- 6) In this case, the physician should first strongly encourage the man to tell his wife. If that fails, the last resort is for the physician to tell the wife because of the risk of harm to future children.
- 7) In all HIV cases, the physician must make sure that anybody at risk (e.g., through sexual contact or IV drugs) is notified. Whenever patients say they are going to do the notification, the physician must ensure it is done. Usually, this obligation is taken care of by the state health department.
- 8) This patient can be held against her will for the good of public welfare.

PALLIATIVE CARE

PREVIEW | REVIEW

- What is palliative care?
- What are the mechanisms for neuropathic and nociceptive pain?
- Which opioids should be avoided in renal failure?
- What should always also be started when starting an opiate?
- Describe the adjuvant medications that can be used for each source of pain.
- Which drugs are helpful to treat metastatic bone pain?
- Which drugs are used to treat visceral pain?
- Which antiemetics target the chemoreceptor zone?
- What is hospice care?

- What is the principle of “double effect” in symptom relief?
- Describe the steps in a terminal extubation.
- Which opiate causes neurotoxic effects when used in end stage renal disease?

PALLIATIVE CARE DEFINED

Palliative care provides an extra layer of support for patients with advanced illness and their families through an interdisciplinary team that focuses on improving quality of life and reducing suffering. It aims to alleviate physical, emotional, social, and spiritual suffering, regardless of a patient’s treatment preferences, and to educate the patient about the natural disease trajectory. The quality of life in patients with advanced illness is considerably improved by proper pain and symptom control.

SYMPTOM MANAGEMENT IN ADVANCED ILLNESS

Good symptom management at the end of life requires understanding the patient’s goals and preferences as you evaluate and treat their symptoms. Patients focused on life-prolonging treatments require a thorough evaluation of the cause of their symptoms. Patients with a comfort focus require less evaluation. Understanding and treating the reversible causes of symptoms in the context of the patient’s goals is the key to good symptom management. Do **not** just give morphine!

PAIN MANAGEMENT IN ADVANCED ILLNESS

Source of Pain

Understand the mechanisms:

- **Neuropathic pain** is caused by damage to the peripheral or central nervous system tissues. Patients use words such as burning, shooting, tingling, stabbing, and painful numbness to describe their pain.
- **Nociceptive pain** is caused by potential or actual damage to tissues that activates nociceptors. The 2 types of nociceptive pain are somatic and visceral:
 - **Somatic pain** is caused by the activation of nociceptors when damage to the body surface or musculoskeletal tissues occurs. Patients use words such as aching, stabbing, throbbing, or squeezing to describe deep tissue damage. “Stabbing” is used if superficial tissues are involved. Pain involving bone is often worse with movement.
 - **Visceral pain** is caused by the activation of nociceptors because of compression, obstruction, ischemia, stretching, or inflammation of the viscera. This pain is usually nonspecific and described as spastic, gnawing, cramping, or vague pressure.

- Nonphysical pain is caused by psychosocial and spiritual factors related to a patient's life-limiting illness. This pain does not respond to medication but can be lessened by exploring the following phrases recommended by Dr. Ira Byock: "Please forgive me," "I forgive you," "Thank you," and "I love you."

Opioids in Advanced Illness

Opioids play a key role in pain management in advanced illness and are used adjunctively to treat neuropathic sources of pain.

National Comprehensive Cancer Network (NCCN) Guidelines for Adult Cancer Pain

The 2020 NCCN guidelines for treating adult cancer pain and opioid titration can be applied when treating most patients with advanced illness. The 1st step in opioid titration is to determine the patient's level of pain using the numerical 1–10 pain scale:

- **Mild pain** (pain score 1–3): Use acetaminophen, an NSAID, or other adjuvant pain medication. Consider titrating short-acting opioids if pain persists. Begin a bowel regimen.
- **Moderate pain** (pain score 4–6): Titrate short-acting opioid. Consider adding a long-acting medication if the patient needs > 3 doses of short-acting opioids in a day. Begin a bowel regimen.
- **Severe pain** (pain score 7–10): Rapidly titrate short-acting opioid using IV opioids and hospitalization if necessary. Convert to long-acting medication once the opioid dose need is determined (see [Opioid Titration](#)). Begin a bowel regimen.

Equivalent Dosing

All classes of opioids have different potencies in both the oral and IV form. Use [Table 15-9](#) when switching from one class or route to another. If using large doses, have another physician or pharmacist double-check your work.

Table 15-9: Opioid Equivalents

Drug	Oral (mg)	IV/SQ (mg)
Morphine	30	10
Oxycodone	20	N/A
Hydromorphone	7.5	1.5
Hydrocodone	30	N/A
Fentanyl	N/A	0.1
Oxymorphone	10	1

Example: A patient is on 45 mg bid of sustained-release (SR) morphine for a total of 90 mg in a 24-hour period. If you switch her to oxycodone, she will require 60 mg of oxycodone in a 24-hour period or 30 mg of oxycodone

SR bid. (90 mg of oral morphine = 60 mg of oral oxycodone because the ratio is 30:20.)

Use the table only as a guide since patients have variations in tolerance to individual opiates. A patient may receive more effective pain relief at a lower-than-equivalent dosage of another opioid, known as **incomplete cross-tolerance**. To account for this effect, reduce the dose by 1/3 when switching from one opioid to another, then up-titrate based on response (see [Opioid Titration](#)). In the example above, instead of switching the patient to 60 mg of oxycodone in a 24-hour period, start the patient on 40 mg of oxycodone (1/3 reduction from 60 mg) to account for the effect of incomplete cross-tolerance.

Fentanyl patches are a long-acting form of fentanyl and are useful in patients who cannot swallow pills or have significant kidney disease. 25 mcg/hour of fentanyl equals 50 mg of oral morphine in a 24-hour period. Only use patches in patients with known opioid requirements and avoid in opioid-naïve patients. Patches take 48–72 hours to reach steady state. **Do not adjust the dose more often than every 3 days!** Additionally, fevers can cause increased release of fentanyl, and cachectic patients may not have full absorption.

Opioid Titration

Patients with advanced illness usually have increasing pain as their disease progresses, and opioid titration is expected. Oral opioids come in 2 forms:

- 1) Short-acting: morphine instant release (IR);
e.g., oxycodone IR, hydromorphone
- 2) Long-acting: morphine sustained release (SR);
e.g., oxycodone SR, fentanyl patch

The 2016 NCCN guidelines for opioid titration include the following key points:

- Use **short-acting** opioids to determine a patient's 24-hour need. Never start an opioid-naïve patient on a long-acting opioid! Once you determine the 24-hour opioid need by adding together the total daily short-acting doses, convert to a long-acting opioid that includes all their prn usage. For example, a patient is started on oral morphine 10 mg q 2 hours prn. She uses 6 doses a day or 60 mg in a 24-hour period. Start her on morphine SR 30 mg q 12 hours.
- Increase a short-acting opioid dose by 50–100% if the pain remains **severe**. When titrating opioids, always start at low doses. If they get no relief with 10 mg of oxycodone IR, you can safely increase to 15 or 20 mg of oxycodone IR with the next dose.
- Short-acting opioids reach peak effect within 60–90 minutes and last 4 hours. Therefore, do not make the prn interval less frequent than every 4 hours.
- Short-acting opioid doses can be safely increased with each dose given. Only increase long-acting opioids every 48 hours. Do not increase a fentanyl patch more frequently than every 3 days.

- Long-acting opioids are typically dosed every 12 hours. Some patients require every 8 hours. Do **not** dose long-acting opioids more frequently than every 8 hours.
- A short-acting opioid for breakthrough pain should be available to all patients on long-acting opioids. This allows the patient to get relief if their long-acting opioid is not fully effective.
- The breakthrough dose is 10% of the 24-hour long-acting dose. For example, a patient is on 160 mg of oxycodone SR and has a 24-hour oxycodone dose of 320 mg. The breakthrough dose is 30 mg of oxycodone IR every 3–4 hours as needed.
- Stick to only 1 long-acting opioid and 1 short-acting opioid prescription. Avoid confusion, polypharmacy, and unnecessary math!
- Pay attention to the bowels! All patients on chronic opioids need a stimulant laxative in addition to stool softeners. Osmotic laxatives like polyethylene glycol are also helpful.

PCA Dosing

IV/SQ opioids onset is < 5 minutes; they are the quickest way to achieve analgesia. Patient-controlled analgesia (PCA) provides a safe and efficient way to determine a patient's opioid need. Elements of a PCA include an opioid, the basal rate, and the demand dose.

Basal rate (mg/hour): This is the amount of medication infused at a continuous rate. Be cautious with the basal rate. The basal rate continues to infuse even if the patient is sedated. It takes 8 hours for a basal rate to reach steady state, so do not adjust the basal rate more frequently than every 8 hours. Avoid an initial basal rate in opioid-naïve patients. Use the first 24 hours to determine their opioid need; then start a basal rate based on that need. For example, if a patient uses 24 mg of IV morphine in a day, start a 1 mg/hour basal rate.

Demand dose: This is the amount of medication given to the patient each time the button is pushed. In opioid-naïve patients, start low (e.g., 0.5 mg IV morphine, 0.1 mg IV hydromorphone). Adjust the demand dose upward by 50–100% if a patient does **not** achieve adequate analgesia. The **lockout interval** is the time between demand doses. Typical lockout intervals are 8–10 minutes based on the drug's time to peak effect. Do not shorten the interval below 8 minutes. Intervals < 8 minutes risk stacking doses before the patient receives the full effect of the drug.

Other Opioid Considerations

Renal Failure

Most opioids are renally cleared. Avoid codeine and morphine when creatinine clearance is < 30 mL/min/1.73 m² (0.50 mL/s/m²). Neurotoxic metabolites can occur. Fentanyl and methadone are the safest in renal failure.

Liver Failure

Most opioids are at least partially metabolized by the liver, so there are no “safer” options. When initiating opioids in patients with end-stage liver disease, start low and go slow. Consider longer dosing intervals and do not add scheduled opioids until the patient tolerates their prn usage.

Opioids to Avoid

Meperidine has a low potency when given orally. Metabolites accumulate in renal failure, with increased risk of seizures.

Methadone can be a very effective agent when used appropriately; however, it has a long half-life and many drug interactions. It also prolongs QT_c. Do not use unless you thoroughly understand the pharmacokinetics and pharmacodynamics.

Managing Opioid Side Effects

Patients develop tolerance to most opioid side effects within the 1st week of being on a stable dose. Encourage patients to continue their opioid for at least 1 week before switching to another due to intolerable side effects such as nausea. Nausea can usually be controlled with scheduled antiemetic dosing during the first week. The one side effect that never improves is constipation. Tolerance to constipation does not occur over time, and all patients on chronic opioids need to be on stimulant laxatives. Osmotic laxatives can be of additional help.

If your patient experiences severe respiratory depression or accidental overdose, give the opioid reversal agent naloxone. If the patient has mild to moderate respiratory depression, avoid abrupt reversal and a potential pain crisis by diluting 1 amp (0.4 mg) of naloxone in 9 mL of normal saline. Then give 1 mL/minute until the patient's respiratory rate returns to normal.

Adjuvant Medications

Adjuvant medications are used to reduce the overall opioid requirement and diminish side effects. There are different adjuvants for different pain syndromes.

Neuropathic pain: Several drug classes offer some relief in neuropathic pain syndromes (Table 15-10). In the **antidepressant** class, TCAs or serotonin norepinephrine reuptake inhibitors (SNRIs) are the most effective. If using a TCA, nortriptyline has the fewest anticholinergic side effects. In the **antiseizure** class, gabapentin or pregabalin are most effective; however, valproic acid and carbamazepine have some utility. Steroids and NSAIDs are used when there is inflammation around a nerve. There are no clinical guidelines that specify which drug class is superior. Most adjuvants take several weeks to reach full effect. If one drug is ineffective or is too sedating, transition to a different agent.

Table 15-10: Neuropathic Pain Medications

Drug Class	Examples
TCAs	Nortriptyline: 10–150 mg hs; start at 10–25 mg and slowly increase
SNRI antidepressants	Venlafaxine: 37.5–75 mg bid; increase every 3–4 days Duloxetine: 30–60 mg daily
Antiseizure medications	Gabapentin: 100–300 mg hs; increase every 3–4 days in divided doses as tolerated (3,600 mg max per day) Pregabalin: start at 25–50 mg tid

Tip: When medications are not relieving pain, consider interventional pain options such as nerve blocks, intrathecal pumps, or epidural injections.

Bone pain is most often caused by bone metastasis.

The following are helpful adjuvants for bone pain:

- Steroids
- NSAIDs
- Bisphosphonates
- External beam radiation

Visceral pain: If visceral pain is caused by obstruction or bowel wall distension, use a nasogastric (NG) tube for decompression. Visceral pain can also be improved with anticholinergic agents, such as scopolamine to reduce GI secretions, as well as steroids to reduce swelling and inflammation. Surgical evaluation is appropriate when aligned with the patient's treatment goals and preferences.

NONPAIN SYMPTOM MANAGEMENT IN ADVANCED ILLNESS

Dyspnea

Dyspnea is the subjective feeling of shortness of breath; it is not tachypnea. A person with normal oxygen saturation, respiratory rate, and blood gas can still feel dyspneic. Use the mnemonic **BREATH AIR** to determine causes and possible treatments based on the patient's treatment goals and preferences:

- **Bronchospasm:** Use nebulized albuterol and ipratropium plus steroids.
- **Rales:** Assess for volume overload. Withhold IV fluids and use diuretics.
- **Effusions:** Consider thoracentesis and/or indwelling catheter if it is recurrent.
- **Airway obstruction:** Modify diet if aspirating.
- **Thickness of secretions:** If thick, use nebulized saline. If thin, use anticholinergic agents such as glycopyrrolate, which does not have as many side effects because it does not cross the blood-brain barrier.
- **Hemoglobin low:** In some patients, dyspnea improves with blood transfusion.

- **Anxiety:** It can be the cause of dyspnea or the effect. If it is the cause, use cognitive behavioral techniques, guided imagery, relaxation techniques, and BDZs. If the patient is anxious due to dyspnea, treat the dyspnea with opioids.
- **Interpersonal issues:** Work with a social worker and a chaplain to address issues that are contributing to distress.
- **Religious concerns:** Utilize chaplains for spiritual distress that contributes to anxiety/dyspnea.

Pharmacologic treatment: Opioids are the 1st line treatment for dyspnea after reversible causes are treated. All opioids are equally effective in relieving dyspnea. Titrate opioids as you would for pain and use long-acting opioids when needed. BDZs are not the 1st line therapy for dyspnea even if the patient is anxious. In anxious patients, treat the dyspnea first with opioids. If they remain anxious after their dyspnea is treated, then consider BDZs.

Nonpharmacologic treatment: Oxygen or moving air (i.e., using a fan) relieves dyspnea as does sitting in a more upright position. Additionally, acupuncture relieves dyspnea in some patients.

Nausea

Understand the pathophysiology of nausea including which receptors mediate the vomiting response. Use antiemetics that target the receptors involved (Table 15-11 on page 15-20). Common sources of nausea include:

- **Cortical:**
 - Increased cranial pressure from cancer in the brain: Use steroids and/or radiation therapy for brain metastases.
 - Anxiety: Use BDZs for anticipatory nausea.
- **Vestibular:** presents as vertigo or nausea with head movements. Vestibular nausea involves cholinergic and histamine receptors. Use anticholinergic medications (e.g., scopolamine patch) or antihistamines (e.g., meclizine). BDZs can also be used as a vestibular stabilizer for acute vertigo.
- **Chemoreceptor trigger zone (CTZ):** The CTZ monitors changes in the blood and induces vomiting when toxins are detected. Medications and metabolic derangements are the most common offenders. Dopamine and serotonin Type 3 (5-HT₃) are the two receptor types involved. Use dopamine antagonists, such as haloperidol and prochlorperazine, and 5-HT₃ antagonists, such as ondansetron, when the CTZ is involved.
- **Gastrointestinal tract:**
 - Dysmotility of the upper gut: Patients describe feeling early satiety. Use metoclopramide to stimulate the serotonin Type 4 (5-HT₄) receptors and dopamine D₂ receptors in the upper GI tract.
 - Infection: Treat the underlying infection with antibiotics if a bacterial source is suspected.

Histamine and 5-HT₃ receptors are involved in mediating nausea. Use promethazine for antihistamine activity and ondansetron for 5-HT₃ receptor antagonism.

- Obstruction: Use an NG tube for decompression. Treat pain with opioids and use an anticholinergic agent to reduce gastric secretions.

Table 15-11: Antiemetics

Drug Class	Source	Examples
Prokinetic agents	Gut dysmotility	Metoclopramide
Antihistamines	Vestibular or intestinal irritation	Diphenhydramine Promethazine
Dopamine antagonists	CTZ	Haloperidol Prochlorperazine
Anticholinergic	Vestibular or intestinal obstruction	Scopolamine
5-HT ₃ antagonists	CTZ	Ondansetron
Corticosteroids	Increased intracranial pressure	Dexamethasone Prednisone
Benzodiazepines	Anxiety Acute vertigo	Lorazepam

Constipation

Understand the cause of constipation when selecting your treatment.

Poor fiber diet: Fiber supplements add bulk to the stool and are effective in patients who have a low-fiber diet. Do not use fiber supplements when motility or poor fluid intake is the problem.

Dehydration: Increasing fluid intake improves constipation in patients who are dehydrated. Osmotic agents such as polyethylene glycol or lactulose increase the amount of water in the intestine, which triggers a bowel movement. Note: Avoid magnesium salts in renal failure patients.

Decreased motility: This occurs in patients with advanced illness and can be caused by medications or insufficient physical activity. Stimulant laxatives, such as senna, increase motility in the intestines.

Use of lubricants: Using lubricants, such as docusate, are only helpful when bowel movements are painful. However, lubricants are not enough when intestinal motility is the cause of the constipation.

Opioid-induced constipation: All patients on chronic opioids should be on a stimulant laxative. If this is not effective, add an osmotic agent and try a stimulant laxative suppository. When stimulants and osmotic agents are not working, selective opioid antagonists, such as methylnaltrexone, antagonize mu receptors in the intestine and are effective in relieving opioid-induced constipation—but only in refractory cases. Do not use

methylnaltrexone if there is intestinal obstruction. Lubricants and fiber are not effective in opioid-induced constipation.

DELIRIUM IN ADVANCED ILLNESS

Delirium is a common symptom in patients with advanced illness. Diagnose and treat any reversible causes of delirium (including infection, medication, and metabolic abnormality) if the treatment is aligned with the patient's goals and treatment preferences. Note: A reversible cause of delirium is found in less than half of all patients who are in the last weeks of life. Use antipsychotics like haloperidol as 1st line treatment for delirium or use chlorpromazine if sedation is needed. Avoid BDZs as they make delirium worse.

FACILITATION OF HOSPICE CARE

Hospice care is a subset of palliative care and is a Medicare benefit available to any patient with a prognosis of ≤ 6 months. The focus is on quality of life and, ultimately, death with dignity. The patient chooses to forgo curative or life-prolonging therapy. Care is provided by a team of individuals (RN, social worker, chaplain, CNA, hospice medical director, bereavement counselor, volunteer) wherever a patient resides or in a hospice facility. Patients receiving hospice care forgo hospitalizations for their terminal illness; however, they continue to receive treatment for diseases unrelated to their terminal diagnosis (e.g., hip fracture repair in a patient with advanced HF). Nearly all commercial insurances also have a hospice benefit.

As in palliative care, the goal of care is to provide what the patient needs—not what the team wants to provide.

Physicians certify patients for hospice care when they have a life expectancy of ≤ 6 months and have a provided diagnosis that meets Centers for Medicare and Medicaid Services (CMS) eligibility criteria. In general, a declining functional status is a poor prognostic sign in many diagnoses. Consider hospice care for these patients.

Here are some disease-specific considerations in qualifying for hospice care:

- **Cancer**—patients with cancer qualify for hospice when they have distant metastatic disease either at the time of diagnosis or if they develop metastases after treatment. A person chooses hospice when they decline further cancer-directed therapy. Cancer carries a high-symptom burden in many patients.
- **Dementia due to Alzheimer disease**—patients with dementia qualify for hospice when they are dependent on others for nearly all activities of daily living (ADLs), are incontinent of bowel and bladder, have limited meaningful communication, and, most importantly, have a complication from their advanced dementia. These complications include

a recent history of 1 of the following: aspiration pneumonia, pyelonephritis, bacteremia, Stage 3 or Stage 4 pressure ulcers, or 10% weight loss in the preceding 6 months. Most patients with dementia have significant custodial needs, but their symptom burden is not as high as patients with other advanced illnesses such as cancer, lung disease, and HF.

- **Heart disease**—patients with heart disease qualify for hospice when they have received optimized medical treatment and continue to have New York Heart Association (NYHA) Class IV HF (symptomatic at rest) or an ejection fraction of < 20%. Other factors that carry a poor prognosis include treatment-resistant ventricular arrhythmias, a history of cardiac arrest and resuscitation, and a history of unexplained syncope. Continue cardiac medications in the hospice setting because they improve symptoms of heart disease. One exception is lipid-lowering agents, which have limited use in patients receiving hospice.
- **HIV**—patients with HIV qualify for hospice when their CD4+ count is < 25 cells/μL or they have a persistent viral load > 100,000 copies/mL plus 1 of the following: CNS lymphoma, loss of at least 10% lean body mass, *Mycobacterium avium* complex bacteremia, progressive multifocal leukoencephalopathy, systemic lymphoma, visceral Kaposi sarcoma, renal failure, *Cryptosporidium* infection, or toxoplasmosis.
- **Liver disease**—patients with liver disease qualify for hospice when their INR is > 1.5, their serum albumin is < 2.5 g/dL (25 g/L), and they have 1 of the following complications of liver disease: refractory ascites, primary peritonitis (a.k.a. spontaneous bacterial peritonitis), hepatorenal syndrome, refractory hepatic encephalopathy, or recurrent variceal bleeding. Patients awaiting liver transplant qualify for hospice while they are awaiting a liver transplant. If they receive an organ, they can be discharged from hospice.
- **Pulmonary disease**—patients with pulmonary disease qualify for hospice when they have severe chronic lung disease of any type that results in disabling dyspnea at rest that does not respond to medical therapy and show evidence of disease progression with frequent exacerbations of their lung disease that requires a visit to the emergency department or a hospitalization.
- **Renal disease**—patients with renal disease qualify for hospice when they choose to forgo dialysis and meet 1 of the following criteria: creatinine clearance < 10 mL/minute/1.73 m² (0.12 mL/s/m²), serum creatinine > 8 mg/dL (707.2 μmol/L), or presence of a sign/symptom of end-stage renal disease. These include uremia, oliguria, intractable hyperkalemia, uremic pericarditis, hepatorenal syndrome, and refractory volume overload. (See [Withdrawing](#)

[Dialysis on page 15-22](#) for more information on how to care for patients who choose to forgo dialysis.)

- **Stroke**—patients qualify for hospice after a stroke when they require assistance for all ADLs and are unable to maintain adequate hydration and nutrition. These patients demonstrate > 10% weight loss in the past 6 months, a serum albumin < 2.5 g/dL (25 g/L), and pulmonary aspiration. Additionally, the patient or family has declined a feeding tube.
- **Amyotrophic lateral sclerosis (ALS)**—patients with ALS qualify for hospice if they choose to forgo invasive ventilation and artificial nutrition/hydration and show signs of impaired respiratory function and nutritional insufficiency. Signs of impaired respiratory function include dyspnea at rest, orthopnea, use of accessory muscles, tachypnea, weakened cough, and daytime somnolence.

COMMUNICATING PROGNOSIS

Patients and families use prognosis when making decisions about treatment preferences. Understanding prognosis helps patients plan for the level of care they might need, determine if a treatment is too burdensome, and make decisions about work and travel. Patients deserve to have clear and honest communication about what to expect with their disease.

Determine how much the patient and family want to know. Some patients want very specific information (e.g., median survivals, probabilities of response); other patients want more general information. Some prefer not to discuss prognosis at all and prefer you talk to their family. Tailor your prognosis discussion to what the patient wants to know.

Deliver the information in a straightforward manner. Be honest about what you know and what you do not know. Avoid giving false hope or being overly optimistic. Do not give specific time frames. Instead use ranges such as days to weeks, weeks to a month or two, months to a year.

Acknowledge and support emotions. Prognosis discussions can be emotionally challenging. Pay attention to the emotions you are seeing and respond appropriately. Do not ignore the emotional weight of the conversation.

Assess for understanding and ensure that you have given the information the patient wants. Patients do not always absorb all the information when it is difficult or negative news. Inquire about their understanding and determine if you've given the patient the information they want.

PHYSICIAN-ASSISTED DEATH AND EUTHANASIA

Physician-assisted death (PAD) (a.k.a. physician-assisted suicide [PAS]) is when the physician supplies the means of death to a patient, such as a prescription

for a lethal dose of medication along with instructions on its use for terminating one's own life.

Euthanasia is when the physician directly administers a lethal dose of a medication with the intention of causing death.

As of 2020, Hawaii, Maine, New Jersey, Oregon, Washington, California, Colorado, Vermont, and the District of Columbia have legalized PAD by legislation, and Montana has legal PAD via court ruling. Many other states are considering voting on legalization of PAD. Euthanasia is illegal in all 50 states.

The latest guidelines by the ACP, Ethics Manual 7th Edition 2019, clearly states that ACP does not support PAD or euthanasia.

Know that respecting a patient's choice to refuse life-sustaining treatment is different from either of these.

Good end-of-life care entails treatment based on many issues. For instance, the ACP Ethics Manual says that, when providing comfort to a dying patient, "... the physician may appropriately increase medication to relieve pain, even if this action inadvertently shortens life." This is known as the principle of "double effect." Hospice and palliative care providers are experts at navigating the various needs of the dying patient and assist in dealing with the concerns and loss of control faced by many dying patients.

DISCONTINUATION OF LIFE-SUSTAINING CARE

Patients or their surrogates can also choose to discontinue life-sustaining devices and interventions. There is no ethical difference between choosing to withhold life-sustaining treatment and choosing to withdraw that therapy once it has started. When a family requests withdrawal of life-sustaining devices such as the ventilator or dialysis, physicians and staff need to support the family in this transition by counseling them on what to expect and addressing any symptoms that may arise.

Withdrawing the Ventilator

Follow these steps when withdrawing a ventilator:

- 1) **Prior to withdrawal:** Preparation is key! Counsel families on what to expect during and after the withdrawal of the ventilator, including that the patient may live for a period of time afterwards. Offer for the family to be present during the extubation if they desire. Ensure adequate medication is drawn up and available and that extra sedating medication is available in the event of significant distress. (See [Symptom Management in Advanced Illness on page 15-16.](#)) Remove all monitors and restraints. Stop all other life-sustaining treatments (e.g., artificial nutrition, pressors, dialysis).
- 2) **Withdrawing the ventilator:** Premedicate with an opioid and benzodiazepine. Set the F_iO₂ to room air and observe for respiratory distress. Adjust

medications as necessary to ensure continued comfort. Once the patient is comfortable on room air, silence the ventilator alarms, remove the endotracheal tube, and suction as needed.

- 3) **After withdrawal:** Observe the patient for any signs of distress including facial grimace or labored breathing. Medicate with bolus doses of opioids or BDZs. Answer any other questions the family has. When the patient dies, ensure that the family has time to spend with the patient.
- 4) **Symptom management:** The 2 most common symptoms after ventilator withdrawal are breathlessness and anxiety. Opioids and BDZs, such as morphine and midazolam, are the routine medications used to achieve symptom control. The usual starting doses include morphine 5–10 mg IV push every 10 minutes prn and midazolam 2–4 mg IV push every 10 minutes prn. Bolus dosing is the quickest way to achieve symptom control. Morphine and midazolam drips can be started; however, morphine drips take 6–8 hours to achieve steady state and are only helpful in patients who are comfortable and will live longer than an hour or two.
- 5) **Secretion management:** Dying patients have difficulty clearing oral secretions. This is especially true in patients on the ventilator who have been loaded with fluids during their ICU stay. Anticholinergic medications reduce oral secretions. Glycopyrrolate is a fast-acting anticholinergic that does not cross the blood-brain barrier. Scopolamine patches are longer-acting but take 24 hours to reach full effect.

Withdrawing Dialysis

The Decision

Patients choose to stop dialysis when dialysis is no longer substantially prolonging life (in the case of advanced illness or multiorgan failure) or the burdens of continued dialysis outweigh the life-prolonging benefits. When requests are made, explore the reasons behind them. In patients with a favorable prognosis, make attempts to address concerns that can be fixed (untreated depression, frustration with the mechanics of dialysis, or inadequate social support). However, once you have attempted to address the patient's concerns and you determine the patient has made a fully informed choice based on his/her goals and values, you should honor the patient's decision to stop dialysis.

Communication and Care Planning

Counsel patients on what to expect after dialysis is withdrawn. Median survival after stopping dialysis is 8–10 days but can be several weeks in rare instances. Discuss possible symptoms and how you will address them. Identify a care setting for the patient with the support of hospice services. Discuss stopping other medical treatments that are no longer beneficial once dialysis has stopped.

Symptom Management

Common symptoms after stopping dialysis include:

- Agitation/Restlessness: Address pain and psychosocial distress that may be contributing. Use haloperidol to treat delirium/agitation. Haloperidol is partially eliminated in the urine, so start with a low dose and titrate up.
- Pain: Do not use morphine in patients with creatinine clearance $< 30 \text{ mL/min/1.73 m}^2$ (0.50 mL/s/m^2) due to rapid accumulation of active metabolites that are neurotoxic. Hydromorphone and oxycodone are safer but still can accumulate. Use lower doses of these opioids and monitor closely for side effects. Fentanyl is the safest opioid in renal failure. Remember, certain narcotics are withheld only because their toxic side effects increase discomfort.
- Dyspnea: Use oxygen, positioning, and opioids. Continue fluid restriction. For patients with residual urine output, use high-dose diuretics.
- Restless legs/Muscle cramps: Clonazepam reduces symptoms of restless legs caused by uremia.
- Nausea: Dopamine antagonists such as haloperidol and prochlorperazine treat uremia-associated nausea effectively but can be sedating in this context. Ondansetron is less sedating and is not eliminated by the kidneys.

QUALITY AND SAFETY

PREVIEW | REVIEW

- What is the difference between process measurement and outcome measurement?
- What are balance measures?
- Name the 4 elements of a PDSA cycle.
- Is failure modes and effects analysis used before or after an adverse outcome occurs?
- Define a sentinel event.
- What do six sigma projects attempt to accomplish?
- Name a goal of lean management.
- What is a just culture?
- Why do hospitals use the Hospital Consumer Assessment of Healthcare Providers and Systems (HCAHPS)?
- List 5 accountable care organization (ACO) "never events."
- What is the goal of an ACO?

CLINICAL QUALITY MEASUREMENTS

Performance is measured both in **process** (what we do) and in **outcomes** (what results are achieved). For example,

data showing how often pharmacologic DVT prophylaxis was ordered is a **process measurement**, whereas the number of DVTs that occurred (whether or not prophylaxis was ordered) is an **outcome measurement**.

Balance measures are a set of metrics tracked to show that improvement in one area is not causing problems in a different area.

Well-intentioned measures can have **unintended** outcomes. If a group of doctors is very successful at reducing length of stay in a hospital, it can come at the expense of a higher readmission rate. To balance the length-of-stay measurement, simultaneously evaluate the readmission rate as a balance measurement.

PREVENTION STRATEGIES FOR MEDICAL ERRORS

Preventable Harm

One of the foremost safety goals of all health care providers is to **minimize preventable harm**—a modifiable cause of harm that results from medical care.

There are also adverse events that are considered nonpreventable, meaning the adverse effect occurred as a complication of treatment, not due to a preventable error.

If a patient with pneumonia develops a severe rash after being prescribed a guideline-recommended antibiotic that they haven't previously taken, then the rash is considered a nonpreventable adverse event. Contrast that scenario with the prescribing of an antibiotic that the patient's medical record lists as a severe allergy; that is a case of preventable harm.

The burden of preventable harm on cost and health is unacceptable. A provider can also be crushed by the legal and psychological consequences of harming a patient from a preventable error. The **patient safety-and-quality movement** is heavily focused on reducing the impact of preventable harm.

Plan, Do, Study, Act

The purpose of quality improvement (QI) is to improve service, delivery, and outcomes to a patient population.

QI projects are ideally a team process. Many experienced health care improvement teams utilize a Plan, Do, Study, Act (PDSA) cycle.

The goal of PDSA is to perform small tests of change, analyze those results, and then make adjustments if necessary. When the process is stable and sustainable, it is implemented on a larger scale.

During the **planning** stage, those most familiar with the issue are assembled to work on the project. This includes the frontline providers who have the most knowledge of the problem. By engaging the key stakeholders to work on the plan, they will later be more accepting of solutions they helped create. Planners

identify the current process and outcome and then agree on the desired future outcome. They brainstorm ideas and then develop a plan to achieve that desired outcome.

After identifying an action plan, the team will **do** it by testing the plan on a smaller scale. That provides an opportunity to **study** the results. If data indicates that the hypothesis was unsuccessful, the team needs to revert to the planning stage. However, if results show a favorable outcome, they **act** on it by implementing the improvement for the health care team.

Failure modes and effects analysis (FMEA) fits in the DSA (do, study, act) portion of the PDSA cycle. It is a process improvement (PI) tool used to identify **how** a process might fail and what the **impact** of that failure might be. FMEA is a proactive way to diagnose parts of a new or existing process that need revision before a bad outcome occurs. The hope is to prevent a sentinel event before it happens (see [Sentinel Event](#)).

FMEA example: A team of doctors and nurses decide to do an FMEA on the current ICU pressure ulcer prevention process. They brainstorm various ways the current process may fail and how it can be made safer. They list several items and rate each failure mode on a scale of 1–10 to decide which steps have the highest risk priority. They identify 3 areas the team considers highest risk for an adverse impact on patients at risk for a pressure ulcer and then develop actions for those 3 failure modes to redesign the process ([Table 15-12](#)).

Table 15-12: Pressure Ulcer Risk Assessment

Failure Mode	Cause	Action
Patient not getting turned every 2 hours	Nurses forget	An alarm rings every 2 hours as a reminder
Preventive mattress not getting ordered	Physicians forget	Allow nurses to order for high-risk patients
Skin not inspected daily	Time and staffing; providers forget	Checklist completed at change of shift

Sentinel Event

The Joint Commission definition of a **sentinel event** is “an unexpected occurrence involving death or serious physical or psychological injury, or the risk thereof. Serious injury specifically includes loss of limb or function.”

Any time a sentinel event happens, it must be investigated. After the investigation, there must be a credible plan to prevent a similar event from happening. The root cause analysis and the action plan need to be completed within 45 days of the event.

Root Cause Analysis (RCA)

RCA is a tool used to analyze serious adverse events (or a near miss that could have had a serious outcome). Each RCA uses a structured method that includes data collection, record review, and participant interviews to determine the sequence of events that resulted in the error.

It is not unusual to find multiple contributing root causes. For example, it may be found that a medication error resulted from a combination of poor communication, poor staffing levels, and a flawed system of patient identification. Those identified causes require the implementation of reasonable interventions to alter each faulty process that led to the undesirable outcome.

Lean and Six Sigma

Lean and six sigma are methods used in PI. They are often done together, so the combined term, lean six sigma, is increasingly used in hospitals.

Six sigma projects attempt to reduce variation to increase quality by making a process more predictable and effective.

Sigma is a statistical measurement that indicates performance. When a process achieves six sigma, it means that there will only be 3.4 defects (i.e., errors in health care) per million opportunities. That is a very acceptable rate and is why health care has adopted the six sigma goal from manufacturing industries. Note that achieving six sigma is a goal—and even if the error rate does not achieve six sigma, the point is to improve a process as many sigma levels as possible. (See [Table 15-13](#).)

Table 15-13: Sigma Levels

Sigma Performance Level	Defects Per Million Opportunities
1	691,462
2	308,538
3	66,807
4	6,210
5	233
6	3.4

Lean makes use of the **work team** (as opposed to consultants) to define the problems and find solutions. Lean started in the car manufacturing industry (Toyota) and is increasingly being promoted within the health care industry to perform QI.

The goal of lean management is to enhance customer value by eliminating waste. Steps in a process that do not add value are omitted, with the hope of ultimately improving timely delivery, decreasing the use of supplies, and boosting productivity.

Another ambition of lean is to have a **defect alert system**. Any worker in a Toyota plant can “stop the line” without retribution if they identify a defect or error. Mistakes are easier to fix if caught earlier in the process. Many hospitals have also adopted this safety policy. For example, if somebody notices a break in sterile procedure (emergencies excluded), any associate should feel very comfortable halting the care process to assure the ultimate clinical outcome is defect-free. This concept of “stop the line” is also an initiative throughout the U.S. Department of Veterans’ Affairs (VA) to empower all employees to “speak up” with any concerns to improve patient safety.

Just Culture

Refraining from retribution is an important component of a **just culture**. If employees believe they will be punished for reporting an error (or near error), fear of retribution causes inaccurate reporting, which hinders the redesign of a flawed process.

Having a just culture does not mean that reckless behavior or intentional rule violations are tolerated. Rather, a just culture eliminates punishment for an unintentional human error and instead focuses on redesigning process flaws to improve patient safety.

When the culture of an organization moves from secrecy to transparency, it creates an environment of support. Everyone should be able to speak up without reprisal so that safety vulnerabilities are appropriately exposed. Otherwise, incidents tend to be under-reported, and the same errors are likely to be repeated.

PATIENT EXPERIENCE

Hospital Consumer Assessment of Healthcare Providers

Hospitals throughout the U.S. participate in a patient survey process developed and regulated by the CMS called the Hospital Consumer Assessment of Healthcare Providers and Systems (HCAHPS). There are several tools developed (and being developed) to measure patient experience, but HCAHPS gets a lot of attention because it is tied into hospital reimbursement and the scores are publicly reported. Those are also reasons why physician incentive contracts (particularly for hospitalists) frequently use HCAHPS scores.

While patient satisfaction influences “pay for performance” reimbursement, it has also been shown to improve patient compliance with medications and treatment plans.

HCAHPS surveys, sent to a random sample of patients after discharge, ask patients specific questions about

communication with doctors. There are also measures regarding factors such as nurse communication and cleanliness.

Remember: HCAHPS is a standardized survey that hospitals use to see how patients perceive them. Scores are tied to CMS reimbursement and provide a way for hospitals to compare their patient satisfaction levels to those of other hospitals (since CMS mandates that all hospitals use it!).

Improving the Patient Experience

Physicians are like drivers; we all think we are above average. However, nearly all of us can take some steps to improve patient communication.

Some of the things we can do to help communication include:

- 1) Knock before you enter a room. Ask if it is all right to come in.
- 2) Introduce yourself and leave a card with the patient. A card with your picture helps patients connect a name with a face.
- 3) Explain your role in their care.
- 4) Acknowledge visitors in the room. Ask who they are after you introduce yourself.
- 5) Sit down whenever possible. Standing does not save time, and it gives people the impression that you are in a hurry.
- 6) Use language that patients can easily understand. Medical jargon creates barriers to understanding.
- 7) Always explain what new medications and tests you are ordering.
- 8) Manage patient expectations; e.g., “In a few days, you will be healthy enough to leave the hospital, but you will probably feel fatigued for several weeks.”
- 9) After explaining the plan, always ask if there are any questions.

ACCOUNTABLE CARE ORGANIZATIONS (ACOs)

The accountable care organization (ACO) was introduced in 2009 by the CMS as a shared savings program. It is a health care delivery and reimbursement model that ties the reimbursement to the quality of health care delivered and the total cost of care.

Example: 4 regional hospitals combine their outpatient services to better serve the local population. Primary care physicians and specialists from each of the 4 hospitals participate. The costs of the services are bundled to meet predetermined budgets, which include incentives to meet specific performance improvement objectives.

