



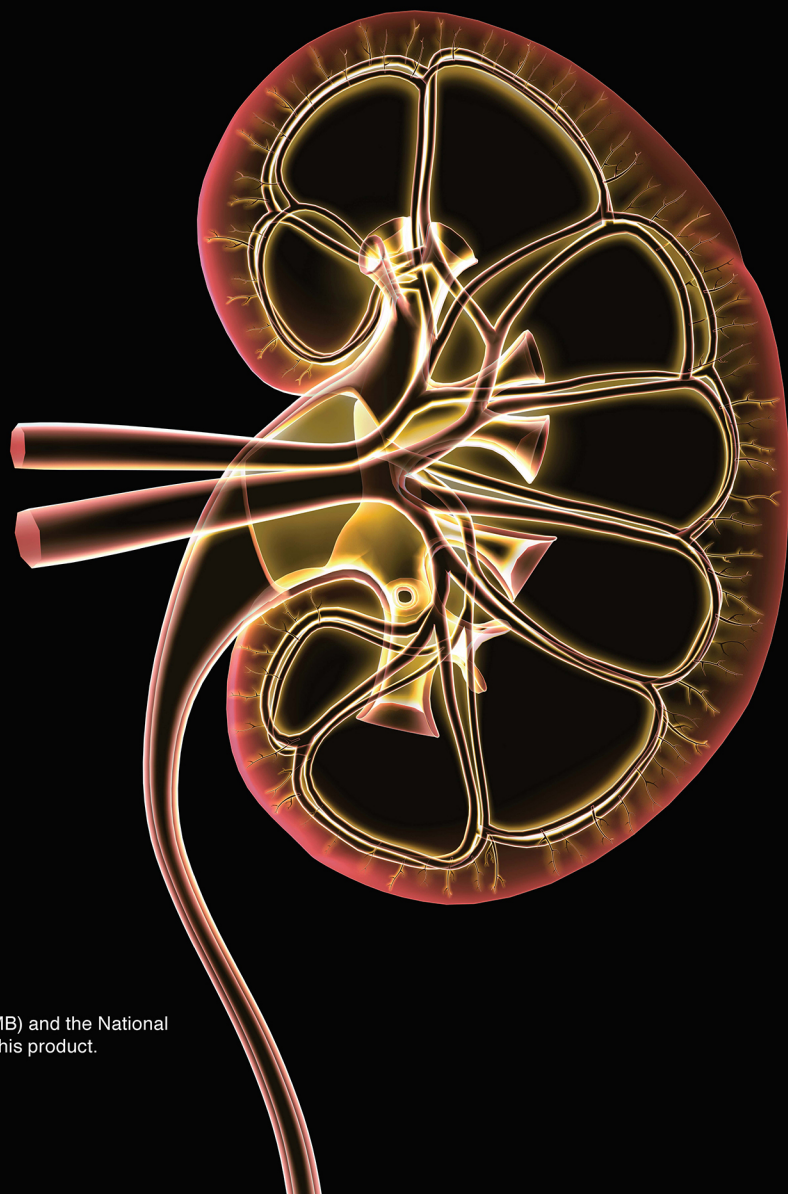
USMLE[®]

Step 2 CK

Lecture Notes

2021

Internal Medicine



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We want to hear what you think. What do you like or not like about the Notes?
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Preventive Medicine

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Learning Objectives

- ❑ Describe appropriate screening methods as they apply to neoplasms of the colon, breast, cervix, and lung
 - ❑ Describe epidemiological data related to incidence and prevention of common infectious disease, chronic illness, trauma, smoking, and travel risks
-

SCREENINGS

For all diseases that have recommended screening:

- Effective intervention must exist
- After a positive test result, course of events must be acceptable to patient
- Screening test must be valid, i.e., it must have proven in trials to decrease overall mortality

For a screening test to be recommended for regular use, it has to be extensively studied to ensure that all of the above requirements are met.

Cancer Screening

A 39-year-old woman comes to the clinic very concerned about her risk of developing cancer. Her father was diagnosed with colon cancer at age 43, and her mother was diagnosed with breast cancer at age 52. She is sexually active with multiple partners and has not seen a physician since a car accident 15 years ago. She denies any symptoms at this time, and her physical examination is normal. She asks what is recommended for a woman her age.

Screening tests are done on seemingly healthy people to identify those at increased risk of disease.



However, even if a diagnostic test is available, that does not always mean it should be used to screen for a particular disease. That is because diagnostic tests may:

- Have adverse (and possibly iatrogenic) effects (e.g., large bowel perforation secondary to a colonoscopy)
- Be expensive, unpleasant, and/or inconvenient
- Lead to ineffective or even harmful treatment

The 4 malignancies for which regular screening is recommended are **cancers of the colon, breast, cervix, and lung**.

Colon Cancer

If there is no significant family history of colon cancer, screen everyone starting age 50.

- Colonoscopy every 10 years (**preferred**)
- Annual fecal occult blood test and sigmoidoscopy with barium enema every 5 years

If there is a single first-degree relative diagnosed with colorectal cancer age <60 or multiple first-degree relatives with colon cancer at any age, screen with colonoscopy starting age 40 or 10 years before the age at which the youngest affected relative was diagnosed, **whichever age occurs earlier**.

- Repeat colonoscopy every 5 years
- Routine screening can stop age >75, as per the U.S. Preventive Services Task Force (USPSTF)

Note

Tamoxifen prevents cancer by 50% in those with >1 family member with breast cancer.

Note

Prostate Screening

USPSTF concludes that the current evidence is insufficient to assess the balance of benefits/risks of prostate cancer screening in men age <75. It recommends against screening in men age >75.

For USMLE, do not screen for prostate cancer.

Breast Cancer

Mammography plus manual breast exam are used to screen for breast cancer. (Self-breast exam by itself is not recommended as a screening tool.)

- Mammography with or without clinical breast exam every 1–2 years from age 50–74
- If there is a very strong family history of breast cancer (i.e., multiple first-degree relatives), consider prophylactic tamoxifen, which prevents breast cancer in high-risk individuals

Cervical Cancer

The screening test of choice for the early detection of cervical cancer is the Papanicolaou smear (the “Pap” test). In average risk women, screen as follows:

- Starting age 21, screen with Pap (regardless of onset of sexual activity) every 3 years until age 65
- Alternatively, screen with Pap + HPV testing every 5 years, age 30–65
- Higher risk women, e.g., HIV, may require more frequent screening or screening age >65

Lung Cancer

Current recommendations for lung cancer screening are as follows:

- For adults age 55–80 with a 30-pack-year smoking history and currently smoke or have quit within 15 years, screen annually with low-dose CT.
- For those who have not smoked for 15 years; age >80; or who have another medical problem which significantly limits life expectancy or the ability to undergo surgery, screening is not necessary.

Clinical Recall

Which of the following patients is undergoing an inappropriate method of screening as recommended by the USPSTF?

- A 50-year-old man gets his first screening for colon cancer via colonoscopy
- A 50-year-old woman gets her first screening for breast cancer via mammography
- A 17-year-old woman is screened for HPV via a Pap smear after her first sexual encounter
- A 65-year-old man with a 30-pack-year smoking history gets a low-dose CT
- A 21-year-old woman with a high risk of developing breast cancer is given tamoxifen

Answer: C

Osteoporosis Screening

A bone density test uses x-rays to measure how many grams of calcium and other bone minerals are packed into a segment of bone. The bones typically tested are the spine, hip, and forearm.

- Screening with a DEXA bone density scan should be given to all women age >65.
- Screening should begin at age 60 if there is low body weight or increased risk of fractures.

Bone density test results are reported in 2 numbers.

- The **T-score** compares the patient's bone density with what is normally expected in a healthy young adult of the same sex. This score is the number of units—standard deviations—that bone density is above or below the average.
 - T-score >2.5 SD indicates the likelihood of osteoporosis and increased risk of fracture.
 - A diagnosis of osteoporosis by DEXA scan also means that treatment should be initiated with bisphosphonates, oral daily calcium supplementation, and vitamin D.

Note

A **pack year** is smoking an average of 1 pack of cigarettes per day for 1 year. A patient with a smoking history of 30 pack years is considered a heavy smoker.

**Note**

Low bone density is very common among older adults, so **Z-score** can be misleading.

- Use Z-score (not T-score) for children/teens/women of childbearing age/younger men.
- In these younger age groups, routine bone density screening is not recommended, nor should a diagnosis of osteoporosis be based on bone density test alone.

- The **Z-score** compares the condition of the patient's bones with those of an average person the same age and body size. It is the number of standard deviations above or below what is normally expected for someone of the same age, sex, weight, and ethnic or racial origin.
 - Z-score ≤ -2 may suggest that something other than aging is causing abnormal bone loss (consider drugs causing osteoporosis such as corticosteroids).
 - The goal in this case is to identify the underlying problem.

Hypertension, Diabetes Mellitus, and Hypercholesterolemia

A 45-year-old man comes to the physician anxious about his health. Five years ago his mother was diagnosed with diabetes and high cholesterol. He is worried about his health and risk for heart disease. Physical examination is within normal limits.

Cholesterol screening should commence at age 35 in men who have no risk factors for coronary artery disease. In both men and women with risk factors, screening should be done routinely after age 20. Management should not be determined by an isolated reading because cholesterol levels may fluctuate between measurements. Repeat in 5 years in low-risk individuals.

Screening for diabetes mellitus should be considered only for patients with hypertension ($>135/80$ mm Hg). Diabetes mellitus is diagnosed in either of these situations:

- Two fasting glucose measurements are >125 mg/dL, HbA1c $>6.5\%$
- Random glucose >200 mg/dL accompanied by symptoms

There is insufficient evidence for or against routine screening. The strongest indication is for those with hypertension and hyperlipidemia.

Screening is recommended for elevated blood pressure in those age >18 , at every visit. Screening is not recommended for carotid artery stenosis with duplex.

Abdominal Aortic Aneurysm

U/S should be done once in men age >65 who have ever smoked. There are no screening recommendations for male nonsmokers and women, regardless of smoking history.

TRAVEL MEDICINE

A 44-year-old man comes to the clinic before traveling to Thailand for business. He has no significant past medical history and is here only because it is required by his company. The patient appears agitated and demands the physician's recommendation immediately.

It is important to set up a pretravel counseling session 4–6 weeks before the patient's departure.