ACO “Never Events”

“Never events” are events that do occur but should never occur. These events are not reimbursed by CMS as part of the Deficit Reduction Act to promote quality of care and reduction of medical errors:

- Foreign object retained after surgery
- Air embolism
- Death or disability from blood transfusion incompatibility
- Acquiring pressure ulcer (Stages 3 or 4)
- Falls and trauma (including fracture, burn, electric shock)
- Catheter-associated UTI or vascular-catheter infection
- Development of poor glycemic control (e.g., diabetic ketoacidosis [DKA], hyperosmolar hypoglycemia) while inpatient
- Surgical site infection, including mediastinitis following coronary artery bypass graft (CABG)
- Surgical site infection following implantable cardiac device
- Iatrogenic pneumothorax
- Infection and/or DVT/PE following hip or knee replacement
- Death/Disability incurred within a health care facility due to medication error, electric shock, burn, fall, use of restraints or bed rails, or contaminated drugs
- Incident due to a line designated for oxygen or other gas to be delivered to a patient containing the wrong gas or contaminated by toxic substances
- Impersonation of a health care worker
- Abduction of a patient
- Sexual assault within or on facility grounds
- Surgery on the wrong body part or patient
- Wrong surgery on a patient
- Implantation of wrong donor egg or use of the wrong donor sperm in artificial insemination
- Infant discharged to wrong person
- Death/Disability due to patient elopement
- Patient suicide or attempted suicide resulting in disability

The overall goal of an ACO is to provide high-quality, coordinated care to CMS patients while avoiding duplication of medical services and serious medical errors during hospitalization.

PERIOPERATIVE CARE

PREVIEW | REVIEW

- Know the 5-step process used in determining if a patient requires a pre-op cardiac evaluation.
- What is a simple, easy method to assess functional capacity?

- Which patients are started on β -blockers before surgery?
- Know the preoperative screening labs and who gets them.
- Who needs endocarditis prophylaxis?
- What is the blood pressure cutoff for treatment in the perioperative period?
- How do you treat postoperative atrial fibrillation?
- Know the strategies used to optimize management of asthma and chronic obstructive pulmonary disease (COPD) around surgery.
- What is the preferred postoperative management for deep vein thrombosis (DVT) prophylaxis?
- Know diabetic perioperative management. How do you manage insulin?
- What is thyroid storm?
- Who should receive stress-dose steroids?
- Know how to manage postoperative delirium.

OVERVIEW

In the U.S., hospitalists are playing an important role in preoperative medical consultation and perioperative comanagement. The goal of the consulting physician is to minimize any potential risks to the patient undergoing the procedure and to address any complications after the procedure.

You must know how to preoperatively evaluate a patient in order to determine the risks of having a cardiac event in the perioperative period!

NONCARDIAC SURGERY PRE-OP GUIDELINES

Different medical societies have produced several guidelines. Let's look at noncardiac surgery. As of this writing, the 2014 AHA/ACC Guidelines for Perioperative Cardiovascular Evaluation for noncardiac surgery is probably the most widely used and addresses 3 levels of risk for noncardiac procedures (Table 15-14).

Table 15-14: AHA / ACC Risk of Procedure

Risk Level	Procedure
Low	Endoscopy, local biopsy, breast biopsy, vasectomy, cataract surgery
Intermediate	Surgeries: carotid endarterectomy, intraperitoneal, intrathoracic, orthopedic, prostate, head/neck
Major	Surgeries: aortic and major vascular, cardiothoracic, emergent major surgery, long procedures with large blood loss and/or fluid shifts

The AHA/ACC guidelines recommend following 5 steps.

Step 1: Does the patient need **emergency** noncardiac surgery?

- If the answer is yes, then the patient should proceed to surgery. Perioperative surveillance, postoperative risk stratification, and risk-factor management should proceed as best as possible.
- If the answer is no, this is not emergent; so, proceed to Step 2.

Step 2: Does the patient have an **active cardiac** condition? Some of the most common are:

- Unstable coronary syndrome (unstable or severe angina or recent MI, defined as lasting > 7 days but ≤ 1 month)
- Decompensated HF
- Significant arrhythmias: 3rd degree AV block, Mobitz 2 AV block, symptomatic ventricular arrhythmias, supraventricular arrhythmias (includes atrial fibrillation) with uncontrolled ventricular rate (> 100 bpm at rest), symptomatic bradycardia, new ventricular tachycardia
- Severe valvular disease: any symptomatic aortic stenosis, asymptomatic aortic stenosis with gradient > 40 mmHg, symptomatic mitral stenosis

If so, then the patient should undergo evaluation and treatment before noncardiac surgery.

If these are not present, proceed to Step 3.

Step 3: Is the patient undergoing **low-risk** surgery (see Table 15-14)? Here, the guidelines get murky. It is clear in defining superficial as very low risk and major vascular procedures as the highest risk. It lists endovascular abdominal aortic aneurysm repair and carotid endarterectomy as intermediate risk. After listing these specifically, it goes on to state: "The physician must exercise judgment to correctly assess perioperative surgical risks and the need for further evaluation." In general, though, any procedure that is "ambulatory" in nature and does not require hospital admission is usually considered low risk. Other surgeries in this category include all breast surgeries, ophthalmologic procedures, and endoscopic procedures.

So, if you get to Step 3 and the surgery is low risk, proceed with noncardiac surgery; if not, go to Step 4.

Step 4: Does the patient have good functional capacity without symptoms? If so, proceed with moderate- to high-risk noncardiac surgery.

What is a simple, easy method to assess functional capacity? The guidelines recommend using a **metabolic equivalent** (MET) level of ≥ 4. Functional capacity is classified as excellent (> 10 METs), good (7–10 METs), moderate (4–7 METs), poor (< 4 METs), or unknown. 1 MET is equivalent to performing normal ADL.

Think of 4 METs as equivalent to walking 4 city blocks (3–4 mph) or up 2 flights of stairs. 4–10 METs is being able to perform house chores such as vacuuming, mowing the lawn, or lifting furniture. > 10 METs is being able to engage in active sports such as tennis, skiing, and swimming.

So, if the patient can run up stairs or mow the lawn without problems, then the patient likely can proceed with the planned surgery. If the patient cannot, then we go to Step 5.

Step 5: Here, we have the patient who has gotten to Step 5 because of either poor or unknown functional capacity, and we must use clinical risk factors to help us determine if we can proceed with surgery.

The 5 clinical risk factors to ask about are:

- 1) History of ischemic heart disease (history of MI, positive exercise stress test, current chest pain, nitrate use, ECG with pathologic Qs)
- 2) HF history (prior or compensated)
- 3) Cerebrovascular disease history
- 4) Diabetes requiring insulin
- 5) Chronic kidney disease (CKD; creatinine > 2 mg/dL)

The **Revised Cardiac Risk Index** (RCRI) is the clinical risk factors plus an additional point for high-risk surgery, defined as intrathoracic or intraabdominal surgery.

If the patient has > 1 clinical risk factors, consider noninvasive cardiac testing if it will change your management. Otherwise, proceed to surgery with heart rate control. Patients with > 3 clinical risk factors undergoing high-risk surgery (e.g., vascular surgery) will undergo noninvasive cardiac evaluation.

In addition, the guidelines suggest that ≥ 60 days should elapse after an MI and before noncardiac surgery in the absence of coronary intervention.

Hold off on elective noncardiac surgery for any of the following:

- Within 4–6 weeks of bare-metal stent placement
- Within 12 months of drug-eluting stent (DES) placement
- Patients with DES should have at least 6 months (12 months preferred) of dual antiplatelet therapy before elective surgery is even considered.
- Within 4 weeks of balloon angioplasty

CARDIAC AND MAJOR VASCULAR SURGERY PRE-OP GUIDELINES

Note

Know that aortic, major cardiovascular, and peripheral vascular surgeries require a cardiac evaluation.

Risk of Procedure

Risk scenarios you are likely to encounter:

- A low-risk patient who can proceed directly to surgery of any type without noninvasive testing
- A moderate-risk patient with good functional capacity who can go directly to a nonvascular surgery
- A major-risk patient who needs further workup, as defined in the health record prior to going to surgery

Preoperative β -Blockers

β -blockers are helpful in the preoperative state because they can improve postoperative outcomes if started in a select group of patients. In these patients, start β -blockers the day prior to surgery.

Who gets β -blockers?

- Vascular surgery patients with positive preoperative stress tests
- Continue these in patients already receiving them for angina, arrhythmias, or HTN.
- Titrate β -blockers when using them to avoid significant bradycardia or hypotension.
- Patients with ≥ 3 RCRI may benefit from β -blockers.

Pre-Op Screening Labs

The following general guidelines are based on areas of agreement in various societies' recommendations.

Hematocrit:

- > 65 years of age for major vascular surgery
- All surgeries that would/could result in major blood loss
- Not needed for minor surgery!
- CBC is not recommended unless it is cheaper than hematocrit alone.

Electrolytes: not recommended unless history suggests there is a reason to check.

Creatinine:

- > 50 years of age
- Major vascular surgery
- Hypotension is likely.
- Nephrotoxic drugs will be used.

Glucose, liver function tests, PT/PTT, U/A: not recommended unless warranted by clinical signs/symptoms.

ECG:

- All vascular procedures
- Nonvascular procedures:
 - Men > 45 years of age
 - Women > 55 years of age
 - Known cardiac disease

- Clinical evaluation suggests possible cardiac disease.
- Diuretic use (electrolyte abnormality possible)
- Diabetes mellitus (DM), HTN, CKD
- Major surgical procedure

Chest x-ray (CXR):

- > 50 years of age for major vascular surgery
- Suspected cardiac or pulmonary disease

Pulmonary function tests (PFTs):

- Not recommended for healthy patients prior to any surgery
- Recommended for unexplained dyspnea

ENDOCARDITIS PROPHYLAXIS

The 2014 AHA/ACC Focused Update for the Management of Patients with Valvular Heart Disease recommends only high-risk individuals receive endocarditis prophylaxis. These include patients with prosthetic cardiac valves; patients with cardiac valve repair with prosthetic materials like annuloplasty rings or chords; previous infective endocarditis; unrepaired cyanotic congenital heart disease; repaired congenital heart defects with residual shunts or valvular regurgitation at the site of or adjacent to prosthetic patch or device; and heart transplant recipients who have a structurally abnormal valve causing valve regurgitation. The European Society of Cardiology (ESC) 2015 guidelines state the same but do not recommend prophylaxis in heart transplant recipients who develop valvulopathy.

Procedures needing prophylaxis are:

- Dental procedures that involve manipulation of gingival tissue or periapical region of teeth or perforation of oral mucosa
- Invasive respiratory tract procedures that involve incision or biopsy
- Procedures involving infected skin or musculoskeletal structures

Routine prophylaxis for GI and GU procedures is no longer recommended.

The most common causative organism is *Streptococcus viridans*. When prophylaxis is needed, give a single dose of oral amoxicillin 2 g 30–60 minutes prior to the procedure. If the patient is unable to take PO, give 2 g IV ampicillin. Alternative regimens for penicillin-allergic patients are clindamycin 600 mg or azithromycin 500 mg.

PERIOPERATIVE HYPERTENSION MANAGEMENT

Good blood pressure control results in less intraoperative lability and fewer postoperative complications. Patients can proceed with elective surgery as long as

their diastolic blood pressure is < 110 mmHg and they undergo close monitoring of intraoperative and postoperative blood pressures to reduce complications. It is less clear what an ideal preoperative systolic blood pressure is. Use IV medications to treat patients with elevated BP who are undergoing emergent surgery.

Patients with HTN should continue their home regimen preoperatively and resume their regimen as soon as possible in the postoperative period, provided they are not hypotensive. Continue β -blockers throughout the perioperative period if patients are already on them. Monitor heart rate and blood pressure closely and make dose adjustments if required. To prevent rebound HTN, do not abruptly discontinue clonidine. There is no established consensus about diuretics, but it may be wise to hold them on the morning of surgery to avoid intraoperative hypotension. To control BP exceeding 180/110 mmHg in the perioperative period, use hydralazine, labetalol, or nicardipine.

Patients without a history of HTN can have postoperative elevated BP due to pain, hypervolemia, and agitation or withdrawal syndromes. Treat the underlying condition unless the BP exceeds 180/110.

PERIOPERATIVE ARRHYTHMIA MANAGEMENT

Patients identified with a new preoperative arrhythmia should be treated and controlled prior to elective surgery. Such arrhythmias include supraventricular tachycardias (SVTs), ventricular tachycardia, atrial fibrillation, atrial flutter, high-grade AV block (2nd degree Type 2 and 3rd degree), and other symptomatic bradyarrhythmia. Patients with an established arrhythmia that is controlled can proceed with surgery. The following arrhythmia can proceed with elective surgery: premature ventricular contractions (PVCs), 1st degree AV block, fascicular blocks, and asymptomatic bundle-branch blocks.

Most postoperative arrhythmias are transient. If they persist, identify the cause and treat. The usual workup for postoperative cardiac arrhythmia looks for cardiac ischemia (check ECG and troponin), electrolyte disturbance (especially K^+ and Mg^{2+}), and hypoxia.

Postoperative tachyarrhythmia:

- PVCs and ventricular bigeminy are most common, rarely degenerate into life-threatening arrhythmias, and do not require intervention. The exception is torsades de pointes, in which hypomagnesemia is the likely cause in a susceptible patient with prolonged QT interval.
- Atrial fibrillation or flutter is often seen after cardiac or thoracic surgery: 15–40% post-CABG, 37–50% after valve surgery, and up to 60% after CABG and valve surgery. It mostly occurs within 48–72 hours of surgery. Use β -blockers, nondihydropyridine calcium channel blockers, or amiodarone to control

heart rate to a goal of < 110 bpm. If the patient cannot tolerate the arrhythmia, cardioversion is recommended. If the arrhythmia lasts beyond 24–48 hours or there are multiple episodes of arrhythmia, consider anticoagulation with warfarin if the bleeding risk is acceptable. Keep INR from 2.0–3.0. Continue anticoagulation for 4 weeks after sinus rhythm has returned.

- Sinus tachycardia does not need treatment. Investigate the underlying cause. Common etiologies to consider are pain, infection, and hypovolemia.

Postoperative bradyarrhythmias are commonly due to excess antihypertensive medications, opioid use, and neuraxial anesthesia. Prescribe atropine or external pacing if the underlying problem cannot be corrected and the patient is symptomatic.

PERIOPERATIVE PULMONARY MANAGEMENT

Pulmonary complications in the postoperative period include atelectasis, bronchospasm, infection such as pneumonia, exacerbation of the underlying lung condition, prolonged mechanical ventilation, and need for reintubation.

Factors that influence these complications are:

- Status of the chronic underlying lung disease (specifically asthma, chronic obstructive pulmonary disease [COPD], pulmonary HTN, and obstructive sleep apnea)
- Age (> 50 years)
- Current respiratory infection
- HF
- Smoking
- High-risk surgery
- Emergent surgery

It is important to perform a detailed preoperative history and physical to identify and treat undiagnosed lung disease and to optimize chronic lung conditions. Routine PFTs, CXR, and arterial blood gas (ABG) are **not** recommended. PFTs and CXR are helpful in preoperative evaluation of suspected undiagnosed lung disease and for lung resection surgery.

Patients with suspected obstructive sleep apnea benefit from evaluation and treatment prior to elective surgery. Recommend smoking cessation at least 8 weeks prior to surgery.

Perioperative Asthma Management

Evaluation and optimization of asthma patients should occur several weeks prior to surgery to allow time for changes in medications to take effect. PFT and CXR are recommended for evaluation of the uncontrolled patient. Optimal control is when the patient is without symptoms and has an FEV₁ (forced expiratory volume in

1 second) > 80% of predicted or personal best. Patients with asthma should continue their home medications prior to surgery and resume them as soon as possible after surgery.

For patients with signs of uncontrolled asthma, you can either postpone elective surgery or give supplemental steroids. If on chronic oral steroids, give stress-dose coverage hydrocortisone 100 mg IV every 8 hours and taper postoperatively.

If you see severe bronchospasm (e.g., due to endotracheal intubation) in the postoperative period, either delay extubation or use noninvasive ventilation. To avoid pulmonary complications, use bronchodilators, incentive spirometry, early mobilization, and good pain control.

Perioperative COPD Management

COPD is an important risk factor for pulmonary complications. These include prolonged intubation, development of pneumonia, and risk for reintubation. There is **no** level of lung function below which surgery is contraindicated. Thus, very high-risk patients may proceed to surgery if there is sufficient benefit. Like that of the asthma patient, preoperative evaluation of the COPD patient should occur several weeks prior to surgery. Postpone elective surgery for patients presenting with a COPD exacerbation.

Employ strategies similar to those for asthmatics to minimize postoperative pulmonary complications. Use noninvasive positive pressure ventilation (NPPV) such as biphasic positive airway pressure (BIPAP) to avoid reintubation. NPPV leads to fewer pulmonary complications in these patients than endotracheal intubation. Patients who develop postoperative COPD exacerbation improve with prednisone or hydrocortisone and bronchodilators.

PERIOPERATIVE HEMATOLOGY

Anticoagulation / Antiplatelet

It is important to note that not all procedures require withholding anticoagulant/antiplatelet agents. These determinations are often made by weighing the bleeding risk of continuing the agents against the thrombotic risk of withholding them.

The following are the 2017 recommendations of the American College of Chest Physicians (ACCP) for non-valvular atrial fibrillation:

- Warfarin: Stop 5 days before surgery and check PT/INR level the day before surgery. If INR ≤ 1.4 , proceeding with surgery is usually okay. If INR ≥ 1.5 , use low-dose oral vitamin K the day prior to surgery, or use fresh frozen plasma for immediate reversal in urgent procedures. Bridging with heparin is only indicated in patients who are at very high thromboembolism risk, e.g., patients who have had a recent stroke or mechanical heart valves, and atrial

fibrillation patients with CHA₂DS₂-VASc (Cardiac left-side HF [or left ventricular systolic dysfunction], Hypertension [blood pressure consistently > 140/90 mmHg or treated HTN on medication], A₂ for age ≥ 75 years, Diabetes mellitus, S₂ for prior stroke [or TIA or thromboembolism], Vascular disease, Age 65–74 years, Sex category) score of 7 or 8. (For more on the CHA₂DS₂-VASc scoring system, see the [Cardiology](#) section.) If bridging is required, start the bridging agent 3 days before surgery.

Warfarin can be started 12–24 hours after surgery, assuming there were no surgical issues that would increase the chances of bleeding. Bridging with low molecular weight heparin (LMWH) is required for high-thromboembolic-risk patients until the INR becomes therapeutic.

- Heparin: Stop 4–6 hours before surgery.
- LMWH: Stop 24 hours before surgery.
- Clopidogrel: Delay elective surgery for 6 months for drug-eluting stents and 6 weeks for bare-metal stents. If surgery is needed, continue antiplatelet therapy with aspirin in the perioperative setting. Patients need 5 days off clopidogrel before elective surgery.
- Direct-acting oral anticoagulants (i.e., dabigatran, rivaroxaban, apixaban, edoxaban): Stop 24–48 hours before surgery if renal function is normal. Use idarucizumab (Praxbind) for reversal of dabigatran in emergent life-threatening surgery. Andexanet alfa can be used to reverse apixaban and rivaroxaban.
- Aspirin (acetylsalicylic acid [ASA]): Continue (ASA 81 mg) for recent MI, stroke, and percutaneous coronary intervention (within 12 months).

Other general recommendations:

- For DVT/PE, recommend delaying elective surgery (e.g., knee replacement, cosmetic surgery) for 3 months after acute venous thromboembolism (VTE). If surgery is needed during the initial 3 months, (e.g., femur fracture, acute cholecystitis, appendicitis), recommend bridging anticoagulation with LMWH.
- NSAIDs, salicylates, and COX-2: Stop 1 week before surgery.

Postoperative Venous Thromboembolism Prophylaxis

VTE is a **preventable** occurrence in the postoperative period. Death due to pulmonary embolism (PE) arising from deep vein thrombosis (DVT) is the most common preventable death in the hospital. It is imperative to employ the appropriate strategies (ACCP 2012 guidelines) to minimize this risk in the appropriate patient population:

- Low-risk patients (laparoscopic surgery, shoulder/elbow surgery, podiatry): early ambulation until hospital discharge
- Moderate- to high-risk patients (general surgery; gynecologic, urologic, and thoracic surgery): Give

prophylactic anticoagulation with unfractionated heparin (UFH) or LMWH until hospital discharge.

- Orthopedic patients:
 - Total knee and hip replacement: Give anti-thrombotic prophylaxis (LMWH preferred, UFH, fondaparinux, warfarin, dabigatran, rivaroxaban, or apixaban) for 10–35 days.
 - Hip fracture surgery: Treat 10–14 days with LMWH, UFH, fondaparinux, warfarin, or ASA (325 mg bid).
 - Extend treatment to 35 days after major orthopedic surgery.
- In general, LMWH is preferred over other agents unless creatinine clearance is $< 30 \text{ mL/min/1.73 m}^2$ (0.50 mL/s/m^2).
- ASA as prophylaxis is only used if the other agents are contraindicated.
- Cancer patients: Check Khorana risk score. The Khorana risk score is the validated risk assessment model to stratify risks of VTE development in ambulatory patients with cancer. If Khorana risk score ≥ 2 , give apixaban 2.5 mg PO bid.
- Patients at high risk for bleeding (neurosurgery and major trauma): Recommend intermittent pneumatic compression and early mobilization.
- Screening U/S to look for asymptomatic DVT is not recommended.
- Patients on oral contraceptives should receive DVT prophylaxis.

they increase the risk of postoperative hypoglycemia. Metformin is discontinued before surgery due to renal function complications that may occur intraoperatively.

- Prevention of ketoacidosis
- Maintenance of physiologic electrolyte and fluid balance

Preoperative Period

Prior to surgery, patients are NPO for 6–8 hours. Appropriate management of diabetic medications is needed to avoid hyper- or hypoglycemia:

- Continue usual oral medications until the morning of surgery.
- Omit any short- or rapid-acting insulin on the morning of surgery.
- Reduce intermediate- or long-acting insulin by 25–50%.
- Patients on continuous insulin infusion pump can continue their basal rate.
- Patients with hyperglycemia can be treated with supplemental short-acting insulin.
- IV insulin infusion is recommended for long (> 4 hours) and complex procedures.
- Baseline evaluation includes ECG, serum creatinine, recent HbA1c, and glucose level.
- Cancel elective surgery for patients in DKA or with a glucose level $> 500 \text{ mg/dL}$ (27.75 mmol/L).

Blood Transfusion

Acute blood loss anemia in the postoperative period is common. Transfuse symptomatic patients regardless of the hemoglobin level. Transfuse asymptomatic patients with an Hgb $< 7.0 \text{ g/dL}$ (70 g/L). After 5 units of packed RBC (PRBC) transfusion, check Ca^{2+} level, aPT, aPTT, and platelet level. Give fresh frozen plasma if aPT and aPTT are $> 1.5\times$ normal. Give 6-pack of platelets for values $< 50,000$ (seen after 10–12 units of PRBC). Transfusion threshold increases to keep Hgb $\geq 10 \text{ g/dL}$ (100 g/L) in postoperative acute coronary syndrome.

PERIOPERATIVE ENDOCRINOLOGY

Diabetes Management

Perioperative Period

Optimal blood glucose control in the surgical patient results in decreased morbidity and mortality. The goals of diabetic management in the perioperative period are:

- Avoidance of severe hyperglycemia or hypoglycemia (goal glucose $140\text{--}180 \text{ mg/dL}$ [$7.77\text{--}9.99 \text{ mmol/L}$]). For patients on a long-acting insulin like insulin glargine, give 50–75% of usual dose on the day of surgery. Short-acting insulins like insulin lispro or aspart should be withheld before surgery because

Postoperative Period

Postoperative tips for the patient with diabetes:

- Postoperative pain and nausea can limit a patient's ability to eat, in which case continue to use IV insulin or subcutaneous correctional insulin.
- Most oral medications can be restarted once the patient is eating well. (Avoid metformin in the hospitalized patient with renal or hepatic impairment or HF. Hold starting sulfonylureas if there is concern for hypoglycemia. Hold thiazolidinediones in patients with fluid overload.)
- Continue insulin infusion postoperatively until the patient can tolerate food and can be converted to subcutaneous insulin.
- The home insulin regimen can be restarted at 25–50% of the home dose once the patient is tolerating food.
- Supplemental correction insulin is given when glucose levels are $> 140\text{--}180 \text{ mg/dL}$ ($8.32\text{--}9.99 \text{ mmol/L}$).
- The preferred insulin regimen is basal-bolus, especially with Type 1 diabetes, to prevent ketoacidosis.
- Treat hypoglycemia (glucose $< 80 \text{ mg/dL}$ [4.44 mmol/L]) with 5% dextrose infusion or 50% dextrose injection.

Thyroid Management

Routine screening with TSH measurement is **not** recommended unless the history and exam are suggestive of thyroid disease. Cancel elective surgery for untreated hypo- or hyperthyroid patients. Order a TSH in controlled thyroid patients if it has not been done in the last 3–6 months. Hold thyroid replacement medication the morning of surgery. Resume home medications once the patient can tolerate oral intake. If the patient is not able to take oral medication, then give 50% of the dose in IV formulation. For emergent surgery, treat the hypo- or hyperthyroid state accordingly:

- Subclinical hypothyroidism: Proceed with surgery without thyroid replacement.
- Moderate hypothyroidism: Give replacement thyroid dose 1.6 mcg/kg prior to surgery. (Reduce the dose to 25–50 mcg for elderly and CV patients.)
- Severe hypothyroidism (i.e., myxedema coma, HF, T_4 level $< 1.0 \mu\text{g/dL}$ [12.871 nmol/L]): Give both T_3 and T_4 thyroid replacement therapy prior to surgery.
- Subclinical hyperthyroidism: Proceed with surgery without intervention.
- Moderate-to-severe hyperthyroidism: Treat with β -blockers, thionamides (methimazole or propylthiouracil), and potassium iodine oral solution.
- **Thyroid storm:** This is a medical emergency (10–30% mortality). The stress of surgery can precipitate thyroid storm (occurs in the first 18 hours after surgery). Patients can present with fever, tachycardia, HF, and CNS and GI/liver dysfunction. In addition to the above treatment for hyperthyroidism, add hydrocortisone 100 mg IV every 8 hours and bile acid sequestrants (cholestyramine) to prevent thyroid hormone enterohepatic recycling.

Obesity

Following noncardiac surgery, obesity is a major risk factor for DVT and PE. Obesity is **not** a risk factor for postoperative complications except for VTE (major risk factor for DVT and PE) following noncardiac surgery.

In cardiac surgery, obesity is a risk factor for patients with prolonged hospital stay, wound infection, prolonged ventilation, and atrial arrhythmias.

In preoperative screening, look for undiagnosed comorbid conditions common among obese patients (obstructive sleep apnea, obesity hypoventilation syndrome, HTN, heart disease, diabetes, metabolic syndrome, and kidney disease).

Steroid Management

Patients on prednisone $> 20 \text{ mg/day}$ for 3 weeks or more should receive stress-dose steroids (hydrocortisone 100 mg IV q 8 hours) starting 12–24 hours prior to surgery.

Cosyntropin stimulation test (a.k.a. adrenocorticotrophic hormone [ACTH] stimulation test) can be done preoperatively for patients at risk for relative adrenal insufficiency.

Taper hydrocortisone over 48–72 hours in the postoperative period. Resume the home steroid dose after hydrocortisone is discontinued.

Patients on a lower prednisone dose (or with recent exposure to prednisone) presenting with unexplained postoperative hypotension can be treated with stress-dose hydrocortisone. The postoperative hypotension is likely due to adrenal insufficiency.

PERIOPERATIVE INFECTIONS

Preoperative infections need to be controlled prior to elective surgery, especially if prosthetic material will be implanted. Postoperative infections most commonly present as fever. Fever in the first 48 hours after surgery usually resolves spontaneously and does not require further investigation.

Causes of postoperative infection include UTI, intravascular line infection, pneumonia, and surgical site infection.

Note: Other noninfectious causes of perioperative fever include medication side effect, gout, VTE, transfusion reaction, surgical site inflammation without infection, MI, and stroke.

Initial workup: Check CXR, U/A, and blood cultures.

Start empiric antibiotics to cover methicillin-resistant *Staphylococcus aureus* (MRSA) and *Pseudomonas* in hemodynamically unstable patients. Stop antibiotics after 48 hours if no source can be identified and the patient is stable. Cefazolin is the drug of choice for antimicrobial prophylaxis to prevent surgical site infection.

PERIOPERATIVE NEUROLOGY

Postoperative Delirium

Risk factors for the development of delirium:

- Age > 65 years
- Baseline cognitive impairment
- Serious illness
- Major orthopedic surgeries

Delirium can be due to pain, hypoxia, hypercapnia (hypercarbia), urinary retention, hypoglycemia, electrolyte imbalance (especially hyponatremia), infection, or medication side effects (especially opiates, BDZs, and drug-induced anticholinergic activity).

Patients with post-op delirium present with acute onset of waxing and waning levels of consciousness. They have disorganized thought and are inattentive.

Direct treatment toward any reversible causes. Use antipsychotics (haloperidol, quetiapine, or risperidone) to control behavioral symptoms. Use BDZs only in delirium related to alcohol withdrawal.

Postoperative Neuropathy

Focal neurologic deficits can be due to a central or a peripheral process. It is more common following cardiac surgery. CT or MRI scan of the brain helps identify if there is a stroke or if another CNS process is involved.

Thrombolytics are often contraindicated in the postoperative period. Aspirin, statin therapy, and supportive care are the mainstay of treatment. Anticoagulation treatment for embolic causes is individualized, weighing risks and benefits in each patient.

Compressive neuropathies following surgery typically present with numbness, weakness, pain, diminished reflexes, and discoordination of an extremity. Symptoms usually resolve within 2–4 weeks.

Malignant Hyperthermia

Malignant hyperthermia (MH) manifests as a hypermetabolic crisis. It occurs when susceptible individuals are exposed to volatile anesthetics or succinylcholine. MH clinically presents with hypercapnia, tachycardia or arrhythmia, muscle rigidity, rhabdomyolysis, and hyperthermia. Treatment involves the following:

- Remove the offending agent.
- Give dantrolene 2.5 mg/kg IV.
- Monitor core temperature, ABG, CK level, and basic metabolic panel (BMP).
- Give supportive care in the ICU.

MH is an autosomal dominant disorder; therefore, it is important to counsel other family members.

Neuropsychiatric Medications

Neuropsychiatric medications are stopped or continued depending on the risks of losing disease control in the postoperative period:

- MAOIs: Stop 10–14 days before surgery.
- Antipsychotics: Continue.
- Antiseizure medications: Continue.
- Antiparkinsonian drugs: Continue, but it is okay to discontinue the night before surgery.
- Alzheimer drugs: Discontinue.
- Antidepressants (i.e., TCAs, SSRIs, SNRIs): Continue.
- Myasthenia gravis drugs: Continue these and avoid medications that can exacerbate the condition.

- What are the screening indications for patients at risk for abdominal aortic aneurysm? Do they apply to women?
- Should you do prostate-specific antigen (PSA) screening in a 75-year-old man?
- At what age should Pap smear screening begin?
- What are the U.S. Preventive Services Task Force (USPSTF) indications for lung cancer screening?
- Which external factors contribute to pressure ulcers in immobilized patients?
- Which prevention strategies can benefit patients at risk for pressure ulcers?
- What is the difference between airborne and droplet precautions?

PATIENT EDUCATION

Know this entire topic. The most authoritative single source for preventive medicine in the U.S. is the United States Preventive Services Task Force (USPSTF).

Because patient education improves outcomes, it is necessary to periodically review and counsel patients on the following:

- Tobacco
- Firearms
- Alcohol/Substance abuse
- Physical activity level
- Obesity

Check the elderly for functional status, gait abnormalities, and osteoporosis risk factors.

Guide all patients about self-examination for skin disease, gum disease, STIs, and nutrition.

Recommend seat belts and good fluid intake.

Teaching women to perform a breast self-exam does **not** reduce their mortality from breast cancer; so, most organizations no longer recommend it and some even recommend **against** it.

When to order a screening mammogram in a woman without known risk factors for breast cancer is also controversial. Expert groups agree that routine screening mammography should be started at least by 50 years of age. However, some expert groups recommend starting mammography as early as 40 years of age. For women 40–49, the most desirable approach is usually shared decision-making that takes into account the benefits and harms of mammography. After the initial screening mammography, for average-risk women, repeat it every 2 years until age 74. After age 74, only do mammography if life expectancy is at least 10 years.

Along similar lines, the USPSTF recommends **against** testicular self-examination for early detection of testicular cancer because it is unlikely to change outcomes.

PREVENTIVE MEDICINE

PREVIEW | REVIEW

- Which patient education topics should you review and counsel patients about periodically?
- Memorize [Table 15-15 on page 15-34!](#)

Firearm-related injuries and deaths are a major public health problem. The physician's ethical role is to counsel patients about firearm safety and to become involved in community efforts to prevent firearm injuries. Some states have passed specific laws prohibiting physicians from inquiring about ownership of a firearm.

Smoking Cessation

Tobacco smoke is responsible for **90%** of all lung cancer deaths; it also contributes to various other cancers (e.g., bladder) and more than 10% of cardiovascular deaths.

The USPSTF 2015 recommendation suggests using a "5-A" framework:

- 1) Ask about tobacco use.
- 2) Advise to quit through clear personalized messages.
- 3) Assess willingness to quit.
- 4) Assist to quit.
- 5) Arrange follow-up and support.

Know that cessation of smoking can exacerbate ulcerative colitis. This is usually because nicotine suppresses the immune system, and a reduction in the activity of the immune system will suppress the inflammation associated with ulcerative colitis. When a patient with ulcerative colitis quits smoking, the reverse happens.

First-line medications for smoking cessation:

- Bupropion SR—inhibits presynaptic reuptake of dopamine and norepinephrine
- Nicotine replacement products (e.g., gum, inhaler, lozenges, nasal spray, patch)
- Varenicline (Chantix)—partial agonist of nicotinic acetylcholine receptors

Counseling plus meds is better than counseling alone.

Drug therapy for smoking cessation is generally safe. Nicotine replacement products do not increase cardiovascular risk, even for those who smoke while wearing the nicotine patch.

Avoid bupropion in patients with a history of seizure disorders.

Both bupropion and varenicline have been associated with serious neuropsychiatric side effects (e.g., behavior changes, suicidal ideation and behavior, depressed mood); bupropion has a black box warning, while the FDA black box warning on varenicline was removed in 2016.

Note that **cigar** smoking increases the risk of coronary heart disease (relative risk = 1.27), COPD (1.45), and cancers of the mouth and throat (2.02).

Other Disease Risks

The following increase the risk of disease:

- High intake of red meat increases risk of colorectal cancer.
- Alcohol increases risk of colon, breast, esophageal, and oropharyngeal cancers.

- Obesity is associated with increased risk of colon, breast, endometrial, kidney, and esophageal cancers—and may increase risk for prostate, ovary and cervix, liver and gall bladder, and pancreatic cancers, myeloma, and lymphoma!
- Bladder cancer is inversely associated with fluid intake. Incidence in the high-fluid intake group is half that of those in the low-fluid intake group.
- Infections that cause or increase the risk of certain cancers: HPV, HBV, HCV, HIV, EBV, and *Helicobacter pylori*.

The following decrease the risk of disease:

- High intake of tomatoes decreases prostate cancer risk.
- Fiber reduces heart disease and diabetes.
- Vitamin D may decrease colorectal and prostate cancer risk.

Note that supplemental vitamins and minerals do **not** decrease cancer risk in patients with adequate diets.

Certain drugs are used to decrease cancer risks in special patient populations:

- Tamoxifen and raloxifene decrease breast cancer.
- NSAIDs and aspirin decrease colon polyps and colon cancer in very high-risk patients.
- Dutasteride and finasteride decrease prostate cancer.

SCREENING TESTS

Every official entity detailing screening protocols has a different (but usually similar) suggested protocol for each disease. [Table 15-15](#) provides a rough summary of screening protocols.

Table 15-15: Screening Exam Recommendations

Screening	Protocol
Counseling about smoking	Each visit
Blood pressure	Each visit; at least every 2 years
Cholesterol	Every 5 years
Breast exams	Proven unreliable; see the Oncology section.
Mammograms	Can begin at age 50; some expert groups start at 40 with shared decision-making approach. For more on screening for breast cancer, see the Oncology section.
Digital rectal exam	No longer recommended
Fecal immunochemical testing	Yearly after 50 years of age (not needed after colonoscopy)
Colonoscopy	See the Gastroenterology section.
Pap smear	Every 3 years*
PSA	Inconclusive*
* See text for more information.	

Cardiovascular Disease

Blood Pressure and Cholesterol

Blood pressure (BP): Check every 2 years and **every** clinical encounter. For treatment of HTN, please refer to the [Nephrology](#) section.

Cholesterol: Screen men 35–65 years of age and women 45–65 years of age every 5 years. If the patient is placed on lipid-lowering agents, then generally they are checked every 6 months to a year thereafter. If the screening total cholesterol is near the threshold, repeat it periodically. For treatment of lipid disorders, see the [Cardiology](#) section.

Cardiovascular Disease in Women

The 2011 AHA updated guidelines for prevention of cardiovascular disease in women recommend the following:

- Hormone therapy should **not** be used as primary or secondary prevention of cardiac disease.
- Antioxidant vitamin supplements should **not** be used as primary or secondary prevention of cardiac disease.
- Folic acid should **not** be used for prevention of primary or secondary cardiac disease.
- Aspirin in **healthy** women < 65 years of age is **not** recommended to prevent MI.

Estimating Cardiovascular Risk

For patients who do not currently have heart disease but have at least 2 risk factors for heart disease (for the primary risk factors for coronary artery disease [CAD], see the [Cardiology](#) section), the 5-year, 10-year, or lifetime risk for heart disease can be estimated using one of the many established risk predictor models (e.g., Framingham risk assessment, ACC/AHA Pooled Cohort Equation). The assessment result gives good insight into how aggressive you need to be about reducing the patient's cardiovascular risk factors.

Diabetes

The 2016 American Diabetes Association (ADA) diabetes management guidelines recommend screening all adults with BMI > 25 and ≥ 1 risk factor (see below) with a venous fasting plasma glucose, HbA1c, or oral glucose tolerance test every 3 years. Start screening people > 45 years of age if they have no risk factors.

Retest in 3 years if results are normal.

The American Association of Clinical Endocrinologists recommends screening in patients with any risk factors or > 45 years of age if no risk factors are present.

Risk factors include:

- BMI > 25
- High-risk ethnic groups
 - African Americans
 - Hispanics

- Native Americans
- Asian Americans
- Pacific Islanders
- Dyslipidemia
- Diabetes in a 1st degree relative
- History of gestational diabetes
- Sedentary lifestyle
- HTN
- Polycystic ovary syndrome
- Vascular disease

Abdominal Aortic Aneurysm

One-time U/S screening for abdominal aortic aneurysm (AAA) is recommended in men 65–75 years of age if they have a history of smoking (ACC/AHA 2013 and USPSTF 2014) or in men > 60 years of age if they had a sibling or parent with AAA (ACC/AHA 2013). Repeat screening is not recommended. CT or MRI ordered for other indications can be used for AAA screening if the infrarenal aorta was visualized and measured. No organization recommends screening in women.

Breast Cancer

Breast cancer screening using breast self-exams and clinical breast exams has not shown a clear benefit. Average-risk patients have the option for mammography screening at age 40 if employing a shared decision-making approach. See more on this topic in the [Oncology](#) section.

Prostate Cancer

Prostate-specific antigen (PSA) testing has contributed to the increased finding and treatment of early prostate cancer. Although no trials have been concluded that indicate its effectiveness as a screening test, consumer demand has made it a commonly performed lab test.

The American College of Physicians (ACP 2013) recommends that annual PSA be **discussed** with men between 50 and 69 years of age to determine if they want the test based on benefits and harms. No PSA screening is recommended for men < 50 or > 69 years of age or whose life expectancy is < 10 years. In general, discuss screening at 40 years of age with African Americans and in patients with a family history of early prostate cancer.

The digital rectal exam, previously combined with serum PSA screening, is no longer recommended by the ACP. The American Urological Association (AUA) 2015 guideline on early detection of prostate cancer does not recommend PSA screening for men up to 54 years of age who are at average risk; those in this age group who are at high risk (African American or family history) should have the decision individualized. The same AUA guidelines recommend shared decision-making for men 55–69 years of age and do not recommend screening after age 69 or in anybody with a < 10- to 15-year life expectancy.

The USPSTF issued a draft recommendation in 2017 regarding men age 55–69 for individualized decision-making about screening for prostate cancer after discussion with a clinician. They recommend against screening in men age > 69. In a large U.S. study in 2012, the Prostate, Lung, Colorectal, and Ovarian Cancer (PLCO) Screening Trial showed no statistically significant mortality benefit with PSA screening. Additionally, false-positive PSA tests (80%!) result in more testing and negative psychological effects, which have also been considered in these recommendations.

Colon Cancer

Colon cancer is discussed in depth in the [Oncology](#) section.

Cervical Neoplasia and Cancer

Pap smears have been proven effective, but the recommended intervals between these tests vary. The U.S. Preventive Services Task Force recommends starting at 21 years of age. For women 21–29 years of age, only cervical cytology should be tested. For women 30–65 years of age, there are 3 options:

- 1) Test every 3 years for cervical cytology alone.
- 2) Test every 5 years with high-risk human papillomavirus (hrHPV) testing alone.
- 3) Test every 5 years with hrHPV testing in combination with cytology (cotesting).

There are 3 categories in which testing is discouraged:

- 1) Screening for women younger than 21 years
- 2) Screening in women who have had a hysterectomy with removal of the cervix and do not have a history of a high-grade precancerous lesion (i.e., cervical intraepithelial neoplasia [CIN] Grade 2 or 3) or cervical cancer
- 3) Screening for cervical cancer in women older than 65 years who have had adequate prior screening and are not otherwise at high risk for cervical cancer

Lung Cancer

About 85% of lung cancers are the result of smoking. The status of lung cancer screening is evolving based largely on the results of the National Lung Screening Trial (NLST). The NLST randomized over 50,000 current and former smokers 55–74 years of age to 3 annual low-dose CT scans (LDCT) vs. 3 annual CXRs. The study was halted early (at 6.5 years) due to a 20% reduction in lung cancer mortality in the group screened with LDCT.

The USPSTF issued a recommendation in 2013 in favor of annual low-dose CT scan screening (Grade B) of individuals who meet **all** of the following criteria:

- Adults 55–80 years of age
- Current smokers or those who have quit within the past 15 years
- ≥ 30 pack years of smoking history

These same guidelines recommend discontinuing screening once a person has not smoked for 15 years or develops a health condition that limits life expectancy or the ability to have curative lung surgery.

False-positive rates are high: In the NLST, 24% of screening CTs were positive, and **over 96% were false positives**. Concerns about the new lung cancer screening recommendation center around the potential of overdiagnosis, excess radiation exposure, and cost. However, the evidence suggests that 1 lung cancer death is averted for every 450–500 scans done.

Tobacco avoidance and cessation continue to be important steps in decreasing the burden of disease. It is essential that all smokers be advised in this regard.

VACCINATIONS

Adult vaccinations are discussed in the [Infectious Disease](#) section.

HOSPITAL-BASED PREVENTION STRATEGIES

Pressure Ulcer Prevention

Patients who are immobile are at increased risk for soft tissue wounds called pressure ulcers. **As the term implies, external pressure injury is a major factor.** Other external factors are friction, moisture, and shearing forces.

If external pressure exceeds capillary perfusion pressure, the tissue becomes ischemic and will progress to necrosis if blood flow is not restored. Pressure ulcers (depending on the stage) are chronic wounds that can take months to years to heal. Therefore, close attention to prevention is critical for those at risk.

Common intrinsic factors that increase the risk of pressure ulcers include malnutrition, sensory neuropathy, incontinence, and vascular disease.

Prevention strategies include mobilization when possible. Ordering complete bed rest when not warranted can increase the risk of pressure ulcers.

When patients are sedated on a ventilator, mobilization is not an option. In these cases, the following strategies are necessary:

- Reposition manually
- Minimize moisture (urine and feces can be particularly irritating to the skin)
- Use positioning aides to redistribute pressure
- Correct any malnutrition

Pressure redistribution—the ability of a support surface to distribute load over the contact areas of the human body—is important. The standard hospital bed is not effective at pressure redistribution. The 2015 ACP guidelines recommend ordering static mattresses or advanced static overlays for patients who are at an increased risk of developing pressure ulcers. A static

mattress doesn't move when a person lies on it. Some static mattresses are made of special memory foam, which reduces pressure by spreading the weight of the body over a larger area and molds to the contours of the body.

Order turning and scheduled repositioning for bed- and chair-bound individuals regardless of the support surface in use. Determine repositioning frequency based on the support surface being used and patient characteristics (e.g., whether or not there is malnutrition, vascular disease, paralysis).

Transmission-Based Precautions

All patients require **standard precautions** (CDC guidelines), which has 8 components:

- 1) Perform hand hygiene.
- 2) Use personal protective equipment when there is a risk of exposure to infectious material.
- 3) Follow respiratory hygiene/cough etiquette principles.
- 4) Ensure appropriate patient placement.
- 5) Properly handle, clean and disinfect patient care equipment, instruments and environment.
- 6) Handle textiles and laundry carefully.
- 7) Follow safe injection practices including wearing a surgical mask when performing lumbar punctures.
- 8) Ensure health care worker safety, including proper handling of needles and sharps.

There are also populations with suspected or confirmed clinical syndromes that require **transmission-based precautions**. These precautions are recommended for patients who may be infected or colonized with certain infectious agents for which additional precautions are needed to prevent infection transmission. These include:

- 1) Place patients in a single-patient space.
- 2) Use personal protective equipment appropriately.
- 3) Limit transport and movement of patients outside of the room to medically necessary purposes.
- 4) Use disposable or dedicated patient-care equipment.
- 5) Prioritize cleaning and disinfection of the rooms of patients on contact precautions.

Contact, droplet, and airborne precautions may be needed, depending on the infectious agents. Sometimes more than one type of precaution is used for the same patient. For example, varicella requires both contact and airborne precautions.

Contact Precautions

Contact precautions moderate the spread of resistant or highly contagious organisms.

Norovirus, hepatitis A, and *Clostridioides difficile* are just a few examples of organisms that require contact precautions.

Organisms requiring contact precautions can sometimes differ between hospitals. Infection prevention departments continuously evolve their understanding of isolation needs. For example, many ICUs have moved away from screening and contact isolation of MRSA. Instead, they utilize **universal decolonization**, in which every patient admitted to the ICU is decolonized with intranasal mupirocin and chlorhexidine bathing, whether or not the patient is a known MRSA carrier. The Department of Veterans' Affairs maintains MRSA screening swabs have significantly decreased MRSA hospital infection rates.

Gowns and gloves are used as barriers to prevent contamination of exposed skin and clothing. **Gowns and gloves must be removed before leaving the patient's room!** It is still very important to use hand hygiene after glove removal. Keep dedicated equipment, such as stethoscopes and blood pressure cuffs, in the patient's room to prevent spread of organisms to other patients.

The following infections require contact precautions:

- Large, draining abscess(es)
- Congenital rubella
- *C. difficile* infection
- Conjunctivitis (acute viral and hemorrhagic)
- Diphtheria (cutaneous)
- Type A hepatitis (if diapered, incontinent)
- Herpes simplex infection (mucocutaneous)
- Herpes zoster infection (if disseminated or in immunocompromised)
- Human metapneumovirus
- Impetigo
- Lice
- Pneumonia (adenovirus)
- Poliomyelitis
- Respiratory syncytial virus (RSV)
- Rotavirus
- Scabies
- Severe acute respiratory syndrome (SARS)
- Staphylococcal scalded skin syndrome
- Major streptococcal skin infection
- MRSA
- Vancomycin-resistant enterococci (VRE)
- Varicella-zoster infection (until lesions dry)

Droplet Precautions

Droplets are large-particle aerosols. Droplets do not remain suspended in the air and do not travel long distances. They cause infection if the droplets land on the mucosal surfaces of the nose, mouth, or eye. Therefore, these patients need to be isolated in a private room, even though no special air handling is necessary. Wear a standard surgical mask when entering the room. The patient should wear a surgical mask when it is necessary to leave the room (e.g., to go to a test or procedure).

Additionally, wear gowns and gloves because touching a contaminated surface followed by touching a mucosal surface spreads infection.

Droplet precautions are required with:

- Diphtheria (pharyngeal)
- Epiglottitis (*Haemophilus influenzae* B)
- Influenza
- Meningitis (*H. influenzae* B or meningococcal suspected)
- Monkeypox
- Mumps
- *Mycoplasma pneumoniae*
- Parvovirus B19
- Pertussis (whooping cough)
- Plague (pneumonic, not bubonic)
- Rhinovirus
- Rubella
- SARS
- Streptococcal infections: pneumonia, scarlet fever, serious invasive disease, pharyngitis in young
- Viral hemorrhagic fever

Airborne Precautions

Small infectious particles that remain suspended in the air can travel long distances, and they require airborne precautions.

These patients must be put in a negative air pressure, private room. High-density masks (N-95) or self-contained breathing systems such as a powered air purifying respirator (PAPR) are recommended. A surgical mask is not adequate protection when seeing a patient requiring airborne precautions.

Airborne precautions are required with:

- Ebola
- Herpes zoster infection (if disseminated or in immunocompromised)
- Measles (rubeola)
- SARS
- TB with pulmonary or laryngeal disease
- Varicella-zoster infection (until lesions dry)

OVERDOSE AND POISONING

PREVIEW | REVIEW

- What procedures and tests should you consider for general management of an obtunded patient?
- Activated charcoal is not used for which overdoses?
- When can cardiopulmonary resuscitation be stopped after hypothermic cardiac arrest?

- Which acid-base disorder is classically found when a patient presents with salicylate overdose?
- Which drug is used to treat acetaminophen overdose?
- What are the findings in an anticholinergic overdose?
- Which electrocardiogram finding correlates most closely with the degree of intoxication with a tricyclic antidepressant?
- For tricyclic overdose, where should you keep the serum pH?
- A 30-year-old man presents with acute myocardial infarction. Which illicit drug should be ruled out as the cause?
- Methanol causes which neurologic deficit?
- Does ethylene glycol cause an increased osmol gap, anion gap, or both?
- Know about carbon monoxide poisoning!
- What are the 3 drugs used to treat cyanide poisoning?
- How do you check for lead exposure in the past 3 months?
- What is the treatment for organophosphate poisoning?

OVERVIEW

Deaths from drug overdose have been steadily rising over the past 2 decades. According to the CDC drug overdose database, 70,237 people died from a drug overdose in the U.S. in 2017. The age-adjusted rate of overdose deaths increased from 19.8 per 100,000 in 2016 to 21.7 per 100,000 in 2017—a 9.6% increase. The highest rates of deaths from drug overdose in the U.S. occur in West Virginia (57.8 per 100,000), Ohio (46.3 per 100,000), Pennsylvania (44.3 per 100,000), the District of Columbia (44.0 per 100,000), and Kentucky (37.2 per 100,000). Opioids were the most common drugs involved, often found in combination with BDZs.

First, we discuss an empiric approach to overdoses; then we focus on individual ingestions. Ingestions involving HAGMA (high anion gap metabolic acidosis) and an increased osmol gap (a.k.a. osmolal gap) are covered completely in the [Nephrology](#) section. Carbon monoxide poisoning and carboxyhemoglobin are discussed in the [Pulmonary Medicine](#) section.

OVERDOSE MANAGEMENT

General management of the obtunded or comatose patient is guided by history, vital signs, and physical exam. Assessment of airway is most important, with immediate intubation of the patient with unstable vital signs and/or inability to protect the airway. Next, assess

cardiac rhythm with an ECG and continuous cardiac monitoring, and assess blood oxygenation with pulse oximetry.

The following interventions are usually empirically performed, except as noted:

- IV D50 if blood glucose is low on capillary measurement
- Thiamine 100 mg IM or IV
- ABG +/- carboxyhemoglobin level, serum basic chemistry, and a urine and serum toxicology screen—remember to calculate the serum anion and osmol gaps.
- Serum salicylate level
- Serum acetaminophen level
- Serum CPK if the patient was immobile for long periods
- CXR and supplemental oxygen prn
- Naloxone IV if you suspect opiate overdose (pinpoint pupils)—but be careful of dosage (see [Opiates](#) on page 15-40).

Be able to characterize the patient's physical exam, determine whether the presentation is most consistent with **excitation** or **depression**, and know which ingestions are associated with the presented scenarios ([Table 15-16](#)).

In clinical practice, many patients present with co-ingestions, and the physical exam can be a mixed bag of signs/symptoms.

Tip: Mydriasis = dilated pupils (big word, big pupils). Miosis = constricted pupils (small word, small/pinpoint pupils).

After the patient is stabilized, consider gastric lavage with a large-bore orogastric tube in special circumstances; this may be effective even hours after ingestion **if** the drug involved is a salicylate, anticholinergic, or narcotic. (These drugs cause decreased gastric motility; gastric lavage is **not** routinely done except for poisoning with drugs that delay gastric emptying.) Lavage with only small amounts of tap water (100 mL) to prevent forcing the stomach contents into the duodenum. Follow with activated charcoal and a cathartic (sorbitol or magnesium citrate).

Activated charcoal is ineffective or contraindicated in the following. Think **CHEMICAL Camp**:

- Caustics
- Hydrocarbons (and most water-soluble compounds)
- Electrolytes
- Metals
- Iron
- Cyanide
- Alcohols
- Lithium
- Camphor
- Phosphorus

Continued dosing with oral charcoal is effective in decreasing the levels of a few drugs by gut dialysis (absorption via the enteric recirculation)—especially digoxin, phenobarbital, theophylline, tricyclics, and salicylates.

Note again! There is a strong trend toward **not** lavaging patients with most overdoses. The thought is that lavage is, in most cases, ineffective; using activated charcoal with cathartics is at least as effective, if not more so.

Table 15-16: Physical Exam in Toxic Ingestions

Physical Exam	Category	Examples
"Excited": agitation, restlessness, HTN, tachycardia, hyperventilation, hyperthermia, mydriasis (usually)	Anticholinergics	Antihistamines Neuroleptics (e.g., chlorpromazine, quetiapine) TCAs Atropine Antispasmodics (e.g., hyoscyamine) Plants: nightshade (belladonna) and jimson weed
	Sympathomimetics	Ephedrine Dextromethorphan (5–10× therapeutic dose) Cocaine Amphetamines Methamphetamine MDMA (Ecstasy) 4-bromo-2,5-dimethoxyphenethylamine (2C-B, Nexus, 2's) 2,5-dimethoxy-4-n-propylthiophenethylamine (Blue Mystic, 2C-T-7)
	Hallucinogens	Lysergic acid diethylamide (LSD) Mescaline (peyote) Phencyclidine (PCP, Angel Dust) Psilocybin (found in certain mushrooms)
"Depressed": obtundation, hypotension, bradycardia, hypoventilation, hypothermia, miosis (usually)	Cholinergics	Organophosphate and carbamate insecticides
	Sympatholytics	Clonidine
	Opiates	Oxycodone (frequently combined with acetaminophen; has extended-release formulations) Hydrocodone (frequently combined with acetaminophen; has extended-release formulations)

Shock is treated with IV fluids and vasopressors if needed.

Alkalinization and acidification of the serum (and hence, the urine) are based on the principle that compounds in their ionized form are less tissue-permeable and more easily eliminated by the kidneys. Weakly acidic substances ionize in an alkaline environment, while weakly alkaline substances ionize in an acidic environment. Alkalinization of the urine to a pH of > 7 with sodium bicarbonate increases excretion of salicylates, tricyclics, and phenobarbital. Acidification of the urine with ammonium chloride (NH_4Cl) increases excretion of amphetamine and phencyclidine (PCP). Mix 2.75 Eq/kg of NH_4Cl in 60 mL NS and give through the gastric tube. Clamp for 1 hour. Repeat every 6 hours until urine pH is < 5.0 .

Important: Hemodialysis may be necessary in patients with severe overdose or renal failure. It is effective in removing drugs with low molecular weights that are **not** lipid soluble, protein bound, or tissue bound (i.e., drugs with a small volume of distribution). These include lithium, chloral hydrate, salicylates, and alcohols (methanol and ethylene glycol). Dialysis is not effective in removing BDZs, opiates, or tricyclics.

Also important: Charcoal hemoperfusion (blood pumped through a charcoal filter), in contrast to dialysis, removes drugs that **are** lipid soluble and protein bound! It can also remove some of the same drugs as dialysis. Also, like dialysis, it is most effective in removing drugs with a low volume of distribution. Charcoal hemoperfusion is especially good for digoxin, theophylline, and salicylate overdoses.

Hypothermia can occur following an overdose of alcohol or drugs (e.g., with prolonged cold air exposure or water submersion). Due to the neuroprotective reflexes of hypothermia, pulseless patients with hypothermia who are brought to the emergency department must be resuscitated to core temperature between 89.6 and 95.0°F (32.0 and 35.0°C) with continued CPR, warmed IVF, and peritoneal and pleural lavages before death pronouncement can be made.

Obtain a psychiatric consult in cases of deliberate drug overdosing or self-poisoning. Observe these patients closely to avoid a repeat attempt at self-harm (e.g., one-to-one nursing).

Overdose — Analgesics

Opiates

According to the CDC, the sale of prescription opioids in the U.S. quadrupled from 1999 to 2014. Opioid overdoses have likewise dramatically increased; opioid overdose killed 67,344 people in 2017.

Think opiate overdose (especially on an exam) when you see the following combination of signs/symptoms: obtundation, hypoventilation (decreased rate and tidal volume), hypotension, bradycardia, decreased bowel sounds, and **constricted pupils**. Know that meperidine

and tramadol are associated with seizures in intoxicated patients, especially those on dialysis. Also know that methadone can increase the QT interval, causing *torsades de pointes*.

Naloxone is usually given by IV in doses of 0.4–2 mg, up to a maximum of 10 mg. Use the drug to reverse hypoventilation induced by opiates; **do not** use it in large doses as a diagnostic tool for opiate intoxication because of the risk of inducing withdrawal in the chronic user. Titrate the dose of naloxone to result in a normal respiratory rate (10–14 breaths per minute), **not** consciousness. A dose too large (i.e., enough to wake someone up completely) can cause rapid reversal and withdrawal. A dose too small can result in the need for intubation. Chronic users of opiates, and those patients who inhaled or ingested a large dose of the drug, may require an IV drip of naloxone because its half-life is very short. Generally, 2/3 of the dose that results in adequate ventilation is given per hour in a drip. Naloxone can also be delivered intranasally, IM, or SQ.

Know that acute lung injury is sometimes seen in opiate addicts who undergo rapid reversal of unconsciousness with naloxone + high-flow oxygen via face mask. Patients usually recover with supportive care.

Also recognize that naloxone is typically **not** the correct answer if a scenario presents a patient with dilated pupils.

See the **Psychiatry** section for more information on opioids.

Salicylates

Salicylates (ASA and salicylic acid [the active ingredient in aspirin]) are found in various herbal supplements, oil of wintergreen salves, and bismuth subsalicylate. They are metabolized in the liver by conjugation with glycine or glucuronide. Enteric formulations can cause a delay in peak absorption rate, so the initial level may be misleading. These pathways are quickly saturated in a person who has overdosed, resulting in **acidemia**. The increased salicylate level initially causes hyperventilation through a **central** effect. There is a protective effect of the resulting respiratory alkalosis because the salicylate crosses the blood-brain barrier (i.e., is more tissue permeable) when the patient is acidemic. Acidosis can worsen if the HAGMA is compounded by lactic acidosis due to pulmonary edema. If the patient stops hyperventilating, it is probably due to respiratory muscle fatigue. If ventilatory support is required, it is mandatory to maintain a high respiratory rate with high tidal volumes to prevent an acute rapid worsening of acidemia with dire clinical outcome.

The classic presentation of the patient with a salicylate overdose is tachypnea, a mixed acid-base disorder (**HAGMA + respiratory alkalosis**), and a history of having taken over-the-counter pain medicine. Patients complain of nausea and vomiting and may even present in an altered mental state or coma. Patients can also complain of tinnitus.

Treatment of salicylate overdose: Decontaminate with activated charcoal with cathartic if patient presents within 2 hours of ingestion or later if enteric-coated ingestion is suspected. If there is altered mentation, give supplemental glucose because of low cerebral levels, even with normal serum levels. Serum/urine alkalinization is needed even with an alkalemic state; use aggressive hydration and sodium bicarbonate to maintain a urine pH of 7.5–8. Both hemodialysis and charcoal hemoperfusion have been used in severe cases (salicylate levels > 100 mg/dL [7.24 mmol/L]). Other indications for dialysis in salicylate poisoning include altered mentation, pulmonary edema, severe acidemia (pH < 7.2), and AKI or CKD that impairs clearance and causes cerebral edema. The charcoal hemoperfusion removes the salicylates better than hemodialysis but does not correct any fluid/electrolyte imbalance, so it is rarely used. Patients are often hypokalemic and are at risk for cardiac arrhythmias. Slow forms of dialysis such as peritoneal dialysis or continuous renal replacement are not substitutes for hemodialysis, as acidemia cannot be rapidly corrected.

Acetaminophen

90% of acetaminophen is metabolized to inactive metabolites by glucuronidation or sulfation in the liver. 5% is excreted unchanged through the kidneys. The last 5% is metabolized to active metabolites by way of the hepatic cytochrome P450 system. One of the active metabolites is *N*-acetyl-*p*-benzoquinone imine (NAPQI), which is highly hepatotoxic. Normally, the small amount of NAPQI is quickly detoxified by reacting with the sulfhydryl group of glutathione, forming nontoxic mercapturic acid. A large overdose results in depletion of the glutathione and subsequent increase in these metabolites. A severe overdose is often followed by mild nausea/vomiting/diarrhea (N/V/D). It is only after 24–48 hours that liver toxicity ensues. Acetaminophen poisoning is the most common cause of acute liver failure in the U.S.

Many intentional overdose patients present with coingestion of multiple substances. Always suspect acetaminophen as part of the clinical picture of any overdose. It is reasonable to check acetaminophen levels **regardless** of the presentation because untreated toxicity is potentially fatal.

Alcohol-acetaminophen syndrome—chronic moderate-to-heavy use of alcohol has a 2-fold effect: The cytochrome P450 system is cranked up (so that more NAPQI is produced), and the amount of glutathione is decreased (so less is available for detoxifying the NAPQI). Therefore, long-time users of moderate-to-heavy amounts of alcohol who take acetaminophen in normal or higher doses are at risk for severe hepatic toxicity or liver failure.

Treatment of acetaminophen overdose: Activated charcoal is beneficial, does not hinder use of *N*-acetylcysteine (NAC), and is typically used if patients

present within 4 hours of ingestion. Although there is great variability in the hepatic response to the overdose, a 4-hour postingestion acetaminophen level of > 250 µg/mL (165 µmol/L) indicates a high probability of hepatotoxicity if left untreated. NAC is an effective antidote that works by increasing the availability of hepatic glutathione.

NAC is effective when given within 8–16 hours after the acetaminophen overdose. Even when given late in the course to a patient with significant ingestion and toxicity, it reduces mortality and improves liver function. Treatment can be initiated with either an IV or oral protocol, each of which varies in duration. IV is favored if patients are vomiting or present in liver failure.

Both protocols continue dosing until the measured acetaminophen level is undetectable or “clearly decreasing” with a minimum of dosing over 20 hours. (The specific definition of “clearly decreasing” is controversial.)

Overdose — Anticholinergics

Remember the presentation of anticholinergic overdose—“red as a beet, dry as a bone, hot as a hare, blind as a bat, mad as a hatter, full as a flask”:

- Red: cutaneous vasodilation
- Dry: anhidrosis
- Hot: hyperthermia
- Blind: mydriasis
- Mad: hallucinations
- Full: urinary retention

Tachycardia is another consistent clinical presentation of anticholinergic overdose. The antidote is physostigmine, which is an anticholinesterase.

See Table 15-16 on page 15-39.

Overdose — Other Prescription Drugs

Lithium

Mental status changes are the most common manifestation of an acute lithium overdose, affecting > 90% of patients. Other CNS changes with severe toxicity include seizures and symptoms due to encephalopathy (e.g., poor memory, incoherence, disorientation). Patients can also get parkinsonian symptoms and movement disorders. Nausea, vomiting, and diarrhea are also common.

Obtain a lithium level if you suspect toxicity. The therapeutic range for acute mania treatment is 1.0–1.5 mEq/L (1.0–1.5 mmol/L). Long-term therapeutic range is 0.6–1.2 mEq/L (0.6–1.2 mmol/L). Mild-to-moderate adverse symptoms usually occur at 1.5–2.5 mEq/L (1.5–2.5 mmol/L), and severe effects can be seen at > 2.0 mEq/L (> 2.0 mmol/L).

Many medications interact with lithium, especially those that affect renal function or water balance (e.g., ACE inhibitors and NSAIDs increase serum levels of

lithium). Diuretics are challenging because thiazide diuretics increase lithium levels, potassium-sparing diuretics decrease lithium levels, and loop diuretics can do both. Likewise, calcium channel blockers can increase or decrease lithium levels. When adding a new medication, monitor lithium levels closely.

Remember: Chronic lithium use can cause renal tubular acidosis, nephrogenic diabetes insipidus, and sicca symptoms.

Treatment: Restore fluid and electrolyte balance; reserve hemodialysis for severe cases. Activated charcoal is **not** an effective treatment for lithium overdose.

Benzodiazepines

Overdose with oral BDZs alone rarely causes severe toxicity, but it is typically ingested with alcohol or opioids. More common scenarios of benzodiazepine toxicity occur in the setting of operative anesthesia. Patients with benzodiazepine toxicity can have CNS depression with otherwise normal vitals and exam ("coma with normal vitals"). Treatment is usually supportive. Activated charcoal is **not** recommended. Use of the antidote flumazenil is controversial because it may precipitate withdrawal seizures in patients who are tolerant to BDZs.

Tricyclic Antidepressants

TCAs are lipophilic and are protein bound, so they have a very large volume of distribution and **cannot** be removed by dialysis. Clinical presentation of toxicity includes sedation or confusion and arrhythmias. Symptoms can be present at low concentrations, so quantitative serum measurements are not helpful to guide acute overdose therapy.

If presentation is within 2 hours of ingestion, treatment includes gastric decontamination with activated charcoal +/- a single dose of a cathartic. Give supportive care and monitor for cardiotoxic side effects. Tricyclics cause tachycardia and PR, QT, and QRS prolongation. The **QRS prolongation** is the ECG change that correlates most closely with the **degree** of intoxication! Ventricular tachycardia and fibrillation are also common. The cardiac problems often respond to maintaining an **alkalemic** state—either by hyperventilation if the patient is intubated or with IV sodium bicarbonate. Keep the serum pH at 7.5–7.55, using sodium bicarbonate. Use BDZs for seizures.

Digoxin

Digoxin toxicity can occur because the drug has a very narrow therapeutic index, so you have to pay close attention to signs and symptoms. Clinical presentation of toxicity includes anorexia, nausea and vomiting, abdominal pain, confusion, weakness, changes in color vision, scotoma, and bradycardia with hypotension.

The presentation can appear as if the patient is being overtreated with an antihypertensive drug; this is important because patients who take digoxin often also take antihypertensives. Labs can show K^+ disturbances (hypokalemia in acute toxicity; hyperkalemia in chronic toxicity) and AKI, which is often the cause of the increase in the serum level.

Commonly used drugs that can increase digoxin levels when coadministered are macrolides and amiodarone. Digoxin is cleared by the kidney; therefore, decreases in glomerular filtration rate (GFR) increase the serum level.

Management includes continuous cardiac monitoring. PVCs are common. Other conduction abnormalities include AV block with junctional escapes and serious ventricular arrhythmias. Evaluate the ECG periodically because digoxin can flatten or invert T waves, shorten the QT interval, and depress lateral ST segments (findings often referred to as a "dig effect").

Treat digoxin overdose with activated charcoal if presented within 2 hours of ingestion. Use Fab fragments (a digoxin-specific antibody) to treat patients who have serious ventricular arrhythmias (tachycardia, fibrillation, complete heart block, Mobitz 2, and symptomatic bradycardia), serum $K^+ > 5 \text{ mEq/L}$ ($> 5 \text{ mmol/L}$), and renal failure or mental status changes. Be aware that the presenting hyperkalemia rapidly reverses with Fab antibodies, so do **not** be overly aggressive in treating hyperkalemia.

Theophylline

Theophylline more often presents as **inadvertent** toxicity rather than intentional overdose. Toxicity often occurs in the context of the patient having been prescribed another drug (or herbal preparation) that increases theophylline levels. Suspect toxicity when you see a clinical history of obstructive lung disease and tremulousness, tachycardia/ventricular arrhythmias, vomiting, +/- seizures, or with a theophylline level $> 20 \text{ } \mu\text{g/mL}$ ($111 \text{ } \mu\text{mol/L}$). This toxicity can look like cocaine or methamphetamine use. Know the drugs that commonly interact with theophylline and increase levels: cytochrome P450 3A4 (CYP3A4) inhibitors, certain macrolides, quinolones, and cimetidine. The hydrocarbons (not nicotine) in cigarette smoke induce an increase in CYP1A2, so theophylline levels can rise with smoking cessation.

Treat supportively (paying attention to hypokalemia because it predisposes to ventricular arrhythmia), and give multiple doses of activated charcoal with a cathartic. If vomiting is too severe to allow for charcoal, give ondansetron +/- famotidine. Treat seizures with diazepam. Treat SVTs with adenosine. Stable ventricular arrhythmias usually respond to amiodarone; treat hypotension with α -agonists (phenylephrine or norepinephrine). Oddly, β -blockers can reverse

hypotension if the α -agonists do not work, but give β -blockers only under the guidance of a medical toxicologist. Call poison control to get such advice. Dialysis is recommended in patients with seizures or ventricular arrhythmias.

Overdose — Illicit Drugs

Table 15-17 on page 15-44 and page 15-45 summarizes key clinical findings for illicit drugs.

Cocaine: Cardiotoxicity can occur no matter what the route of use. Cocaine causes rhythm disturbances (including V-fib/tach), ischemia (irrespective of whether the patient has preexisting atherosclerotic disease), myocarditis, and systolic dysfunction. Suspect use in a young patient presenting with MI. Seizures and stroke are also common with cocaine; consider it in patients with a 1st time seizure. Muscle injury with rhabdomyolysis can occur. Know that β -blockers are **not** used in this group to treat angina or verified myocardial ischemia due to concerns of unopposed α -receptor stimulation. Instead, nitroglycerin, calcium channel blockers, and BDZs are 1st line treatments. Levamisole, a cocaine cutting agent that potentiates cocaine's action, has side effects of agranulocytosis and vasculopathy in genetically susceptible (e.g., HLA-B27) patients.

Methamphetamine is a powerful CNS stimulant that increases the release of epinephrine, norepinephrine, serotonin, and dopamine. Consider methamphetamine toxicity in the **sweaty**, severely agitated, or psychotic patient with tachycardia and HTN. Severe tooth decay occurs in chronic users. Acute treatment of the severely agitated patient is with IV BDZs first and then antipsychotics (e.g., haloperidol) if needed. IM doses are given if unable to give IV. Watch for rhabdomyolysis in these patients by monitoring electrolytes, BUN, creatinine, CPK, serum lactate, liver enzymes, and clotting times.

PCP (phencyclidine) can cause acute psychotic agitation, seizures, dystonia (including laryngospasm), nystagmus, and hypertensive crisis. Severe dystonia can cause rhabdomyolysis. Treat with a calm environment and IV BDZs as needed, with supportive care for complications such as rhabdomyolysis.

Heroin is an opiate from the seed pod of the poppy. Opiate intoxication presents with suppressed respiratory rate and volume, decreased mental status, decreased bowel sounds, and miotic (constricted) pupils. Heroin intoxication is sometimes difficult to differentiate from alcohol intoxication because both substances are CNS depressants, but alcohol does not usually constrict the pupils or decrease the bowel sounds.

LSD (lysergic acid diethylamide) is referred to as **Acid** and causes hallucinations. Fatalities and morbidity during use are unusual and generally attributable to bad decisions being made while intoxicated. It can precipitate serotonin syndrome.

MDMA (3,4-methylenedioxymethamphetamine; a.k.a. **Ecstasy**) use is often seen in young people in the setting of parties or raves. The drug is taken in tablet form. The ingestion of MDMA results in euphoria, loss of inhibitions, cozy feelings of intimacy, and increased sexual arousal due to an increased release of serotonin. The drug is commonly perceived as being very mild with minimal risk and physical effects, but Ecstasy possesses properties that resemble a combination of amphetamines and peyote (stimulant + hallucinogen) and can cause serious side effects.

Side effects of MDMA include bruxism (teeth grinding), anxiety, sweating, HTN, and tachycardia. Dangerous and sometimes fatal complications include hyperthermia, severe hyponatremia (from drinking too much water while sweating heavily), malignant HTN, rhabdomyolysis, DIC, stroke, cardiac ischemia, arrhythmias, aortic dissection, and serotonin syndrome. The hyperthermia, rhabdomyolysis, and hyponatremia especially occur in patients who use Ecstasy and dance all night. The hyperthermia is dose-dependent and usually mild, but can be worsened by prolonged physical exertion, poor fluid intake, and an overheated environment. Severe hyperthermia can cause disseminated intravascular coagulation (DIC) and can be fatal.

Give activated charcoal if the patient presents within 1 hour of ingestion. In intoxicated states, most symptoms (i.e., HTN, tachycardia, agitation) respond to BDZs. Haloperidol can potentially exacerbate hyperthermia. Arrhythmias respond to calcium channel blockers. β -blockers are **not** recommended because of the possibility of unopposed α -adrenergic stimulation. Hyponatremia typically responds to water restriction; treat hyponatremic seizures with IV hypertonic saline and benzodiazepine in the ICU.

POISONING MANAGEMENT

Poisoning — Acid Alcohols Ingestion

Isopropyl alcohol (rubbing alcohol) is a common solvent and disinfectant. Like ethanol, it has CNS-depressant effects. It is 2nd to ethanol in the causes of alcohol overdose. The main metabolite is acetone, which causes a prolonged CNS effect. The acetone causes ketonuria but **no** anion gap acidosis, and the **sweet odor** of acetone is evident on the patient's breath. CNS depression is the major effect, although there can also be cardiac depression. Abdominal pain and vomiting are usually present. An osmol gap of > 35 mOsm/kg is typically seen with toxicity. Treatment: Give supportive care. Make early use of hemodialysis/peritoneal dialysis in severe cases.

Methanol (wood alcohol) toxicity is usually due to contaminated moonshine. It is only mildly inebriating, and many signs of toxicity are delayed > 24 hours—especially visual impairment, from blurring to **blindness**. The toxic metabolites are formaldehyde and formic acid. Serum analysis shows an increased anion and

Table 15-17: Substance Abuse and Key Clinical Findings / Effects

Drug	Symptoms / Signs	Lab Results / Other Effects
Marijuana	Conjunctival injection Gynecomastia Chronic cough, phlegm, wheezing Impairment of short-term memory Decreased performance in driving and other activities requiring coordination Loss of critical judgment Time-perception distortion Nausea and vomiting	Decreased plasma testosterone and spermatogenesis Decreased glucose tolerance Significant drop in intraocular pressures (may be helpful in glaucoma)
Tobacco	Chronic cough, phlegm, and wheezing	Increased hemoglobin/hematocrit Increased platelet aggregation
Toluene (e.g., model airplane glue, paint thinner)	Perioral eczematous changes Relaxation and "pleasant" hallucinations for ~ 2 hours	Excreted rapidly in the urine; can be detected by looking for hippuric acid Hypokalemia Hypophosphatemia Metabolic acidosis
Gasoline	Perioral eczematous changes Euphoria followed by violent excitement and then coma	Pulmonary HTN Restrictive lung defects Peripheral neuropathy Acute rhabdomyolysis Hematuria
Amyl nitrite (Poppers) Butyl nitrite (e.g., room deodorizers)	Euphoria Enhanced musical appreciation Increased libido Headaches Hypoxemia Syncope	Hypotension Transiently inverted T waves and depressed ST segments Methemoglobinemia Increased intraocular pressure
LSD (lysergic acid diethylamide)	Very potent hallucinogen 3 stages: Somatic (physical effects: dizziness, dilated pupils, flushing, increased temperature, tachycardia) Perceptual (changes in vision and hearing: "seeing" smells or "hearing" colors) Psychic (changes in sensorium: delusional ideation, body distortion, psychosis)	Not associated with a withdrawal syndrome "Flashbacks" common years after use
Alcohol	Euphoria Grogginess Talkativeness Impaired short-term memory High levels: result in coma, respiratory depression, death	Elevated GGT and AST Elevated amylase and lipase
Inhalants	Perioral eczematous changes Euphoria Slurred speech Decreased coordination Dizziness Sexual enhancement (amyl nitrate) Profound hypotension Chronic use: possible irreversible damage to the heart, liver, kidneys, lungs, and brain	Methemoglobinemia (amyl nitrate) with decreased oxygen saturation on pulse ox but normal P_aO_2
Dextromethorphan	"Out of body" dream-like state Tachycardia, HTN, lethargy, mydriasis, agitation, and vomiting	Symptoms last 3–6 hours
Mushrooms (psilocybin)	Similar to LSD	Also, prominent gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea)
MDMA (3,4-methylenedioxymethamphetamine; Ecstasy, Molly)	Euphoria, heightened sensual awareness Increased "emotional" energy Nausea, jaw clenching, teeth grinding, blurred vision Anxiety and psychotic episodes At risk for dehydration At risk of hyponatremia secondary to "water-loading" in attempt to avoid dehydration	Rhabdomyolysis Seizures

Table 15-17: Substance Abuse and Key Clinical Findings / Effects (continued)

Drug	Symptoms / Signs	Lab Results / Other Effects
PCP (phencyclidine; Angel Dust)	Cramps, diarrhea, and hematemesis Euphoria, nystagmus, ataxia, and hallucination Higher doses—psychosis with use of verbal abusive language Even higher levels—cardiac arrhythmias and seizures Coma (unique for PCP) with absence of respiratory depression, presence of muscle rigidity, hyperreflexia, and nystagmus	Urine drug screen is helpful
Cocaine	Euphoria Decreased fatigability Paranoid ideation Possible seizures Chest pain	Pupillary dilatation Elevated CK Tachycardia HTN Consider in young person with MI: look for cocaine
Amphetamines/ Methamphetamines	HTN Hyperpyrexia Seizures Increased libido leading to high-risk sexual behavior	Cardiac conduction abnormalities Cerebrovascular damage Withdrawal syndrome presents in stages: • Early: depression, agitation, anergia • Intermediate: loss of energy, limited interest in surroundings, anhedonia • Final: drug-craving returns Do not use phenothiazines for treatment of withdrawal (hypotension and seizures)!
Opiates	Euphoria Decrease in pain Pinpoint pupils Bradycardia Hypersomnolence	Severe vasodilation Respiratory depression Pulmonary edema Loss of libido Constipation Withdrawal occurs 8 hours without opiate over a period of 24–36 hours: 1 st finding seen is yawning ; then lacrimation, mydriasis, insomnia, “goose flesh,” diarrhea, and systolic HTN α -2 agonists helpful
Anabolic steroids	Acne Keloids Striae Hirsutism Gynecomastia Testicular atrophy Azoospermia Rage-like behaviors Depression Mania Libido alterations	Hepatitis Increased risk of hepatocellular carcinoma Fluid retention is common. Growth retardation because of early epiphyseal closure
Benzodiazepines (Downers, Blue Footballs)	Relaxation Drowsiness Adverse effects: flu-like symptoms, paradoxical aggression, anxiety, oversedation	Hypotension Hypotonia Nystagmus Ataxia Withdrawal symptoms: diaphoresis, confusion, agitation, psychosis Abrupt withdrawal: protracted seizures
Synthetic cathinones (Bath Salts)	Stimulant/hallucinogenic effects: diaphoresis, tachycardia, HTN, hyperthermia, psychosis, paranoia, frightening hallucinations	Nosebleeds Increased sociability/sex drive Withdrawal symptoms: depression, tremors, paranoia, anxiety
GHB (γ -hydroxybutyric acid; “date rape” drug)	Euphoria Disinhibition Enhanced libido Agitation	Nausea Decreased respirations
Methylphenidate (psychostimulant used to treat ADHD)	Agitation Irritability Psychosis	Hyperthermia

osmol gap. Treat with fomepizole, folic acid, and immediate dialysis. Give folic acid to increase metabolism of the formic acid.