Recommendations are as follows:

- **Hepatitis A** vaccination: recommended for all travelers to less developed nations
 - If patient is departing within 2 weeks of being seen, give both the vaccine and immune serum globulin
 - Booster shot given 6 months post-initial vaccination provides immunity for approximately 10 yrs
- **Hepatitis B** vaccination: recommended for patients who work closely with indigenous populations
 - If patient plans to engage in sexual intercourse with the local populace or to receive medical/dental care, vaccinate
 - If patient plans to remain abroad for >6 months, vaccinate
- **Malaria**
 - Mefloquine is the agent of choice for malaria prophylaxis (given 1×/week); side effects include neuropsychiatric effects such as hallucinations, depression, and unusual behavior
 - Doxycycline is an acceptable alternative; side effects include photosensitivity
 - In pregnancy, chloroquine is the preferred regimen for prophylaxis
- **Rabies** vaccination is recommended only for those traveling to areas where rabies is common among domesticated animals (India, Asia, Mexico). It is not considered a routine vaccine for most travelers.
 - Chloroquine can blunt the response to the **intradermal** form of rabies vaccine
 - Therefore, if both malaria prophylaxis and rabies prophylaxis are required, give the intramuscular form of the vaccine
- **Typhoid** vaccination is recommended for those traveling to developing nations, who may have prolonged exposure to contaminated food and water; side effects include irritation at the injection site and rarely headache and fever
 - Live attenuated form: given orally (needs refrigeration; contraindicated for HIV patients)
 - Capsular polysaccharide form (**preferred**): given intramuscularly 1× (needs no refrigeration; safe for HIV patients; well-tolerated)

Polio vaccination is recommended for those traveling to developing nations.

- If patient has not previously received a polio vaccine, give 3 doses of the inactivated polio vaccine.
- If patient has previously been immunized, give a one-time booster.
- The live attenuated polio vaccine is no longer recommended because of the risk of vaccine-associated disease.

Note

- The global health approach to disease prophylaxis is to provide treatment to travelers whose destination is an area where the disease is endemic.
- Because disease distribution shifts over time, country-specific questions are not likely to be on the exam.

Note

Hepatitis A infection is the most common vaccine-preventable disease in travelers. It can occur wherever there is fecal contamination of food/drinking water.



Other general travel recommendations are as follows:

- **Polysaccharide vaccination** is recommended for those traveling to areas where meningococcal meningitis is endemic or epidemic (Nepal, sub-Saharan Africa, northern India).
 - Meningococcal vaccine is now routinely administered at age 11
 - Saudi Arabia requires immunization for pilgrims to Mecca
 - Immunize those with functional (or actual) asplenia and those with terminal complement deficiencies
- To prevent **traveler's diarrhea**, patients should be advised to avoid raw and street vendor salads, unwashed fruit, and tap/ice water. Patients who experience mild loose stools without fever or blood can safely take loperamide. Treatment with a fluoroquinolone or azithromycin is reserved for patients with moderate to severe symptoms.

IMMUNIZATIONS

A 52-year-old man comes to the clinic for a health maintenance evaluation. His recent colonoscopy showed no evidence of carcinoma. Recent serum fasting glucose, serum cholesterol, and blood pressure are all within normal limits. The patient has a history of smoking and continues to smoke 2 packs per day. He was diagnosed with COPD 3 years ago.

Immunization is the best method available for preventing serious infectious disease. Between 50,000–70,000 adults die every year from preventable infectious disease (influenza, invasive pneumococcal disease, and hepatitis B).

Surveys have shown that among patients who have an indication for any vaccination, very few actually receive it (pneumococcal vaccination 20%, influenza 40%, hepatitis B 10%). For this reason, the American College of Physicians recommends that **every patient's immunization status be reviewed at age 50**; evaluate risk factors for specific vaccinations at that time.

- Most patients received a primary immunization against tetanus and diphtheria as children.
- For those adults who were never vaccinated, give 3 doses. The principle is that adults require a total of 3 vaccinations against tetanus and diphtheria.
 - Give the first 2 doses 1–2 months apart
 - Give the third dose 6–12 months later
 - Give a booster vaccination every 10 years for life; one of the boosters should use Tdap instead of Td booster; if wound is dirty, revaccinate after 5 years

Influenza Vaccine

- Recommended annually for all adults, regardless of age
- Those who will see the greatest benefit from an annual vaccination include:
 - Patients with a history of cardiopulmonary disease, DM, or hemoglobinopathy
 - Residents of a chronic care facility, age 50+
- Pregnant women who will be in their second or third trimester during the influenza season should also receive the vaccine.

Pneumococcal Vaccine

Pneumococcal vaccine is indicated for all adults age ≥ 65 . Additionally, the following individuals should receive the vaccine regardless of age:

- Those with history of sickle-cell disease or splenectomy
- Those with history of cardiopulmonary disease, alcoholism, or cirrhosis
- Alaskan natives and certain Native American populations
- Immunocompromised patients (patients with hematologic malignancies, chronic renal failure, or nephrotic syndrome; HIV-positive patients; or patients receiving immunosuppressive medications)

Revaccination should be performed in healthy patients who received their initial vaccination age < 65 and were age < 60 at the time of primary vaccination. Patients with a high risk of fatal infection (chronic kidney disease patients, asplenic patients, immunocompromised patients) should be revaccinated 1 $\times$ after 5 years. No one gets > 1 booster shot per lifetime.

Hepatitis B Vaccine

Hepatitis B vaccine is recommended when there is a history of the following:

- IV drug abuse
- Male homosexuality
- Household or sexual contact with hepatitis B carriers
- Frequent exposure to blood/blood products
- History of chronic liver disease

The hepatitis B vaccine is also recommended for the following individuals:

- All children through age 18
- Those with STIs
- Those who are sexually active but not monogamous
- Workers with occupational exposure to blood
- Prison inmates

Immunity is confirmed serologically.

Note

Patients must get Pneumovax, meningococcal, and *Haemophilus* vaccines 2 weeks before a splenectomy.



Hepatitis A Vaccine

The hepatitis A vaccine protects against the virus in >95% of cases. There are 2 types of vaccine, both of which stimulate active immunity against a future infection.

- One contains inactivated hepatitis A virus
- One contains a live but attenuated virus

For the best protection, give the vaccine in 2 doses: initial dose and then a booster 6–12 months later. Protection against hepatitis A begins approximately 2–4 weeks after the initial vaccination.

In the United States, the vaccine is strongly recommended for all children age 12–23 months in an attempt to eradicate the virus nationwide. There are also recommendations that the following populations be vaccinated:

- All children age >1 year
- People whose sexual activity puts them at risk
- People with chronic liver disease
- People who are being treated with clotting factor concentrates
- People who are living in communities where an outbreak is present

Hepatitis A is the most common vaccine-preventable virus acquired during travel, so people traveling to places where the virus is common (Indian subcontinent, Africa, Central America, South America, the Far East, and Eastern Europe) should be vaccinated.

Varicella Vaccine

The varicella vaccine is a live attenuated vaccine recommended for use in all adults who lack a history of childhood infection with varicella virus. Being a live attenuated vaccine, varicella vaccine should not be given to immunocompromised patients, HIV-positive patients when symptomatic or <200 CD4 cells, or pregnant women.

Patients age ≥60 are recommended to receive the varicella zoster (shingles) vaccine, which has been shown to reduce the risk of zoster and its associated pain (post-herpetic neuralgia). It is indicated regardless of whether there is a history of shingles, as it is possible to have a second herpes zoster infection.

Measles, Mumps, Rubella Vaccine

The measles, mumps, rubella (MMR) vaccine is a live attenuated vaccine usually given in childhood. Healthy adults born after 1956 should receive 1 dose of the vaccine. Pregnant women and immunocompromised patients should not be vaccinated. HIV-positive patients who are asymptomatic may receive the vaccine.

Meningococcal Vaccine

The meningococcal vaccine is recommended for everyone at age 11 visit. It is also recommended for young adults living in dormitories or barracks, people exposed to outbreaks, those with asplenia or terminal complement deficiencies, those who travel to endemic regions (traveling to Mecca), and those exposed to *Neisseria meningitidis*.

Human Papillomavirus (HPV) Vaccine

The HPV vaccine is recommended for women age 9–26, regardless of sexual activity. The regimen is in 3 doses: 0, 2, and 6 months.

Do not administer the HPV vaccine in pregnancy.

Herpes Zoster Vaccine

The zoster vaccine is a live vaccine that has been shown to reduce the incidence of shingles by 50%. It has also been shown to reduce the number of cases of post-herpetic neuralgia, as well as the severity and duration of pain/discomfort associated with shingles. The vaccine is, basically, a larger-than-normal dose of the chickenpox vaccine, as both shingles and chickenpox are caused by the same virus, varicella zoster virus (VZV).

The shingles vaccine (Zostavax), a live vaccine given as a single injection, is recommended for adults age ≥ 60 , whether they have already had shingles or not. Some people report a chickenpox-like rash after receiving it. The vaccine should not be given to the following individuals:

- Those with a weakened immune system due to HIV/AIDS or another disease that affects the immune system
- Those who are receiving immune system-suppressing drugs or treatments such as steroids, adalimumab (Humira), infliximab (Remicade), etanercept (Enbrel), radiation or chemotherapy
- Those who have neoplasia, which affects the bone marrow or lymphatic system, such as leukemia or lymphoma

Recombinant zoster vaccine (Shingrix) (**preferred over Zostavax by the CDC**) is a newer vaccine for healthy adults age ≥ 50 (with no maximum age). It is not indicated for the prevention of primary varicella infection (chickenpox).

Shingrix is given in 2 doses, 2–6 months apart. Side effects include skin rash, joint pain, flu-like symptoms, headaches, and fatigue.

Patients can receive Shingrix even if they have had shingles, have already received Zostavax vaccine, or are not sure if they have ever had chickenpox.

Clinical Recall

In which of the following patients will the vaccination have the greatest benefit?

- Routine hepatitis A vaccination in a 2-month-old infant
- Influenza vaccine in a 16-year-old asymptomatic high school student
- VZV vaccination given to an AIDS patient with CD4 count 100
- Pneumococcal vaccination given to a 48-year-old male COPD patient
- HBV vaccination given to a heart failure patient

Answer: D



LIFESTYLE MEDICINE

Alcohol

Physicians should screen for alcohol abuse by using the CAGE questionnaire.

Have you ever felt the need to:	Cut down on your drinking?
Have you ever felt:	Annoyed by criticism of your drinking?
Have you ever felt:	Guilty about your drinking?
Have you ever taken a morning:	Eye opener?

A positive screen is 2 “yes” answers. One “yes” should raise the possibility of alcohol abuse.