Ethylene glycol (antifreeze): Alcohol dehydrogenase breaks down ethylene glycol to its very toxic metabolites, especially oxalate. Presence of oxalate is indicated by **calcium oxalate crystals** in the urine and **hypocalcemia** (oxalate chelates Ca^{2+}). Suspect if a patient appears intoxicated but without an alcohol smell, and with a high anion gap metabolic acidosis and increased osmol gap. Treat with fomepizole, HCO_3^- for the acidosis, Ca^{2+} prn, and immediate dialysis.

Poisoning — Miscellaneous

Carbon monoxide: Carbon monoxide (CO) quickly binds with hemoglobin, with an affinity of ~ 250× greater than O_2 . This carboxyhemoglobin (COHb) decreases arterial oxygen content, which leads to tissue hypoxia.

Symptoms are progressive and range from headache and lightheadedness to lethargy to unconsciousness to coma to death.

Be especially suspicious if the patient has been working around cars, gas/oil heating units, or generators. Typical real-life scenarios:

- Car exhaust (e.g., bandmates practicing in the garage on a cold winter day and using a running car to warm up the garage—with the door closed)
- Exhaust from gasoline-powered generators: Especially suspect after a power outage, such as after a flood, hurricane, or ice storm; or among people from low socioeconomic status, who often use gasoline-powered generators.
- Poor combustion in heating unit:
 - Suspect when a patient calls from home in winter (especially near start of the cold season) and says the family members are suffering from headache and lightheadedness. The patient may sound slow to respond.
 - Or, suspect when the patient calls in the winter and complains of headache and lightheadedness that improves after going outside.

What to do? The answer to any scenario in which the patient calls you with suspected symptoms, and especially with suspected environmental factors, is to tell the patient to leave and get the family out of the house immediately; then, send an EMS unit there.

CO poisoning is responsible for most deaths in patients with smoke inhalation, so do not forget to check COHb levels when managing smoke inhalation.

The brain and heart are especially sensitive to CO. Poisoning often causes **long-term to permanent** CNS impairment with cognitive deficiencies (i.e., memory and learning), as well as personality and movement disorders.

Fetal hemoglobin has especially high affinity for CO, so treat pregnant patients aggressively.

If you suspect CO poisoning, get a COHb level. A handheld breath analyzer can quickly rule out CO poisoning, but ethanol causes false positives:

- Mild-to-moderate CO toxicity occurs at 15–30%.
- Moderate-to-severe toxicity occurs if > 30%.
- > 50% is often fatal.

“Cherry red” coloration is rare.

Treat CO poisoning with 100% O_2 —this decreases the half-life of COHb from about 5 hours to 1 hour. Hyperbaric O_2 further decreases the half-life to 30 minutes, but its main benefit is that it decreases the CO-induced ischemic reperfusion injury to the brain.

Hyperbaric oxygen is generally used to treat moderate-to-severe CO poisoning. Indications for hyperbaric oxygen (give within 6 hours):

- COHb > 25% and > 20% in pregnant women
- Loss of consciousness or any focal neurologic deficit
- Acidosis with pH < 7.1
- End-organ damage
- Smoke inhalation: Respiratory impairment results from the noxious chemicals in the lungs or laryngeal/airway edema. Suspect laryngeal involvement if face or airways are burned (e.g., singed nasal hairs). Remember the association between CO poisoning and smoke inhalation.

Cyanide poisoning clues: The patient’s breath has an **almond odor**, and the lab draw shows **bright red venous blood**. Cyanide immediately binds to the ferric molecule in the mitochondrial cytochrome oxidase complexes, thereby blocking cellular aerobic metabolism. These patients very quickly develop headache, tachycardia, and tachypnea. This can quickly progress to coma, various cardiac arrhythmia, and shock. Think about cyanide poisoning in patients who have been in a fire or who have received sodium nitroprusside or amygdalin (the chemical derived from apricot and peach pits that is used often in herbal compounds). Laboratory evaluation routinely shows significant lactic acidosis. Diagnosis is clinical, after excluding CO poisoning and other causes of lactic acidosis. Assays exist to find the chemical in the blood, but these are reference tests that take a long time for results.

The treatment goal is to induce methemoglobinemia because cyanide preferentially binds methemoglobin and produces a less toxic reaction. Treatment for cyanide poisoning is the following 3-step cyanide antidote sequence:

- **Step 1:** Hold amyl nitrite under the patient’s nose for 30 seconds.
- **Step 2:** Administer 3% sodium nitrite IV. The nitrites convert hemoglobin to methemoglobin (the ferric form of hemoglobin), which more effectively competes with the cytochrome oxidases for the cyanide.

Amyl nitrite inhalation causes a 3–5% methemoglobinemia, while the sodium nitrite causes 20% methemoglobinemia.

- **Step 3:** Administer sodium thiosulfate IV, which acts as a substrate for the enzyme rhodanese. This enzyme converts the cyanide released from hemoglobin to inactive thiocyanate, which is excreted renally.

Significant toxicity can result in a parkinsonian-type syndrome because cyanide is toxic to the basal ganglia.

Inorganic lead poisoning: Symptoms include anemia, basophilic stippling on peripheral smear, abdominal pain, and irritability, and can progress to neurologic and renal decline. If blood lead level is $> 25 \mu\text{g/dL}$ ($1.2 \mu\text{mol/L}$), then measure zinc protoporphyrin and free erythrocyte protoporphyrin levels, which indicate if exposure occurred over the preceding 120-day lifespan of the RBCs.

X-ray fluorescence can be used to reflect bone lead concentration over the past 10–30 years. Cumulative lead exposure increases risk for Parkinson disease, ALS, cataracts, and renal cancer.

Organic lead is lipid-soluble and rapidly excreted, and previous exposure is not detectable!

Insecticide: Exam questions give occupational exposure clues (e.g., agricultural or industrial settings)! Organophosphate and carbamate poisonings present identically. Muscarinic symptoms include increased salivation, miosis (small pupils), N/V/D, bronchorrhea, bronchospasm, bradycardia, and abdominal cramps. Organophosphates are more toxic than carbamates; they bind **irreversibly** to acetylcholinesterase, whereas the carbamate binding is reversible. This is reflected by a decrease in the level of RBC (not plasma!) acetylcholinesterase for several months after organophosphate poisoning, whereas it returns to normal within hours after carbamate poisoning.

Treatment for organophosphate and carbamate insecticide poisoning: The route of the poison into the body is dermal absorption (especially organophosphates), so decontaminate by removing and discarding clothes and irrigating with soap and water. Health care providers should wear protective clothing. For moderate-to-severe symptoms, give atropine 1–2 mg IV; repeat q 5 minutes prn. To prevent delayed neurotoxicity, also give a slow IV infusion of pralidoxime.

SPECIFIC TOXINS

Refer to [Table 15-16 on page 15-39](#) and [Table 15-17 on page 15-44 and page 15-45](#) for information on the physical exam in toxic ingestions, and see [Table 15-18](#) for a summary of common drug overdoses, poisoning agents, and the usual antidotes.

Table 15-18: Toxins and Antidotes

Toxin	Antidote(s)
Acetaminophen	N-acetylcysteine (NAC)
Digoxin	Antigen-binding fragments of digoxin-specific antibodies
Opiates	Naloxone
Benzodiazepines	Flumazenil*
Nitrates	Methylene blue
Iron	Deferoxamine
Carbon monoxide	Oxygen
Ethylene glycol	Fomepizole
Methanol	Fomepizole
Organophosphates	Atropine, pralidoxime (2-PAM)
Cyanide	Nitrates, sodium thiosulfate

* May precipitate withdrawal seizures in patients who are tolerant to BDZs or in tricyclic antidepressant overdose

DRUG WITHDRAWAL SYNDROMES

PREVIEW | REVIEW

- What are the pupillary findings in heroin withdrawal?
- What is the difference between alcohol withdrawal hallucinosis and delirium tremens (DT)?
- Which medication can precipitate seizures in patients with DT?

So far, the discussion has focused on intoxication. Know the following presentations of specific drug withdrawal.

Opiate withdrawal: Heroin is the major opiate that causes physiologic withdrawal; it also has the most addictive potential. Symptoms usually start within 6–24 hours after the last dose of opiate, or a patient can develop symptoms immediately after receiving opiate antagonists (e.g., naloxone, buprenorphine). Early symptoms include agitation, rhinorrhea, tearing, muscle aches, nausea, vomiting, abdominal pain, and diarrhea. Definitely think about this entity in the **tearful patient who is yawning**—two activities that typically do not go together.

Physical exam shows **dilated** pupils, yawning, hyperactive bowel sounds, and piloerection (from which the term “quitting cold turkey” is derived!). Vital signs can be normal; however, patients in severe distress can have tachycardia, tachypnea, and HTN.

Methadone is given to patients who are chronically addicted to opiates and present in acute withdrawal. If the patient desires to stop opiate use entirely because

of addiction and refuses methadone, symptoms can be ameliorated with clonidine and diazepam. Give promethazine for vomiting and loperamide for diarrhea.

Benzodiazepine withdrawal can be fatal. It presents with anxiety, tremulousness, agitation, and sometimes psychosis and/or seizures. Time of withdrawal from last dose depends on whether the drug used has a short or long half-life (up to 3 weeks for diazepam). Ideally, these drugs are tapered over a prolonged period when a patient is discontinuing chronic use. Withdrawal is treated with long-acting BDZs.

Ethanol: Patients severely addicted to ethanol start having withdrawal within about 6–24 hours from the last drink. (This can happen even though the patient still has a measurable blood alcohol level; if it's lower than the patient is accustomed to having, then they can withdraw.) Symptoms get more severe as time passes. Seizures can occur. Hallucinations may occur within 12 to 24 hours of abstinence, during which the patient's sensorium is intact and BP/pulse are normal, but they see, hear, and feel nonexistent phenomena. Alcohol hallucinosis is not synonymous with delirium tremens (DT). DT begins between 48 and 96 hours of abstinence and is marked by autonomic instability and delirium. Untreated, it lasts about 5 days. Complications include volume depletion, hypokalemia, hypomagnesemia, hypophosphatemia, and aspiration pneumonia. For DT, give good supportive care, replace thiamine before glucose, and use BDZs with alcohol withdrawal protocols. Replace electrolytes prn. Watch out for refeeding hypophosphatemia (discussed in the [Nephrology](#) section). Despite treatment, DT carries a mortality rate up to 15%.

For patients who can be frequently observed, give repeat BDZ doses when symptoms recur. The Clinical Institute Withdrawal Assessment (CIWA) protocol is commonly used to direct BDZ dosing and has been shown to result in lower total BDZ doses when compared with unstructured clinician assessment. In situations where observation is not feasible, fixed dosing schedules are used. **Do not use haloperidol in patients with DT because it can precipitate seizures.** To prevent alcohol withdrawal, give chlordiazepoxide orally to patients who desire to quit drinking and are not in DT.

Nicotine withdrawal syndrome peaks 3 days after stopping nicotine. Symptoms include insomnia, weight gain, depression, anxiety, and irritability. These symptoms subside over 3–4 weeks and can be reduced by nicotine replacement products (i.e., varenicline or bupropion).

Caffeine withdrawal symptoms occur 12–24 hours after stopping caffeine, peaking at 1–2 days. Fatigue, irritability, difficulty concentrating, and headache are the most common symptoms. Resumption of caffeine reverses symptoms in 30–60 minutes. Patients wishing to stop caffeine can be tapered off over 1–2 weeks if they develop withdrawal symptoms with abrupt discontinuation (occurs in only 50% of patients).

OSTEOPOROSIS

PREVIEW | REVIEW

- What are the risk factors for primary osteoporosis?
- How do you screen for osteoporosis?
- How are the Z-score and T-score used in the evaluation of osteoporosis?
- What are the common recommendations for all patients with osteoporosis?
- Which patients should be treated with drug therapy for osteoporosis?
- For how long can teriparatide be used? Why?
- A patient on alendronate presents with difficulty swallowing. What is the likely etiology?
- What is the most serious consequence of osteoporosis?

OVERVIEW

Osteoporosis is decreased bone strength, predisposing patients to bone fractures. One-half of all postmenopausal women suffer an osteoporosis-related fracture during their lifetime. Most fragility fractures (fractures that occur with a fall from standing height or less) occur in those without a prior radiographic diagnosis of osteoporosis.

Primary prevention of osteoporosis is controversial. As of 2018, the USPSTF concluded that for the primary prevention of fractures, the evidence is insufficient to assess the balance of the benefits and harms of:

- Combined vitamin D and Ca^{2+} supplementation, in premenopausal women or in men
- Daily supplementation with > 400 IU of vitamin D and $> 1,000$ mg of Ca^{2+} in noninstitutionalized postmenopausal women

For postmenopausal women, the common practice of supplementation with a combination of 1,000 mg of Ca^{2+} and 400 IU of vitamin D was found to have **no** effect on the incidence of fractures. Supplementation at this level was found to increase a woman's risk of developing kidney stones. For these reasons, the USPSTF recommends **against** daily use of low-dose Ca^{2+} (1,000 mg) and vitamin D (400 IU) in postmenopausal women for primary prevention of fractures. At present, evidence is lacking for support of higher doses of supplemental Ca^{2+} and vitamin D in these women. In its 2018 guideline on preventing falls in the elderly in a community-dwelling setting, the USPSTF recommends multifactorial interventions, primarily exercise, and recommends **against** using vitamin D supplementation. For more information on falls in the elderly, see the [Geriatric Medicine](#) section.

In contrast to the USPSTF, the 2014 National Osteoporosis Foundation guidelines recommend vitamin D and Ca^{2+}

supplements to prevent fractures in **all** adults ≥ 50 years of age. The Institute of Medicine report issued in 2010 also calls for dual supplementation.

From an exam standpoint, it is reasonable to accept that evidence is insufficient at present to recommend for or against vitamin D and Ca^{2+} supplementation for primary prevention of osteoporosis and falls.

RISK FACTORS

Osteoporosis is common in the elderly and is generally suspected by clinical presentation. (Fragility fracture is a clinical diagnosis if postmenopausal.)

There are many risk factors for primary osteoporosis, but the following connote highest risk:

- Age
- Personal history of fragility fracture (no trauma or fall from standing height or less)
- History of fragility fracture in a 1st degree relative
- Weight < 127 lb or BMI < 21
- Alcohol intake of 2 or more drinks/day
- Menopause before age 40
- History of glucocorticoid therapy equivalent to ≥ 5 mg/day of prednisone for > 3 months
- Cigarette smoking
- Malabsorption

SCREENING

The National Osteoporosis Foundation guidelines of 2014 recommend screening all women ≥ 65 years of age and all men ≥ 70 years of age with dual energy x-ray absorptiometry (DXA) scans—and selectively screening women and men > 50 years of age **if** they have **any** osteoporosis risk factors, particularly those listed above. The USPSTF 2018 guidelines are the same for women, but they do not promote screening in men, stating that the evidence is insufficient for assessing the balance of risks and benefits in men. Evidence for the optimal interval for repeat screening is lacking. Data suggests that the degree of osteopenia found on the initial scan should dictate appropriate screening intervals.

Screen patients with the following conditions regardless of age and gender:

- GI diseases: ulcerative colitis, Crohn's, celiac, gastric bypass, malabsorption
- Endocrine disorders: hyperparathyroidism, Cushing syndrome, hypogonadism, hyperthyroidism
- Medications: glucocorticoids, thyroxine, lithium, phenobarbital, phenytoin, cyclosporine
- Rheumatoid arthritis, systemic lupus erythematosus (SLE)
- Anorexia nervosa
- Prolonged bed rest or wheelchair bound
- Multiple vertebral compression fractures noted on x-ray (2/3 of vertebral fractures are painless)

DXA is the preferred method for screening. It is quick (~ 15 minutes), inexpensive, and quite accurate.

Bone mineral density (BMD) reports generated by the DXA have the T-score and the Z-score:

- The **T-score** compares results with normal, young, healthy bone; a T-score of -1.0 means the BMD is 1 standard deviation less than normal—about 10% low. A T-score of **-2.5 or lower** is the definition of osteoporosis (about 25% below normal), whereas those between -1.0 and -2.5 indicate osteopenia.
- The **Z-score** compares the BMD result to age- and sex-matched controls (usually used in premenstrual women).

BMD by DXA is an excellent predictor of fracture risk, but it does not consider other risk factors for fracture. In 2008, the University of Sheffield developed a more comprehensive risk assessment tool called **FRAX**. FRAX is a well-validated tool that incorporates both BMD and clinical risk factors (such as age, weight, smoker, glucocorticoids, rheumatoid arthritis, and alcohol use) and calculates the 10-year risk of developing a fragility fracture. FRAX requires using the calculation tool at shef.ac.uk/FRAX.

TREATMENT

Common recommendations for all patients with osteoporosis:

- Dietary Ca^{2+} 1,200 mg daily (Include supplements if necessary, but higher amounts are not recommended due to increased risk of kidney stones and cardiovascular disease.)
- Vitamin D 800 IU daily
- Regular weight-bearing exercise
- Fall prevention
- Avoiding tobacco
- Avoiding excess alcohol use—no more than 1 drink/day for women and 2 drinks/day for men

The 2014 National Osteoporosis Foundation guidelines recommend that drug therapy be considered in postmenopausal women and in men > 50 years of age presenting with these findings:

- A hip or vertebral fracture (clinical or radiographic)
- T-score between -1.0 and -2.5 with other prior fractures (not hip or vertebral)
- T-score < -2.5 : This means a score like -3.0 or -2.7 because we are dealing with “less than” and negative numbers. **A T-score < -2.5 defines osteoporosis!**
- T-score between -1.0 and -2.5 and secondary causes associated with high risk of fracture (steroid use or total immobilization)
- T-score between -1.0 and -2.5 and a 10-year probability of hip fracture $> 3\%$ or a 10-year probability of any major osteoporosis-related fracture $> 20\%$ based on the U.S.-adapted WHO algorithm FRAX calculation

Drug Therapy for Osteoporosis

All drugs that increase bone density do so by their effects on bone remodeling. They can either increase buildup (stimulate osteoblasts) or decrease breakdown (inhibit osteoclasts). The drugs can be categorized as anabolic vs. anticatabolic based on these effects on bone remodeling. Anabolic agents stimulate both osteoblasts and osteoclasts but stimulate the osteoblasts more, leading to a net increase in bone building and increased bone density. Anticatabolic agents inhibit osteoclasts, thereby decreasing the resorptive process.

Anabolic agents (stimulate osteoblasts): Parathyroid hormone (PTH) causes both an increase in bone buildup and an increase in bone resorption—but the net effect is to build more bone than it breaks down. It is **not** a 1st line treatment; PTH is reserved for patients with severe disease (T-score < -2.5 and an osteoporosis-related fracture or T-score < 3.5 without a fracture). Teriparatide and abaloparatide are injectable synthetic PTH. These agents (which are not used together) can be used for only 2 years because of cumulative increased risk of osteosarcoma; when one agent is discontinued, patients need to use a bisphosphonate. The major side effect is hypercalcemia.

Anticatabolic/Antiresorptive agents (inhibit osteoclasts) include the rest of the osteoporosis drugs:

- Bisphosphonates
 - Oral bisphosphonates: alendronate (Fosamax), ibandronate (Boniva), and risedronate (Actonel, Atelvia)
 - Injectable bisphosphonates: zoledronic acid (Reclast, Zometa) and ibandronate
- Hormone replacement therapy (HRT) may prevent or reverse the development of osteoporosis, **but** its use in the peri- and postmenopausal woman is a two-edged sword. 2018 USPSTF recommends **not** using HRT as 1st line therapy! For more on HRT, see the [Women's and Men's Health](#) section.
- Denosumab (Prolia, Xgeva)
- Calcitonin-salmon (Miacalcin)
- Raloxifene (Evista)

Bisphosphonates are analogs of pyrophosphate and, like estrogen and other anticatabolic agents, inhibit bone resorption. Bisphosphonates and HRT appear to have an **additive effect** and effectively act as antagonists of PTH. (Recall, PTH causes resorption—a release of Ca^{2+} from the bone into the serum.)

Severe muscle/joint/bone pain can occur between 1 day and several months after starting the drug. Treatment is to stop the bisphosphonate.

Bisphosphonates, especially IV, increase risk of osteonecrosis (i.e., avascular necrosis) of the jaw (ONJ); although it is not common (0.001–0.01%, with incidence in general population of < 0.001%), ONJ presents as pain and sometimes fracture of the mandible. Be cautious of using

these drugs in patients who are having extensive dental or mandibular surgery; using glucocorticoids; or have poor oral hygiene, diabetes, and ill-fitting dentures. If dental risk factors are present, repair and stabilize them prior to initiation of bisphosphonates. X-rays, CT, MRI, and positron emission tomography (PET) can help with diagnosis of ONJ, but plain radiographs are usually obtained first. Treatment includes good oral hygiene, antibiotics, and sometimes surgical debridement, as well as stopping the bisphosphonates.

Atypical subtrochanteric femoral fractures can occur in patients receiving bisphosphonates for a median of 7 years and usually present with an aching in the groin or thigh. These look like stress fractures. Get radiographs to determine if an atypical fracture is present with cortical lucency and periosteal thickening. If so, stop the bisphosphonates and request an orthopedic consult.

Notes on the bisphosphonates:

- They are considered 1st line therapy for treatment in most patients.
- **Alendronate** is poorly absorbed and, rarely, causes severe esophagitis (although this is **less** of a problem with weekly dosing). Recommend that patients take it with a full glass of water on an empty stomach and do not eat or lie down for 30 minutes after ingestion. It has been shown to reduce the risk of hip fractures.
- **Ibandronate** is the 1st once-monthly oral medication approved for postmenopausal osteoporosis. It is given every 3 months via IV.
- **Risedronate** was FDA-approved in 1998 for the prevention and treatment of postmenopausal osteoporosis. It has the same clinical effect as alendronate but may have fewer GI side effects. Even so, take the same dosing precautions as with alendronate.
- **Zoledronic acid** is given by IV once a year.

Denosumab is a monoclonal antibody that inhibits the receptor activator of nuclear factor kappa-B ligand (RANKL) receptors, preventing preosteoclasts from maturing into osteoclasts and thereby decreasing bone resorption. It is given as an SQ injection every 6 months. Although denosumab is still a relatively new agent, in 2017 the FDA published a new update to the warnings and precautions section of the denosumab drug label regarding the risk of atypical femur fractures during and after treatment.

Calcitonin, administered via nasal spray, SQ, and IM routes, increases BMD; however, the FDA advisory statement says the risks outweigh benefits in prevention of osteoporosis. Both the nasal and injectable forms are an effective analgesic in the setting of an acute osteoporotic fracture. There is no evidence that either the injections or nasal spray decrease hip fracture risk.

Raloxifene: During the development of antiestrogens, scientists discovered substances that blocked the effect of estrogen on some tissues but mimicked estrogen on

others. These are called selective estrogen receptor modulators (SERMs). Examples are tamoxifen and raloxifene. The effect of raloxifene on bone and lipid levels is similar to, but less than, estrogen; however, it exerts estrogen-antagonistic effects on the breast and uterus and may be less likely to cause cancer than traditional HRT. Raloxifene is FDA approved for both prevention and treatment of postmenopausal osteoporosis.

There is no consensus on the appropriate duration of drug therapy for osteoporosis.

FRACTURES

Fractures are the most serious consequence of osteoporosis. There are 1.5 million fractures/year due to osteoporosis, with 300,000 of those due to proximal femoral fracture. Mortality due to proximal femoral fractures is about 20% within the 1st year! Femoral neck and intertrochanteric fractures account for 97% of proximal femoral fractures.

Femoral neck fractures are **intracapsular** and have a significant risk of osteonecrosis from disruption of blood supply to the femoral head; therefore, the treatment of choice is either femoral head replacement or total hip arthroplasty.

Intertrochanteric fractures are **extracapsular** and have a lower risk of osteonecrosis but a higher risk of hip displacement than do intratrochanteric fractures. If there is a complete fracture and patients are ambulatory, they are typically treated with internal fixation; if nonambulatory with an incomplete fracture, treat with conservative measures.

In both types of fracture, the main goals are:

- To achieve mobility and function as soon as possible to avoid morbidity and spiraling complications due to poor mobility
- To reduce mortality if surgery is done within 72 hours of fracture, especially in patients without significant comorbidities

DVT, which is usually asymptomatic, occurs in up to 48% of hip fracture patients without anticoagulants. Prophylactic anticoagulation with various agents (i.e., low-molecular-weight heparin [LMWH], warfarin, fondaparinux [Arixtra]) reduces this risk by 50–65%.

The estimated risk of symptomatic VTE occurring without prophylaxis within 35 days of surgery is 4.3%. The direct oral anticoagulants are approved for VTE prophylaxis in knee and hip replacement surgery but **not** for hip fracture surgery, as this has not been sufficiently studied.

Other complications of hip fractures are pressure ulcers, hospital-acquired delirium, constipation, and fecal impaction. Fat embolism is a rare but potentially fatal complication.

OPHTHALMOLOGY

PREVIEW | REVIEW

- What is the treatment for primary open-angle glaucoma? Angle-closure glaucoma?
- What is the difference between open-angle and angle-closure glaucoma? Which is a medical emergency?
- Describe the ocular findings with angle closure glaucoma.
- Describe the findings with retinal detachment.
- What is the treatment for retinal detachment?
- How do retinal artery occlusion and retinal vein occlusion differ?
- What is the leading cause of acquired legal blindness in the U.S.?
- Optic neuritis can signal the development of which neurologic disorder?
- What is vitreous hemorrhage?
- Know the eye movements controlled by the 3rd, 4th, and 6th cranial nerves and the symptoms of their associated dysfunctions.
- Which virus is usually responsible for conjunctivitis?
- A contact lens wearer presents with severe keratitis and says she uses tap water frequently for lens care. Which organism should you consider?

OVERVIEW

The ciliary body produces aqueous humor, which flows through the pupil into the anterior chamber, and then goes through the trabecular meshwork and into the Schlemm canal (Figure 15-4). The greater the resistance to this flow in the trabecular meshwork and the Schlemm canal, the greater the intraocular pressure. Normal pressure is < 21 mmHg.

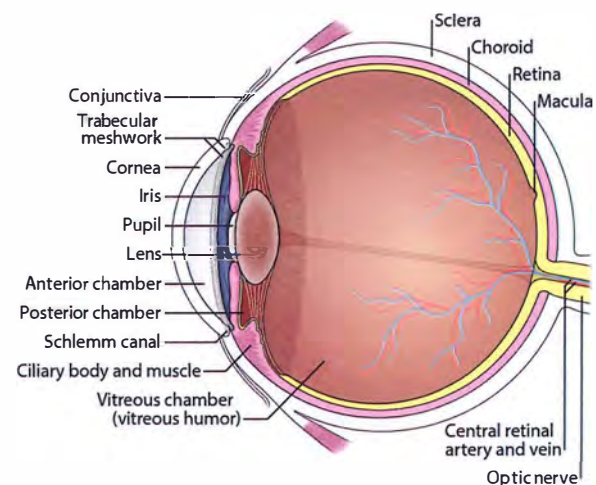


Figure 15-4: Structures of the eye

CAUSES OF SUDDEN VISION LOSS

Sudden loss of vision may be painless or painful and may be monocular or binocular in nature:

- Painless monocular loss
 - Retinal detachment
 - Central retinal artery occlusion
 - Branch retinal vein occlusion
 - Central retinal vein occlusion
 - Vitreous hemorrhage
 - Giant cell arteritis
 - Psychogenic
 - Hyphema
- Painful monocular loss
 - Keratitis
 - Corneal ulcers
 - Closed-angle glaucoma
 - Trauma and hyphema
 - Optic neuritis
 - Ischemic optic neuropathy
- Sudden loss of vision binocular
 - Migraine headaches
 - Psychogenic
 - Bilateral occipital cortical infarct
 - Vertebrobasilar ischemia

We will discuss these in more depth later in this section.

Note: **Gradual** vision loss is often caused by presbyopia. **Presbyopia** is a normal aspect of aging that occurs between 40 and 50 years of age as the lens slowly loses its ability to accommodate for near vision. Patients usually need bifocals or reading glasses for near vision.

GLAUCOMA

Glaucoma is an insidious disease in which a prolonged, elevated intraocular pressure causes progressive visual field loss due to optic nerve damage. There are 4 broad classifications of glaucoma: primary open-angle (POAG), angle-closure, congenital, and secondary. Know the specifics about POAG and angle-closure glaucoma.

Primary Open-Angle Glaucoma

POAG is the most common type. It is called “open-angle” because the globe has elevated pressure with **no** closure of the inlet of the trabecular meshwork. Patients suffer **unnoticed** gradual loss of peripheral vision (tunnel vision) that can progress to blindness before it is detected.

Risk factors include advanced age, family history, increased intraocular pressure, and African American race (5× increased risk compared to other races).

Be suspicious and refer for ophthalmologic evaluation those patients with risk factors and/or those who have “**cupping**” on fundoscopic exam. (Cupping = cup occupying > 50% of the optic disc; normal cup occupies < 50%.)

Screening of POAG: The American Academy of Ophthalmology (AAO) 2015 comprehensive adult medical eye evaluation guidelines recommend a comprehensive eye exam by an ophthalmologist or skilled optometrist after 40 years of age. After the initial screening exam, repeat screening is usually recommended every 3–5 years in patients without risk factors and every 1–2 years for those with ≥ 1 risk factor (borderline intraocular pressure, cupping, African American race, and family history). Patients with DM should be seen yearly. The AAO also recommends that African Americans have periodic exams between 20 and 39 years of age. For all individuals > 60 years of age, perform a complete exam every 1–2 years. However, the USPSTF 2013 recommendations found insufficient evidence to recommend for or against screening adults for glaucoma.

Treat POAG with medications or laser surgery. The following meds are used:

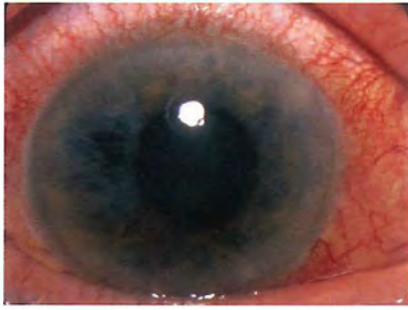
- **Prostaglandins** (topical) are 1st line drugs because of the once-daily dosing and the few systemic side effects, especially compared to the topical β -blockers. These are expensive!
- **β -blockers** (topical) dramatically decrease intraocular pressure, probably by decreasing production of aqueous humor. Aqueous humor production is thought to be mediated by tonic sympathetic (β) stimulation. β -blocker options are:
 - Nonselective (i.e., timolol, carteolol, levobunolol, metipranolol)—can cause lethargy, bradycardia, and exacerbations of COPD
 - β_1 -selective (betaxolol)

Angle-Closure Glaucoma

Primary angle-closure glaucoma (a.k.a. closed-angle glaucoma, narrow-angle glaucoma; see A in Table 15-19) is the most severe form of narrow-angle glaucoma. It is an **ocular emergency**—know it well. Risk factors include age > 40 years, female, hyperopia (farsightedness), Asian race, and positive family history.

In contrast to primary open-angle glaucoma, elevated intraocular pressure in angle-closure glaucoma is caused by mechanical obstruction of aqueous outflow through the trabecular meshwork, due to an anomalous iris configuration or iris neovascularization. The resulting rapid increase in intraocular pressure causes redness, severe eye pain, nausea, and halos around lights. It can also cause headache and present similarly to migraine. Onset can be triggered by low-light conditions that precipitate pupillary dilatation (e.g., nighttime or in a movie theater).

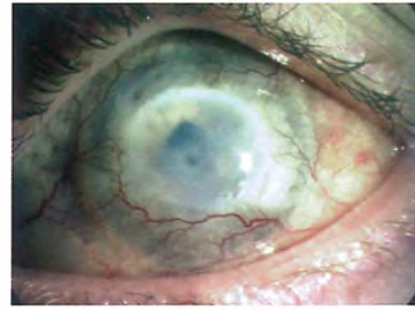
Physical exam shows decreased vision, increased intraocular pressure (often > 30 mmHg), a narrow angle and shallow anterior chamber (seen with gonioscopy with lens), corneal edema, conjunctival hyperemia, and a fixed, mid-dilated pupil.

Table 15-19: Ophthalmology — Treat Emergently and Immediately Refer

A. Angle-closure glaucoma. Image shows corneal edema, conjunctival hyperemia, and a fixed, mid-dilated pupil.



B. Central retinal artery occlusion (CRAO). Retinal edema, sparing the relatively thin fovea, creates pallor and the appearance of a cherry red spot in the macula.



C. Alkali burn. Findings may involve corneal opacification and ischemia of the conjunctival and scleral vessels.



D. Anterior uveitis (severe). Findings include ciliary flush with normal cornea, distorted pupil, and hypopyon.



E. Optic nerve infarction in giant cell arteritis. Funduscopy shows a pale and swollen disc, peripapillary hemorrhages, and cotton-wool spots.



F. Orbital cellulitis (severe). Image shows dysconjugate gaze, diplopia, proptosis, and chemosis (conjunctival swelling), and swelling of the eye and eyelid.

Ideal treatment includes immediate ophthalmologic referral for a laser iridotomy. If an ophthalmologist cannot see the patient immediately and the patient has decline in vision, **treat immediately** with these steps in the following order:

- 1) Place patient supine.
- 2) Give timolol 1 drop and wait 1 minute.
- 3) Give apraclonidine 1 drop.
- 4) Give pilocarpine 1 drop.
- 5) Give prednisone 1 drop.
- 6) Give acetazolamide.

Instructions with over-the-counter medications (decongestants) often include admonitions to “avoid use in patients with glaucoma.” These warnings apply only to patients with angle-closure glaucoma **not** already treated with iridotomy.

THE RETINA

Retinal Detachment

Retinal detachment can occur spontaneously (see A in Table 15-20 on page 15-54). It often presents as flashes or streaks of light (photopsias), showers of black dots (hemorrhage), or a “shade coming down” or “waving curtain” in a portion of the visual field. Visual acuity can be normal

initially. Myopia (nearsightedness) is the biggest risk factor. Other risk factors include male sex, 40–60 years of age, and recent head trauma.

Presumptive diagnosis is based on history, but occasionally a portion of the retina appears elevated or folded on ophthalmoscopy exam.

Treatment: This condition requires an **emergent referral** because untreated partial detachment can progress over hours to total retinal detachment with permanent blindness. Surgical repair or vitrectomy is beneficial.

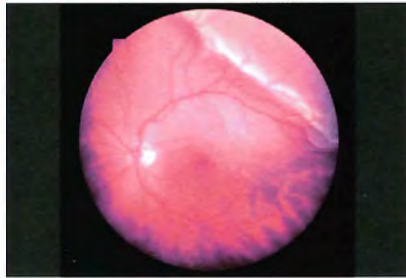
Retinal Vascular Occlusion

Central Retinal Artery Occlusion

Occlusion of the central retinal artery—usually embolic—causes sudden, painless, **unilateral** blindness (see B in Table 15-19). This is a true ocular emergency in which every minute counts. Retinal edema, sparing the relatively thin fovea, creates pallor and the appearance of a **cherry red spot** in the macula.

Treatment is directed toward dislodging the embolus and includes ocular massage and/or paracentesis of the anterior chamber and ocular hypotensive agents (to lower pressure). You can massage the affected globe with your index fingers (5 seconds pressure, 5 seconds no pressure, repeat). Laser or surgery-mediated

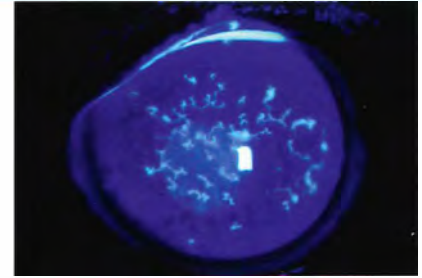
Table 15-20: Ophthalmology — Refer Immediately Without On-Site Treatment



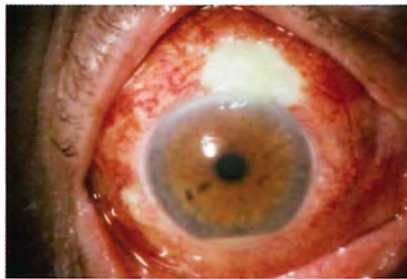
A. Retinal detachment. Retina is pulled away from the blood vessel layer.



B. Keratoconjunctivitis. Conjunctiva is inflamed (conjunctivitis) with mucoid discharge and visible white opacifications in cornea (keratitis).
Source: CDC



C. Herpes keratitis of the cornea. Fluorescein dye under UV light reveals the herpetic ulcerations.



D. Endophthalmitis. Note the hazy cornea and hypopyon.

embolectomy can help. Unfortunately, all these temporary measures are rarely effective. Patients subsequently require a thorough systemic evaluation for embolic and carotid disease (i.e., an acute stroke workup).

Retinal Vein Occlusion

Retinal vein occlusion is more likely to occur in patients with HTN, diabetes, high cholesterol, and hyperviscosity syndromes (e.g., polycythemia vera, Waldenström macroglobulinemia).

Central retinal vein occlusion (CRVO) is blockage of the main retinal vein. It results in sudden, painless, near-total loss of vision. The main cause is HTN, but it is also seen with diabetes and with hyperviscosity syndromes. It has been associated with history of primary open angle glaucoma in Western populations and with angle closure glaucoma in Asian populations.

Branch retinal vein occlusion (BRVO) involves blockage of a smaller branch retinal vein, which can be thought of as AV nicking with the artery pinching off the vein, producing venous dilation and wedge-shaped focal retinal hemorrhages. In contrast to CRVO, these patients may have only mildly blurred vision.

Diagnosis is made with an ophthalmoscopy exam. CRVO has a “blood and thunder” fundus with multiple hemorrhages (see A in Table 15-21). This is in contrast to the cherry red spot found in central retinal artery occlusion. BRVO reveals itself as AV nicking (see B in Table 15-21).

Evaluate patients with retinal vein occlusion for HTN and hyperviscosity states, and refer them to an ophthalmologist.

Macular Degeneration

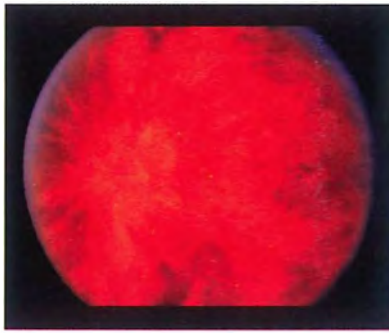
Age-related macular degeneration (AMD) is the leading cause of irreversible acquired legal blindness in developed countries. The macular area of the retina consists of the fovea and the surrounding area. The fovea is responsible for fine (20/20) visual acuity. Although the macula comprises only 2% of the visual field, 25% of the cone photoreceptors are here, and it correlates with 50% of the primary visual area of the brain.

There are 2 types of AMD:

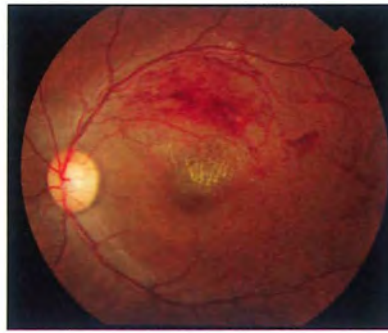
- 1) **Atrophic** (or “dry”): This is the most common type. It causes a gradual loss of central acuity down to 20/400 (peripheral vision is spared).
- 2) **Neovascular** (or “wet”): This type is somewhat amenable to treatment with laser photocoagulation, photodynamic therapy, and/or intravitreal ranibizumab or bevacizumab.

Risk factors for both types include smoking and low levels of zinc and antioxidants in the diet. The Age-Related Eye Disease Study (AREDS) in 2001 and the AREDS2 in 2013 both showed that, in patients with moderate to advanced AMD, use of antioxidant vitamins plus zinc, β -carotene, lutein, and omega-3 fatty acids reduced the risk of developing more advanced AMD.

Table 15-21: Ophthalmology — Refer to Be Seen Within 1–2 Days



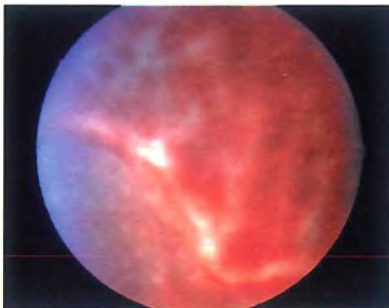
A. Retinal vein occlusion. Central retinal vein occlusion (CRVO). Funduscopy shows “blood and thunder” fundus.



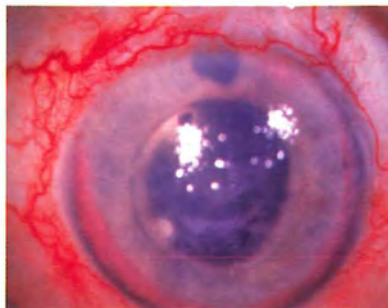
B. Retinal vein occlusion. Branch retinal vein occlusion (BRVO). Funduscopy shows venous dilatation and wedge-shaped focal retinal hemorrhages (apex of the hemorrhage is at the region of AV nipping).



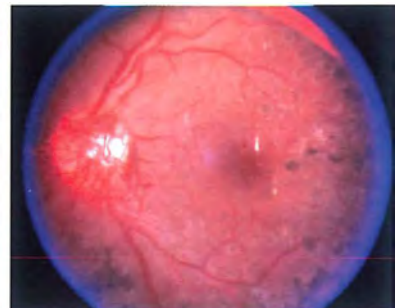
C. Optic neuritis. Findings: Initially the optic disc is normal, but it later develops pallor.



D. Vitreous hemorrhage. Findings: may have a decreased red reflex; when dense (as shown here), the retina is obscured by the hemorrhage.



E. Rubeosis. Blood vessels grow onto the iris, causing worsening glaucoma. Associated with proliferative diabetic retinopathy.



F. Proliferative diabetic retinopathy with disc neoplasia

OPTIC NERVE

Optic Neuritis

Optic neuritis (ON) is an inflammation and demyelination of the optic nerve. It is a frequent presentation of **multiple sclerosis (MS)**.

ON presents with ocular pain, especially with eye movement. On exam, the optic disc is usually normal **initially** (“the doctor sees nothing, the patient sees nothing”) and only later develops pallor (see C in Table 15-21). Refer the patient to an ophthalmologist. IV glucocorticoids improve vision more quickly, but patients not given steroids ultimately regain vision as well. Typically, an MRI is done, looking for evidence of MS.

Ischemic Optic Neuropathy

Ischemic optic neuropathy is the feared complication of giant cell (temporal) arteritis (GCA). On funduscopy, look for a pale swollen disc, peripapillary hemorrhages, and cotton-wool spots. Up to 50% of patients with GCA have polymyalgia rheumatica: malaise, fever, weight loss, muscle aches, jaw claudication, and elevated ESR (erythrocyte sedimentation rate). Start corticosteroids as presumptive treatment even before the diagnostic temporal artery biopsy is done.

VITREOUS HUMOR

Vitreous degeneration occurs in all geriatric persons. They tend to get bothersome floaters, brief unilateral flashing lights (from the vitreous traction on the retina), and **vitreous detachment** (with a sudden shower of floaters and flashing lights). Vitreous detachment is not dangerous **unless** it damages the retina.

Vitreous hemorrhage is a cause of sudden, painless loss of vision; see D in Table 15-21. There may be a decreased red reflex; and, when dense, the retina can be obscured by the hemorrhage. B-scan U/S may be needed if the view is obscured by blood. Hemorrhaging is caused by either a vitreous detachment tearing a retinal vessel, CRVO, or a breakage of the fragile blood vessels in diabetics with neovascularization (proliferative diabetic retinopathy; see E and F in Table 15-21). In proliferative diabetic retinopathy, blood vessels grow onto the retina, which may cause intractable glaucoma.

Promptly refer any patient with vitreous detachment to an ophthalmologist, who will look for current retinal detachment (retina is pulled away from the blood vessel layer) and defects that, when repaired, may forestall future retinal detachment. The eye with vitreous hemorrhage must be examined by U/S to check for retinal detachment.

OCCIPITAL CORTEX INFARCT

Acute bilateral occipital cortex infarct can affect the visual context bilaterally and lead to binocular blindness. This can occur due to embolic posterior circulation infarcts, posterior reversible encephalopathy syndrome (PRES; from hypertensive encephalopathy), and cortical hypoperfusion. The ophthalmological exam is normal. On occasion, the patients deny that they are blind and confabulate to cover for their blindness (Anton syndrome). There is usually good visual recovery in hypertensive encephalopathy and hypoperfusion of the cortex; in cases of ischemic infarcts, visual recovery is variable.

CATARACTS

The crystalline lens of the eye is a clear, biconvex structure behind the iris and is supported by the zonules. The lens is normally clear, pliable, and reactive to accommodation. As the lens ages, it gets less pliable and can get less clear. Any lens opacity is called a cataract (see A in Table 15-22). Risk factors for cataracts include advanced age, DM, HTN, positive family history, and excessive alcohol intake. Cataracts cause a very gradual, painless, progressive loss of vision. Treatment is cataract extraction with replacement of the lens.

Arcus senilis is common in older patients as a white, gray, or blue opaque ring in the corneal margin. In patients < 40 years of age, it may be a sign of a lipid disorder. (See B in Table 15-22.)

Heterochromia and ocular melanosis is a normal finding in darkly pigmented persons and is rarely caused by Fuchs heterochromic iridocyclitis. (See C in Table 15-22.)

Pterygium is a triangular growth of conjunctiva on the sclera toward the cornea associated with exposure to ultraviolet light and dry wind. It can grow over the pupil and cause loss of vision. (See D in Table 15-22.)

CRANIAL NERVE DYSFUNCTION

Suspect cranial nerve (CN) involvement in the patient who presents with sudden onset of painless double vision (Figure 15-5):

- **6th CN** (abducens; CN6) supplies the lateral rectus. Paralysis prevents lateral eye movement.
- **4th CN** (trochlear; CN4) innervates the superior oblique muscle; paralysis results in the eye deviating upward and the head tilting toward the uninvolved side (Bielschowsky sign).
- **3rd CN** (oculomotor; CN3) has 2 motor branches that innervate extrinsic eye muscles: the superior branch supplies the superior rectus, as well as the levator palpebrae superioris (upper-eyelid muscle), and the inferior branch innervates the inferior rectus, inferior oblique, and the medial rectus. A parasympathetic branch of CN3 provides tonic constriction of the pupil. Complete paralysis of CN3 results in an eye that is deviated “down and out” (due to unopposed activity of the superior oblique [CN4] and lateral rectus

[CN6]), a ptotic eyelid, and a dilated pupil. If the eye is **not** dilated, the patient probably has diabetic vascular disease affecting only the somatic branches. Always order MRI/MRA when the pupil is involved to evaluate for a posterior communicating aneurysm.

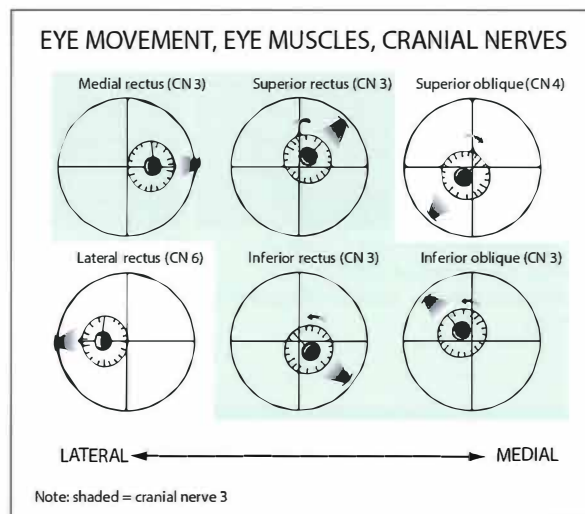


Figure 15-5: Cranial nerves associated with eye movements

Though not a cranial nerve defect, lesions of the sympathetic chain will produce ipsilateral ptosis and anhidrosis. Moreover, agents like cocaine that produce mydriasis by local release of sympathomimetic substance will also not work.

EYE INJURY

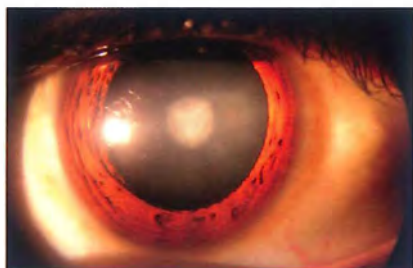
Trauma

Check acuity. Look for layered blood (hyphema) in the anterior chamber, corneal laceration, and subconjunctival hemorrhage, which may occur after blunt trauma or puncture wounds. Penetrating eye injuries break the surface of the eye but are not through and through (i.e., no exit wound), which is in contrast to perforating (through-and-through) injuries. Both types of injury may lead to foreign body insertion; look for overt pupil distortion, deformation of the lens and iris with vitreous hemorrhage, shallow or flat anterior chamber, and hyphema. Try to obtain visual acuity and assess both pupillary and extraocular muscle functions. Use ophthalmoscopy to confirm a clear view of the retina and that there are no other signs of hemorrhage. If there is pain, instill fluorescein to check for corneal abrasion and evert, inspect, and swab the upper lid, looking for a **foreign body**. Any abnormal finding, except perhaps a small corneal abrasion, requires consultation. Never patch corneal abrasions in contact lens wearers.

Corneal Ulcers

Ulcerative keratitis is the group of painful disease processes that lead to corneal ulcers. Most corneal ulcer formation is due to bacterial infection, either as a primary infection from HSV (ocular herpes) or

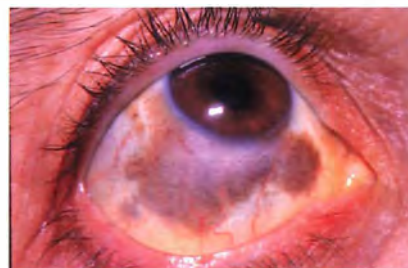
Table 15-22: Ophthalmology — Nonemergent



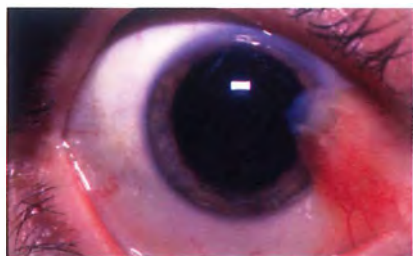
A. Cataract. Image shows the lens opacity.



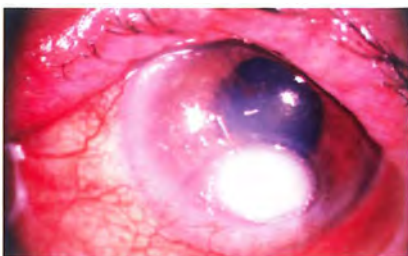
B. Arcus senilis. Finding: white, gray, or blue opaque ring in the corneal margin. Common in older patients; in patients < 40 years of age, it may be a sign of a lipid disorder.



C. Heterochromia and ocular melanosis. This is a normal finding in darkly pigmented persons. Rarely, it can be caused by Fuchs heterochromic iridocyclitis.



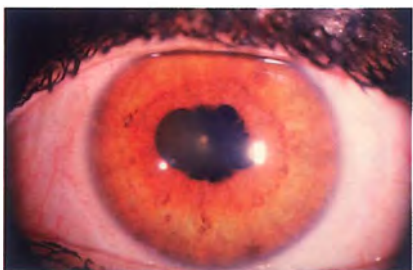
D. Pterygium. Finding: pinkish, triangular growth on the cornea, typically starting near the nose. Associated with exposure to ultraviolet light and dry wind. Seen in outdoor professions such as farmers and professional golfers.



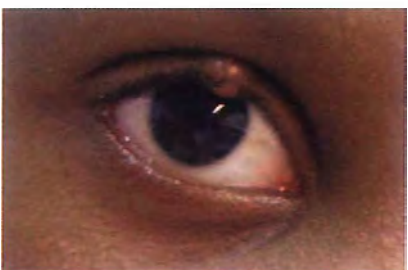
E. Corneal ulcer. Painful open sore on cornea. Most are due to bacterial infection. It is especially seen with the extended-wear contact but may follow eye injury or trauma. If the ulceration is on the **central** cornea, emergent treatment is required.



F. Conjunctivitis. Viral conjunctivitis (shown here) has profuse, watery discharge; findings for allergic conjunctivitis resemble viral conjunctivitis. Bacterial conjunctivitis typically has profuse purulent discharge and should be treated aggressively.



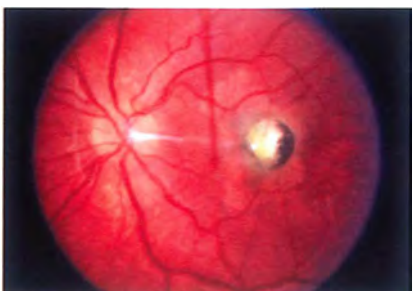
G. Synechiae. Iris is distorted due to iritis causing adhesions to the cornea or lens.



H. Chalazion. Obstruction of a tarsal (Meibomian) gland forms a nodule under the eyelid.



I. Stye. Abscess at the base of an eyelid.



J. Ophthalmic toxoplasmosis. Ophthalmologic exam reveals chorioretinitis with yellow-white cotton-like retinal lesions in a nonvascular distribution.



K. CMV retinitis. Finding: white granular lesion adjacent to retinal vessels; hemorrhages, with overall minimal vitreous inflammation.



L. Hard exudate as seen in nondiabetic retinopathy. This is caused by leakage of protein and lipids from capillaries. Treatment is photocoagulation of the leaking capillaries.

as a secondary infection after trauma or epithelial abrasion (e.g., contact lens, sicca). It is especially seen with extended-wear contact lenses. (See E in [Table 15-22 on page 15-57](#).)

Ulceration of the **central** cornea can lead to vision loss. Rapid treatment is required.

Alkali Injury

Alkali injury is a special form of trauma where a treatment delay of minutes can devastate the eye. Alkali rapidly penetrates the cornea and enters the anterior chamber, where it wreaks havoc (see C in [Table 15-19 on page 15-53](#)). Alkali burns may involve corneal opacification, and the eye appears white due to ischemia of the conjunctival and scleral vessels. This follows the initial conjunctival redness from the immediate injury.

Treatment is immediate, consisting of profuse irrigation with water or isotonic saline, with lid eversion to remove any alkali-containing particles. Check pH of tears to confirm that it is normal before discontinuing irrigation. Vessels can be blanched by alkali solution in severe injury, paradoxically creating the appearance of a “white and quiet” eye.

RED EYE

Assessment

The prevailing cause of a red eye is conjunctivitis. Conjunctivitis can be viral (the most common cause; see F in [Table 15-22 on page 15-57](#)), bacterial, chemical, or allergic (the latter is usually seasonal). A red eye also can indicate more urgent conditions. Work up by evaluating certain key differentiating features: visual acuity, pain, and photophobia (light sensitivity). Also assess other features: preauricular adenopathy, amount and type of discharge, and the location and amount of redness.

Significant symptoms and signs:

- **Decreased visual acuity** can indicate a **serious** problem (e.g., glaucoma, iridocyclitis, uveitis) requiring prompt consultation. Check for an afferent pupillary defect, which is seen more often in serious eye conditions.
- **Photophobia** is a key feature of iridocyclitis (and other more serious conditions). Evaluate promptly (within 24 hours) for possible intensive topical steroid treatment.
- **Type of redness:**
 - Bright red, confluent blood is seen with subconjunctival hemorrhage.
 - Ciliary flush (red near corneal limbus only in a sunray-like pattern) suggests iridocyclitis, keratitis, or angle-closure glaucoma; it warrants referral to an ophthalmologist.
 - Diffuse conjunctival hyperemia is nonspecific.
- **Pain** is **not** common in typical infectious causes of red eye. In patients who have photophobia, foreign body

sensation, and/or vision complaints, consider the more serious conditions of anterior uveitis, keratitis, or acute closed-angle glaucoma.

- **Preauricular adenopathy**, which may be tender, is highly suggestive of adenoviral conjunctivitis.
- **Discharge**, if purulent (typically profuse), suggests a bacterial etiology. Clear, watery exudate more likely suggests a viral etiology. White, stringy exudate can be allergic, especially if associated with pruritus. If there is no pruritus, it is more likely dry eye. (More information on dry eye is available under [Keratoconjunctivitis Sicca \(Keratitis Sicca\)](#)).

Anterior Uveitis

Anterior uveitis is the **autoimmune** or infectious (viral) inflammation of the anterior eye structures (iris and ciliary body). It can occur as a solitary problem but is also seen with many diseases (e.g., spondyloarthropathies, sarcoidosis, lupus, syphilis, vasculitides; see D in [Table 15-19 on page 15-53](#)).

Make a presumptive diagnosis with symptoms of ocular pain, photophobia, and a ciliary flush with a normal cornea, distorted pupil, hypopyon (layering of white cells at the bottom of the anterior chamber), and normal intraocular pressure. Slit lamp exam reveals inflammatory cells floating in the aqueous humor or deposited on the corneal epithelium. **This presentation requires emergent referral!**

Treat with steroids to reduce inflammation and scarring and cycloplegics to prevent synechiae (see G in [Table 15-22 on page 15-57](#)). Synechiae (adhesions of iris to lens) are a possible sequela of iritis (iridocyclitis). 90% of iritis is idiopathic, but it is also seen in inflammatory diseases such as viral infections and connective tissue diseases.

Keratoconjunctivitis Sicca (Keratitis Sicca)

Keratitis sicca refers to excessively dry eyes. This is most common in the older patients and in middle-aged women. It can be an early sign of systemic inflammatory disease, including Sjögren syndrome, Graves disease, rheumatoid arthritis, and sarcoidosis. The conjunctiva appears inflamed (conjunctivitis) with mucoid discharge and visible white opacifications in cornea (keratitis). Treat most cases with artificial tears (electrolyte solutions, methylcellulose, or other formulations).

Viral Conjunctivitis

Viruses are by far the most common cause of red eye, with adenovirus being the most likely pathogen. Patients have diffuse conjunctival hyperemia and profuse, watery discharge (often with other signs/symptoms of a viral infection). Infection can occur by coming in contact with swimming pool water. There is no specific treatment—just practice strict hygiene and do not wear contact lenses until the infection has completely resolved. Resolution should occur in 5–7 days.

Bacterial Conjunctivitis

Bacterial conjunctivitis can be caused by *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Pseudomonas aeruginosa*, *Moraxella catarrhalis*, or *Neisseria* species. Most cases of bacterial conjunctivitis resolve in 5 days even without treatment, but we **do** treat and follow closely because the patient can develop vision loss.

Red eye with profuse purulent discharge is the typical presentation.

Treat uncomplicated cases with topical erythromycin, sulfa, or polymyxin/trimethoprim drops or ointment. Drops are preferred for adults because vision is blurry for ~ 20 minutes after insertion of ointments. Remember: Some patients have sulfa allergy, so worsening conjunctivitis after sulfa treatment can be due to allergy. Reserve quinolones for the more serious cases.

For complicated cases, obtain cultures, initiate treatment with gatifloxacin or moxifloxacin, **and** refer to an ophthalmologist.

Neisseria conjunctivitis (can be gonococcal or meningococcal) is a “hyperacute” conjunctivitis (i.e., severe conjunctival discharge and redness) that requires early recognition and aggressive topical treatment to prevent progression to corneal perforation. Systemic therapy is also indicated.

Patients who use extended-wear contact lenses have an impaired ability to fight conjunctivitis and are at high risk for developing vision-threatening complications. Always consider an ophthalmology referral at presentation if the patient wears contact lenses. *Pseudomonas* conjunctivitis can progress to corneal perforation overnight in these patients. Any contact lens wearer with conjunctivitis should **immediately** discontinue use of the lenses. Start these patients on topical gatifloxacin to cover *Pseudomonas* and gram-positives, and refer them to an ophthalmologist.

Infectious Keratitis

Consider **bacterial keratitis** in patients who wear **contact lenses** and who present with a painful eye that is difficult to keep open. Non-lens wearers can also get bacterial keratitis, especially if immunocompromised. *Staphylococcus*, *Streptococcus*, and *Pseudomonas* are the organisms usually responsible.

On exam, the eye is red with a **mucoïd** discharge and a visible **white spot** (corneal opacity) that is easily seen with a penlight (see B in Table 15-20 on page 15-54). Fluorescein staining shows the area as well. Treatment includes emergent referral to an ophthalmologist.

Viral keratitis can be caused by reactivation of latent herpes simplex; herpes keratitis frequently recurs. Its presentation can be similar to bacterial conjunctivitis (red eye with profuse purulent discharge). Fluorescein staining shows a characteristic dendritic branching pattern of herpetic ulcerations (see C in Table 15-20 on page 15-54).

Risk factors for reactivation include laser eye treatments and immunocompromised states.

Diagnosis is clinical because most patients have antibodies to HSV and viral culture takes days. Treat with oral or topical antivirals (**but not both**). Know that topical steroids can seriously exacerbate the infection, so do not prescribe any topical steroids for an eye unless you are certain that the underlying diagnosis is **not** herpes keratitis. Some patients have problems with recurrent disease (similar to fever blisters from HSV); these patients can be managed with chronic oral antivirals.

Acanthamoeba is a known cause of infection with contact lens wearers, especially if the patient uses tap water for lens cleaning. Usually, it progresses rapidly to keratitis.

Optic Nerve Infarction in Giant Cell Arteritis

Giant cell arteritis causes an arteritic ischemic optic neuropathy (see E in Table 15-19 on page 15-53). Patients complain of reduced vision, and funduscopy shows pallor and swelling of the disc. Flame hemorrhages are sometimes seen adjacent to the swollen disc, as are cotton-wool exudates. Patients eventually develop optic atrophy. Visual loss tends to be irreversible. Diagnosis is usually made with visual loss in the context of GCA (clinical or biopsy confirmed) and high ESR. Sometimes central retinal artery occlusion (CRAO) is also apparent. Prompt treatment with high-dose steroids helps improve visual acuity.

OTHER EYE INFECTIONS

Endophthalmitis

Endophthalmitis (infection inside the eye) can have an ocular (traumatic/surgical) or systemic (blood stream seeding) source and can be bacterial or fungal. The most common presentation is bacterial infection after cataract surgery (with intraocular lens [IOL] replacement), and the organism is usually a coagulase-negative *Staphylococcus*. Remember: If trauma to the orbit is involved, suspect *Bacillus cereus*!

Patients present with decreased visual acuity, hazy cornea, pain, and hypopyon; see D in Table 15-20 on page 15-54.

Treatment: Refer **immediately**. The ophthalmologist does vitrectomy and cultures the vitreous fluid; then intraocular antibiotics are injected (vancomycin + ceftazidime or amikacin). Systemic antibiotics are added in severe cases, although utility is controversial. It is important to choose antibiotics that cross the blood-brain barrier; otherwise, the drugs do **not** reach the vitreous fluid. A cataract IOL does not have to be removed unless the infecting organism is a fungus.

Candida endophthalmitis is seen more commonly because of the widespread use of prolonged IV access and cases of fungemia. *Candida* can reach the eye via trauma or bloodstream infection. The cornea is hazy and has a hypopyon. Bacterial and fungal endophthalmitis

present similarly, which is why cultures are of paramount importance in postsurgical patients. Risk factors for candidemia include long-term venous access, neutropenia, immunocompromised states, long-term broad-spectrum antibiotics use, and corticosteroid treatment. Treatment includes removal of the IOL and systemic azole antifungal treatment (not amphotericin B because it does not achieve high levels in the eye).

Periorbital and Orbital Cellulitis

Periorbital or preseptal cellulitis is usually a rapidly progressive cellulitis of the periorbital area, which can become orbital if not treated (see F in Table 15-19 on page 15-53). Patients present with warmth, redness, and swelling of the eye and eyelid. In contrast to preseptal cellulitis, orbital cellulitis causes swelling and inflammation of the extraocular muscles and therefore causes painful eye movements. Untreated sinusitis is an important risk factor for orbital cellulitis. The key physical exam finding in preseptal cellulitis is normal extraocular muscle movement, with no associated diplopia and no pain with eye movement.

If the patient has disconjugate gaze, proptosis, diplopia, or pain with eye movement, it is probably the result of infection that has moved into the orbital space. This warrants a periorbital CT or MRI and IV antibiotics with MRSA and streptococcal coverage, such as vancomycin and ceftriaxone. ID and ophthalmology should be consulted urgently.

Chalazion

Chalazion is caused by obstruction of 1 of the tarsal (Meibomian) oil glands forming a small nodule in the tarsus under the eyelid (see H in Table 15-22 on page 15-57). Treat with warm compresses. Chalazion is not a problem unless secondary infection occurs. Such infections often require ophthalmologic surgery.

Stye

Stye is an infection of an oil gland or hair follicle at the base of an eyelid (see I in Table 15-22 on page 15-57). Treat it with warm compresses and a topical ophthalmologic antibiotic. Occasionally, it requires drainage.

Ophthalmologic Complications of HIV

Ocular disease manifestations with HIV infection correlate with CD4 count. In early stages of HIV, patients can manifest cotton wool spots without hemorrhage on fundoscopic examination, termed HIV retinopathy. Kaposi sarcoma,

herpes zoster ophthalmicus, candidiasis, and lymphoma are common in early stages as well. Tuberculosis, toxoplasmosis, and *Pneumocystis jiroveci* pneumonia occur later in the disease course. Ophthalmic toxoplasmosis (see J in Table 15-22 on page 15-57) is diagnosed by ophthalmologic exam, which reveals chorioretinitis with white retinal lesions, along with anterior uveitis and vitritis. Retinal detachment and glaucoma may occur.

CMV retinitis (the most common and serious ocular manifestation in AIDS; see K in Table 15-22 on page 15-57) is seen in more profound immunosuppressed states, typically with CD4 count < 50 cells/ μ L. CMV retinitis is diagnosed by visualization of a white granular lesion adjacent to retinal vessels, as well as hemorrhages with overall minimal vitreous inflammation. The use of CMV serology and blood CMV DNA by PCR is not helpful diagnostically. Treat with ganciclovir or valganciclovir.

EYE EMERGENCIES — REVIEW

Briefly, here is how to approach ophthalmologic emergencies.

Treat emergently and immediately refer (Table 15-19 on page 15-53):

- Alkali burns
- Trauma: blunt, perforating, and penetrating
- Orbital cellulitis
- Bilateral occipital artery infarct
- Central retinal artery occlusion
- Angle-closure glaucoma
- Anterior uveitis
- Optic nerve infarction in giant cell arteritis

Refer immediately without on-site treatment (Table 15-20 on page 15-54):

- Penetrating ocular injury
- Endophthalmitis
- Retinal detachment
- Infectious keratitis/keratoconjunctivitis

Refer to be seen within 1–2 days (Table 15-21 on page 15-55):

- Retinal vein occlusion
- Optic neuritis
- Corneal ulcers
- Vitreous detachment/hemorrhage
- Proliferative diabetic retinopathy (with acute vision changes)

See Table 15-22 on page 15-57 for some nonemergent findings.

HEARING LOSS

PREVIEW | REVIEW

- What is the best way to diagnose an acoustic neuroma?
- A Rinne test is done. The patient can hear the tuning fork more loudly when it is on the bone. What does this mean?
- A Weber test is done on the same patient. He can hear sounds more loudly on the left side. What does this mean?

CONDUCTIVE HEARING LOSS

Hearing loss is conductive, sensorineural, or both. Conductive hearing loss occurs when something blocks sound from reaching the inner ear (e.g., otitis media, eustachian tube blockage, otosclerosis, invasive external otitis, tympanic membrane [TM] perforation, ceruminosis—or any other impaction of the external canal).

Otosclerosis is abnormal bone growth in the middle ear that may result in hearing loss. It is an autosomal dominant trait with poor penetrance. It is much more common in Caucasians than in African Americans. 10% of Caucasians develop otosclerosis; 1% become symptomatic.

Cholesteatoma is a collection of built-up layers of keratinized squamous epithelium trapped within the middle ear and/or mastoid. It can be congenital or acquired following tympanic membrane perforation. Cholesteatoma presents with foul-smelling ear discharge and conductive hearing loss; it can also present with headache and dizziness (less common) and is unresponsive to antibiotics. Rarely, it can lead to meningitis or epidural abscess. Diagnosis is by CT scan, which is pretty sensitive. If local extension is a concern, obtain an MRI. Audiometry will reveal conductive deafness. Treatment is by surgical excision: This prevents further hearing loss, as well as progressive infection and cranial nerve palsies.

SENSORINEURAL HEARING LOSS

Sensorineural hearing loss is caused by damage to either the cochlea or the vestibulocochlear nerve (CN 8). It can be caused by viral infections, ototoxic drugs such as aminoglycosides and high-dose furosemide infusions, meningitis, cochlear otosclerosis, Ménière disease, acoustic neuromas, aging (presbycusis), or environmental exposure to chronic loud noise.

Presbycusis is characterized by bilateral symmetrical sensorineural hearing loss in the frequencies > 2,000 Hz. 1/3 of persons > 65 years of age have some form of presbycusis.

Ménière disease is an uncommon condition that stems from excess production or decreased drainage of endolymphatic fluid. Affected patients have recurrent, severe attacks of vertigo that persist for several hours and often

are associated with vomiting and prostration. Patients have tinnitus, fullness in the ear, and, in more severe cases, progressive hearing loss (which is frequently one-sided) until deafness occurs, at which time the symptoms stop!

Diagnosis is made with the combination of typical clinical symptoms and demonstration of sensorineural hearing loss on audiometry.

Symptomatic treatment during acute episodes uses BDZs, antiemetics, anticholinergics (e.g., scopolamine) and antihistamines (e.g., meclizine). Chronic treatment includes avoidance of caffeine, nicotine, and salt, with the addition of diuretics if symptoms continue. Middle-ear gentamicin injections are the next step if symptoms persist and are effective in 80–90% of patients treated. A surgical approach with labyrinthectomy or vestibular nerve ablation is helpful for persistent vertigo but carries a higher risk of hearing loss. (Alan Shepard, the 1st American astronaut to fly in space, suffered from Ménière disease and was grounded from space flight for 5 years. He eventually made it to the moon after a corrective surgery.)

Acoustic neuromas (vestibular schwannomas) are benign, very slow-growing tumors of the 8th cranial nerve. Patients commonly present with tinnitus, unilateral hearing loss, and gait imbalance. Bilateral acoustic neuromas are caused by neurofibromatosis Type 2. MRI is the diagnostic test of choice. Treatment is radiosurgery or surgical resection.

ACUTE HEARING LOSS

Acute sensorineural hearing loss should be evaluated and treated immediately. If the patient cannot be seen immediately, prescribe prednisone (40–80 mg/day) and evaluate as soon as possible. Early steroids are considered standard of care and may allow hearing return for a larger percentage of patients; however, studies have failed to prove their effectiveness.

RINNE AND WEBER TESTS

Know how to use the Rinne and Weber tests to differentiate between conductive and sensorineural hearing loss (Figure 15-6 and Table 15-23 on page 15-62).

The **Rinne test** is based on the fact that air-conducted sound is normally louder than bone-conducted. The base of the best vibrating tuning fork (256 Hz) is placed over the mastoid, and the sound of this bone-conducted hearing is compared to the air-conducted sound the patient hears when the tuning fork is placed next to the ear on the same side.



Weber: forehead
Rinne: mastoid

Figure 15-6: Rinne (R) and Weber (W) tests

Table 15-23: Diagnosing Conductive vs. Sensorineural Hearing Loss with the Rinne and Weber Tests

Type of Hearing Loss	Rinne Test (A = air; B = bone)*	Weber Test†
None	Sound A > B	Sound does not lateralize
Sensorineural loss (in left ear)	Left ear: Both air and bone conduction decreased equally: sound A > B	Lateralizes to the right ear
Conductive loss (in left ear)	Left ear: B > A	Lateralizes to the left ear

*Rinne test:
Position A = air (i.e., fork held next to ear)
Position B = bone (i.e., tuning fork base held on mastoid)

†Weber test:
Tuning fork base held at middle of forehead

To summarize:

- With no hearing loss, the air-conducted sound is loudest.
- With conductive hearing loss, the bone conduction is louder.
- With sensorineural hearing loss, both air and bone conduction are decreased, but the air conduction is perceived as being louder.

The Weber test consists of placing the base of a 256-Hz or 512-Hz tuning fork on the middle of the forehead. The patient tells you whether the sound lateralizes to one side or stays in the middle:

- If the sound is perceived as being in the middle, the patient either has normal hearing or the hearing loss is symmetrical.
- If the sound lateralizes, there is either a conductive hearing loss in the ipsilateral ear or sensorineural loss in the opposite ear.

The Weber test can be simulated by asking the patient to hum and stick a finger in one ear (causing a conductive hearing loss). If hearing is normal, the sound lateralizes to the plugged ear.

EPISTAXIS

Most epistaxes are uncomplicated and can be controlled with a few simple techniques. The majority of epistaxes arise from the anterior region, and bleeding is stopped with pinching of the nose. If unable to achieve hemostasis, use silver nitrate or electrocautery if a bleeding source can be seen on examination. Ultimately, nasal packing is required if bleeding persists. Patients should be evaluated within 24–48 hours by an ENT specialist after nasal packing. Posterior bleeding is suspected in patients with continued bleeding despite anterior packing. These patients require posterior packing and hospitalization. Patients on antiplatelet and/or anticoagulant therapies should be assessed for risks and benefits of stopping these agents. Antibiotics for nasal packing is controversial and should be individualized.

DEEP INFECTIONS OF THE HEAD AND NECK

PREVIEW | REVIEW

- What is the most common cause of parotid space infection?
- Which common organisms cause a peritonsillar abscess?
- What is Ludwig angina?

Deep infections of the head and neck mostly originate from an infective focus in dentition, tonsillar tissue, salivary glands, cervical lymph nodes, sinuses, or the middle ear.

In most cases, the causative organisms are anaerobes like *Fusobacterium nucleatum*, *Peptostreptococcus* species, *Actinomyces*, and *Prevotella melaninogenica*. *S. aureus*, *Pseudomonas*, Enterobacteriaceae, and *Klebsiella* have also been isolated from neck infections.

Diagnosis generally involves a proper ENT exam and use of imaging, with CT scanning being the modality of choice. MRI scans may be preferred if vascular involvement is a concern. Send blood cultures, and send purulent material from the infective collections for culture at the time of drainage.

Some specific locations of infections include the parotid gland and space, the peritonsillar region, and the submandibular space.

Parotid gland and space infection is commonly due to suppurative parotitis, which may complicate viral parotitis or parotid gland stones. Patients present with asymmetric facial swelling, pain, and fever. The parotid gland is swollen at the angle of the jaw. *S. aureus* is the most common culprit, followed by anaerobes. Treatment is with nafcillin or vancomycin + clindamycin or metronidazole. The swelling can be so severe that it compromises the airway. Incision and drainage may be needed if there is no response to IV antibiotics. See also [Parotid Gland Disease](#).

Peritonsillar abscess occurs when a collection of purulent material collects between the palatine tonsil and pharyngeal muscle. It is usually due to strep, staph, and anaerobes. Patients present with a sore throat, which is soon followed by swelling and an inability to swallow solids; eventually they cannot even swallow their own saliva. They often have facial pain and fever. Exam will reveal a swelling in the tonsillar area, often with uvula deviation to the opposite side. Treatment is initially with IV ampicillin-sulbactam (Unasyn) and observation for 24 hours; if there is no improvement in fever, swelling, pain, or the ability to swallow, then surgical intervention is indicated.

Submandibular space infection (Ludwig angina) begins in the floor of the mouth. The infection spreads rapidly to involve the submylohyoid sublingual spaces. The infection is always bilateral. The source of infection is mostly in the teeth. As infection spreads, the tongue enlarges. The most common organisms here are anaerobes. Patients complain of drooling, neck pain, dysphagia, and fevers; breathing may be compromised, with stridor occurring. CT identifies the planes of infection. Treatment is protection of airway by an ENT specialist or anesthesiologist and administration of broad-spectrum antibiotics (Unasyn or Zosyn). If CT shows an abscess collection (which can take 48 hours to develop), then drainage is indicated.

PAROTID GLAND DISEASE

PREVIEW | REVIEW

- What is the most common salivary gland tumor?
- What concern does facial nerve involvement in pleomorphic adenoma raise?
- What are 3 causes of parotitis?
- Most salivary gland stones occur in which gland?

For the internist, the important parotid gland diseases to know include tumors (pleomorphic adenoma and cancer), parotitis, parotid space infections, and salivary gland stones.

Pleomorphic adenoma is the most common salivary gland tumor. It tends to originate in the superficial lobe of the parotid gland. Symptoms are chronic and progressive, with patients presenting with asymmetric facial swelling, pain, and inability to fully open their mouths. Most of these adenomas are benign, but malignant transformation can occur. Facial nerve involvement raises concern for malignant change. Treatment is with superficial parotidectomy, which has a recurrence rate of 5% (as opposed to simple enucleation, which has a recurrence rate of 20–45%).

Parotitis: Patients present with inflammation and bilaterally swollen and painful parotid glands; they may have fever and difficulty swallowing. Mumps is the commonest

cause, but other viruses and bacteria can also cause parotitis, including Sjögren syndrome and Heerfordt syndrome. (The latter is an acute and rare form of sarcoidosis that includes parotid gland enlargement, uveitis, and facial nerve palsy.) Imaging with CT shows parotid inflammation and swelling. For mumps, treatment is supportive only; for sarcoidosis, including Heerfordt syndrome, steroids are helpful; and use of saliva stimulants are helpful in Sjögren syndrome.

The parotid space danger zone—the parotid gland or duct—can be injured during head and neck surgery (e.g., plastic surgery, tumor resection), as it lies deep and is covered by its own fascia. Postoperative patients may complain of facial pain or swelling.

Suppurative parotitis occurs when the gland becomes infected with polymicrobial organisms, causing unilateral swelling, fevers, and chills. Treat with IV antibiotics and, if not improved, surgical incision. See the discussion on parotid gland and space infection in [Deep Infections of the Head and Neck](#).

Salivary gland stones: Most salivary gland stones (80–90%) occur in the submandibular glands, and 5–20% occur in the parotid glands. Patients present with pain and swelling in ≥ 1 salivary gland, especially on eating, when the stones may block the flow of saliva. Examine the submandibular glands, parotid glands, and the opening of the Stensen duct on the affected side(s) (look next to the second upper molar)—a stone may even be felt in the duct. The stones can lead to infective sialadenitis. Stones can be diagnosed by CT, U/S, or MRI. Treatment of salivary gland stones is initially conservative, with use of lemon drops to promote saliva flow. Avoid anticholinergic agents that dry the mouth. If symptoms are troublesome or patients have recurrent infections, remove the stones via an endoscopic approach or open surgery.

GENETICS

PREVIEW | REVIEW

- What is the risk of disease in each child of a parent affected with an autosomal dominant disease?
- What chance does the daughter of a male with an X-linked disease have of being a carrier?
- What is the Philadelphia chromosome? Why is it important?

Histocompatibility antigens are the antigens involved in graft rejection. These are the markers that identify “self” vs. “nonself” for the body’s immune surveillance system. Many of the histocompatibility genes are closely grouped on chromosome 6, and this area is called the major histocompatibility complex (MHC). The human MHC is termed **human leukocyte antigen (HLA)**.

General review of transcription and translation: The DNA has coding sequences called exons, separated by very small noncoding sequences called introns. The full gene (introns + exons) is transcribed into RNA by DNA-dependent RNA polymerase. The introns are then spliced out of the RNA before it leaves the nucleus, thereby forming the messenger RNA (mRNA). The mRNA is then translated into protein: Each 3-base sequence comprises a codon, which determines the amino acid that attaches when it is translated.

Point mutations are a change to a single base and can result in either a missense or a nonsense mutation. Missense mutation occurs when a point mutation causes a different amino acid to be produced, as in sickle cell disease with hemoglobin S, which results from valine substitution for glutamic acid. Nonsense mutation produces a stop codon, which stops the translation.

Insertion and deletion mutations cause a “frame shift,” which produces an abnormal protein from that point to the end.

Splicing mutations result from a point mutation at the area defining the junction between the intron and the exon. This results in dysfunctional proteins. β -thalassemias often are caused by splicing mutations.