Smoking

Smoking is responsible for 1 in every 5 deaths in the United States. Smoking cessation is the most preventable cause of disease. Physicians can take the following steps to assist:

- **ASK** about smoking at every visit.
- **ADVISE** all smokers to quit at every visit.
- **ATTEMPT** to identify those smokers willing to quit.
- **ASSIST** the patient by setting a quit date (usually within 2 weeks) and using nicotine patches/gum, the oral antidepressant bupropion or varenicline as supportive therapy. Varenicline and bupropion are more effective than patches.
- **ARRANGE** follow-up. If the quit attempt was successful, then provide positive reinforcement. If it was not successful, then determine why the patient smoked and elicit a recommitment to smoking cessation. Most patients require several attempts before being successful.

Monotherapy treatment for smoking cessation includes nicotine replacement therapy (transdermal nicotine patches, gum, lozenges, inhalers), bupropion, and varenicline.

- Bupropion lowers the seizure threshold so do not use in cases of alcohol abuse.
- Varenicline causes an increased rate of suicidal thoughts, so first screen for depression.

Place a follow-up call 1–2 weeks after quit date. The use of pharmacotherapy doubles the effect of any tobacco cessation intervention.

Note

Do not use varenicline in patients with a history of psychiatric disease.

VIOLENCE AND INJURY

A 27-year-old woman presents to the ED with right-arm pain. When asked how she sustained the injury, she states that she fell down the steps in front of her house. The patient appears anxious and nervous. On physical examination there are various 2 cm wide lacerations on her buttocks.

Injuries are the most common cause of death in those age <65. The role of the physician is to advise patients about safety practices that can prevent injury, e.g., using seat belts, wearing bicycle helmets, and not driving after drinking alcohol.

Identifying women who are at increased risk of physical or sexual abuse is an essential role for a physician. Simply asking them if they have been hit, kicked, or physically hurt can increase identification by >10%.

Clinical Recall

Which of the following is indicated in a 65-year-old male smoker?

- A. Digital rectal examination with prostatic specific antigen level
- B. Meningococcal vaccination
- C. Varicella-zoster vaccination
- D. Varicella-zoster vaccination and hepatitis A vaccination
- E. Varicella-zoster vaccination and abdominal ultrasound

Answer: E

Learning Objectives

- ❑ List presenting signs and therapeutic approaches to disease of the anterior pituitary, posterior pituitary, thyroid, parathyroid, and adrenal glands
 - ❑ Describe disorders that cause hypogonadism or affect the testes
 - ❑ Describe disorders of carbohydrate metabolism
-

DISEASES OF THE PITUITARY GLAND

The pituitary is surrounded by the sphenoid bone and covered by the sellar diaphragm, an extension from the dura mater. It lies in the sella turcica near the hypothalamus underneath the optic chiasm.

The pituitary is divided into 2 lobes:

- Adenohypophysis (anterior lobe) (80% of pituitary)
- Neurohypophysis (posterior lobe) (20%)
 - Stores hormones produced by neurosecretory neurons (supraoptic and paraventricular nuclei) within the hypothalamus
 - Hypothalamus secretes ADH (antidiuretic hormone or vasopressin) and oxytocin

There is a close relationship between the hypothalamus and the pituitary. The hypothalamus regulates the release of hormones from the anterior pituitary by different hypothalamic releasing and inhibiting hormones (hypothalamic–pituitary axis).

The hypothalamus secretes releasing factors for each respective pituitary stimulatory hormone. Each pituitary hormone stimulates release of the active hormone from the final target gland. The active hormones then inhibit release of releasing factors and stimulatory hormones from the hypothalamus and pituitary gland, respectively. This is feedback inhibition, and it leads to a steady state of both respective hormones involved in the axis.

Note

- The posterior lobe does not actually produce hormones.
- It stores and secretes hormones produced by the hypothalamus.

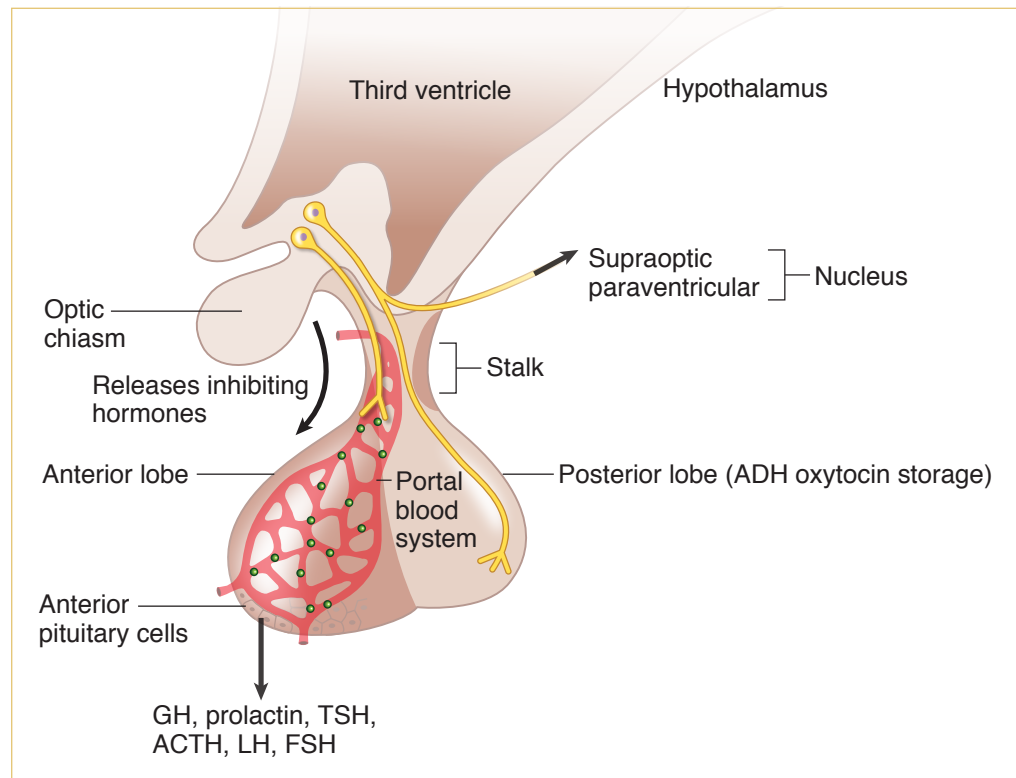


Figure 2-1. Pituitary Gland

Clinically, note the following when diagnosing disease:

- Disease states involving **overproduction of target hormones** lead to **suppressed levels** of pituitary hormones.
- Disease states involving **underproduction of target hormones** lead to **increased levels** of pituitary hormones.

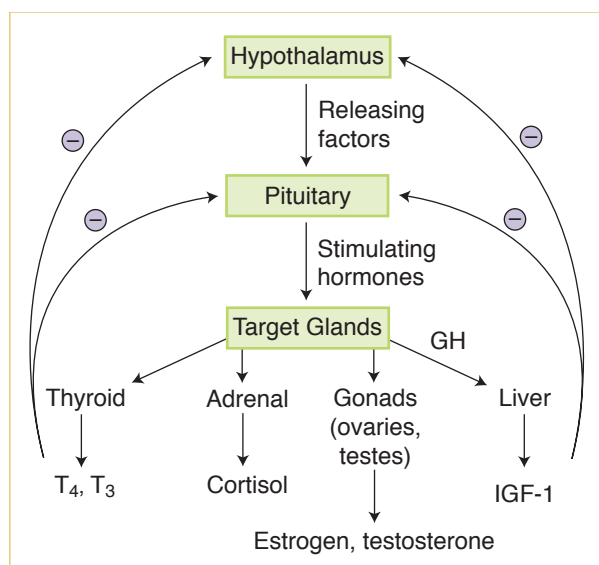


Figure 2-2. Summary of Action

Anterior Pituitary

Syndromes causing excess production of hormones usually arise from benign tumors of a single cell type.

- **Microadenomas (more common)** are <1 cm in diameter.
- **Macroadenomas** (less common) are >1 cm in diameter; larger tumors sometimes compress the optic chiasm and cause visual deficits.

The frequency of pituitary adenomas by function is as follows.

- Prolactin: 50–60%
- Growth hormone (GH): 15–20%
- ACTH: 10–15%
- Gonadotroph: 10–15%

Hyperprolactinemia

A 32-year-old woman presents with milk-like discharge from her breasts for the past 4 weeks. She explains that she has not menstruated in 2 months. Physical examination is normal with the exception of galactorrhea.

Excess prolactin secretion (**common in women**) causes the syndrome of galactorrhea-amenorrhea. The amenorrhea appears to be caused by inhibition of hypothalamic release of gonadotropin-releasing hormone (GnRH), with a decrease in luteinizing hormone (LH) and follicle-stimulating hormone (FSH) secretion. Prolactin inhibits the LH surge that causes ovulation. The LH/FSH-producing cells are not destroyed, just suppressed.

Note

Gynecomastia, and especially galactorrhea, are much rarer in men than is hyperprolactinemia. The most common presenting symptoms of hyperprolactinemia in men are erectile dysfunction and decreased libido.



Hyperprolactinemia can be caused by the following conditions:

- Natural physiologic states such as pregnancy, early nursing, hypoglycemia, seizure, exercise, stress, sleep, cirrhosis, nipple stimulation, and chronic renal failure (due to PRL clearance)
- Pituitary adenomas: autonomous production of prolactin (“prolactinomas”) are the most common functioning pituitary adenomas (60% of all pituitary tumors)
 - In **women**, usually microadenomas
 - In **men**, usually macroadenomas (usually present with visual field deficits, obstruction of pituitary stalk, and increased prolactin release by blocking dopamine transport from hypothalamus (stalk effect))
- Other tumors such as craniopharyngioma/meningioma/dysgerminoma; empty sella; and trauma
- Decreased inhibitory action of dopamine, seen in dopamine-blocking agents (phenothiazines, metoclopramide) and dopamine-depleting agents (α -methyldopa, reserpine)
- Tricyclic antidepressants, narcotics, cocaine, CCBs, protease inhibitors, SSRIs, risperidone
- Stimuli which overcome the normal dopamine inhibition, e.g., primary hypothyroidism (causing increased thyrotropin-releasing hormone [TRH]) and subsequent increased prolactin release)

Note

Always check TSH in patients with elevated prolactin.

Clinical Presentation.

- Galactorrhea (mostly women)
- Menstrual abnormalities amenorrhea/oligomenorrhea (results in earlier detection in women; thus, microadenomas are more common in women)
- Osteopenia and osteoporosis (in chronic cases)
- Infertility
- Gynecomastia
- Hypogonadism, erectile dysfunction, decreased libido (men)

Diagnosis. To diagnose, first exclude pregnancy, lactation, hypothyroidism, and medication. Prolactinomas may co-secrete GH.