Clues for autosomal dominant disease:

- Vertical transmission involving several generations
- Risk to each child of an affected individual is 50%.
- Male-male transmission is observed.
- Normal parents do not transmit the trait (unless a new mutation occurs).

Clues for X-linked inheritance:

- Inheritance of the trait is father to daughter—**all** daughters of affected males are carriers; no sons of the father are affected.
- If the mother is a carrier, she has a 50% risk of transmitting the gene to her sons, and each son with a resulting abnormal X chromosome would therefore be affected. A carrier mother also has a 50% risk of transmitting the gene to her daughters who, in turn, become unaffected carriers.

Acquired chromosomal abnormalities: A viral gene that can transform DNA is called a viral oncogene. The human chromosomes also contain genes that are associated with malignancy, called cellular oncogenes or protooncogenes. These protooncogenes probably have something to do with embryonal development and are otherwise silent; but they become active with certain chromosomal rearrangements. In both Philadelphia chromosome and Burkitt's, the protooncogene becomes active by an acquired reciprocal translocation.

The Philadelphia (Ph1) chromosome t(9;22) was the 1st chromosomal abnormality found to be associated with malignancy (first found in chronic myelocytic leukemia [CML]). The switch causes the *c-ABL* protooncogene to be moved from chromosome 9 to 22.

Burkitt lymphoma and its leukemic analog, ALL (FAB Type 3), have a reciprocal translocation that switches the protooncogene *c-MYC* on chromosome 8 to chromosome 14, 22, or 2; i.e., t(8;14), t(8;22), or t(8;2). Chromosome 14 has the heavy chain locus. The lambda light chain locus is on chromosome 22, and the kappa light chain locus is on chromosome 2.

Many leukemia and lymphoma patients have a chromosomal abnormality. Solid tumors rarely have abnormal chromosomes.

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SUICIDE

PREVIEW | REVIEW

- What are the means by which males and females commit suicide?
- What is the demographic for who commits suicide?
- What are the risk factors for suicide?

Suicide ranks as the 10th leading cause of death in the U.S., and globally, an estimated 1 million individuals commit suicide annually. It is 1 of the top 3 causes of death in adolescents and young adults. While females have a higher rate of depression and attempt suicide more frequently, males have the highest rate of completed suicide. Poisoning by medication overdose is the most common means of suicide among women and use of firearms is the most common among men. 95% of people who commit suicide have a mental illness diagnosis.

Risk factors for suicide include the following (remember the mnemonic **SAD PERSONS**):

- Sex (male)
- Age (bimodal: < 25 years of age in both genders, and > 45 years in men and > 55 years in women), access to guns
- Depressed mood, including MDD, bipolar depression, and borderline personality disorder
- Previous attempt
- Excess alcohol or substance use
- Race (White)
- Social support lacking
- Organized plan
- No partner
- Sickness (chronic illness and chronic pain), stressful life events

The relationship between antidepressant use and suicide varies with age: While there is a slight increase in suicidality in children and adolescents < 18 years of age, no increased risk of suicidality has been shown in adults > 24 years of age. Antidepressants have shown to be protective against suicidality in adults ≥ 65 years of age.

MAJOR DEPRESSIVE DISORDER (MDD)

PREVIEW | REVIEW

- What are the diagnostic criteria for major depressive disorder (MDD)?
- How is adjustment disorder with depressed mood different from MDD?

- How is persistent depressive disorder different from MDD?
- What is the clinical course of MDD?
- Which laboratory tests should be considered when an individual presents with depressive symptoms?

OVERVIEW

MDD is associated with high mortality, much of which is accounted for by suicide (see [Suicide](#)). It has a lifetime prevalence of 20%, with a female-to-male ratio that ranges from 1.5:1 to 3:1. The average age of onset is 29 years of age. The twin concordance rate is 40–50%, and individuals with a 1st degree relative have a 3-fold risk for developing depression. Depression is more common in females 40–60 years of age than in any other age group, and rates of depressive symptoms are lower among non-Hispanic individuals.

DIAGNOSIS

According to the *American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders*, 5th edition (DSM-5), major depressive episodes are characterized as ≥ 5 of the following symptoms within the same 2-week period, and 1 of the symptoms must be either a depressed mood or anhedonia (the loss of pleasure or interest in nearly all activities):

- Depressed mood
- Anhedonia
- Significant weight loss or gain or significant loss or increase in appetite
- Hypersomnia or insomnia
- Psychomotor retardation or agitation
- Loss of energy or fatigue
- Feelings of worthlessness or excessive guilt
- Decreased concentration ability or marked indecisiveness
- Preoccupation with death or suicide; patient has planned or attempted suicide.
- ≥ 1 major depressive episodes do not occur with mania or hypomania, and symptoms are not due to another medical condition, substances, or another mental disorder.

Remember the mnemonic **SIG E CAPS**:

- Sleep disturbance (insomnia or hypersomnia)
- Interest diminished
- Guilt
- Energy loss or fatigue
- Concentration diminished
- Appetite changes
- Psychomotor retardation (or agitation)
- Suicidal thoughts

Adjustment disorder with depressed mood occurs **within 3 months of a stressful event** (e.g., divorce) as the major trigger. In MDD, no specific trigger is identified.

Persistent depressive disorder (PDD; a.k.a. dysthymia) is a mild and chronic form of depression characterized with low mood lasting for at least two years. Unlike MDD, PDD has less than 5 depressive symptoms and does not meet the full criteria for MDD.

CLINICAL COURSE AND PROGNOSIS

MDD typically starts during puberty and peaks in the 20s. It is a recurrent illness, with a 50% relapse after 1 episode and 80% relapse after 3 episodes. The duration of each episode is ~ 3 months. In 6 months, about 60% of individuals have recovered, and in 2 years, 80% have recovered with proper treatment. 80% of individuals with MDD can achieve a significant reduction in symptoms with proper treatment. Up to 50% of individuals do not respond to the initial treatment trial. Those with comorbid anxiety, borderline personality disorder, and substance use may have a complicated recovery course.

RISK FACTORS

Comorbidities include anxiety disorder, substance use disorder, impulse control/disruptive behavior disorders (e.g., intermittent explosive disorder, attention deficit hyperactivity disorder [ADHD], conduct disorder, oppositional defiant disorder), sleep disorders (e.g., insomnia, sleep apnea), obsessive-compulsive disorder (OCD), bulimia nervosa, anorexia nervosa, panic disorder, borderline personality disorder, stressful life events, and chronic/disabling medical conditions in addition to genetics and family history.

ASSESSMENT

The diagnosis of MDD is clinical. General assessment includes psychiatric and social history of depressive, manic, hypomanic, or anxiety symptoms; substance use; stressors; and suicidal and homicidal ideation. Perform a physical exam/laboratory assessment for the following to rule out medical causes of depression:

- Complete blood count (CBC), comprehensive metabolic panel (CMP), liver function tests (LFTs), thyroid-stimulating hormone (TSH; free T₃, T₄ if TSH abnormal), glucose, vitamin B₁₂, vitamin B₁, folate, creatinine, glucose, Ca²⁺, Mg²⁺
- Pregnancy testing (woman of childbearing age)
- Toxicology—drugs, heavy metal screen
- Infections—chest x-ray (CXR), urine culture, rapid plasma reagin (RPR), human immunodeficiency virus (HIV)
- Magnetic resonance imaging (MRI)—if any neurologic or cognitive signs

MANAGEMENT

Both cognitive behavioral therapy (CBT) and medications are equally effective treatments for mild-to-moderate cases of MDD. A combination of CBT and medications has been proven to be more effective than either treatment alone. An adequate trial of an antidepressant medication is 3–6 months. Treatment-resistant depression (failure to respond to 2 antidepressants) occurs in 10–30% of patients. Antipsychotics and mood stabilizers can be added for treatment-resistant depression. Consult a psychiatrist if there is a suspicion of hypomania, mania (see [Bipolar Disorder](#)), psychosis, or treatment-resistant depression. Transfer individuals to emergency care for suicidal ideation.

ANTIDEPRESSANTS

Selective serotonin reuptake inhibitors (SSRIs; e.g., fluoxetine, paroxetine, sertraline, citalopram, escitalopram) are also effective for treating anxiety disorders at higher doses. They may cause moderate weight gain and decreased libido. Side effects to consider are nausea and diarrhea, which usually resolve after 1–2 weeks.

Serotonin-norepinephrine reuptake inhibitors (SNRIs; e.g., venlafaxine, desvenlafaxine, duloxetine) are also effective for treating anxiety and chronic pain. Side effects are similar to SSRIs.

Monoamine oxidase inhibitors (MAOIs; e.g., phenelzine, selegiline, isocarboxazid, tranylcypromine) are effective for treating depression and anxiety. MAOIs tend to cause severe weight gain and decreased libido.

Tricyclic antidepressants (TCAs; e.g., imipramine, amitriptyline, doxepin, desipramine) tend to cause severe weight gain and decreased libido. They are also sedative due to anticholinergic effect and may cause confusion in the elderly.

Bupropion is a **norepinephrine and dopamine reuptake inhibitor** also used for smoking cessation. It does **not** cause weight gain or sexual dysfunction, but it is contraindicated for patients with a history of seizures or eating disorders.

Mirtazapine is a **presynaptic α₂-receptor antagonist** and enhances neurotransmitter release. It is very sedative and also increases appetite.

BIPOLAR DISORDER

PREVIEW | REVIEW

- What are the diagnostic criteria for bipolar disorder?
- How is bipolar 1 (mania) different than bipolar 2 (hypomania)?
- What is cyclothymia?

- What are the rates of suicide attempts and completion in bipolar disorder?
- What types of substances can cause a manic episode?

OVERVIEW

Bipolar disorder (a.k.a. bipolar affective disorder, manic-depressive illness) is a chronic and persistent mental illness consisting of alternating episodes of mania/hypomania and severe depression. Mixed states (concurrent mania/hypomania with depression) also occur. For diagnostic criteria, see [Diagnosis for Hypomanic and Manic Episode](#). The lifetime prevalence is 1–4%. Males and females are affected equally. There are no racial differences. There is a 10-fold risk of bipolar disorder in 1st degree relatives with bipolar 1 or bipolar 2; offspring of a parent with bipolar disorder have a 50% chance of having bipolar disorder or another major psychiatric disorder (e.g., MDD, schizophrenia). The concordance rate is 33–90% in monozygotic twins.

The etiology of bipolar disorder is multifactorial. Genetic, biochemical, and environmental factors contribute to bipolar disorder.

DIAGNOSIS FOR HYPOMANIC AND MANIC EPISODE

According to the *DSM-5*, a manic or hypomanic episode is a distinct period of an abnormally and persistently elevated, expansive, or irritable mood and persistently increased goal-directed activity or energy plus the presence of ≥ 3 symptoms (4 if mood is only irritable):

- Inflated self-esteem or grandiosity
- Decreased need for sleep
- More talkative or pressure to keep talking
- Flight of ideas or subjective racing thoughts
- Distractibility
- Increase in goal-directed activity
- Activities with high potential for bad consequences
- The symptoms are not better explained by a psychotic disorder, substance, or medical condition.

Remember **DIG FAST** for bipolar:

- Distractibility
- Increased goal-oriented activity
- Grandiosity (inflated self-esteem)
- Flight of ideas (racing thoughts)
- Activities with potential for consequences
- Sleep decreased
- Talkativeness

MANIC EPISODE (BIPOLAR 1)

In a manic episode, there is marked impairment in functioning for at least 7 days or the manic symptoms necessitate hospitalization.

HYPOMANIC EPISODE (BIPOLAR 2)

A hypomanic episode is milder and lasts < 7 days, whereas a manic episode is more severe and lasts ≥ 7 days. The changes in functioning are severe in a manic episode and may require psychiatric hospitalization; during a hypomanic episode, the individual experiences mild changes in functioning that do **not** lead to psychiatric hospitalization. If, during an episode, the functioning of an individual rapidly declines and the patient requires inpatient psychiatric hospitalization, the episode is considered to be manic regardless of episode duration.

MANIC OR HYPOMANIC EPISODE WITH MIXED FEATURES

In a mixed episode, symptoms for both a manic and a depressive episode are met (i.e., SIG E CAPS and DIG FAST). See [Diagnosis on page 16-1](#) under [Major Depressive Disorder \(MDD\) on page 16-1](#) and [Diagnosis for Hypomanic and Manic Episode](#).

DIAGNOSIS FOR CYCLOTHYMIA

Per the *DSM-5*, cyclothymia is a subcategory of mood disorders. It is characterized by numerous periods with hypomanic symptoms that do not meet criteria for a hypomanic episode and numerous periods with depressive symptoms that do not meet criteria for a major depressive episode for at least 2 years. The symptoms must have been present at least 50% of the time, and the patient must not have been symptom free for > 2 months at a time.

DIAGNOSIS FOR BIPOLAR DISORDER

Bipolar disorder is not associated with any clear laboratory result. The diagnosis is **clinical**. Perform the following to rule out other or concomitant illnesses:

- CBC, CMP, LFTs, TSH (free T_3 , T_4 if TSH abnormal), glucose, vitamin B_{12} , vitamin B_1 , folate
- Pregnancy testing (woman of childbearing age)
- Toxicology: drugs, heavy metal screen
- Infections: CXR, urine culture, RPR, HIV
- Imaging/electroencephalography (EEG): subdural hematomas, vasculitis, tumors, seizure disorder
- Medication reconciliation: corticosteroids (psychosis, depression, or mania), levodopa (L-DOPA; hallucinations or insomnia), antidepressants (mania)

RISK FACTORS

Risk factors for a poorer prognosis include poor premorbid functioning, substance use, depression, psychosis, and male gender. Factors suggesting a better prognosis include those contrary to those listed for a poor prognosis, as well as a shorter duration of mania, later age of onset, fewer comorbidities, and less suicidal ideation.

CLINICAL COURSE

The disorder typically has an onset in late teens and early 20s with depressive symptoms as the first episode, and medical causes or substance ingestion/withdrawal should be investigated. > 90% of individuals who have a single manic episode go on to have recurrent mood episodes. Approximately 60% of manic episodes occur immediately before a major depressive episode. Rapid cycling is characterized by > 4 mood episodes (major depressive, manic, or hypomanic) within 1 year. 50% of individuals with bipolar attempt suicide, and 20% complete it. 50% of individuals have psychotic symptoms at one point.

PROGNOSIS

Bipolar disorder has significant morbidity and mortality rates. Up to 50% of individuals experience another manic episode within 2 years of the initial episode. While lithium is a gold-standard medication, it controls symptoms in only 50% of individuals. Mania and depression tend to cycle faster with increasing age. Comorbid issues include anxiety and substance use disorders. Comorbid medical conditions, including cardiovascular disease, diabetes, and obesity, can result from therapeutic medication side effects and lack of follow-up with primary care providers.

MANAGEMENT

The treatment of bipolar disorder is directly related to the phase of the episode (i.e., depression or mania) and the severity of that phase, and involves a combination of psychotherapy and medication. Always screen for suicidal and homicidal ideation (e.g., presence of dangerous weapons) and psychosis. Consider transferring patients presenting with these symptoms to the nearest emergency department for evaluation.

Medical management of bipolar disorder includes antipsychotics for treatment of acute manic episodes, mood stabilizers for mood maintenance and prevention of mania, and antidepressants for depressive episodes.

Unopposed antidepressants (i.e., those not used in combination with a mood stabilizer or antipsychotic) are generally not helpful in individuals with bipolar disorder, as they carry the risk of “switching” the patient into a manic phase of the illness. Dopaminergic substances of abuse, including *Cannabis*, cocaine, and methamphetamines, can also trigger mania. Dopaminergic medications, including Parkinson’s medication, may also induce a manic episode.

MOOD STABILIZERS

Lithium is the gold standard for treating bipolar disorder, as it is effective for mood and decreases the risk of suicide at therapeutic levels (> 0.8 mEq/L). It is a teratogen during pregnancy. The major side effects are lethargy, intention tremor, and diabetes insipidus. Lithium therapy can cause goiter and either hyper- or

hypothyroidism. Check TSH routinely. Know that thiazide diuretics, angiotensin-converting enzyme (ACE) inhibitors, and nonsteroidal antiinflammatory drugs (NSAIDs) increase the serum lithium concentration.

Valproic acid is also a teratogen and may cause liver toxicity.

Lamotrigine is an effective mood stabilizer; however, the dose must be increased gradually over weeks to prevent Stevens-Johnson syndrome.

Carbamazepine, like lamotrigine, is an antiseizure medication (ASM; a.k.a. antiepileptic drug, anticonvulsant) that is an effective mood stabilizer.

PSYCHOSIS

PREVIEW | REVIEW

- What are risk factors for schizophrenia?
- How is schizophrenia diagnosed?
- What is delusional disorder, somatic type?
- What is the management of delusional disorder?

Schizophrenia and related disorders are a subcategory of psychiatric conditions with psychotic features (e.g., disconnection from reality, delusions, hallucinations) as primary symptoms while other psychiatric symptoms, including mood symptoms, may or may not be present. While with schizophrenia the psychotic symptoms are the primary symptoms, in “major depressive disorder with psychosis” or “bipolar disorder with psychosis,” the mood (depressed or manic) is the clinically significant symptom. Intensity of mood indicates risk of psychosis.

Schizoaffective disorder is a condition where both psychotic and mood symptoms are equally severe and present. In substance-induced psychosis or psychosis secondary to a medical condition, the psychotic symptoms are secondary to the underlying cause. In delusional disorder, symptoms are mild—limited to the presence of a delusion—with minimal changes in the individual’s functioning.

SCHIZOPHRENIA

Schizophrenia is a disorder of chronic or recurrent psychosis affecting 1% of the population. Males and females are affected equally, but the peak age of onset for males is between 15 and 25 years of age and for females is between 25 and 35 years of age. Clinical manifestations present later in life in females (possibly due to the antidopaminergic influence of estrogen). There are no racial differences. The risk of schizophrenia in 1st degree relatives is 10%, and the concordance rate is 40–50% in monozygotic twins.

Several genes involving dopamine, serotonin, and glutamate metabolism/control are involved in schizophrenia. Risk factors include birth in winter (5–10%), influenza

during pregnancy, obstetric complications, major maternal stressor during pregnancy, advanced paternal age, immigration, and living in an urban area. *Cannabis* use in susceptible individuals increases schizophrenia by 2–3×, whereas chronic psychostimulant use increases the odds by 10-fold.

Diagnosis

The *DSM-5* criteria for schizophrenia include the presence of ≥ 2 of the following during a 1-month period for ≥ 6 months, with ≥ 1 of the first 3 being required:

- Delusions
- Hallucinations
- Disorganized speech
- Grossly disorganized or catatonic behavior
- Negative symptoms

Schizophrenia is no longer categorized into subtypes. Symptoms fall into 3 categories: positive, negative, and cognitive (Table 16-1).

Table 16-1: Symptoms of Schizophrenia

Category	Symptoms	Special Note
Positive	Auditory or visual hallucinations	If olfactory or tactile, consider other medical causes.
	Delusions, including fixed false beliefs	e.g., the belief one is under police surveillance
	Thought disorder	e.g., derailment, poverty of speech, tangentiality, illogical speech, perseveration
	Movement disorders	Agitated body movements
Negative	Flat affect	Reduced expression of emotions
	Reduced speaking	
	Reduced feelings of pleasure	
Cognitive	Difficulty initiating and sustaining activities	
	Poor executive functioning	Inability to understand information to make decisions
	Inattention	
	Poor working memory	Inability to use information immediately after learning it

Schizophrenia is not associated with any clear laboratory results. The diagnosis is **clinical**. Perform the following to rule out other or concomitant illnesses:

- CBC, CMP, LFTs, TSH, glucose, vitamin B₁₂, vitamin B₁, folate, methylmalonic acid (MMA)
- Pregnancy testing (woman of childbearing age)
- Toxicology: drugs, heavy metal screen
- Infections: CXR, urine culture, RPR, HIV
- Imaging/EEG: subdural hematomas, vasculitis, cerebral abscesses, tumors, seizure disorder
- Medication reconciliation: corticosteroids (psychosis, depression, or mania); L-DOPA (hallucinations or insomnia)

Clinical Course

People with schizophrenia have low rates of employment, marriage, and independent living. They often face poverty, limited access to medical care, homelessness, and incarceration. Co-occurring conditions include depression, anxiety, alcohol, and substance use disorder. Factors contributing to mortality include suicide (5% risk), cigarette smoking, poor nutrition, lack of exercise, and medication complications. See [Overview on page 16-28](#) under [Complications of Drug Therapy on page 16-28](#).

Prognosis

The prognosis is guarded, and full recovery is unusual. A poor prognosis is associated with a family history of schizophrenia, early onset of illness, structural brain abnormalities, lack of social support, and cognitive symptoms. Positive symptoms respond fairly well to antipsychotic medication.

Management

Treatment includes antipsychotics and psychotherapy. Comprehensive care with a primary care physician, psychiatry, and therapy is helpful in managing symptoms.

Antipsychotics

First generation (a.k.a. typical) **antipsychotics** (e.g., chlorpromazine, fluphenazine, haloperidol, perphenazine) can cause **extrapyramidal symptoms** (EPS)—dystonia, akathisia, parkinsonism, and tardive dyskinesia—as part of their side effect profile. They may also cause hyperprolactinemia and **prolonged QT_c** (corrected QT interval). Neuroleptic malignant syndrome is a rare but life-threatening side effect.

Second generation (a.k.a. atypical) **antipsychotics** (e.g., aripiprazole, clozapine, lurasidone, olanzapine, quetiapine, risperidone, ziprasidone) are less likely to cause EPS but have a higher risk of causing weight gain and **metabolic syndrome**. They are also less likely to cause hyperprolactinemia (except risperidone).

Clozapine is the gold standard for managing schizophrenia. Monitor CBC routinely due to the rare but life-threatening side effect of **agranulocytosis**.

DELUSIONAL DISORDER

In delusional disorder, patients have false beliefs that are bizarre or nonbizarre. These false beliefs last ≥ 1 month, the patient does not meet the criteria for schizophrenia, and **daily functioning is preserved**. There have not been large studies done on delusional disorder, but it affects roughly 0.05–0.1% of the population, with an average onset of 40 years of age.

Delusional Disorder — Somatic Subtype

Presentation

In delusional disorder, somatic subtype, patients are delusional about bodily functions and sensations. Patients believe they are infested with insects or parasites, they are emitting an odor, parts of their body are not functioning, or parts of their body are misshapen/ugly. Patients typically see other doctors (e.g., dermatologists, cosmetic surgeons, urologists, gastroenterologists) before being referred to a psychiatrist.

Management

Avoid direct confrontation of the delusion, and establish a therapeutic alliance with the patient and family to assist with treatment compliance. If a delusion is suspected and it is permitted by the patient, seek corroborative information from family or doctors. Treatments include antipsychotics, antidepressants, and psychotherapy (individual/family).

DIAGNOSIS

DSM-5 criteria for substance use disorder describe a problematic pattern of substance use leading to impairment/distress, occurring for ≥ 1 year, and including ≥ 2 of the criteria listed in Table 16-2.

Table 16-2: DSM-5 Criteria for Substance Use Disorder

Impaired Control
Use in larger amounts or longer than intended
Desire or unsuccessful effort to cut down/discontinue use
Great deal of time obtaining, using, or recovering
Craving or strong urge to use
Social Impairment
Role obligation failure at work, school, or home
Continued use despite social/interpersonal problems
Sacrificing important social, occupational, or recreational activities to use or because of use
Risky Use
Recurrent use in situations where it is physically hazardous
Continued use despite knowledge of physical or psychological problem caused or exacerbated by use
Neuroadaptive / Physiologic
Tolerance
Withdrawal

SUBSTANCE USE DISORDER

PREVIEW | REVIEW

- What are the criteria for substance use disorder?
- What is a useful screening tool for alcohol use disorder?
- What is a guideline for drink limits for males, females, and individuals > 65 years of age?
- What are the FDA treatments for alcohol and opiate use disorders?
- What is the timeline for alcohol withdrawal, and what are the risk factors for alcohol withdrawal delirium?
- What is delirium tremens?
- What are the symptoms of opiate withdrawal?

OVERVIEW

Substance use disorder is a cluster of cognitive, behavioral, and physiological symptoms indicating that the individual continues using the substance despite significant problems.

CLINICAL PEARLS

Intravenous injection, smoking, and intranasal administration produce a more rapid rate of absorption into the bloodstream, result in a more intense intoxication than ingestion of a substance, and increase the likelihood of withdrawal.

Rapidly acting substances produce immediate intoxication.

Relatively short-acting substances have a higher potential for the development of withdrawal.

Longer-acting substances have longer withdrawal duration with a less intense syndrome.

ALCOHOL USE DISORDER (AUD)

Alcohol is a central nervous system (CNS) depressant. It affects several neurotransmitter systems in the brain, including opiates, GABA (γ -aminobutyric acid), glutamate, serotonin, and dopamine. Increased opiate levels help explain the euphoric effect of alcohol, and the effects on GABA cause anxiolytic and sedative effects.

Alcohol inhibits the glutamate receptor, and long-term use of alcohol results in upregulation of glutamate receptor synthesis. If alcohol is withdrawn, the CNS has increased excitability.

2017 guidelines for alcohol consumption for a standard drink (14 g pure alcohol) from the Centers for Disease Control and Prevention (CDC):

- 12-oz beer (5% alcohol)
- 8-oz malt liquor (7% alcohol)
- 5-oz wine (12% alcohol)
- 1.5-oz spirits (40% alcohol)

AUD affects 12.4% of males and 4.9% of females. 12-month prevalence varies markedly across race/ethnic subgroups in North America. See Table 16-3.

Table 16-3: Demographics of Alcohol Use Disorder in Adults

Race	Percentage
Native American/Alaska Native	12.1%
White	8.9%
Hispanic	7.9%
African American	6.9%
Asian American/Pacific Islander	4.5%

The 2018 statistics from the National Survey on Drug Use and Health (NSDUH) indicate that 14.4 million adults ≥ 18 years of age (9.2 million males and 5.2 million females) met criteria for AUD, and about 6.7% of adults received treatment for AUD at a specialized facility.

The disorder is inherited at a rate of 40–60%, and genes involved in the dopamine reward system likely contribute to this predisposition. Risk and comorbid factors include preexisting schizophrenia, bipolar disorder, depression, anxiety, antisocial personality disorder, impulse control disorders, and cultural influences.

Development and Course

The 1st episode of alcohol intoxication is likely to occur during the midteens, and alcohol-related disorders develop in the late 30s in those who continue use. It has a varying course characterized by periods of remission and relapse. There is an increased rate of suicidal behavior, as well as of completed suicide, among individuals with the disorder.

Physiologic effects of chronic alcohol use include those listed in Table 16-4.

Alcohol Morbidity and Mortality

AUD causes significant morbidity and mortality. Roughly 10–30% of individuals who present to the emergency department complain of AUD. It leads to 100,000 annual unexpected deaths as a result of suicide, domestic violence, medical complications, and motor vehicle accidents.

Table 16-4: Physiologic Effects of Chronic Alcohol Use

System	Symptoms
Neurologic	Wernicke encephalopathy, Korsakoff psychosis, dementia, peripheral neuropathy
Psychiatric	Depression, anxiety
Gastrointestinal	Cirrhosis, peptic ulcer disease, gastritis, pancreatitis, carcinoma
Cardiovascular	Hypertension, atrial fibrillation, cardiomyopathy
Immunologic	Suppression of neutrophil function and cell-mediated immunity
Endocrinologic	Erectile dysfunction, testicular atrophy, gynecomastia (high estrogen and low testosterone in males), menstrual irregularities
Obstetric	Spontaneous abortion, fetal alcohol syndrome

Screening

A useful screening tool is the **CAGE** questionnaire:

- **C**—Has anyone ever felt you should cut down on your drinking?
- **A**—Have people annoyed you by criticizing your drinking?
- **G**—Have you ever felt guilty about your drinking?
- **E**—Have you ever had a drink first thing in the morning (eye-opener) to steady your nerves or to get rid of a hangover?

2 “yes” responses indicate AUD at a rate of 90% sensitivity and specificity.

An alternative screen is when drinking reaches these levels:

- Men: > 14 drinks/week or > 4 drinks/occasion
- Women: > 7 drinks/week or > 3 drinks/occasion
- > 65 years of age: > 7 drinks/week or > 3 drinks/occasion

Alcohol Assessment

Lab tests include CBC, triglycerides (TGL), electrolytes, Mg^{2+} , liver enzymes (γ -glutamyl transferase [GGT]; aspartate aminotransferase [AST] > alanine aminotransferase [ALT]), urine drug screen, pregnancy test, and breathalyzer or blood alcohol level.

Other useful tests are skin test for tuberculosis (TB), CXR, electrocardiogram (ECG), and tests for viral hepatitis, HIV, or other sexually transmitted infections (STIs).

Sequelae

Complications of severe AUD include Wernicke encephalopathy and Korsakoff psychosis, as described in Table 16-5.

Management

Psychotherapy (e.g., Alcoholics Anonymous, individual) in addition to the U.S. Food and Drug Administration (FDA)-approved medications naltrexone, disulfiram, and acamprosate are treatments for AUD. Naltrexone blunts the opiate receptors in the reward pathway activated by alcohol use; acamprosate modulates glutamate neurotransmission; and disulfiram is an aversive agent. Naltrexone and acamprosate have been shown to reduce return to heavy drinking and the number of drinking days in the short term; however, longer-term studies show a less significant impact. Assess and treat comorbid psychiatric and physical illnesses. Screen for suicidal and homicidal ideation, and send to emergency department for psychiatric assessment when indicated.

Alcohol Withdrawal

Criteria

DSM-5 criteria for alcohol withdrawal (which can also be seen with benzodiazepines [BDZs] and barbiturates):

- Cessation of (or reduction in) alcohol use that has been heavy and prolonged
- ≥ 2 of the following, developing within several hours to a few days after the cessation of (or reduction in) alcohol use:
 - Autonomic hyperactivity (e.g., sweating, pulse rate > 100 bpm)
 - Increased hand tremor
 - Insomnia
 - Nausea or vomiting
 - Transient visual, tactile, or auditory hallucinations or illusions
 - Psychomotor agitation
 - Anxiety
 - Generalized tonic-clonic seizures
- The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning and are not due to another medical condition, mental disorder, or intoxication or withdrawal from another substance.

Alcohol withdrawal symptoms typically begin around 6 hours following the last drink, are the worst at 24–72 hours, and improve by 7 days.

Symptoms vary and can be categorized by the following:

- Alcohol hallucinosis
- Transient visual, auditory, or tactile hallucinations
- Withdrawal seizures—seizures occur within 48 hours of alcohol cessation and occur either as a single generalized tonic-clonic seizure or as a brief episode of multiple seizures.
- Delirium tremens:
 - Medical emergency with mortality up to 20%
 - Hyperadrenergic state, disorientation, tremors, diaphoresis, impaired attention/consciousness, and visual and auditory hallucinations
 - Occurs 3–10 days after alcohol cessation
 - Most severe form of withdrawal, occurring in 5–20% of patients experiencing detoxification and 30% of patients experiencing withdrawal seizures

Predictors of alcohol withdrawal delirium include prior history of severe withdrawal symptoms, high blood alcohol level without signs of intoxication, withdrawal signs with high blood alcohol level, concurrent use of sedative-hypnotics, and medical comorbidities (e.g., hepatitis, pancreatitis).

Management

The typical treatment of alcohol withdrawal is with BDZs with a long half-life, such as chlordiazepoxide (a.k.a. chlordiazepoxide taper). Delirium tremens is treated with IV lorazepam in the intensive care unit (ICU). Assess and treat with folic acid, vitamin B₁₂, and thiamine; correct electrolyte abnormalities.

OPIATE USE DISORDER (OUD)

Epidemiology of Opioid Use in the U.S.

Although the U.S. has ~ 5% of the world’s population, Americans consume 80% of the world’s opioid supply. Heroin and synthetic opioids are the most commonly abused opiates. The General Internal Medicine section has additional information on opioid overdose.

Table 16-5: Wernicke Encephalopathy vs. Korsakoff Psychosis

	Wernicke Encephalopathy	Korsakoff Psychosis
Etiology	Thiamine deficiency	Impaired short-term memory (sequela of Wernicke's)
Timeline	Acute symptoms	Chronic condition
Features	Triad: ataxia, nystagmus, ophthalmoplegia	Anterograde amnesia +/- confabulation
Treatment	Thiamine 100 mg IM/IV × 3 days; 100 mg PO tid × 2 weeks	Consider memantine (no controlled studies)

Burden of Opioid Use in the U.S.

Significant medical and social problems are associated with OUD, including infections (e.g., HIV/AIDS, hepatitis B and C, TB, skin abscess at an injection site, cellulitis, mycotic aneurysms, endocarditis), psychosocial problems (e.g., unemployment, family stressors, crime), and mental health issues (e.g., suicide, violence). The economic burden is \$100 billion annually due to medical care, unemployment, absenteeism, and crime.

Diagnosis of Opioid Intoxication

The *DSM-5* criteria for opioid intoxication include the following:

- Recent opioid use
- Clinically significant problematic behavior (e.g., euphoria followed by apathy, dysphoria, psychomotor agitation/retardation, impaired judgment)
- Pupillary constriction and ≥ 1 of the following:
 - Drowsiness
 - Slurred speech
 - Impairment in attention or memory
- Causes significant distress or impairment in functioning and is not due to another mental illness or medical condition

Diagnosis of Opioid Withdrawal

The *DSM-5* criteria for opioid withdrawal include:

- Either the cessation or the reduction in opioid use or the administration of opioid antagonist after a period of opioid use
- ≥ 3 of the following:
 - Dysphoric mood
 - Nausea or vomiting
 - Muscle aches
 - Lacrimation or rhinorrhea
 - Pupillary dilation, piloerection, or sweating
 - Diarrhea
 - Yawning
 - Fever
 - Insomnia
- Causes significant distress or impairment in functioning and is not due to another mental illness or medical condition

Workup

Lab tests include CBC, urine toxicology screen, TB, viral hepatitis, HIV, or other STIs.

Management

Treatment (Table 16-6) includes managing comorbid psychiatric and medical illnesses. Psychotherapy and Narcotics Anonymous are also encouraged. FDA-approved medications include methadone and extended-release injectable naltrexone and buprenorphine/naloxone for OUD. Methadone and buprenorphine/naloxone reduce euphoria/cravings, block the effects of illicit opiates, and prevent withdrawal. Use buprenorphine/naloxone as a 1st line if available. Methadone can be dispensed at a clinic, and providers prescribing buprenorphine/naloxone require special training and regulation by the FDA.

OTHER SUBSTANCES — INTOXICATION / COMPLICATIONS

Cocaine

Cardiotoxicity can occur no matter what the route of use. Cocaine causes rhythm disturbances (including ventricular fibrillation/tachycardia), ischemia (irrespective of whether the patient has preexisting atherosclerotic disease), myocarditis, and systolic dysfunction. Suspect use in a young patient presenting with myocardial infarction (MI). Stroke is also common with cocaine. Muscle injury with rhabdomyolysis can occur. Know that β -blockers are **not** used in this group to treat angina or verified myocardial ischemia, due to concerns of unopposed α -receptor stimulation. Instead, nitroglycerin, calcium channel blockers, BDZs, and antipsychotics (for agitation) are 1st line treatments.

Amphetamines

Methamphetamine is a powerful CNS stimulant that increases the release of epinephrine, norepinephrine, serotonin, and dopamine. Consider methamphetamine toxicity in the sweaty, severely agitated, or psychotic patient with tachycardia and hypertension. Severe tooth decay occurs in chronic users. Acute treatment of the severely agitated patient is BDZs and antipsychotics (e.g., haloperidol) if needed. Watch for rhabdomyolysis in these patients by monitoring electrolytes, blood urea nitrogen (BUN), creatinine, creatine kinase (CK; a.k.a. creatine phosphokinase [CPK]), and serum lactate.

Table 16-6: Opioid Intoxication Treatment

Type of Intoxication	Signs and Symptoms	Approach
Acute	Euphoria, pupillary constriction, depression of respiration and gag reflex, bradycardia, hypotension, constipation	Airway protection, naloxone
Chronic	Complications of IV use, including hepatitis B, hepatitis C, HIV/AIDS, endocarditis, brain abscesses	Discontinue use, treat medical conditions.
Overdose	Acute overdose can cause respiratory arrest and death.	Intubation and ventilation, naloxone

Hallucinogens

PCP (phencyclidine) can cause acute psychotic agitation, seizures, dystonia (including laryngospasm), nystagmus, and hypertensive crisis. Severe dystonia can cause rhabdomyolysis. Treat with a calm environment and antipsychotics as needed for agitation, with supportive care for complications such as rhabdomyolysis.

LSD (lysergic acid diethylamide; a.k.a. Acid) causes hallucinations. Fatalities and morbidities during use are unusual and generally attributable to bad decisions being made while intoxicated. LSD can precipitate serotonin syndrome.

MDMA (3,4-methylenedioxymethamphetamine; a.k.a. Ecstasy) use is often seen in young people in the setting of parties or raves. The ingestion of MDMA results in euphoria, loss of inhibitions, cozy feelings of intimacy, and increased sexual arousal due to an increased release of serotonin. The drug is commonly perceived as being very mild with minimal risk and physical effects, but MDMA possesses properties that resemble a combination of amphetamines and peyote (stimulant + hallucinogen). The drug is taken in tablet form, and overdoses can result in death. Side effects of MDMA include bruxism (teeth grinding), anxiety, sweating, hypertension, and tachycardia. Dangerous complications include severe hyponatremia, malignant hypertension, stroke, cardiac ischemia, arrhythmias, and serotonin syndrome. Hyperthermia and rhabdomyolysis are possibilities, especially in patients who use MDMA and dance all night. In intoxicated states, most symptoms (i.e., hypertension, tachycardia, agitation) respond to BDZs and antipsychotics for severe agitation.

Cannabis

Δ^9 -tetrahydrocannabinol (Δ^9 -THC) is the cannabinoid that is primarily responsible for the psychoactive effects of *Cannabis*. It is converted to 11-hydroxy- Δ^9 -THC in the CNS. *Cannabis* intoxication can cause impaired motor coordination, euphoria, anxiety, sensation of slowed time, impaired judgment, social withdrawal, conjunctival injection, increased appetite, dry mouth, and tachycardia. Complications include psychosis with chronic use. Treat with abstinence and antipsychotics for psychosis.

ANXIETY DISORDERS

OVERVIEW

Anxiety disorders are classified in 2 ways:

- 1) Generalized anxiety disorder, which is chronic and low grade
- 2) Panic disorder, with brief and dramatic panic attacks

GENERALIZED ANXIETY DISORDER (GAD)

PREVIEW | REVIEW

- What are the diagnostic criteria for generalized anxiety disorder (GAD)?
- Describe the clinical course of GAD.

GAD is an anxiety disorder characterized by persistent and excessive worry about events or activities. Individuals with GAD find it difficult to control their worry, and this excessive worry often interferes with daily functioning. GAD affects 3-4% of individuals, and females are affected 2× more than males. Although it starts gradually and can begin at any age, it typically starts between childhood and middle age, with median age of onset of 30 years of age (later than other anxiety disorders). In some cultures, somatic symptoms predominate, whereas in other cultures, cognitive symptoms predominate.

Diagnosis

See Table 16-7.

Table 16-7: DSM-5 Criteria for Generalized Anxiety Disorder

Excessive anxiety and worry (apprehensive expectation) for ≥ 6 months about a number of events or activities

The individual finds it difficult to control the worry.

The anxiety and worry are associated with > 3 of the following 6 symptoms (with some symptoms present for a majority of the past 6 months):

- Restlessness or feeling keyed up or on edge
- Easily fatigued
- Difficulty concentrating or mind going blank
- Irritability
- Muscle tension
- Sleep disturbance (difficulty falling or staying asleep or experiencing restless, unsatisfying sleep)

Symptoms cause distress in functioning and are not due to a substance, medical condition, or another mental disorder.

GAD also can co-occur with conditions associated with stress, which in turn can lead to gastrointestinal or cardiovascular sequelae. Worrying impairs scholastic and employment progress. Risk factors include parental overprotectiveness, anxiety, sensitivity, and genetics. GAD is 30-50% comorbid with other anxiety disorders, depression, and Cluster C personality disorders. Patients are at risk for alcohol or sedative-hypnotic use disorder.