- Prolactin level >100 ng/mL suggests probable pituitary adenoma
- Prolactin level should be commensurate with tumor size
 - Prolactin 100 ng/mL correlates with tumor ~ 1 cm
 - Prolactin 200 ng/mL correlates with tumor ~ 2 cm
- Prolactin level influenced by drugs and other nonprolactinoma conditions are usually <150 ng/mL. If someone is on a psychotropic agent and prolactin >150 ng/mL, do a brain MRI.

Treatment. Dopamine normally inhibits prolactin release.

- Treat initially with dopamine-agonists (cabergoline [**preferred**] or bromocriptine), which will reduce prolactin level to <10% of pretreatment level (90% success rate)
 - Dopamine-agonists are always **first line**, even when there are mass effects compressing the optic chiasm or invasion of cavernous sinus or vessels.
 - Cabergoline has fewer side effects than bromocriptine, so is preferred for galactorrhea.
- If no response to cabergoline or bromocriptine, or if significant compressive neurologic effects, consider surgery
 - Surgery is more effective for microadenomas than macroadenomas.
 - Only 30% of macroadenomas can be successfully resected, with long-term recurrence >50%.
- If no response to drug therapy or surgery, consider radiation therapy

Clinical Recall

Which of the following options is most appropriate in the treatment of prolactinoma?

- A. Somatostatin
- B. Surgical resection
- C. Transsphenoidal resection
- D. Radiation therapy
- E. Cabergoline

Answer: E

Acromegaly

Acromegaly (called gigantism in children) is a syndrome of excessive secretion of GH. It is an insidious, chronic debilitating disease associated with bony and soft tissue overgrowth, and increased mortality.



Wikimedia, Philippe Chanson and Sylvie Salenave

Figure 2-3. Acromegaly Facial Features

Note

A basal, fasting, morning PRL >100–200 mg/L (normal <20 mg/L) in a nonpregnant woman indicates a need for a pituitary MRI.



Acromegaly is caused by a pituitary adenoma (usually macroadenoma in 75% of the cases that produce GH). Rarely, ectopic tumors can produce growth hormone-releasing hormone (GHRH) and cause this syndrome. Less than 1% of cases are malignant. GH is produced by 20% of pituitary tumors.

Clinical Findings. GH excess occurs most frequently around decades 3–5. The following symptoms may be seen.

- Enlargement of hands/feet, coarsening of facial features, and thickened skin folds; increase in shoe/hat/glove/ ring size
- Enlarged nose and mandible (prognathism and separation of teeth), sometimes causing underbite
- Deeper voice
- Increased sweating
- Obstructive sleep apnea
- Enlarged internal organs, including heart, lung, spleen, liver, and kidneys
- Interstitial edema, osteoarthritis, and entrapment neuropathy (carpal tunnel syndrome)
- Menstrual problems (**common**) due to co-secretion of prolactin by GH-producing tumor
- Cardiac anomalies (10–20%) such as hypertension, arrhythmia, hypertrophic cardiomyopathy, and accelerated atherosclerosis
- Metabolic changes, i.e., impaired glucose tolerance (80%) and diabetes (13–20%)
- Hypertension (35%)
- Headaches and visual field loss

Note

The most common cause of death in acromegaly is cardiovascular mortality.

Diagnosis. Patients with acromegaly have symptoms for ~9 years before the diagnosis is made. Measurement of insulin-like growth factor (IGF) or somatomedin correlates with disease activity.

- Significantly elevated IGF-1 (**best initial test**)
- Confirmatory test is GH measurement (after 100 g of glucose is given orally)
 - If GH remains high (>5 ng/mL), it is positive and suggests acromegaly.
 - Normally, glucose load should completely suppress levels of GH.
- MRI (**preferred**; highly diagnostic) and CT to localize the tumor, but only after GH excess is documented biochemically

Treatment. The goals of treatment are to decrease GH levels to normal, stabilize/decrease tumor size, and preserve normal pituitary function (hypopituitarism is a side effect in 10–20% of cases).

- Transsphenoidal surgery provides a rapid response
- Somatostatin analogues (**drugs of choice**)
 - Octreotide (**preferred**) and lanreotide reduce GH (70% success rate) and cause partial tumor regression (20–50% success rate).
 - Main side effect is cholestasis, leading to cholecystitis

- If surgery is not curative, dopamine-agonists such as bromocriptine and cabergoline (10% success rate)
- Pegvisomant (**second-line**), a GH analogue that antagonizes endogenous GH by blocking peripheral GH binding to its receptor in the liver
- If surgery and drug therapy are not curative, radiotherapy can slow resolution of disease and hypopituitarism (20% success rate)

Complications of acromegaly include pressure of the tumor on the surrounding structures or invasion of the tumor into the brain or sinuses; cardiac failure (**most common cause of death**), DM, cord compression, and visual field defects.

Hypopituitarism

Hypopituitarism is partial/complete loss of anterior function resulting from any lesion that destroys the pituitary or hypothalamus or interferes with the delivery of releasing and inhibiting factors to the anterior hypothalamus. GH and gonadotropins (FSH, LH) are typically lost early.

Causes include:

- Large pituitary tumors or cysts
- Hypothalamic tumors (craniopharyngiomas, meningiomas, gliomas)
- Pituitary adenomas (**most common cause of panhypopituitarism**); the mass compresses the gland, causing pressure, trauma, and necrosis
- Pituitary apoplexy (**medical emergency**), a syndrome associated with acute hemorrhagic infarction of a preexisting pituitary adenoma; symptoms include severe headache, nausea/vomiting, and depression of consciousness
- Inflammatory disease
 - Granulomatous disease (sarcoidosis, TB, syphilis), eosinophilic granuloma, and autoimmune lymphocytic hypophysitis (usually associated with other autoimmune diseases such as Hashimoto thyroiditis and gastric atrophy)
 - Trauma, radiation, surgery, infections, and hypoxia, which may damage both the pituitary and hypothalamus
 - Vascular disease such as Sheehan postpartum necrosis (initial sign is the inability to lactate) and infiltrative diseases, e.g., hemochromatosis and amyloidosis
 - Stroke, which can cause central diabetes insipidus (DI) due to damage of hypothalamus and/or posterior pituitary

Clinical Findings. The following hormones appear in the **order in which they are lost in hypopituitarism**.

- Gonadotropin deficiency (LH and FSH) can occur in women and lead to amenorrhea, genital atrophy, infertility, decreased libido, and loss of axillary and pubic hair.
- In men, decreased LH and FSH results in impotence, testicular atrophy, infertility, decreased libido, and loss of axillary and pubic hair.



- GH deficiency occurs next.
 - Not clinically detectable in adults, though it may manifest as fine wrinkles and increased sensitivity to insulin (hypoglycemia)
 - Causes an asymptomatic increase in lipid levels and a decrease in muscle, bone, and heart mass
 - May accelerate atherosclerosis
 - Increases visceral obesity
 - In children, results in growth failure and short stature
- TSH deficiency results in hypothyroidism with fatigue, weakness, hyperlipidemia, cold intolerance, and puffy skin without goiter.
- Adrenocorticotropin hormone (ACTH) deficiency occurs last. It causes secondary adrenal insufficiency caused by pituitary disease (and does not result in the salt-wasting, hyperpigmentation, hyperkalemia, and death associated with aldosterone deficiency)
- Decreased cortisol, which results in fatigue, reduced appetite/weight loss, decreased skin/nipple pigment, and decreased response to stress (as well as fever, hypoglycemia, hypotension, and hyponatremia).

Electrolyte changes like hyperkalemia and salt loss are minimal in secondary adrenal insufficiency because aldosterone production is mainly dependent on the renin-angiotensin system.

Diagnosis. The first step in diagnosing pituitary insufficiency is to measure GH, TSH, LH, and IGF-1.

Note

Random GH and IGF levels are not sensitive enough to diagnose GH deficiency, which is why a provocative test is used.

- To diagnose **GH deficiency**, the most reliable stimulus for GH secretion is insulin-induced hypoglycemia.
 - After injecting 0.1 μ /kg of regular insulin, blood glucose declines to <40 mg/dL (in normal conditions that will stimulate GH levels to >10 mg/L and exclude GH deficiency).
 - Arginine infusion can also stimulate GH release. Measure GH after infusing arginine. This is less dangerous because it does not cause hypoglycemia.
- To diagnose **ACTH deficiency**, basal cortisol levels may be normal (the problem could be only in response to stress). Insulin tolerance test is diagnostic (give 0.05–0.1 U/kg of regular insulin and measure serum cortisol); plasma cortisol should increase to >19 mg/dL. Metyrapone tests for decreased ACTH production.
 - Metyrapone blocks cortisol production, which should increase ACTH. Failure of ACTH to increase after metyrapone administration would indicate pituitary insufficiency.
 - Cosyntropin (ACTH) stimulation may give abnormally low cortisol output if pituitary insufficiency has led to adrenal atrophy.
- To diagnose **gonadotropin deficiency**
 - LH, FSH, and estrogen (women)
 - LH, FSH, and testosterone (men)
- To diagnose **TSH deficiency**, measure serum thyroxine (T4) and free triiodothyronine (T3), which are low, with a normal/low TSH.

Treatment. Treat the underlying cause. Multiple hormones must be replaced, the most important of which is cortisol.

- Cortisol must be given before T4; otherwise an adrenal crisis can occur.
- Cosyntropin stimulation test must be done before T4 to rule out adrenal insufficiency if secondary hypothyroidism is suspected (risk factors include radiation to the head, sarcoidosis, hemochromatosis, Sheehan syndrome, or TSH that is not elevated).

Empty Sella Syndrome (ESS)

ESS is in the differential diagnosis of enlarged sella caused by pituitary tumors. In ESS, the sella has no bony erosion. It is caused by herniation of the suprasellar subarachnoid space through an incomplete diaphragma sellae.

The syndrome can be primary (idiopathic) and is also associated with head trauma and radiation therapy.

Most patients are obese, multiparous women. Symptoms include:

- Headaches (**common**)
- Hypertension (30% of patients)
- Endocrine symptoms are absent.
- No pituitary gland is visible on CT or MRI.

Treatment is reassurance.

Note

- In **primary hypothyroidism**, TSH will always be elevated due to loss of negative feedback inhibition.
- In **secondary hypothyroidism**, TSH can be normal.

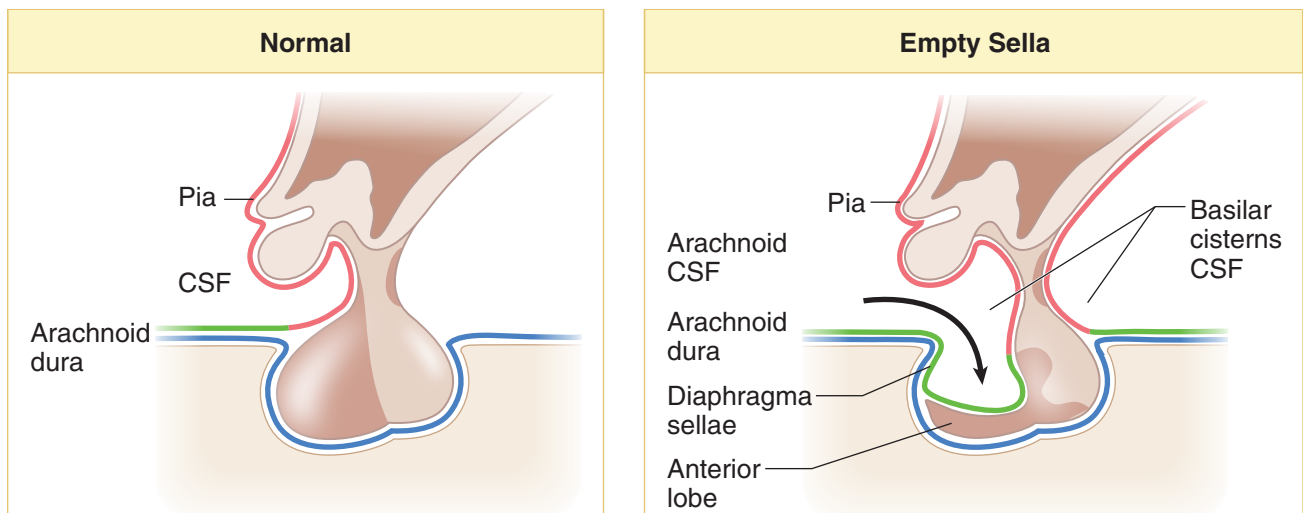


Figure 2-4. Empty Sella Syndrome



Clinical Recall

What is the best initial test to diagnose acromegaly?

- A. 100 g oral glucose tolerance test
- B. Insulin-like growth factor-1 levels
- C. MRI of the brain
- D. Pituitary biopsy
- E. Adrenal venous sampling

Answer: B

Posterior Pituitary

Vasopressin (or ADH) and oxytocin are synthesized in neurons of the supraoptic and paraventricular nuclei in the hypothalamus, then transported to the posterior pituitary lobe to be released into the circulatory system.

- ADH deficiency will cause DI.
- ADH excess will cause syndrome of inappropriate secretion of ADH (SIADH).

Diabetes Insipidus

DI often starts in childhood or early adult life. Men > women.

- **Central DI** is a disorder of the neurohypophyseal system caused by partial or total deficiency of ADH. It leads to excessive, dilute urine and increased thirst associated with hypernatremia.
 - Causes include neoplastic or infiltrative lesions of the hypothalamus or pituitary (60% also have partial or complete loss of anterior pituitary function); in the hypothalamus these lesions can be secondary to adenoma, craniopharyngioma, etc.; in the pituitary gland, adenoma, leukemia, or sarcoid histiocytosis can lead to DI
 - Other causes include pituitary or hypothalamic surgery, radiotherapy, severe head injuries, anoxia, hypertension, meningitis
 - Idiopathic DI starts in childhood
 - Encephalitis, TB, and syphilis may affect the pituitary as well
- **Nephrogenic DI** is caused by renal resistance to the action of vasopressin. It can be idiopathic or it can be secondary to hypercalcemia, hypokalemia, sickle cell disease, amyloidosis, myeloma, pyelonephritis, sarcoidosis, or Sjögren syndrome.
 - Causes include drugs (lithium, demeclocycline, colchicine)

Clinical Findings. Clinical findings of DI include polyuria, excessive thirst, polydipsia (16–20 L/d), hypernatremia with high serum osmolarity and coexisting low urine osmolarity and urine specific gravity <1.010. Nocturia is expected.

Hypertonicity is not usually present if the patient has an intact thirst mechanism and can increase water intake to keep up with urinary loss.

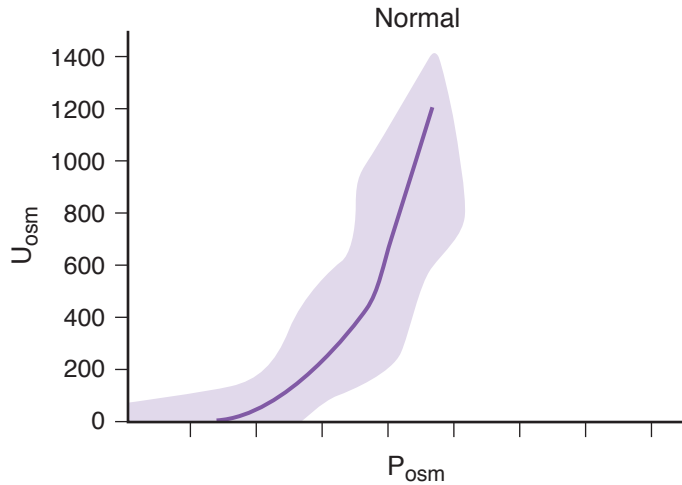


Figure 2-5. P_{osm} versus U_{osm} during Dehydration in Normal Subjects

Diagnosis. The water deprivation test compares U_{osm} after dehydration versus U_{osm} after vasopressin.

- In a healthy person, the response to fluid restriction is decreased urine volume and increased urine osmolality.
- In a person with DI, urine volume remains increased and urine osmolality remains low (<200 mOsm/kg H₂O) despite volume depletion.
- ADH will be decreased in central DI and increased in nephrogenic DI. If a patient falls to the right of the shaded area, the diagnosis is DI.

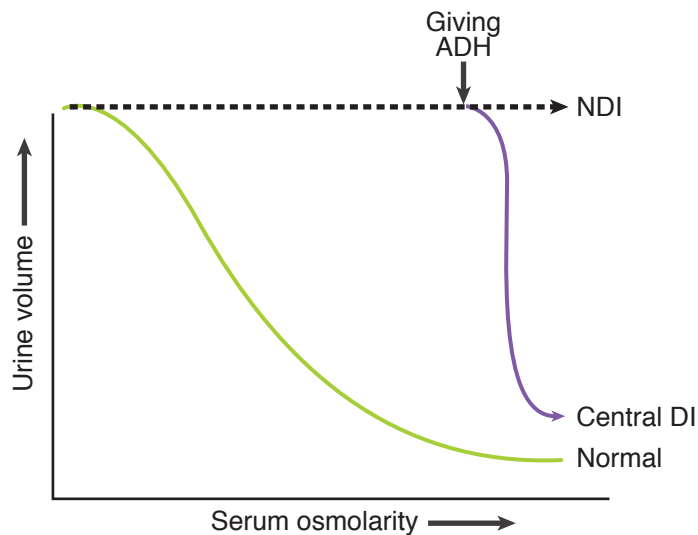


Figure 2-6. Water Restriction Test



The differential diagnosis of DI includes primary disorders of water intake (psychogenic polydipsia, drug-induced polydipsia from chlorpromazine, anticholinergic drugs, or thioridazine) and hypothalamic diseases.

Treatment.

- Hormone replacement with vasopressin subcutaneously or desmopressin subcutaneously, orally, or intranasally
- Drugs to stimulate the secretion of ADH or increase release (chlorpropamide, clofibrate, or carbamazepine)
- HCTZ or amiloride (for nephrogenic DI) to enhance the reabsorption of fluid from proximal tubule
- Chlorthalidone
- Correction of any calcium and/or potassium abnormalities

Syndromes associated with ADH excess involve a mechanism of defense against hypovolemia or hypotension. This includes adrenal insufficiency, excessive fluid loss, fluid deprivation, and probably positive-pressure respiration.

Excessive release of ADH from the neurohypophysis is associated with drugs or diseases (SIADH).

Syndrome of Inappropriate Antidiuretic Hormone

Causes include:

- Malignancy, e.g., small cell carcinoma, carcinoma of the pancreas, ectopic ADH secretion
- Nonmalignant pulmonary disease, e.g., TB, pneumonia, lung abscess
- CNS disorder, e.g., head injury, cerebral vascular accident, encephalitis
- Drugs, e.g., chlorpropamide, clofibrate, vincristine, vinblastine, cyclophosphamide

In general, increased ADH causes water retention and extracellular fluid volume expansion without edema or hypertension, owing to natriuresis. Symptoms include:

- Hyponatremia (**key feature in SIADH**) as a result of water retention and sodium loss
 - Concentrated urine ($U_{osm} > 300$ mOsm)
 - If hyponatremia is severe (sodium < 120 mOsm) or acute in onset, symptoms of cerebral edema will be seen: irritability, confusion, seizures, coma
- No signs of edema or dehydration

Diagnosis. Lab findings in SIADH include:

- Hyponatremia < 130 mEq/L (possible causes include hypothyroidism and adrenal insufficiency)
- $P_{osm} < 270$ mOsm/kg
- Urine sodium concentration > 20 mEq/L (inappropriate natriuresis)
- Urine osmolality > 300 mOsm/kg
- Euvolemia (normal volume) on physical exam

Note

Syndromes associated with an excess of ADH involve a mechanism of defense against hypovolemia or hypotension such as adrenal insufficiency, excessive fluid loss, fluid deprivation, and probably positive-pressure respiration. Excessive release of ADH from the neurohypophysis is associated with drugs or diseases e.g., SIADH.

- Suppression of renin–angiotensin system
- No equal concentration of atrial natriuretic peptide
- Low blood urea nitrate (BUN), low creatinine, low serum uric acid, and low albumin

Management. Treat underlying causes.

- Restrict fluid to 800–1,000 mL/d to increase serum sodium
- For **chronic SIADH**: loop diuretics and oral salt tablets or demeclocycline, which inhibits ADH action at the collecting duct [V2])
- For **moderate/severe** SIADH: V2 receptor blockers conivaptan and tolvaptan
- For **severe symptoms** (severe confusion, convulsions, coma): IV hypertonic saline (3%) 200–300 mL in 3–4 h (if acute, increase by 2.0–4.0 mEq/L)

Never correct sodium >10 mEq/L/24 hrs, which could lead to osmotic demyelination syndrome (central pontine myelinolysis). If correction has been too rapid, give desmopressin and IV 5% dextrose in water.

Clinical Recall

Which of the following lab findings is suggestive of central DI?