Associated features of GAD include:

- Headaches
- Upset stomach, vomiting, diarrhea
- Numbness in hands and feet
- Hot flashes, sweating
- Difficulty breathing or swallowing
- Difficulty concentrating

Clinical Course

Many individuals with GAD report feeling anxious and nervous their whole life. The content of an individual's worry tends to be age appropriate: Children/adolescents worry about school and sporting performance, while older adults report concern about the well-being of family or their own physical health. Younger adults experience greater severity of symptoms than older adults, and individuals have higher comorbidity and impairment when diagnosed at an earlier age. GAD is overdiagnosed in children. Rule out separation anxiety disorder, social anxiety disorder, or OCD. GAD tends to be chronic and waxes and wanes. The prognosis is good when treatment is implemented early and effectively. The prognosis is guarded for those where symptoms are not diagnosed.

There are several differential diagnoses to consider for GAD. A few include ADHD, anorexia nervosa, bipolar disorder, MDD, OCD, posttraumatic stress disorder, phobias, panic disorder, personality disorder, somatic symptom disorder, and substance use disorder.

Workup

Few findings are noted on physical examination. Order urine drug screening (use of and/or withdrawal from substances), TSH, and less common laboratory tests based on history and physical findings. Avoid excessive laboratory screening for somatic complaints. Perform a medication reconciliation, as prescribed medications can contribute to anxiety.

Management

CBT and serotonergic antidepressants (e.g., SSRIs, SNRIs), alone or in combination, are the treatment for GAD. Antidepressants are effective medications to manage anxiety disorders in the long run; however, antianxiety medications (e.g., buspirone, hydroxyzine) are also effective in resolving anxiety symptoms and are commonly used. Long-term use of BDZs can worsen anxiety, and subsequent reduction of BDZs improves anxiety.

PANIC DISORDER

PREVIEW | REVIEW

- What are the symptoms of a panic attack?
- What medical conditions can mimic a panic attack?

Panic disorder is characterized by recurrent, unexpected panic attacks. It usually develops between 18 and 45 years of age, with an average age of onset of 24 years of age. Lifetime prevalence is 2–6%, with an inheritance rate of 43% in 1st degree relatives. Women are affected 2–3× more often than men. There is an increased risk for panic disorder among offspring of parents with anxiety, depressive,

and bipolar disorders. Recognize that symptom manifestations differ among races, whereby some individuals present with classic symptoms while others may present with somatic or cognitive symptoms.

Diagnosis

DSM-5 diagnosis for panic disorder:

- Recurrent unexpected panic attacks. A **panic attack** is an abrupt surge of intense fear or intense discomfort that reaches a peak within minutes, with ≥ 4 of the following symptoms:
 - Feeling dizzy, lightheaded, or faint
 - Palpitations or pounding heart
 - Nausea or abdominal distress
 - Sweating
 - Trembling or shaking
 - Sensations of shortness of breath, smothering, or choking
 - Chest pain/ discomfort
 - Chills or heat sensations
 - Paresthesias (numbness or tingling sensations)
 - Derealization (feelings of unreality) or depersonalization (being detached from oneself)
 - Fear of losing control, going crazy, or dying
 - Note: Culture-specific symptoms (e.g., tinnitus, neck soreness, headache, uncontrollable screaming or crying) may be seen. These symptoms should **not** count as 1 of the 4 required symptoms.
- ≥ 1 attack has been followed by ≥ 1 month of 1 or both of the following:
 - Persistent concern or worry about additional panic attacks or their consequences (e.g., losing control, having a heart attack, going crazy)
 - A significant maladaptive change in behavior related to the attacks (e.g., avoidance)
- The disturbance is not attributable to the physiological effects of a substance, to a medical condition, or to another psychiatric disorder.

Risk factors include family history of anxiety and mood disorders, childhood sexual and physical abuse, smoking, stress, and comorbid medical issues. Culture also plays a role in perception of symptoms. Patients with panic disorder have an 80% chance of having other psychiatric disorders, including mood, depressive, anxiety, and substance use disorders.

The diagnosis of panic disorder is clinical and a diagnosis of exclusion. Be sure to rule out substance exposure/withdrawal as a cause of panic attacks. Rule out conditions also seen in GAD. Medical conditions associated with panic disorders include asthma, obstructive sleep apnea, ulcers, and migraines.

For differential diagnoses for panic disorder, see Table 16-8 on page 16-12.

Table 16-8: Differential Medical Diagnoses for Panic Disorder

Medical	Substance Exposure	Intoxication	Withdrawal
Cardiac: myocardial infarction, angina, anemia, arrhythmia	Carbon dioxide	Stimulants	Sedative-hypnotics
Pulmonary: asthma, pulmonary embolism	Cholecystokinin	Cocaine	Antidepressants
Endocrinologic: pheochromocytoma, Addison disease, Cushing syndrome, hyperthyroidism, hypoparathyroidism	Yohimbine	Hallucinogens	Opiates
Neoplasm: carcinoid syndrome, brain lesion	Caffeine	<i>Cannabis</i>	Alcohol
Neurologic: temporal lobe epilepsy, Huntington disease, Wilson disease, systemic lupus erythematosus	Sodium lactate	Amyl nitrates	Benzodiazepines
Other: electrolyte disturbances, vitamin B ₁₂ deficiency, heavy metal poisoning	Cholecystokinin	Organophosphates	Barbiturates

Clinical Course

Panic disorder is associated with poor social and family relationships and lower educational and occupational achievement and absenteeism, resulting in lower income. If compounded by the presence of agoraphobia, the effects are magnified. Individuals have the highest number of medical visits among all the anxiety disorders. Cardiovascular disorders (e.g., hypertension, stroke, mitral valve prolapse) are comorbid factors, and individuals have 2× the risk of coronary artery disease, MI, and death with panic attack. Individuals with panic attacks/disorder have a high rate of suicidal ideation and suicide attempts.

Panic disorder has a chronic waxing and waning course, with ~ 50% of individuals reporting improved symptoms and a small percentage achieving full remission. The course is typically complicated by anxiety, depression, and substance use. Good prognostic factors include brief duration of symptoms and good premorbid functioning, whereas those associated with poor outcomes are low socioeconomic class, unmarried status, divorce, and death of a parent during childhood. Poor outcomes are also associated with those who do not want to tolerate the sensations of panic or medication side effects.

Management

Refer all patients with panic attacks/disorder to a mental health professional for management. Brief follow-up appointments, CBT, and anxiolytics (selective serotonin reuptake inhibitors [SSRIs], serotonin-norepinephrine reuptake inhibitors [SNRIs], benzodiazepines [BDZs], and buspirone) are the treatment of choice for outpatient management. SSRIs and SNRIs are preferred over BDZs, but if ineffective, a short course of a longer-acting BDZ (e.g., clonazepam) is preferred over alprazolam (a short-acting BDZ) due to alprazolam's potential for abuse and higher toxicity in overdose. Buspirone is useful as a BDZ substitute. Indications for inpatient hospitalization include sedative-hypnotic intoxication, withdrawal, self-injurious behaviors, suicidal or homicidal ideation, severity of a disorder to the extent that it is crippling the individual, or need for investigation of medical issues contributing to presentation.

PHOBIAS

PREVIEW | REVIEW

- What is agoraphobia?
- What are the risk factors for agoraphobia?
- What is social anxiety disorder?
- What are the features of social anxiety disorder?
- What labs are ordered to rule out a medical cause of a phobia?
- What are the treatments for phobias?

Agoraphobia

Agoraphobia is characterized by anxiety in situations where the person perceives the environment to be unsafe with no easy way to escape when panic-like symptoms or other incapacitating or embarrassing symptoms occur.

It affects 1.7% of adolescents/adults, and the female-to-male ratio is 2:1. Onset in childhood is rare (although children may have difficulty expressing symptoms). The initial onset of agoraphobia is < 35 years of age in 66% of cases. There is bimodal distribution with presentation at ~ 17 years of age then again after 40 years of age. There are no racial differences. Inheritance is 60% in 1st degree relatives.

Diagnosis

DSM-5 diagnosis of agoraphobia includes marked fear or anxiety in ≥ 2 of 5 situations:

- 1) Using public transportation
- 2) Being in open spaces
- 3) Being in enclosed places
- 4) Standing in line or being in a crowd
- 5) Being outside of the home alone

An affected individual fears or actively avoids these situations or requires the presence of a companion because escape might be difficult or help unavailable. Such situations almost always provoke fear or anxiety. Fear or

anxiety is out of proportion to the actual danger posed. It is persistent (≥ 6 months), causes significant distress/impairment, and cannot be explained by another mental disorder, substance, or medical condition. If another medical condition is present, the fear/anxiety/avoidance is excessive.

Note: Agoraphobia is diagnosed irrespective of the presence of panic disorder.

Features and Risk Factors

Roughly 30–50% of individuals report panic attacks/disorder before agoraphobia. If agoraphobia occurs with panic attacks, agoraphobia might not necessarily resolve when panic stops. Risk factors include childhood stressors, such as death of a parent; adult stressors, such as being attacked; genetic predisposition to anxiety disorders; and personal history of anxiety.

Clinical Course

Age-specific concerns occur; for example, children may fear getting lost, adults may fear having a panic attack, and older adults may have a fear of falling. The clinical course is persistent and chronic. Complete remission is rare, and comorbid conditions of anxiety, depressive, personality, and substance use disorders complicate the clinical course.

Social Anxiety Disorder / Social Phobia

Social anxiety disorder/social phobia is characterized by extreme fear in social situations causing distress and inability to function in certain aspects of daily life. Fears are triggered by perceived or actual scrutiny from others. It affects 7% of children, adolescents, and adults, with a median age of onset at 13 years of age. It affects 2–5% of older adults. Females are 1.5–2.2 $\times$ more likely to suffer from social anxiety disorder than are males. There are racial differences, with higher incidence in Native Americans and Whites than in those of Asian, Hispanic, or African American descent.

Diagnosis

The *DSM-5* diagnosis of social anxiety is defined by:

- Marked, persistent fear of social or performance situations because it can lead to humiliation or scrutiny
- Person fears showing anxiety symptoms that could lead to being negatively evaluated.
- Exposure almost always provokes anxiety and/or panic attack.
- Situations are avoided or endured with anxiety.
- Fear is out of proportion with actual threat.

Social anxiety typically lasts > 6 months, causes significant distress or impairment, and is not due to a substance, mental disorder, or another medical condition. If due to another medical condition, the fear is unrelated or excessive.

Features

Blushing is a hallmark of social anxiety. Individuals avoid conversation and dating, display rigid posture, exhibit low eye contact and soft voice, and are shy and nondisclosing. Situations that provoke anxiety include social interactions (e.g., having a conversation), being observed (e.g., eating, drinking), and performing in front of others (e.g., giving a speech). Risk factors include having a parent with an anxiety disorder and having a tendency to experience distress and then withdraw from unfamiliar situations, people, or environments.

Clinical Course

Social anxiety disorder has a chronic, lifelong course. It may be precipitated by a humiliating social event, or the person may have a history of childhood anxiety. Males have a higher comorbidity with oppositional defiant and conduct disorders, and females have a higher comorbidity with depressive and bipolar disorders. Individuals with social anxiety have lower educational and professional achievement levels and are more likely to resort to substances to calm anxiety. Approximately 30% of individuals with social anxiety disorder experience remission within 1 year, and $\sim 50\%$ experience remission within a few years of treatment. It takes several years for remission in individuals who do not seek therapy.

Specific Phobia

Specific phobia is an irrational fear or anxiety due to the presence of a particular situation or object, resulting in avoidance of the situation or object. The disorder affects 5% of children, 16% of adolescents, and 2–9% of adults. The female-to-male ratio is 2:1. In the U.S. and in European countries, the prevalence is 7–9%, while it is 2–4% in Asian, African, and Latin American countries. The median age at onset is between 7 and 11 years of age. Specific phobias that occur in childhood/adolescence are likely to wax and wane during that period but rarely remit when they persist into adulthood.

Diagnosis

The *DSM-5* diagnosis of specific phobia is characterized by:

- Marked fear/anxiety cued by presence or anticipation of a specific object or situation
- Exposure to phobic stimulus provokes anxiety.
- Situation is avoided or endured with anxiety.
- Anxiety is out of proportion to actual danger posed by object or situation.
- Persistent (typically lasts ≥ 6 months), causes significant distress or impairment, and is not better explained by another mental disorder, substance, or medical condition

Examples of specific phobias include:

- Animal type (includes insects)
- Natural environment type: e.g., storms, heights
- Blood-injection-injury type: e.g., needles, invasive medical procedures
- Situational type: e.g., airplanes, elevators, enclosed spaces
- Other type: e.g., fear of choking, fear of vomiting

Clinical Course

Phobias are associated with decreased rates of academic and employment achievement; lower socioeconomic status; higher likelihood of living at home or being homebound; being single, unmarried, divorced, or with no children; and lower quality of life.

Clinical Considerations

The diagnosis is clinical. Consider the following tests to rule out anxiety secondary to medical conditions:

- Drug screen
- Thyroid function tests
- Fasting glucose

Management

SSRIs (e.g., sertraline, paroxetine) and SNRIs (e.g., venlafaxine, duloxetine) are FDA approved for social anxiety disorder and agoraphobia. There are no FDA-approved medications for specific phobia, but SSRIs and a short course of BDZs (i.e., 30 minutes prior to a flight) have been used with good effect. Exposure therapy can assist with extinguishing specific fears. CBT is also recommended for all 3 phobias.

OBSESSIVE-COMPULSIVE DISORDER (OCD)

PREVIEW | REVIEW

- What is obsessive-compulsive disorder (OCD)?
- What are obsessions?
- What are compulsions?
- What are the risk factors for OCD?
- What is the management of OCD?

OCD is characterized by distressing, intrusive, obsessive thoughts and/or repetitive compulsive physical or mental acts.

It affects 1.2–2.5% of the population. Males and females are affected equally, but it presents in males during childhood/adolescence and in females in their 20s. Males are more likely to have a comorbid tic disorder. There are no racial differences. There is an 80–87% concordance rate in monozygotic twins and a 47–50% concordance in

dizygotic twins. Those with 1st degree relatives who have OCD are at a higher risk for developing OCD themselves. The risk is higher if the 1st degree relative developed OCD as a child or teen.

Diagnosis

The *DSM-5* diagnosis for OCD is guided by the following concepts.

Obsessions are defined as recurrent and persistent thoughts, urges, or images that are intrusive and inappropriate and cause marked anxiety and distress. The individual attempts to suppress or ignore these thoughts, impulses, or images or to neutralize them with some other thought or action.

Compulsions are defined as repetitive behaviors or mental acts performed in response to an obsession or according to rules that must be applied rigidly. The behaviors or mental acts are aimed at preventing or reducing distress or preventing some dreaded event or situation, but they are not connected in a way that could realistically neutralize or prevent whatever they are meant to address, or they are clearly excessive.

The individual recognizes that the obsessions or compulsions are excessive or unreasonable; they cause marked distress, take > 1 hour per day, or significantly interfere with the individual's daily functioning. The behaviors are not due to a substance or a general medical condition.

Development and Course

OCD has a chronic gradual course, with a waxing and waning of symptoms. While up to 70% of patients entering treatment improve, the remainder worsen over time. 5% of patients remit completely between episodes of exacerbation. Full remission rate is ~ 20% without treatment. 40% of individuals with onset of OCD in childhood or adolescence experience remission by early adulthood, while the rest experience lifetime symptoms. Refractory cases may require combinations of medications (see [Management](#)). OCD is associated with reduced quality of life and social and occupational impairment as individuals spend time obsessing and doing compulsions and avoiding situations triggering obsessions and compulsions. Individuals with OCD minimize relationships with family and friends, perform poorly at school or work, and may fail to progress or get fired. Individuals delay treatment for years as they spend much time concealing symptoms from loved ones and health care providers.

Risk and Prognostic Factors and Comorbid Disorders

In addition to genetic factors, risk factors for OCD include physical and sexual abuse in childhood, stressful/traumatic events, infectious agents, autoimmune diseases, and mood lability. OCD is comorbid with mood and anxiety disorders, somatoform disorders (e.g., somatic

symptom disorder), eating disorders, impulse control disorders (e.g., kleptomania, trichotillomania [hair-pulling], excoriation disorder [skin-picking]), ADHD, obsessive-compulsive personality disorder (OCPD), and tic disorder.

Differential Diagnosis

Do not confuse OCD with OCPD. Whereas individuals with OCD are aware their behavior is not rational and are unhappy about their obsessions but nevertheless feel compelled by them, those with OCPD are not aware of anything abnormal, consider their actions rational, and derive pleasure from their obsessions/compulsions.

Management

The treatment of OCD includes high-dose SSRIs, atypical antipsychotics, CBT, and exposure and response prevention therapy (teaching the person to deliberately come into contact with the situations that trigger the obsessive thoughts and fears ["exposure"], without carrying out the compulsive acts associated with the obsession ["response prevention"]).

POSTTRAUMATIC STRESS DISORDER (PTSD)

PREVIEW | REVIEW

- What is the diagnosis of posttraumatic stress disorder (PTSD)?
- Why do females have a higher rate of PTSD than males?
- What is the natural history of PTSD?
- What are the treatments for PTSD?

PTSD can develop after an individual witnesses or experiences a serious threat of violence or death, resulting in disturbing thoughts, flashbacks, and nightmares related to the event and the so-called fight-or-flight response in an attempt to avoid triggers. Individuals also suffer from negative thoughts and mood.

Prevalence is about 3.5–9%, but rates of PTSD are higher among military veterans (up to 75%) and others whose vocation increases the risk of traumatic exposure. PTSD is more prevalent in females than in males, and females experience symptoms for a longer duration. The increased risk for PTSD in females is likely due to a greater exposure to traumatic events, such as rape and other forms of interpersonal violence, while males are likely to suffer from PTSD due to combat exposure.

Diagnosis

Table 16-9 shows the 4 conditions necessary for a diagnosis of PTSD. Symptoms and impairment lasting < 1 month are diagnosed as **acute stress disorder**.

Table 16-9: DSM-5 Criteria for Posttraumatic Stress Disorder

Traumatic event is persistently reexperienced:

Nightmares

Intrusive thoughts of the traumatic event(s)

Flashbacks

Marked emotional distress when exposed to traumatic reminders

Strong physiologic reaction when exposed to traumatic reminders

Avoidance in 1 of 2 ways:

1) Avoidance of thoughts, feelings, or conversations associated with the event(s)

2) Avoidance of people, places, or activities that may trigger recollections of the event(s)

Negative alterations in cognition and mood (2 of the following):

Inability to remember an important aspect of the event(s)

Persistent and exaggerated negative beliefs about oneself, others, or the world

Persistent distorted cognitions about the cause or consequences of the event(s)

Persistent negative emotional state

Markedly diminished interest or participation in significant activities

Feelings of detachment or estrangement from others

Persistent inability to experience positive emotions

Hyperarousal (2 of the following):

Irritable behavior and angry outbursts

Reckless or self-destructive behavior

Hypervigilance

Exaggerated startle response

Concentration problems

Sleep disturbance

The duration of symptoms is > 1 month, the symptoms cause distress or impairment in functioning, and symptoms are not due to a substance or medical condition.

Risk and Prognostic Factors and Comorbid Disorders

Risk factors for the development of PTSD include lower socioeconomic status, education, and intelligence; exposure to prior trauma (especially during childhood); childhood adversity (e.g., economic deprivation, family dysfunction, parental separation or death); minority racial/ethnic status; dissociation during trauma; witnessing atrocities; interpersonal violence; personal injury; and a family psychiatric history of PTSD. Social support prior to trauma is a protective factor. PTSD is associated with poor social and family relationships, work absenteeism, lower income, and lower educational and occupational

achievement. Comorbid conditions include major depressive, substance-related, panic, and generalized anxiety disorders as well as specific or social phobias.

Clinical Course

PTSD can occur at any age, manifesting within the first 3 months after the trauma, or there may be a delay of months or years before criteria are met. The duration of symptoms varies over time. 50% of adults recover within 3 months, while others can have symptoms for the rest of their lives based on the original trauma, ongoing stressors, or other traumatic experiences. Expression varies across age groups. Children have nightmares, engage in symbolic play of the trauma, and are irritable and reclusive. Adolescents are reckless, aggressive, and reclusive and lose future aspirations. Individuals who continue to experience PTSD into adulthood have fewer symptoms of hyperarousal, avoidance, and negative cognitions and mood compared with younger adults. Adults exposed to traumatic events during later life display more avoidance, hyperarousal, sleep problems, and crying spells than younger adults exposed to the same traumatic events. They also have negative health perceptions, more primary care interactions, and suicidal ideation and attempts.

Management

FDA-approved medications include sertraline and paroxetine to target symptoms of hyperarousal, avoidance, and reexperiencing. Venlafaxine is also effective, as is prazosin for nightmares. BDZs worsen the clinical course and should be avoided. 66% of individuals improve with CBT and eye movement desensitization and reprocessing (EMDR) therapy, an exposure therapy desensitizing an individual to traumatic memories.

PERSONALITY DISORDERS (PDs)

PREVIEW | REVIEW

- What is a personality disorder (PD)?
- What are the 10 PDs?
- Which PDs are associated with suicide?

OVERVIEW

According to the *DSM-5*, a PD is an enduring pattern of inner experience and behavior that differs markedly from the expectations of the individual's culture, is pervasive and inflexible, has an onset in adolescence or early adulthood, is stable over time, and leads to distress or impairment. PDs affect 10–15% of the adult U.S. population. Concordance for PDs in monozygotic twins is several times that of dizygotic twins, and the incidence of PDs in monozygotic twins reared apart is similar to that in those reared together.

CLUSTERS

There are 10 recognized PDs grouped into 3 clusters (A, B, and C):

- Cluster A ("mad": odd and eccentric)
 - Paranoid personality disorder
 - Schizoid personality disorder
 - Schizotypal personality disorder
- Cluster B ("bad": dramatic and emotional)
 - Antisocial personality disorder
 - Borderline personality disorder
 - Narcissistic personality disorder
 - Histrionic personality disorder
- Cluster C ("sad": anxious, needy, or fearful)
 - Dependent personality disorder
 - Avoidant personality disorder
 - Obsessive-compulsive personality disorder

Clusters A, B, and C

See [Table 16-10](#), [Table 16-11](#), and [Table 16-12](#) for details on Cluster A, B, and C personality disorders, respectively.

Other

Personality change due to another medical condition is a persistent personality disturbance that is judged to be due to the direct physiological effects of a medical condition (e.g., frontal lobe lesion).

Medical conditions that can cause personality changes include CNS tumors, head trauma, cerebrovascular disease, Huntington disease, epilepsy, infectious conditions with CNS involvement (e.g., HIV), endocrine conditions (e.g., hypothyroidism, hypoadrenocorticism, hyperadrenocorticism), and autoimmune conditions with CNS involvement (e.g., SLE). Rule out these causes of personality changes with history, physical examination, imaging, and laboratory findings.

DIAGNOSIS

PDs cannot be diagnosed in individuals ≤ 18 years of age because personality development is not complete and symptoms may not persist into adulthood. Conversely, PDs are not reliable in the elderly population as the disorders are related to young adulthood behaviors.

PROGNOSIS

PDs are lifelong conditions. Individuals are at high risk for comorbid mood disorders. Clusters A and B personality disorders become less severe and intense in middle age and late life, while Cluster C disorders tend to worsen later in life. Individuals with a Cluster B PD are at high risk for substance use disorder, impaired impulse control, depression, suicide, and homicide (paranoid and antisocial

personality disorders). Risk of death is related to conditions/behaviors resulting from the disorder. Individuals may die from suicide, substance use, trauma from motor vehicle accidents, or fighting.

TREATMENT

Overall, individuals often resist treatment. CBT is the treatment of choice. Use medications to target symptoms. BDZs are not helpful for personality disorders. Refer to [Table 16-10](#), [Table 16-11](#), and [Table 16-12](#) for further details.

Table 16-10: Cluster A Personality Disorder Characteristics

	Paranoid	Schizoid	Schizotypal
DSM-5 Descriptor	Distrust and suspiciousness such that others' motives are interpreted as malevolent	Detachment from social relationships and a restricted range of emotions	Discomfort in close relationships, cognitive/perceptual disturbances, eccentric, inflexible
Treatment	Patients avoid treatment. Offer CBT; low-dose, short course antipsychotics; short-term BDZs during extreme stress.	Supportive therapy; social skill and assertiveness training SSRI for anxiety and depression	Supportive and cognitive behavioral therapy Low-dose, short-course antipsychotics

Table 16-11: Cluster B Personality Disorder Characteristics

	Antisocial	Borderline	Histrionic	Narcissistic
DSM-5 Descriptor	Disregard for and violation of the rights of others	Instability in interpersonal relationships and self-image Marked impulsivity	Excessive emotionality and attention seeking	Grandiosity Need for admiration Lack of empathy
Comorbidities	Anxiety Substance use disorder Somatization disorder Pathologic gambling Other Cluster B characteristics	Substance use disorder Bulimia PTSD Suicide (10–15%) Depression Other Cluster B characteristics	Somatoform disorders Substance use disorder Psychosis Other Cluster B characteristics	Anorexia nervosa Substance use disorder Depression Other Cluster B characteristics
Development	Variable: Symptoms and criminal activity decrease after 30 years of age with shift to somatization.	Dissociation or transient psychosis with stress, trauma, or substances	Variable with age Aging may threaten self-image and worsen prognosis.	Chronic and difficult to treat Prone to severe midlife crises Aging and medical illness are narcissistic injuries.
Risk Factors	Early childhood sexual, emotional, or physical abuse and/or neglect			
Treatment	Rarely seek treatment Hard to treat: deceitful and lack motivation Treat with CBT. Treat comorbid psychiatric disorders with medication.	SSRI, dialectical behavioral therapy, antipsychotics, mood stabilizer Avoid BDZs. Treat comorbid psychiatric disorders.	Limited response—refer to Borderline column (left) and Narcissistic column (right). SSRI for anxiety and irritability	Patients avoid treatment. Individual CBT

Table 16-12: Cluster C Personality Disorder Characteristics

	Avoidant	Obsessive-Compulsive	Dependent
DSM-5 Descriptor	Social inhibition Feelings of inadequacy Hypersensitivity to negative evaluation	Preoccupation with orderliness, perfectionism, and control	Submissive and clinging behavior related to excessive need to be taken care of
Treatment	Supportive and cognitive behavioral therapy SSRI for depression and anxiety	Unaware of disorder and unlikely to seek treatment Offer CBT with skills training. Treat comorbid psychiatric issues.	Supportive therapy; CBT with assertiveness skill training Treat comorbid psychiatric disorders.

ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD)

PREVIEW | REVIEW

- What is attention deficit hyperactivity disorder (ADHD)?
- What is the workup for ADHD?
- What is the treatment for ADHD?

OVERVIEW

ADHD is a condition that affects some individuals starting in preschool and can persist into or develop in adulthood. It is characterized by diminished attention, increased hyperactivity/impulsivity, or a combination of both.

ADHD occurs in 5% of children and 2–7% of adults and has a male-to-female prevalence of 1.6:1 in adults. Females typically present with inattention. Individuals have a > 50% chance of ADHD if either parent has it.

The disorder affects individuals in most cultures around the world, but identification of ADHD for African Americans and Hispanics in the U.S. tends to be lower than for Whites, possibly as a result of diagnostic practices, cultural variation, or interpretation of children's behaviors.

DIAGNOSIS

According to the *DSM-5*, the diagnosis of ADHD is based on symptoms during childhood and adolescence. As such, diagnosing ADHD in adults requires the clinician to examine various features of their behavior; there are different expressions in adults of the same underlying behaviors that exist in children. Adults display hyperactivity (e.g., verbal outbursts; poor task control, memory, self-inhibition), impulsivity (e.g., labile moods, labile speech, traffic violations, easily frustrated), and inattention (e.g., difficulty with prolonged focus, prioritizing, organizing, time management, completion of tasks).

ETIOLOGY

ADHD is a heterogeneous neurodevelopmental disorder with multiple possible etiologies, including environmental, genetic, CNS insults, neuroanatomical, and neurochemical. Neuroimaging findings include smaller volumes of the cerebrum, cerebellum, corpus callosum, frontal lobes, and caudate. Aberrant dopamine and norepinephrine signaling has been found in the nucleus accumbens; frontal, prefrontal, and parietal lobes; and cerebellum.

DEVELOPMENT AND COURSE

Inattention starts in elementary school, impairs daily functioning, and can persist into or even develop in adulthood. Hyperactivity is noted in preschool and decreases

as the individual progresses into adolescence and adulthood; however, the internal feeling of hyperactivity (e.g., restlessness, impatience, jitteriness), poor planning, and impulsivity may persist. Children may develop conduct disorder in adolescence and antisocial personality disorder in adulthood, with possible substance use disorder and incarceration. ADHD is associated with reduced academic and occupational performance and achievement and a higher level of unemployment. Family and peer relationships are strained due to rejection, neglect, or teasing as the individuals are viewed as lazy, irresponsible, or uncooperative as a result of inattention. Hyperactivity and impulsivity are associated with accidental injury, most notably from car accidents in adulthood.

While the above-stated symptoms and comorbidities can develop in or persist into adulthood, they may also ameliorate or disappear. An estimated 20% of children with ADHD maintain a diagnosis into adulthood.

ASSESSMENT

In adults, the World Health Organization (WHO) uses the Adult ADHD Self-Report Scale, consisting of 18 items and using a 5-point scale for each item, to assess ADHD.

TREATMENT

Treatment for ADHD includes psychotherapy and in some cases, use of stimulant medications, such as methylphenidate and amphetamines. Atomoxetine (an SNRI) is also effective and has less potential for abuse. Clonidine is also used to treat hyperactivity. Monitor ongoing medical therapy to ensure that doses are decreased as symptoms diminish with age.

EATING DISORDERS

ANOREXIA NERVOSA (AN)

PREVIEW | REVIEW

- What is anorexia nervosa (AN)?
- True or false? AN has the highest morbidity and mortality rate of all psychiatric disorders.

AN is a potentially life-threatening eating disorder characterized by the inability to maintain a normal weight, a devastating fear of weight gain, dietary habits that prevent weight gain, and a distortion of body weight and shape experienced over the past 3 months.

AN presents with 2 peaks of age in females: at 12–14 years and 18 years of age. Similar peak age of risk appears likely in males. There are some cases diagnosed after 40 years of age. AN affects 0.3–1% of females and 0.1–0.3% of males and is found in all developed countries and in all socioeconomic classes. There is a 50% concordance rate in monozygotic twins and 10% rate for dizygotic twins.

There are 2 subtypes of AN:

- 1) Restricting: weight loss accomplished by fasting and/or excessive exercise
- 2) Binge-eating/purging type: recurrent episodes of binge-eating or purging behavior (i.e., self-induced vomiting, laxatives, diuretics, enema misuse)

Note: There is crossover with these subtypes.

Diagnosis

Diagnosis is clinical. Per the *DSM-5*, typically, diagnosis of AN consists of a combination of the following:

- **Weight loss** has resulted in a weight at least 15% < ideal.
- Patients have a preoccupation with food, have an intense fear of becoming fat, and have persistent behavior patterns that interfere with weight gain.
- There are disturbances in the way body weight and size are experienced. These patients have a distorted self-image, and despite often extreme weight loss they not only deny thinness but also complain of feeling fat. This is a soft criterion because many young individuals have a similar self-perception, although without the weight loss.
- Anorexic patients often purge. This can lead to hypokalemic, hypocalcemic metabolic alkalosis due to vomiting—similar to patients with bulimia nervosa.

Severity: The minimum level of severity is based on the WHO categories for thinness in adults (Table 16-13). Use body mass index (BMI) percentiles for children and adolescents. **Caveat:** An increase in symptom severity reflects the degree of functional disability and the need to consider supervision.

Table 16-13: WHO BMI Severity Scale for Eating Disorder

Severity	BMI (kg/m ²)
Mild	17–18.49
Moderate	16–16.99
Severe	15–15.99
Extreme	< 15

BMI: calculated as weight in kilograms/height in meters²; per WHO/CDC, 18.5 kg/m² is the lower limit of normal body weight.

Presentation

Individuals typically present with the encouragement of family members who have noted marked weight loss or when the individual has somatic and psychological distress as a result of starvation. They rarely present with complaint of weight loss. The intense fear of becoming fat is usually not alleviated by weight loss, and concern about weight gain often increase as weight falls. Individuals may not recognize/acknowledge a fear of weight gain. Gather

history regarding patient behaviors to prevent weight gain, monitor patient's evaluation of body weight, perform a physical exam, and analyze laboratory findings.

Diagnostic markers and physical exam disturbances seen in AN are listed in Table 16-14.

Table 16-14: Diagnostic Markers and Physical Exam Disturbances in Anorexia Nervosa

System	Symptoms
Serum chemistry	Dehydration: blood urea nitrogen elevation
	Hepatic enzyme elevation
	Low Mg ²⁺ , low zinc, low phosphate, high amylase, and low Na ⁺ (with diuretic or laxative abuse)
	Metabolic alkalosis, hypochloremia, and hypokalemia (due to vomiting)
	Metabolic acidosis (due to laxative abuse)
Hematologic	Pancytopenia, anemia
Dental	Caries, tooth enamel erosion
Endocrinologic	Parotid gland hypertrophy, low follicle-stimulating hormone and luteinizing hormone leading to hypogonadism (low estrogen/testosterone), amenorrhea, low leptin, hypothyroidism, hypercortisolemia
Cardiovascular	Sinus bradycardia, mitral valve prolapse, pericardial effusion, orthostatic hypotension, arrhythmias, prolongation of the QT _c
Gastrointestinal	Delayed motility, transaminitis, superior mesenteric artery syndrome, constipation
Renal	Insufficiency
Musculoskeletal	Low bone mineral density, resulting in osteopenia/osteoporosis with 50% fracture risk
Central nervous system	Metabolic encephalopathy (due to fluid and electrolyte disturbances), ventriculomegaly, headaches, seizures
Dermatologic	Emaciation, Russell sign (calluses on knuckles), acrocyanosis, lanugo (fine, downy hair), petechiae or ecchymoses (indicates bleeding diathesis), hypercarotenemia (yellowing of the skin), peripheral edema (during weight restoration or cessation of laxatives/diuretics)
Psychiatric	Depressed mood, social withdrawal, irritability, insomnia, diminished interest in sex, obsessive-compulsive features

Clinical Course

Adults have a longer duration of illness, and their clinical presentations demonstrate signs and symptoms of long-standing disorder. Many individuals have a period of changed eating behavior, increased physical activity, anxiety, and medication misuse prior to meeting full criteria.

Prognosis

Some individuals with AN recover fully after a single episode, with some exhibiting a fluctuating pattern of weight gain followed by relapse and others experiencing a chronic course over many years. Hospitalization may be required to restore weight and to address medical complications (see [Management](#)). Co-occurring conditions include depression, bipolar disorder, OCD, anxiety, and alcohol and substance use disorders. While some individuals remain functional socially and professionally, others demonstrate significant social isolation and/or failure to fulfill academic or career potential.

AN has the highest morbidity and mortality rate of all psychiatric illnesses; mortality rate is 5–10× > the general population. The higher mortality is a result of suicide (1 in 5 who attempt suicide complete it) or medical complications (the most common cause of mortality is due to cardiac complications and refeeding syndrome).

Management

A team approach, including psychiatrist, psychologist, and nutritionist/dietitian/gastroenterologist, is required. It is important to establish a supportive advisor role. Individuals are very resistant to psychotherapy, but outpatient supportive care often works just as well as inpatient therapy. Explain the dangers of starvation (such as sudden death), and set realistic, short-term goals for weight gain. Acknowledge the individual's perception, and counsel them that they are not getting fat as they gain weight.

Outpatient management includes taking weekly weight measurement, ensuring health is maintained, and confirming the patient has not developed bad eating habits. Treatment is long term, with frequent failures and setbacks.

Inpatient hospitalization is necessary for those with profound malnutrition ($\text{BMI} < 15 \text{ kg/m}^2$), cardiac dysfunction (e.g., bradycardia, hypotension, $\text{QT}_c > 0.499 \text{ ms}$), hypothermia, dehydration, and purging behaviors. The goal is to reestablish a normal eating pattern to encourage a 1–2 lb/week weight gain. Electrolyte and nutritional repletion must be undertaken slowly to avoid refeeding syndrome—cardiovascular collapse, starvation-induced hypophosphatemia, and dangerous fluctuations in Na^+ , K^+ , and Mg^{2+} levels. Repletion can be done orally or parenterally.

Medications includes fluoxetine after weight restoration and low-dose olanzapine to assist with ruminations, anxiety, and treatment-resistant individuals. Cyproheptadine, an appetite stimulant, may help a little. Do not use bupropion, as it can lower the seizure threshold. Cognitive behavioral and family therapy are used in conjunction with medications.

BULIMIA NERVOSA (BN)

PREVIEW | REVIEW

- What is the typical weight class for individuals with bulimia?
- What is the FDA-approved medication for bulimia?

BN is a type of eating disorder characterized by binge eating and purging—either with vomiting or with laxatives. It can be a variant of AN, and many bulimic patients have a history of anorexia in their past. Bulimic patients are typically 20–30 years of age (older than anorexic patients). These patients usually do **not** present with a BMI as low as patients with AN. Bulimia nervosa affects 1–1.5% of adolescent and young adult females, with a female-to-male ratio of 10:1. There are no racial differences, and it is inherited at a rate between 30% and 80%.

Diagnosis

Diagnostic criteria for BN from the *DSM-5* include:

- Recurrent episodes of binge eating: eating more than the average person in a 2-hour period, accompanied by a sense of loss of control
- Repetitive, inappropriate compensatory behaviors to avoid weight gain, such as excessive exercise, fasting, laxative use, and diuretic use
- Eating behavior occurs $\geq 1 \times/\text{week}$ for a period of 3 months.
- Body shape and weight influence self-evaluation. This does not occur with episodes of AN.

Individuals with BN typically are within the normal weight or overweight range ($\text{BMI} \geq 18.5$ and < 30 in adults). Individuals with bulimia restrict their total caloric consumption between eating binges.

Physical exam can show erosive skin lesions on the fingers where the teeth cause injury during attempts to induce vomiting (Russell sign). Dental erosions and salivary gland enlargement are also seen. The most common laboratory abnormalities are hypokalemia and metabolic alkalosis from vomiting and laxative use. Consider bulimia in young patients presenting with a Mallory-Weiss tear or severe gastroesophageal reflux disease.

Risk factors include weight concerns, low self-esteem, depressive symptoms, social anxiety disorder, childhood sexual/physical abuse, childhood obesity, early pubertal maturation, genetics, and occupation/hobbies requiring rapid weight gain and weight loss.

A comprehensive history and physical examination and laboratory tests can yield findings similar to those seen in AN (see [Table 16-14 on page 16-19](#)). Electrolyte, cardiac, gastrointestinal, and pulmonary symptoms are present in severe cases.

Workup is similar to that of AN.

Clinical Course

BN commonly begins in adolescence or young adulthood. Onset before puberty or after 40 years of age is uncommon. The binge eating frequently begins during or after an episode of stress or dieting to lose weight. The clinical course is chronic or intermittent with remissions after binge eating, but symptoms can wane, with or without treatment, after several years. 10–15% of individuals cross over from BN to AN and may also revert back to bulimia. Others may cross over to binge eating disorder, and treatment should be initiated for that disorder if it persists for > 3 months. The crude mortality rate for BN is nearly 2% per decade.

Management

Treatment is supportive, with the focus on slowly decreasing the amount of food eaten and decreasing the frequency of binge-eating episodes. As with AN, treatment is long term, with frequent failures and setbacks. Fluoxetine is the FDA-approved medication for BN and should be used in conjunction with CBT. Treat any comorbid psychiatric illnesses as well, and screen for suicide, as suicide risk is elevated. See [Anorexia Nervosa \(AN\)](#) on page 16-18 for indications for hospitalization.

SOMATIC SYMPTOM DISORDER AND RELATED DISORDERS

OVERVIEW

This category of disorders includes somatic symptom disorder, conversion disorder (a.k.a. functional neurological symptom disorder), and factitious disorder. Individuals who suffer from these disorders have somatic symptoms that cause much distress and impair daily functioning.

Hypochondriasis is no longer a recognized diagnosis.