- Increased serum osmolarity, decreased urine osmolarity, decreased ADH
- Decreased serum osmolarity, increased urine osmolarity, increased ADH
- Increased serum osmolarity, decreased urine osmolarity, increased ADH
- Increased serum osmolarity, increased urine osmolarity, increased ADH
- Decreased serum osmolarity, decreased urine osmolarity, decreased ADH

Answer: A

DISEASES OF THE THYROID GLAND

The normal function of the thyroid gland is directed toward the secretion of L-thyroxine (T4) and L-3,5,5'-triiodothyronine (T3), which influence a diversity of metabolic processes.

Diseases of the thyroid can be quantitative or qualitative alterations in hormone secretion, enlargement of thyroid (goiter), or both.

- Insufficient hormone secretion will lead to **hypothyroidism**.
- Excess hormone secretion will lead to **hyperthyroidism**.
- Generalized enlargement can be associated with increased, normal, or decreased function of the gland, depending on the underlying cause.
- Focal enlargement of the thyroid can be associated with tumors (benign or malignant).

**Clinical Pearl**

Always check **free** T4 to assess thyroid function.

The most sensitive test in thyroid diseases is the TSH. If TSH is normal, then the patient is euthyroid.

Total T4 and T3, however, does not always reflect actual thyroid function.

- **Increased TBG levels are seen in pregnancy** and the use of oral contraceptives. Total T4 will increase but free or active T4 level will be normal.
- **Decreased TBG levels** are seen in nephrotic syndrome and the use of androgens. Total T4 will decrease but free or active T4 will be normal, with the patient being euthyroid.

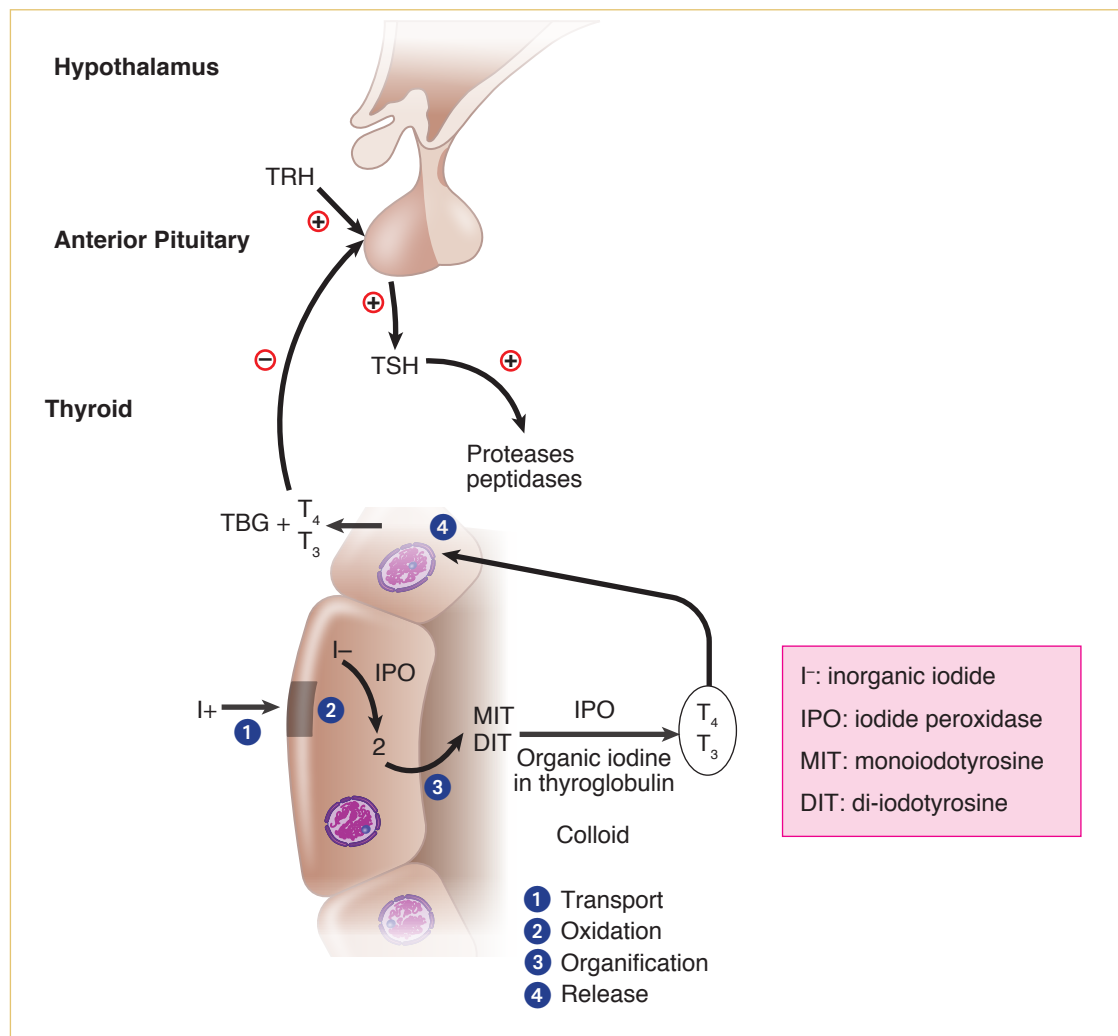


Figure 2-7. Pathways for Synthesis and Secretion of Thyroid Hormones

RAIU (thyroid-reactive iodine uptake) varies directly with the functional state of the thyroid. After 24 hours, normal uptake is 5–30% of administered dose.

- RAIU is **increased** in Graves disease and toxic nodule.
- RAIU is **decreased** in thyroiditis and surreptitious ingestion of thyroid hormone.

Table 2-1. Evaluating Thyroid Function

Thyroid Hormones and TSH	RAI Uptake Scan	Diagnosis
• Decreased TSH • Free increased T_4; increased T_3	Increased RAIU	De novo synthesis of hormone (primary hyperthyroidism)
• Decreased TSH • Free increased T_4; increased T_3	Decreased RAIU	Factitious hyperthyroidism or inflammation/destruction of the gland releasing preformed hormone into the circulation (subacute thyroiditis)
• Decreased TSH • Free decreased T_4; decreased T_3	Decreased RAIU	Secondary or tertiary hypothyroidism

Other tests include antimicrosomal and antithyroglobulin antibodies, which are detected in Hashimoto thyroiditis. In Graves disease, thyroid-stimulating immunoglobulin (TSI) is found. Serum thyroglobulin concentration can be used to assess the adequacy of treatment and follow-up of thyroid cancer, and to confirm the diagnosis of thyrotoxicosis factitia.

Note

Factitious use of thyroid hormone will suppress thyroglobulin levels.

Hyperthyroidism (Thyrotoxicosis)

Graves disease (toxic diffuse goiter) is the **most common cause** of hyperthyroidism. Graves is an autoimmune disorder which causes the production of antibodies (TSI). Autoantibodies form and bind to the TSH receptor in thyroid cell membranes, stimulating the thyroid to hypersecrete T_4 and T_3 .

- Commonly affects patients age <50
- Women > men
- Significant genetic component, i.e., a person is more likely to be affected if they have family member with the disease
- Commonly triggered by stress, infection, and pregnancy
- Risk factors include having another autoimmune disease such as type 1 diabetes or pernicious anemia and smoking



Courtesy of Tom D. Thacher, MD



Wikimedia, Jonathan Trobe, MD/University of Michigan Kellogg Eye Center

Figure 2-8. Pretibial Myxedema

Figure 2-9. Proptosis and Lid Retraction

Note

For treatment purposes, it is important to distinguish **primary hyperthyroidism** (Graves disease or toxic adenoma) from **thyroiditis**.

Note

- Because of the high relapse rate (>50%) associated with antithyroid treatment, many clinicians prefer to use radioactive iodine as first-line therapy. Patients currently taking antithyroid drugs must discontinue the medication at least 2 days prior to taking the radiopharmaceutical, since pretreatment with antithyroid drugs reduces the cure rate of radioiodine therapy in hyperthyroid diseases.
- With radioactive iodine, the desired result is hypothyroidism due to destruction of the gland, which usually occurs 2–3 months post-administration, after which hormone replacement treatment is indicated.

Clinical Findings. Graves is associated clinically with diffuse painless enlargement of the thyroid. Additionally:

- Nervous symptoms (younger patients)
- Cardiovascular and myopathic symptoms (older patients)
- Atrial fibrillation
- Emotional lability, inability to sleep, tremors
- Frequent bowel movements
- Excessive sweating and heat intolerance
- Weight loss (despite increased appetite) and loss of strength
- Proximal muscle weakness (prominent symptom in many patients, and the primary reason why they see a physician)
- Dyspnea, palpitations, angina, and possible cardiac failure
- Warm and moist skin
- Palmar erythema, along with fine and silky hair in hyperthyroidism
- Ocular signs such as staring, infrequent blinking, and lid lag
- Menstrual irregularity such as oligomenorrhea
- Osteoporosis and hypercalcemia, as a result of increases in osteoclast activity
- Dermopathy (rare but hallmark sign)
- Proptosis (protrusion of the eyes), pretibial myxedema (specific to Graves)

Diagnosis of Graves is made on history and physical exam. Lab studies include the following:

- Decreased TSH (but elevated TSH in secondary hyperthyroidism)
- High serum free T₄ and T₃
- Elevated RAIU (but decreased RAIU in subacute thyroiditis and factitious hyperthyroidism)
- Elevated TSI, antithyroglobulin, and antimicrosomal antibodies

Treatment of Graves is relief of symptoms and correction of the thyrotoxic state.

- Beta-adrenergic blockade (propranolol) for adrenergic hyperfunction
- Anti-thyroid medication (methimazole (**preferred**) or propylthiouracil) for high thyroid levels (blocks the synthesis of thyroid hormones and/or by treatment with radioactive iodine)
 - **Methimazole:** long half-life, few side effects; taken 1×/day (often given before radioactive iodine treatment)
 - **Propylthiouracil:** severe side effects (potential liver damage); taken 2–3×/day (use only when methimazole is not appropriate)
- Radioactive iodine (**most commonly used ‘permanent’ treatment**): indications for its use (overusing antithyroid agents alone) include large thyroid gland; multiple symptoms of thyrotoxicosis; elevated thyroxine; and high titers of TSI
- Subtotal thyroidectomy (and rarely, total thyroidectomy), only in pregnancy (second trimester), in children, and in cases when the thyroid is so large that there are compressive symptoms

To monitor response to treatment, check free T4 and T3—not TSH—because it will be suppressed for a very long time and is not a reliable marker of treatment response.