SOMATIC SYMPTOM DISORDER

PREVIEW | REVIEW

- What symptoms suggest somatic symptom disorder?
- What are risk factors for somatic symptom disorder?
- What is the treatment of somatic symptom disorder?

Somatic symptom disorder is characterized by thoughts, feelings, or behaviors related to somatic symptoms. **Features suggesting this disorder versus**

a medical condition include involvement of multiple organ systems and a history of extensive workup with unremarkable physical examination and laboratory findings, all in the absence of psychiatric disorders. It has a female-to-male ratio of 10:1. Etiology is unclear but likely is multifactorial.

Diagnosis

The *DSM-5* diagnostic criteria for somatic symptom disorder describe somatic symptoms that are distressing or disruptive to daily life. Patients experience excessive thoughts, feelings, or behaviors related to somatic symptoms or health concerns, as evidenced by ≥ 1 of the following symptoms that last for ≥ 6 months:

- 1) Disproportionate and persistent thoughts about the seriousness of symptoms
- 2) Persistently high level of anxiety about health or symptoms
- 3) Excessive time and energy devoted to these symptoms or health concerns

Diagnosis is clinical. Take a careful history. Avoid high-risk or invasive tests during evaluation.

Risk Factors, Clinical Course, and Prognosis

Risk factors include mood and anxiety disorders (50%), childhood sexual abuse and neglect (30–70%), substance use disorder, and male relatives with antisocial personality disorder. The disorder is exacerbated in stressful situations and is more common in individuals with little education and a heightened attention to their bodies and response to pain. Symptoms start in adolescence with a chronic and fluctuating course, with symptoms lasting for decades. Prognosis is poor when the disorder persists for decades, whereby only 30% remit after 15 years. Individuals have high medical utilization (economic burden of \$30 billion per year), and symptoms persist if the individual feels misunderstood by medical staff. Individuals are subjected to unnecessary diagnostic examinations.

Treatment

The individual's primary care physician should be the primary contact. Schedule regular appointments (biweekly or monthly) to decrease emergency department visits, and choose 1 symptom to focus on during the appointment. Use nonpharmacologic therapies (e.g., heat, range-of-motion exercises) for medical issues, based on history and physical examination; avoid using narcotics for pain. Refer for CBT, and treat comorbid anxiety and depression with an SSRI or SNRI (if pain is an issue).

CONVERSION DISORDER

PREVIEW | REVIEW

- What are the diagnostic criteria for conversion disorder?
- Describe demographics for an individual with conversion disorder.
- What is the management of conversion disorder?

Conversion disorder (a.k.a. functional neurological symptom disorder) involves symptoms or deficits affecting voluntary motor or sensory function, suggesting a neurologic or general medical condition; however, after a thorough evaluation, no neurologic or medical explanation is found, or the examination findings are inconsistent with the complaint.

Diagnosis

The *DSM-5* diagnosis of conversion disorder includes:

- ≥ 1 symptoms of altered voluntary motor or sensory function
- Clinical findings providing evidence of incompatibility between the symptom and recognized neurological or medical conditions
- Significant distress caused by the symptom/deficit that is not better explained by another medical or mental disorder

Common examples of conversion symptoms include:

- Psychogenic nonepileptic seizures (PNES)
- Blindness; diplopia
- Pseudocyesis
- Unresponsiveness, paralysis
- Difficulty walking

Conversion disorder is more common in rural populations and in individuals with lower socioeconomic status, lack of education, low psychological sophistication, and a history of sexual or physical abuse. Individuals with this disorder deny emotional problems and resist consultation with psychiatry. Onset may be preceded by stress or trauma. Risk factors include dissociative and personality disorders. Panic, depressive, somatic symptom, personality, and neurologic/medical disorders co-occur with conversion disorder.

Workup and Differential Diagnoses

Organic etiologies must be excluded, and thorough medical and neurologic evaluations and appropriate diagnostic testing are warranted prior to diagnosing conversion disorder. See [Table 16-15](#).

Table 16-15: Workup of Conversion Disorder

Hemiparesis	MRI of brain
Psychogenic Nonepileptic Seizures	MRI of brain
	Electroencephalography (EEG)
	Prolonged video-EEG monitoring
	Echocardiography
	Holter monitor
Psychogenic Movement Disorders	Tilttable test
	Prolactin level 30 minutes after the event
	MRI of brain
	24-hour urine studies for copper, serum ceruloplasmin, and slitlamp examination for evidence of Kayser-Fleischer rings if Wilson disease is suspected
	Thyroid-secreting hormone (TSH), thyroid peroxidase antibodies, thyroglobulin antibodies
	CBC count with smear for acanthocytes
	Erythrocyte sedimentation rate (ESR), antinuclear antibodies (ANA), anticardiolipin antibody, lupus anticoagulant
	HIV antibody, Lyme antibody, antistreptolysin O (ASO) antibody
	Human chorionic gonadotropin (hCG)
	Urine and serum drug toxicology screens
	Drug levels (e.g., antiseizure medications, digoxin)

The diagnosis of conversion disorder can be made in the presence of another mental and medical disorder. Neurological disease is the main differential diagnosis. See [Table 16-16](#) for a list of other differential diagnoses to consider. Reassess if symptoms progress.

Clinical Course and Prognosis

Symptoms of conversion disorder are self-limiting and do not lead to physical changes or actual disabilities—but unnecessary diagnostic or therapeutic interventions can cause morbidity and a decreased quality of life. Still, conversion symptoms may affect disability similar to that experienced by those with comparable medical diseases. Further, practitioners may limit driving privileges in patients with PNES. While maladaptive personality traits, comorbid physical disease, and the receipt of disability benefits can be negative prognostic factors, short duration of symptoms and acceptance of the diagnosis are positive prognostic factors.

Table 16-16: Differential Diagnoses for Conversion Disorder

Factor	Example
Neurologic (high on differential list)	Epileptic seizures
Environmental exposures	Chemicals or heavy metals
Syncope	Cardiogenic, hypovolemic, orthostatic, convulsive
Movement disorders	Tics, startle attacks, tremors, myoclonus
Sleep disorders	Narcolepsy, night terrors, restless legs syndrome (RLS), rapid eye movement (REM) sleep behavioral disorder
Other psychiatric disorders	Depressive disorders, anxiety disorders, panic disorder, PTSD, dissociative disorders, psychotic disorders, other somatic disorders, intermittent explosive disorder
Medications	Toxicity (e.g., tremors from high levels of valproic acid); akathisia (from neuroleptics and possibly antidepressants); extrapyramidal symptoms from neuroleptics; withdrawal from medications such as BDZs, opiates, and occasionally antidepressants such as SSRIs or SNRIs
Drugs of abuse	Inhalants, hallucinogens
Malingering disorder	e.g., a man demands you fill out disability paperwork for back pain but posts pictures online of himself skiing that night.
Factitious disorder	e.g., a nurse repeatedly presents to the emergency department with hypoglycemia; C-peptide reveals she is injecting insulin.

Management

Develop a good therapeutic alliance with frequent check-ins to reassure patients that testing indicates no underlying neurological disorder and that the prognosis is good to avoid emergency department visits and unnecessary invasive diagnostic and therapeutic interventions. CBT, stress management training, and treatment of comorbid psychiatric illnesses may help reduce symptoms. The affected body part or physical function may need physical or occupational therapy until the symptoms dissipate.

FACTITIOUS DISORDER

PREVIEW | REVIEW

- What is the primary demographic for factitious disorder?
- How does factitious disorder differ from malingering?
- What responsibility do physicians have when suspecting factitious disorder imposed on another?

Factitious disorder (a.k.a. Munchausen syndrome) is the falsification of medical or psychological signs and symptoms in oneself or others for the principal purpose of assuming the sick role. Persons in the medical field and the unmarried are more likely to have factitious disorder (imposed on self). Factitious disorder imposed on another (a.k.a. Munchausen syndrome by proxy) primarily victimizes the pediatric population (though the perpetrator receives the diagnosis). The exact prevalence is unknown as a result of the deceit, but it is estimated that 1% of individuals who present to the hospital meet the criteria for factitious disorder.

Factitious disorder is divided into the following 2 types:

- 1) Factitious disorder
- 2) Factitious disorder imposed on another (a.k.a. factitious disorder by proxy)

Diagnosis

The *DSM-5* provides the following criteria for factitious disorder (imposed on self):

- Falsification of physical or psychological signs or symptoms, or induction of injury or disease, associated with identified deception
- Self-presentation to others as ill, impaired, or injured
- Deceptive behavior is evident in the absence of obvious secondary gain (in contrast to malingering, where the patient feigns symptoms for the purpose of receiving secondary gain).
- Behavior is not better explained by another mental or psychotic disorder, such as delusional disorder.

The *DSM-5* provides the following criteria for factitious disorder imposed on another:

- Falsification of physical or psychological signs or symptoms, or induction of injury or disease, in another, associated with identified deception
- Victim is presented to others as ill, impaired, or injured.
- Deceptive behavior is evident even in the absence of obvious secondary gain (unlike malingering).
- Behavior is not better explained by another mental or psychotic disorder, such as delusional disorder.

The perpetrator, not the victim, receives this diagnosis.

Factors suggesting an illness is factitious:

- Employment/education in medical field
- Atypical or dramatic presentation
- Inconsistencies between history and physical exam findings
- Knowledge of textbook presentation of illness
- Extensive or difficult-to-access medical record
- Admission to multiple hospitals or working with multiple doctors
- Pseudologia fantastica (i.e., compulsive lying)

Physical exam findings suggesting an illness is factitious:

- Inconsistent physical exam findings
- Multiple surgical scars
- Self-induced physical signs
- Physical signs that appear worse during physical exam rather than during observation with ancillary staff
- Absent signs of dehydration when complaining of diarrhea or vomiting

The diagnosis is given when the individual is taking surreptitious actions to misrepresent, simulate, or cause signs or symptoms of illness/injury in the absence of obvious external rewards. Examples of falsification of symptoms in factitious disorder include:

- Manipulating samples (e.g., adding blood to urine)
- Ingesting substances to induce abnormal lab results (e.g., insulin)
- Physically injuring or inducing illness in themselves/others (e.g., self-injecting fecal matter)
- Falsifying medical records

Development and Course

Factitious disorder is usually in intermittent episodes, but recurrent episodes result in a lifelong course. Onset is usually in early adulthood after hospitalization for a medical or mental health condition. When imposed on another, the disorder may begin after hospitalization of the individual's child or other dependent.

Assessment

Falsification of symptoms can be suspected when the patient has excessively high rates of hospital utilization (often different facilities), multiple drug allergies, numerous surgical scars, and signs and symptoms that do not add up clinically. If factitious disorder is suspected, gather collateral evidence, avoid excessive diagnostic tests, and perform tests to confirm suspicion (e.g., exogenous insulin injections lead to increased serum insulin/C-peptide ratios; test composition of kidney stones).

Treatment

There is no cure for factitious disorder, but identifying the disorder early can reduce morbidity and mortality. Do not confront the individual singly, but approach him or her in a supportive fashion with laboratory data. Refer most to CBT/family therapy; for motivated individuals and those with suicidal ideation, refer to psychiatric inpatient hospitalization. Treat comorbidities. Adult or child protective services must be alerted in the case of factitious disorder imposed on another. Legal issues may ensue if the individual makes legal threats or is breaking laws.

GENDER DYSPHORIA

PREVIEW | REVIEW

- What is gender identity?
- What is gender dysphoria?
- What are the mandatory criteria for gender dysphoria?

OVERVIEW

Important definitions:

- **Gender identity**—an individual's perception and self-awareness of being male or female
- **Gender dysphoria**—occurs when a person feels distress (conflict) because the gender assigned at birth (i.e., natal gender) is contrary to the one with which the individual identifies
- **Transgender**—describes an individual whose gender identity differs from the sex the person was assigned at birth. It is a term used by members of the transgender community to describe themselves.
- **Transsexual**—an older medical term that describes a person with the biological characteristics of one sex who identifies as the other sex and is taking action to align their body with their gender identity. This term is offensive to some members of the transgender community and the medical community is moving away from using this term.
- **Gender nonconformity**—a variation from the cultural norms of gender behavior or expression
- **Sexual orientation**—a term used to designate an individual's desire for intimate, emotional, and/or sexual relationships with people of the same gender/sex, another gender/sex, or multiple genders/sexes. It is a concept separate from gender identity.

Evidence confirms that gender nonconformity is likely due to structural brain changes. Similarly, biologic and genetic factors are gaining prominence as the etiology for same-sex attraction. Therefore, neither gender identity nor sexual orientation is considered a "choice."

Prevalence of gender dysphoria in the U.S. is 0.3–0.5%, and it usually presents in late puberty or adulthood. Adults often report gender incongruity before puberty. While the exact percentages are not known, there is an increased concordance of transgender individuals in monozygotic twins when compared with dizygotic same-sex twins. In addition, some degree of gender dysphoria may be heritable; so, a family history of gender dysphoria may inform a diagnosis.

Because transgender individuals are a heterogeneous group, keep in mind that each individual experiences gender conflict uniquely.

DIAGNOSIS

Expression of gender dysphoria varies with age, and thus there are separate criteria sets for children versus adolescents/adults.

DSM-5 diagnosis for gender dysphoria in adolescents and adults requires marked incongruence between the patient's experienced/expressed gender and assigned gender lasting ≥ 6 months. It must also cause significant distress or impairment and include ≥ 2 of the following 6 criteria:

- 1) Incongruence between one's experienced/expressed gender and primary or secondary sex characteristics (mandatory)
- 2) Strong desire to be rid of primary and/or secondary sex characteristics due to this incongruence
- 3) Strong desire for primary and/or secondary sex characteristics of other gender
- 4) Strong desire to be a different gender
- 5) Strong desire to be treated as the other gender
- 6) Strong conviction that one has the typical feelings and reactions of the other gender

The condition must cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

FEATURES

Distress and impairment vary with age. Adolescents and adults express extreme anatomic dysphoria resulting in impairment in social functioning (e.g., school or work absenteeism, depression, anxiety, substance use). Individuals who identify as transgender girls/women (despite being assigned male gender at birth) can display feminine behavior with little interest in male pursuits. Likewise, individuals who identify as transgender boys/men (despite being assigned female gender at birth) can display masculine behavior with little interest in female pursuits, often referred to as tomboys. The individual may bind the penis or breasts to make them less visible.

Adolescents and adults with gender dysphoria are at an increased risk for suicidal ideation/attempts (40%). They deal with comorbid anxiety (31%) and depression.

MANAGEMENT

The 2012 World Professional Association for Transgender Health standards of care strive to provide clinicians with the best available expert consensus on care, including therapeutic approach, options for treatment, social support, psychotherapy, hormonal therapy (including its risks), and surgery. Keep in mind the following points:

- Gender dysphoria treatment should involve a multidisciplinary team.
- People with gender dysphoria should have access to high-quality care without unnecessarily long waits.
- People with gender dysphoria have a right to psychotherapy and counseling as part of their treatment.

- Treatment should recognize the preferences, needs, and circumstances of the particular patient.
- Treatments that have been initiated for adolescents should continue into adulthood without interruption.

The goal of gender dysphoria treatment is to help alleviate the patient's acute feelings of distress generated by the dissonance between natal gender and gender identity. Treatment includes therapy (individual and family), nonpharmacologic therapies (e.g., communication specialists), gender confirmation surgery, and pharmacologic therapy (i.e., hormones). Involve endocrinologists in assisting with hormone therapy. Male sex characteristics can be suppressed with hormones, including medroxyprogesterone, spironolactone, flutamide, and luteinizing hormone-releasing hormone (LHRH) agonists in transgender women, while ethinyl estradiol and conjugated estrogen can be used to feminize the body (e.g., breasts, body fat). Testosterone promotes facial- and body-hair growth in transgender men.

Satisfaction rate of gender confirmation surgery is 80%.

SLEEP DISORDERS

INSOMNIA

PREVIEW | REVIEW

- What are the diagnostic criteria for insomnia?
- What is the most common symptom of insomnia?
- What medical and psychiatric illnesses are comorbid with insomnia?
- What is the 1st line treatment for insomnia?

Insomnia is defined as repeated difficulty with sleep initiation, maintenance, consolidation, or quality that occurs despite adequate time and opportunity for sleep, resulting in daytime impairment. It is the most prevalent of all sleep disorders, with 30–60% of individuals reporting some symptoms and 10–15% experiencing chronic daytime impairments. It is slightly more prevalent in females, with a female-to-male ratio of 1.44:1. Approximately 40–50% of individuals with insomnia also have a comorbid mental disorder. African Americans have a higher prevalence and greater severity of sleep-disordered breathing (e.g., sleep apnea), while Whites report more symptoms of insomnia.

Diagnosis

DSM-5 diagnostic criteria for insomnia include dissatisfaction with sleep quantity or quality associated with > 1 of the following:

- Difficulty initiating sleep
- Difficulty maintaining sleep, characterized by frequent awakenings or problems returning to sleep after awakenings
- Early-morning awakening with inability to return to sleep

The sleep disturbance causes clinically significant distress or impairments in daily functioning; is present for ≥ 3 months and occurs $\geq 3\times/\text{week}$; occurs despite adequate opportunity for sleep; and is not due to another sleep-wake disorder (e.g., narcolepsy, a breathing-related sleep disorder, a parasomnia, a circadian rhythm sleep-wake disorder), a substance, or another mental disorder.

A diagnosis of insomnia disorder is for those individuals with significant daytime distress/impairment related to their nighttime sleep difficulties, including impairment in cognition (i.e., attention, concentration, memory) and mood with fatigue and daytime sleepiness. Difficulty maintaining sleep is the most common symptom of insomnia.

Different manifestations of insomnia can occur at different times of the sleep period:

- **Sleep onset insomnia** (or **initial insomnia**): difficulty initiating sleep at bedtime (≥ 30 minutes)
- **Sleep maintenance insomnia** (or **middle insomnia**): frequent or prolonged awakenings throughout the night (up to 30 minutes)
- **Late insomnia**: early-morning awakening with an inability to return to sleep (30 minutes before the scheduled time)

See Table 16-17 for primary sleep disorders causing insomnia and the sleep phases they affect. Table 16-18 shows the international classification of sleep disorders.

Table 16-17: Primary Sleep Disorders Causing Insomnia and Sleep Phase Affected

Primary Sleep Disorder	Sleep Phase Affected
Restless legs syndrome (RLS)	Sleep onset insomnia
Periodic limb movement disorder (PLMD)	Sleep maintenance insomnia
Obstructive sleep apnea	Multiple awakenings or sleep maintenance difficulties
Circadian rhythm disorder	Sleep maintenance insomnia

Insomnia is a clinical diagnosis. Perform the following diagnostic studies to clarify comorbid disorders:

- Studies for hypoxemia (cardiopulmonary cause of insomnia)
- Actigraphy and iron studies to rule out PLMD and RLS
- Polysomnography and daytime multiple sleep latency testing (MSLT) to rule out sleep apnea

Risk Factors and Comorbidities

Risk factors for insomnia include female gender, increased age, depression, unemployment, economic inactivity, and widowed, divorced, or separated status. Individuals suffering from insomnia are $10\times$ and $17\times$ more likely to suffer from depression and anxiety, respectively, than counterparts without insomnia. Persistent insomnia represents a risk factor/early symptom of subsequent **bipolar disorder**.

Table 16-18: International Classification of Sleep Disorders

Type of Insomnia	Description
Adjustment insomnia	Sleep disturbance due to an acute stressor Sleep improves with resolution of acute stressor or with adaptation.
Idiopathic insomnia	No identifiable etiology Onset during infancy or early childhood Chronic course
Inadequate sleep hygiene	Activities/behaviors that increase arousal or decrease sleep propensity (e.g., TV- and clock-watching, late night snacks)
Paradoxical insomnia	Sleep misperception Patient reports minimal or no sleep during most nights. No daytime napping or impairment of daytime functioning Normal sleep architecture and quality during sleep study
Psychophysiologic insomnia	Associated with excessive worrying leading to tension and anxiety May take pills or drink alcohol to assist with sleep

Individuals with insomnia may misuse medications or alcohol to help with nighttime sleep, anxiolytics to combat tension or anxiety, and caffeine or other stimulants to combat excessive fatigue. Substance use can progress to substance use disorder.

Medical comorbidities include diabetes, coronary heart disease, chronic obstructive pulmonary disease (COPD), arthritis, fibromyalgia, and other chronic pain conditions.

Assessment

The American Academy of Sleep Medicine (AASM) 2017 guidelines for the assessment of insomnia include:

- A general medical and psychiatric questionnaire to detect comorbid disorders
- A sleepiness assessment, such as the Epworth Sleepiness Scale (ESS)
- A 2-week sleep log to define sleep-wake patterns and their variability

Sleep history:

- Timing of insomnia
- Patient's sleep habits (i.e., sleep hygiene)
- Presence or absence of symptoms of sleep disorders associated with insomnia (i.e., RLS, sleep apnea)
- A medical*, family, social, and psychiatric history; physical exam*; and medication reconciliation**

* Pay attention to history and physical exam findings to rule out medical causes of insomnia or daytime fatigue, including head and neck exam (sleep apnea), neurologic exam (e.g., RLS, PLMD), or lung exam (e.g., asthma, COPD).

** Certain medications can cause insomnia. These include SSRIs (e.g., escitalopram, fluoxetine); β -blockers by blocking melatonin; α -blockers (e.g., doxazosin, tamsulosin) by decreasing rapid eye movement (REM) sleep; ACE inhibitors by increasing bradykinins; bronchodilators; decongestants (e.g., pseudoephedrine); steroids; stimulants (e.g., caffeine, nicotine, amphetamines, 3,4-methylenedioxymethamphetamine [MDMA], energy drinks); and over-the-counter and herbal remedies.

Prognosis

Treatment of insomnia can improve an individual's quality of life, function, and health perception. Individuals with insomnia are at an increased risk of depression, anxiety, motor vehicle accidents (2 $\times$ the risk), poor cognition and memory, stress, mortality (with < 5 hours nightly; cardiovascular disease), impaired social and occupational performance, and an absenteeism rate that is 10-fold > peers without sleep disturbances. Furthermore, insomnia is associated with higher health care use, including a 2-fold higher frequency of hospitalizations and office visits. The estimated annual cost of insomnia is \$12 billion for health care and \$2 billion for sleep-promoting agents.

Management

1st line therapy for insomnia per AASM guidelines is CBT to improve sleep quality and daytime impairments. The AASM published updated pharmacologic guidelines in 2017.

Medications and therapy are noted in Table 16-19.

Avoid medications that could exacerbate medical issues (e.g., avoid BDZs in elderly patients because of the potential worsening of dementia and/or delirium). Advise patients on side effects and addictive potential.

NARCOLEPSY

PREVIEW | REVIEW

- What is the pentad of narcolepsy?
- What triggers cataplexy?
- How is narcolepsy diagnosed?

Narcolepsy is a chronic sleep disorder caused by the brain's inability to regulate the sleep-wake cycle. Narcolepsy-cataplexy affects 0.02–0.04% of the general population and affects both genders. Monozygotic

twins are 25–32% concordant for narcolepsy, and the prevalence of narcolepsy is 1–2% in 1st degree relatives. It is thought to result from genetic predisposition, abnormal neurotransmitter functioning and sensitivity, and abnormal immune modulation. Narcolepsy manifests as a **pentad** of symptoms:

- Excessive daytime sleepiness
- Cataplexy
- Hypnagogic/hypnopompic hallucinations
- Sleep paralysis
- Disturbed nocturnal sleep

Clinical Features

Excessive daytime sleepiness (EDS) is the primary symptom of narcolepsy. It must persist for at least 3 months for a diagnosis of narcolepsy.

There are multiple modalities for evaluating EDS. They include:

- Sleep history
- Sleep diary
- Subjective measures of sleepiness (e.g., ESS)
- MSLT (mean sleep-onset latency < 8 min and 2 sleep-onset REM periods)
- Maintenance of wakefulness test (mean sleep-onset latency < 40 min)

Severe EDS leads to involuntary paroxysms of falling asleep without warning (i.e., sleep attacks) during activities such as driving, eating, or talking. Cataplexy is a condition of diminished responsiveness usually characterized by a trance-like state and constantly maintained immobility. It is triggered by emotions (such as laughing or anger) and can be as subtle as partial loss of tone (e.g., head nodding, knee buckling) and as severe as falling down. Respiratory and extraocular muscles are spared in narcolepsy. Sleep paralysis is the inability to move upon waking. It is accompanied by hypnagogic (going to sleep) hallucinations and is relieved by sensory stimuli, such as touching or talking to the person. Co-occurring disorders include bipolar, depressive, and anxiety disorders; psychosis; and sleep apnea.

Diagnosis

Per the *DSM-5*, a diagnosis of narcolepsy requires recurrent episodes of irrepressible need to sleep, lapsing into sleep, or napping occurring within the same day. These must have been occurring $\geq 3\times$ /week over

Table 16-19: Treatments for Insomnia

Sedating Antidepressants	Sedative-Hypnotics	Agonists	Other
Trazodone Nortriptyline Amitriptyline Doxepin Mirtazapine	Short- and intermediate-acting BDZs (e.g., triazolam, temazepam, estazolam)	Melatonin receptor agonists (e.g., ramelteon) Orexin receptor agonists (e.g., suvorexant) Benzodiazepine receptor agonists (e.g., eszopiclone, zaleplon, zolpidem)	CBT (1 st line) Sleep hygiene Dietary modification Exercise Acupuncture

the past 3 months. There also must be the presence of ≥ 1 of the following:

- Episodes of cataplexy occurring at least a few times per month
- Episodes of sudden bilateral loss of muscle tone with maintained consciousness that is precipitated by laughter or joking
- In children, or within 6 months of onset in any individuals, spontaneous grimaces or jaw-opening episodes with tongue thrusting or a global hypotonia, without any obvious emotional triggers
- Cerebral spinal fluid (CSF) hypocretin deficiency (< 110 pg/mL)
- REM sleep latency ≤ 15 minutes, or a mean sleep latency ≤ 8 minutes and ≥ 2 sleep-onset REM periods

Narcolepsy with cataplexy can be diagnosed by history alone. If cataplexy is absent, perform a sleep study followed by MSLT (sleep latency of ≤ 8 minutes and also to rule out other sleep disorders). It can also be diagnosed by hypocretin CSF levels of ≤ 110 pg/mL.

Differential Diagnoses

See Table 16-20 for narcolepsy differential diagnoses.

Table 16-20: Differential Diagnoses for Narcolepsy

Signs / Symptoms	Discussion Points
Hypersomnolence	Longer and less disrupted nocturnal sleep Little/no dreaming during daytime naps Greater difficulty awakening Longer and less refreshing daytime sleep episodes More persistent daytime sleepiness
Major depressive disorder	Cataplexy not present MSLT is normal.
Movement disorder	Cataplexy can be misdiagnosed as chorea or pediatric autoimmune neuropsychiatric disorder associated with <i>Streptococcus</i> infection.
ADHD	Sleepiness can cause aggression and inattention, leading to this diagnosis.
Seizures	Misdiagnosed with cataplexy Not triggered by emotions Hurts self with falling Rule out with EEG.
Psychosis	Vivid hypnagogic hallucinations Stimulant treatment can cause hallucinations. Rule out narcolepsy before diagnosing schizophrenia.
Conversion disorder (a.k.a. functional neurological symptom disorder)	Unusual triggers present May report dreaming and sleeping, but MSLT is normal. Pseudocataplexy can occur, but reflexes are normal.

Management

The treatment of narcolepsy includes sleep hygiene and stimulants, including methylphenidate, modafinil, armodafinil, and dextroamphetamines. Medications for cataplexy include γ -hydroxybutyrate (GHB; 1st line) and antidepressants, which are REM-suppressing agents.

COMPLICATIONS OF DRUG THERAPY

OVERVIEW

Beware of the possible complications of drug therapy:

- **Extrapyramidal symptoms** occur most often with haloperidol and are a constellation of symptoms that include the following:
 - Acute dystonia—intermittent but sustained spasms and torsion of the head and neck; it is treated with cessation of the medication and IV/IM diphenhydramine or benztropine.
 - Akathisia—sensation of motor restlessness associated with a strong desire to move the lower extremities (highest with aripiprazole)
 - Parkinsonism—rigidity, bradykinesia, tremor, masked facies, shuffling gait
 - Tardive dyskinesia—involuntary movements of the mouth, tongue, upper extremities
- **Anticholinergic effects**—low-potency antipsychotics (chlorpromazine and clozapine)
- **Endocrinologic:**
 - Weight gain, Type 2 diabetes mellitus, dyslipidemia (highest with quetiapine, olanzapine, and clozapine)
 - Hyperprolactinemia and gynecomastia with atypical antipsychotics, especially risperidone
- **Hematologic**—leukocytosis, leukopenia, agranulocytosis with clozapine
- **Ophthalmologic:**
 - Glaucoma
 - Pigmentary retinopathy—can cause blindness
- **Gastrointestinal**—sialorrhea (excessive drooling) with clozapine
- **Cardiovascular:**
 - QT_c prolongation, torsades de pointes, and sudden death seen with haloperidol, chlorpromazine, and atypical antipsychotics (e.g., ziprasidone, risperidone, olanzapine); sudden death with stimulants
 - Orthostasis with chlorpromazine
 - Arrhythmia
 - Myocarditis or cardiomyopathy (rare but serious) with clozapine
 - Hypertension and tachycardia with stimulants
- **Renal:**
 - Hyponatremia (i.e., carbamazepine, thiazide diuretics, MDMA)
 - Syndrome of inappropriate antidiuretic hormone secretion (i.e., fluoxetine)

- **Mental health:**
 - Increased risk of suicide with stimulants and antidepressants
 - Risk of mania with antidepressants in individual with bipolar disorder

NEUROLEPTIC MALIGNANT SYNDROME (NMS)

PREVIEW | REVIEW

- What is neuroleptic malignant syndrome (NMS), and what is the etiology?
- Describe the clinical features of NMS.
- What are complications of NMS?
- What is the treatment of NMS?

NMS is a rare but life-threatening reaction occurring shortly after a marked reduction of dopamine activity, either from the blockade of dopamine receptors or the withdrawal of dopaminergic agents, such as those used for treating Parkinson disease. It is characterized by muscular rigidity, fever, and autonomic dysfunction. It affects 0.07–2.2% of individuals taking neuroleptics.

Diagnosis

While NMS can start up to 2 weeks after starting a neuroleptic or withdrawal of anti-Parkinson agents, it can also occur several years into therapy. The diagnosis is **clinical** and based on historical, physical, and laboratory findings. Symptoms typically evolve over 24–72 hours.

A 2011 multispecialty consensus for NMS diagnosis provides the following priority scoring system (no absolute score has been defined):

- Known exposure or recent withdrawal of dopaminergic in past 72 hours—20 points
- Elevated temperature $> 100.4^{\circ}\text{F}$ (38.0°C)—18 points
- Muscle rigidity—17 points
- Altered mental status—13 points
- 4-fold elevation in creatine kinase (CK; a.k.a. CPK)—10 points
- Labile sympathetic nervous system—10 points; need 2 of the following:
 - Elevated systolic or diastolic blood pressure (BP) $\geq 25\%$ above baseline
 - Fluctuation of diastolic BP ≥ 20 mmHg or systolic BP ≥ 25 mmHg
 - Sweating
 - Bladder incontinence
- Heart rate $\geq 25\%$ baseline and respiratory rate $\geq 50\%$ baseline—5 points
- No other cause identified—7 points

Other laboratory findings include:

- Increased: AST and ALT, hyperkalemia, hyperphosphatemia, protein, alkaline phosphatase, platelets, lactate dehydrogenase (LDH), uric acid, myoglobin, CSF protein
- Decreased: Low Ca^{2+} , low serum iron

Remember the mnemonic **FEVER** for NMS:

- **F**ever—hyperthermia
- **E**ncephalopathy—mental status changes
- **V**itals—autonomic instability (e.g., tachycardia, hypertension, hypotension)
- **E**levated creatine kinase (CK)—rhabdomyolysis and myoglobinuria
- **R**igidity (a.k.a. lead pipe rigidity)—causing elevated CK

Pathophysiology

Dopamine D2 receptor blockade in the regions listed in [Table 16-21 on page 16-30](#) causes the symptoms of NMS.

All classes of antipsychotics have been associated with NMS, but it is most frequently associated with haloperidol and chlorpromazine. Consider other medications, including metoclopramide. There are other medications without antidopaminergic activity that are associated with NMS, including lithium, reserpine, phenelzine, tetrabenazine, and desipramine. Other risk factors include:

- Dehydration
- Inconsistent use of neuroleptics
- Postpartum period
- Agitation
- Mental illness other than schizophrenia
- Past history of electroconvulsive therapy (ECT)
- Warm and humid environments
- Malnutrition
- Organic brain syndromes
- Catatonia

Prognosis

The prognosis for recovery is good if the condition is recognized and treated promptly. Mortality ranges between 5 and 11.6% but is up to 50% if complicated by renal failure. Other complications include:

- Respiratory failure
- Disseminated intravascular coagulation (DIC)
- Seizure
- Decompensation of psychiatric disease following the withdrawal of neuroleptics
- Pulmonary embolism and deep venous thrombosis (DVT)
- Rhabdomyolysis
- Hepatic failure
- Cardiovascular arrhythmias and collapse
- Aspiration pneumonia

Table 16-21: Pathophysiology of Neuroleptic Malignant Syndrome

Dopamine D2 Receptor Blockade Location	Definition	Symptom
Hypothalamus	Connects the nervous system to the endocrine system	Elevated temperature set point and impairment of sweating
Nigrostriatum	Pathway between substantia nigra and corpus striatum	Muscular rigidity
Antipsychotics in the peripheral muscles	Skeletal muscle fibers	Increased Ca^{2+} release from sarcoplasmic reticulum → contractility → hyperthermia, rigidity, muscle breakdown
Sympathetic nervous system (SNS)	Pathway between SNS and adrenal medulla	Removal of inhibition of SNS leads to hyperactivity, and dysregulation leads to autonomic dysfunction.

Management

Perform medication reconciliation. Discontinue neuroleptics and monitor patients in the ICU. Use supportive measures to control rigidity and hyperthermia and to prevent respiratory failure, rhabdomyolysis, and renal failure. Specific treatments include lorazepam and ECT in severe cases.

SEROTONIN SYNDROME

PREVIEW | REVIEW

- What is serotonin syndrome?
- What are the precipitants of serotonin syndrome?
- What are the Hunter Serotonin Toxicity Criteria for serotonin syndrome?
- What is the difference between serotonin syndrome and neuroleptic malignant syndrome?

Serotonin syndrome is a group of symptoms that may occur following administration of certain serotonergic agents. It is caused by excessive serotonergic activity within the CNS. Its symptoms range from mild to severe; if not treated, severe cases can lead to cardiovascular collapse and death.

Serotonin syndrome is characterized by a clinical triad of:

- 1) Mental status changes—confusion, anxiety, extreme agitation, delirium, coma
- 2) Neuromuscular hyperactivity—hyperreflexia, clonus (including myoclonus and ocular clonus), shivering, status epilepticus, akathisia, bilateral Babinski sign
- 3) Autonomic instability—tachycardia, tachypnea, arrhythmia, hypertension, mydriasis, diaphoresis, diarrhea, vomiting

Symptoms typically develop within 6–24 hours of serotonergic initiation, addition, dose change, or overdose.

Common precipitants of serotonin syndrome (alone or in combination) include:

- Antidepressants—SSRIs, SNRIs, tricyclic antidepressants (TCAs), MAOIs, trazadone, mirtazapine, lithium, buspirone, bupropion
- Antimigraine—triptans
- Antibiotics—linezolid
- Opioids/analgesics/muscle relaxants—tramadol, meperidine, fentanyl, methadone, oxycodone, cyclobenzaprine
- Antiemetics—ondansetron, metoclopramide
- Supplements—St. John's wort, tryptophan
- Cold medications—dextromethorphan
- Drugs of abuse—amphetamines, MDMA, LSD, cocaine, ethanol
- Antiseizure medications (ASMs)—valproic acid, carbamazepine
- Other—L-DOPA and bromocriptine

Pathophysiology

The role of serotonin is to modulate body temperature, and thus SSRIs and SNRIs can cause a derangement in thermoregulation.

Serotonin syndrome is the consequence of overactive serotonin receptors affecting behavior, thermoregulation, and attention in the brain and gastrointestinal motility and vasoconstriction in the periphery.

Diagnosis

The diagnosis is clinical. Perform a thorough history (including medication reconciliation and illicit substance and dietary supplement use) and physical examination. Nonspecific laboratory abnormalities include elevation in white blood cells, creatinine, CK with rhabdomyolysis, and LFTs, as well as metabolic acidosis.

Symptoms of serotonin syndrome:

- Mild—mild hypertension and tachycardia, mydriasis, diaphoresis, shivering, tremor, myoclonus, and hyperreflexia; no hyperthermia
- Moderate—hyperthermia to 104.0°F (40.0°C), hyperactive bowel sounds, agitation, pressured speech, and horizontal ocular clonus
- Severe—hyperthermia > 105.8°F (> 41.0°C), vital sign instability, delirium, and muscle rigidity

Hunter Serotonin Toxicity Criteria for serotonin syndrome help in the diagnosis of the syndrome. They describe the consumption of a serotonergic agent plus 1 of the following groups:

- Spontaneous clonus
- Inducible clonus with agitation or diaphoresis
- Ocular clonus with agitation or diaphoresis
- Tremor and hyperreflexia
- Hypertonia, temperature > 100.4°F (38.0°C), and ocular or inducible clonus

Management

Assessment and treatment of serotonin syndrome consists of ECG to evaluate QT_c and QRS durations, removing the offending agent(s), treatment in ICU, mechanical ventilation, IV hydration, nitroglycerin, cyproheptadine, dantrolene, BDZs, ASMs, methysergide, paralyzing agents, and cooling blankets. Contact the local poison control center in the case of intentional overdose.

Prognosis

Overall, the prognosis is good, as most cases resolve within 24 hours with proper treatment (except in cases with agents with longer half-lives and metabolites [e.g., fluoxetine, half-life up to 6 days; norfluoxetine, metabolite active up to 16 days]). Delirium may persist for a few days. Symptoms of antidepressant discontinuation can occur.

Serotonin Syndrome vs. Neuroleptic Malignant Syndrome

Serotonin syndrome and NMS have similar presentations. Whereas serotonin syndrome presents with shivering, hyperreflexia, myoclonus, ataxia, nausea, vomiting, and diarrhea, NMS presents with bradykinesia and lead pipe rigidity.

ANTIDEPRESSANT DISCONTINUATION SYNDROME

PREVIEW | REVIEW

- What is antidepressant discontinuation syndrome?
- List the symptoms of antidepressant discontinuation syndrome.
- How is antidepressant discontinuation syndrome treated?

Antidepressant discontinuation syndrome (a.k.a. SSRI discontinuation syndrome) is the clinically significant effect of withdrawal from antidepressants—including tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), selective serotonin reuptake inhibitors (SSRIs), and serotonin-norepinephrine reuptake inhibitors (SNRIs)—by dose reduction, interruption, or discontinuation.

Accepted criteria for antidepressant discontinuation syndrome require ≥ 2 of the following symptoms developing within 1–7 days of discontinuation or reduction in antidepressant dose after at least 1 month's use:

- Dizziness, light-headedness, vertigo, or feeling faint
- Electric shocklike sensations or paresthesia
- Anxiety
- Diarrhea
- Fatigue
- Gait instability
- Headache
- Insomnia
- Irritability
- Nausea or emesis
- Tremor
- Visual hallucinations
- Reemergence of mood/anxiety symptoms

Antidepressant discontinuation syndrome is likely to occur with the potent and shorter-acting SSRIs paroxetine and fluvoxamine and the SNRI venlafaxine. It is important to taper antidepressant medications slowly.

Treatment

Educate patients about the self-limiting nature of symptoms. Treatment approaches include symptomatic treatment (allowing the syndrome to run its course in mild cases); restarting the medication (symptoms resolve within 24 hours upon reintroduction) then tapering at a slower rate (over 6–8 weeks); or, in more severe cases, switching the medication to one with a longer half-life (e.g., fluoxetine) then tapering. Follow up with patients to ensure symptom resolution. Consider consulting a psychiatrist if cross-titration is needed.

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