Other causes of hyperthyroidism include:

- Hyperfunctioning adenoma (toxic adenoma)
- Toxic multinodular goiter (Plummer disease, a non-autoimmune disease of the elderly associated commonly with arrhythmia and CHF)
- Simple goiter
- Subacute thyroiditis (painful) or by lymphocytic thyroiditis (painless, postpartum), which can cause transient hyperthyroidism
- Drugs such as amiodarone, alpha interferon, and lithium, which can induce thyrotoxicosis
- Excess iodine (as with expectorants or an iodine-containing contrast agent for imaging)
- Extrathyroid source of hormones, i.e., thyrotoxicosis factitia and ectopic thyroid tissue (struma ovarii, functioning follicular carcinoma)
- Excess production of TSH (secondary hyperthyroidism) (rare)

Thyroid Storm

Thyroid storm is an extreme form of thyrotoxicosis, and an **endocrine emergency**. It is precipitated by stress, infection, surgery, or trauma. It manifests with extreme irritability, delirium, coma, tachycardia, restlessness, vomiting, jaundice, diarrhea, hypertension, dehydration, and high fever.

Treatment is supportive therapy with saline and glucose hydration, glucocorticoids, and oxygen cooling blanket. Therapy for hyperthyroidism is also used:

- First, give propylthiouracil.
- Next, give iodine to inhibit hormone release.
- Follow with adrenergic antagonists (e.g., β -adrenergic blockers).

Clinical Correlate

For years propylthiouracil was the drug of choice for Graves during pregnancy, because it causes fewer severe birth defects than methimazole. However, after it caused a few cases of liver damage, experts now give propylthiouracil during the first trimester only. Use methimazole after the first trimester. For the same reasons, use methimazole for nursing mothers. Both drugs can cause agranulocytosis.



Clinical Pearl

When large quantities of iodide are ingested by patients with hyperthyroidism, the result is thyroid hormone suppression (**Wolff-Chaikoff effect**).

Clinical Correlate

Amiodarone is an antiarrhythmic drug used to treat ventricular and supraventricular tachyarrhythmia.

- Structurally similar to T₄ and contains approximately 40% iodine
- Highly lipid-soluble and concentrated in the adipose tissue, muscle, liver, lung, and thyroid gland
- Has a high elimination half-life (50–100 days) so total body iodine stores can remain increased for up to 9 months after drug is discontinued

- Finally, give dexamethasone to provide adrenal support.
- Stop the antithyroid drugs 1–2 weeks before and after the RAI treatment, as they block the uptake of the radioactive iodine.

Subacute Thyroiditis

Thyroiditis includes disorders of different etiologies characterized by inflammation of the thyroid. Each has a different clinical course and can be associated at one time or another with euthyroid, thyrotoxic, or hypothyroid state.

Subacute thyroiditis, most likely viral in origin, includes granulomatous, giant cell, or de Quervain thyroiditis. It is commonly seen in decades 4 and 5.

- Follows upper respiratory infection symptoms, e.g., malaise, fever, pain over the thyroid, and pain referred to the lower jaw, ears, neck, or arms
- Thyroid gland is enlarged and firm
- Lab findings include elevated erythrocyte sedimentation rate, decreased radioactive iodine uptake, initial elevation in T₄ and T₃ (due to leak of hormone from the gland) followed by hypothyroidism as the hormone is depleted
- Differential diagnosis includes mostly Graves disease

Treatment is symptomatic with NSAIDs, prednisone, and propranolol. The disorder may smolder for months but eventually subsides with return to normal function.

Hypothyroidism

The far majority of hypothyroidism has a thyroid etiology (primary). Causes include:

- Chronic lymphocytic thyroiditis (Hashimoto disease) (**most common cause of goitrous hypothyroidism**; associated with antimicrosomal antibodies) is a chronic inflammatory process of the thyroid with lymphocytic infiltration of the gland.
 - Commonly seen in middle-aged women; in children, is the most common cause of sporadic goiter
 - Most likely caused by autoimmune factors, as evidenced by lymphocytic infiltration, increased immunoglobulin, and antibodies against components of thyroid tissue (antithyroglobulin Abs)
 - Hallmark feature is a goiter that is painless; rubbery; not always symmetric; diagnosis is suggested by finding a firm, nontoxic goiter on examination
 - Lab findings include metabolically normal values in early stages, then increased TSH and decreased T₃ and T₄; high titers of antithyroid antibodies, namely antimicrosomal antibodies, are found, as are antithyroperoxidase antibodies
- Postablative surgery or radioactive iodine, heritable biosynthetic defects, and iodine deficiency
- Drugs such as lithium and acetylsalicylic acid
- Suprathyroid causes of hypothyroidism include pituitary induced (secondary hypothyroidism) or hypothalamic induced (tertiary hypothyroidism)

- Amiodarone, interferon, and sulfonamides
 - Thyroid abnormalities are seen in up to 20% of patients receiving long-term amiodarone treatment. (However, other research has shown that with lower doses of amiodarone, incidence of thyroid dysfunction is around 4%.) The effects range from abnormal thyroid function test findings (without clinical hyper- or hypothyroidism) to overt thyroid dysfunction, which may be amiodarone-induced thyrotoxicosis or amiodarone-induced hypothyroidism (both can develop in apparently normal thyroid glands or in glands with preexisting abnormalities).
 - Amiodarone-induced thyrotoxicosis **type 1** occurs in patients with underlying thyroid pathology, e.g., autonomous nodular goiter or Graves (treatment is anti-thyroid therapy), while **type 2** is a result of amiodarone causing a subacute thyroiditis, with release of preformed thyroid hormones into the circulation (treatment is glucocorticoids).
 - Amiodarone-induced hypothyroidism is due to inhibition of peripheral conversion of T4 to T3.

Clinical Findings.

- In the **newborn**, cretinism (in 1/5,000 neonates) and juvenile hypothyroidism; persistent physiologic jaundice, hoarse cry, constipation, somnolence, and feeding problems
- In **later months**, delayed milestones and dwarfism, coarse features, protruding tongue, broad flat nose, widely set eyes, sparse hair, dry skin, protuberant abdomen, potbelly with umbilical hernia, impaired mental development, retarded bone age, and delayed dentition
- In the **adult**, there are stages:
 - **Early stages** may include lethargy; constipation; cold intolerance; stiffness/cramping of muscles; carpal tunnel syndrome; menorrhagia
 - **Later stages** may include slowing intellectual and motor activity; decreased appetite; weight gain, dry hair/skin, deeper, hoarse voice; deafness; elevated cholesterol and slow, deep tendon reflexes; hyponatremia and anemia
 - **Ultimately**, myxedema (expressionless face, sparse hair, periorbital puffiness, large tongue, and pale, cool skin that feels rough and doughy)
- Hypercholesterolemia and diastolic hypertension (increase in vascular resistance) (**common**)
- Myositis (**very common**) (everyone with myopathy should have TSH checked, even if on a statin)
- Weakness, cramps, and myalgias
- Elevated serum CK
- Increased CPK, AST, hyponatremia, and LDH (associated with 10% pernicious anemia)

Diagnosis of hypothyroidism is made with symptoms and physical findings. Lab tests confirm diagnosis.

Note

- In primary hypothyroidism, TSH will always be elevated due to loss of negative feedback inhibition.
- If TSH is normal with low T4 or T3, that is **secondary** (pituitary-induced) hypothyroidism, not primary!

**Table 2-2. Confirmation of Hypothyroid Diagnosis**

Primary Hypothyroidism	Secondary or Tertiary Hypothyroidism
Increased TSH	Normal or decreased TSH
Decreased T_4 and FT_4	Decreased T_4 and FT_4
Mildly decreased T_3	Decreased secretion of other hormones

Note

Increase T4 dose by 30–50% during pregnancy.

Treatment. The goal with hypothyroidism is to restore the metabolic state with T4.

- In the elderly and those with CAD, this should be done gradually: start with 25–50 mcg and slowly increase.
- In young patients without CAD, start with a weight-based dose of T4, ~100 ug/d.
 - Monitor TSH, T3, and T4 (it takes 6 weeks to equilibrate).
 - T4 must be taken on an empty stomach with no other drugs or vitamins (e.g., calcium, iron, PPIs), as they can decrease its absorption.
- If there is a strong suspicion of supratyroid hypothyroidism with a hypothalamic or pituitary origin, give hydrocortisone with thyroid hormones. If there is known supratyroid hypothyroidism, use T4 level—not TSH—to guide treatment.
- If patients require very high doses of T4 and still have elevated TSH, they have malabsorption, so look for celiac sprue.
- During pregnancy, demand for thyroid hormones may increase, so monitor closely. Treat hypothyroidism with T4 (may need 30–50% increase), and target TSH in the lower reference range. Measure TSH at 4–6 weeks' gestation, then every 4–6 weeks until 20 weeks' gestation.

Subclinical hypothyroidism

Subclinical hypothyroidism is an early, mild form of hypothyroidism, with increased TSH and normal T4.

Treat when TSH >10 uU/mL, patient has difficulty conceiving, or there are symptoms of hypothyroidism. Repeat TSH in 6–8 weeks to confirm.

Myxedema coma

Myxedema coma can result if severe, chronic hypothyroidism is left untreated. It is precipitated by cold exposure, trauma, infections, and CNS depressants. It is associated with respiratory depression (CO_2 retention), hypotension, bradycardia, hypoglycemia, and hyponatremia.

Patients develop a hypothermic, stuporous state that is frequently fatal.

Treatment is very high doses of T4 and hydrocortisone (until concomitant adrenal insufficiency has been ruled out with a cosyntropin stimulation test).

Lymphocytic thyroiditis

Lymphocytic thyroiditis (silent, painless, or postpartum thyroiditis) is a self-limiting episode of thyrotoxicosis associated with chronic lymphocytic thyroiditis. It is common in women of any age. The etiology and pathogenesis are unclear.

- Thyroid is nontender, firm, symmetric, and slightly enlarged.
- Characteristic sequence of symptoms is hyperthyroidism, followed by hypothyroidism, and then recovery.
- Lab findings include elevated T3/T4, low RAIU, and normal ESR.
- If antithyroid antibodies are present, they are only in low titer.
- May last for 2–5 months and be recurrent (as in postpartum thyroiditis)

Reidel thyroiditis

Reidel thyroiditis results from intense fibrosis of the thyroid and surrounding structures (including mediastinal and retroperitoneal fibrosis).

Treatment is symptomatic with propranolol.

Neoplasia of the Thyroid

- **Papillary carcinoma** (most common thyroid cancer, nearly 70%) is associated with history of radiation exposure. Women > men by 2–3×.
 - Bimodal frequency: peaks occur in decades 2 and 3, and then again later in life
 - Slow-growing; spreads via lymphatics after many years
 - Treatment is surgery (for small tumors limited to single area of thyroid) or surgery plus radiation (for large tumors); TSH suppression therapy with T4 is also used
- **Follicular carcinoma** (15–20% of all thyroid cancers) is common in the elderly. Women > men.
 - More malignant than papillary carcinoma
 - Spreads hematogenously with distant metastasis to the lung and bone
 - Treatment is near total thyroidectomy with postoperative radioiodine ablation
- **Medullary carcinoma** (5% of all thyroid cancers) occurs as a sporadic form or familial form. It arises from parafollicular cells of the thyroid.
 - More malignant than follicular carcinoma
 - In familial form, families have no other associated endocrine dysfunctions
 - Often produces calcitonin (is the only thyroid cancer with elevated calcitonin)
 - Is the component of 2 types of MEN (multiple endocrine neoplasia)
 - In MEN type IIa (Sipple syndrome), pheochromocytoma, medullary thyroid carcinoma, and (in 50% of cases) parathyroid hyperplasia occur.
 - In MEN type IIb, pheochromocytoma, medullary carcinoma, and neuromas occur.

Note

With **nonthyroidal illness syndrome** (previously called *euthyroid sick syndrome*), acutely ill patients have low free T4, low TSH and very low T3. The condition will normalize in 4–8 weeks. No treatment is needed.

Note

Estrogen increases liver production of TBG, while testosterone reduces liver production of TBG.

Note

Calcitonin can be elevated with cancer of the lung, pancreas, breast, and colon. However, of the **thyroid cancers**, **calcitonin is elevated only with medullary carcinoma**.



Clinical Correlate

RET mutations are the mutations associated with MEN2 and familial medullary thyroid carcinomas.

Note

Thyroglobulin is secreted by papillary and follicular carcinoma and is a marker for recurrent/persistent disease. After thyroidectomy, check thyroglobulin at 6 months and then annually.

- **Thyroid adenoma (benign tumor)** may be nonfunctioning or hyperfunctioning.
 - Categorized as follicular (**most common**; highly differentiated, autonomous nodule), papillary, or Hürthle.
 - Slow-growing
 - Treatment for hyperfunctioning adenoma is ablation containing radioactive iodine.

Thyroid carcinoma should be suspected with the following:

- Recent growth of thyroid or mass with no tenderness or hoarseness
- History of radiation to the head, neck, or upper mediastinum in childhood (takes ~30 years to develop thyroid cancer)
- Presence of a solitary nodule or calcitonin production
- Calcifications on x-ray such as psammoma bodies suggest papillary carcinoma.
- Do thyroid function tests first; cancer is never hyperfunctioning.
- Increased density on x-ray suggest medullary carcinoma.

For a solitary nonfunctioning nodule, diagnostic tests include:

- TSH; if normal, then proceed to FNA
- FNA for cytology in most cases
 - Nonfunctioning thyroid nodules prove to be malignant in a small number of cases.
 - Functioning nodules are very seldom malignant.
- U/S to distinguish cysts from solid nodules

Clinical Recall

Which of the following is the best initial step (most sensitive test) for the diagnosis of suspected hyperthyroidism?

- A. RAIU scan
- B. Free T4 level
- C. Free T3 level
- D. TSH level
- E. TSI including antithyroglobulin and antimicrosomal Ab

Answer: D

PARATHYROID GLANDS

The function of parathyroid hormone (PTH) is to maintain extracellular fluid calcium concentration.

- Acts directly on the bone and kidney, and indirectly on intestine (through its effects on synthesis of 1,25-dihydroxycholecalciferol [$1,25(\text{OH})_2\text{D}_3$]) to increase serum calcium
- Is closely regulated by the concentration of serum-ionized calcium
- Increases osteoclast activity, which releases calcium
- Inhibits phosphate reabsorption in the kidney tubule, also favoring bone dissolution and calcium release from bones
- Activates vitamin D, which increases the GI absorption of calcium

Calcium regulation involves the following:

- **Three tissues:** bone, kidney, intestine
- **Three hormones:** PTH (hypercalcemic), calcitonin (hypocalcemic), and activated vitamin D (hypercalcemic)

Hypocalcemia

Hypocalcemia is insufficient calcium in the blood. Causes include:

- Hypoparathyroidism (the parathyroid glands secrete insufficient amounts of PTH, leading to hyperphosphatemia [causes phosphate to elevate because PTH is essential for renal excretion of phosphate])
 - Surgical removal of the thyroid (**most common cause of hypoparathyroidism**)
 - Hereditary hypoparathyroidism (DiGeorge syndrome)
 - Acquired hypoparathyroidism (surgical removal)
- Hypomagnesemia (magnesium deficiency, seen with decreased GI absorption and alcoholism; prevents release of PTH from the gland)
- Autosomal dominant hypocalcemia (genetic disorder with an activating mutation in the CaS receptors)
 - Usually when CaS receptors are activated by calcium, PTH is suppressed (negative feedback inhibition)
 - When there is an activating mutation of the CaS receptor, it is always activated, so PTH is always suppressed, leading to low calcium and hyperphosphatemia

Hypocalcemia is also seen in:

- Renal failure (*hyperphosphatemia*, elevated PTH, and low 1,25-dihydroxyvitamin D)
- Vitamin D deficiency (*hypophosphatemia*) (vitamin D is needed for intestinal absorption of calcium and phosphate)
- Drugs such as loop diuretics, phenytoin, alendronate, and foscarnet
- Pseudohypoparathyroidism (resistance to PTH), elevated PTH, and hyperphosphatemia
- Massive blood transfusion, due to binding of the calcium to the citrate in the transfused blood



- Low magnesium, due to malnutrition with alcoholism (preventing the release of PTH from the parathyroid glands)
- Alkalosis, decreasing free calcium by causing increased binding of calcium to albumin
- Pseudo hypocalcemia, which occurs with low albumin; normal free calcium, and decreased total calcium

Clinical Findings. Hypocalcemia results in increased neural hyperexcitability. Symptoms depend on the level of calcium, duration, acid-base disorder, and age at onset.

- Neuromuscular irritability: tetany, laryngospasm, cramping, seizures, impaired memory function
- Possible positive Chvostek sign (percussion of the facial nerve in front of ear, which elicits a contraction of facial muscles and upper lip)
- Possible positive Trousseau sign (inflation of a BP cuff on the arm to a pressure higher than patient's systolic BP for 3 min elicits flexion of the metacarpophalangeal joints and extension of interphalangeal joints)
- Ocular findings: cataracts, soft tissue calcifications
- Possible cardiovascular effects: QT prolongation, refractory CHF, and/or hypotension

Diagnosis is suggested when serum calcium is low; it is important to check albumin and make the correction in calcium level.

- Low calcium may be due to low albumin; for a 1.0 g/dL drop in albumin, total calcium will decrease by 0.8 mg/dL. It is better to measure ionized calcium.
- PTH can be low (hypoparathyroidism) or high.
- **Low calcium + high phosphorous** can be due to renal failure, massive tissue destruction, hypoparathyroidism, or pseudohypoparathyroidism. **Low calcium + low phosphorous** can be due to absent/ineffective vitamin D.

Treatment.

- Acute disease: IV calcium gluconate
- Chronic disease
 - Kidney failure: calcitriol (1,25-dihydroxyvitamin D)
 - Liver failure: 25-hydroxycholecalciferol and calcium
 - Vitamin D deficiency: high dose cholecalciferol (D3) or ergocalciferol (D2) and calcium
 - Hypoparathyroidism: calcitriol and calcium

Correct hypomagnesemia if present. Overtreatment can cause kidney stones.

Hypercalcemia

Hypercalcemia is elevated total or free calcium in the blood.

- About 98% of calcium is stored in bone. Calcium is absorbed from the proximal portion of the small intestine, particularly the duodenum.
- About 80% of an ingested calcium load in the diet is lost in the feces, unabsorbed.
- Of the 2% of calcium that is circulating in blood, free calcium is 50%, protein bound is 40%, with only 10% bound to citrate or phosphate buffers.

Causes of hypercalcemia include:

- Primary hyperparathyroidism (**most common**), usually asymptomatic and found on routine testing
- Malignancy such as SCC, renal cell, bladder, breast cancer, which produce a PTH-related protein
- Granulomatous disease such as sarcoidosis, TB, berylliosis, histoplasmosis, and coccidioidomycosis or lymphoma
- Vitamin D intoxication, thiazide diuretics, lithium, and Paget disease, as well as prolonged immobilization (all rare)
- Hyperthyroidism, due to a partial effect of thyroid hormone on osteoclasts
- Acidosis, due to increased free calcium (because albumin buffers acidosis, and increased binding of hydrogen ions to albumin results in the displacement of calcium from albumin)
- Multiple myeloma, due to lytic bone disease (cytokines activate osteoclasts)

Familial hypocalciuric hypercalcemia (FHH)

- Benign form of hypercalcemia
- Presents with mild hypercalcemia, urine calcium to creatinine ratio <0.01 , and urine calcium <200 mg/day (hypocalciuria)
- Most patients have a family history of hypercalcemia
- Associated with a loss of function mutations in the CaSR gene, which encodes a calcium-sensing receptor (expressed in kidney and parathyroid tissue); the perceived lack of calcium level by the parathyroid leads to high levels of parathyroid hormone
- Indicated by the presence of both hypercalcemia and hypocalciuria
- No treatment is needed, since patients typically asymptomatic

Clinical Presentation.

- Neurologic: decreased mental activity such as lethargy and confusion
- GI: decreased bowel activity such as constipation and anorexia but also possible nausea and vomiting; pancreatitis due to precipitation of calcium in the pancreas
- Possible ulcer disease (unclear reasons)
- Renal: polyuria and polydipsia due induction of NDI; calcium precipitation in the kidney, causing kidney stones and nephrolithiasis
- Cardiovascular: hypertension (30–50% of patients); ECG will show a short QT

Note

In granulomas, macrophages have their own 25-vitamin D hydroxylation, producing active 1,25 vitamin D (**high-yield fact**).

Note

- FHH will result in both hypercalcemia and hypocalciuria.
- In all other causes of hypercalcemia, elevated blood calcium is correlated with elevated urine calcium (as a properly sensing kidney works to excrete calcium).

Note

While pancreatitis is associated with *hypercalcemia*, **severe pancreatitis** is associated with *hypocalcemia* because calcium binds to malabsorbed fat in the intestine.

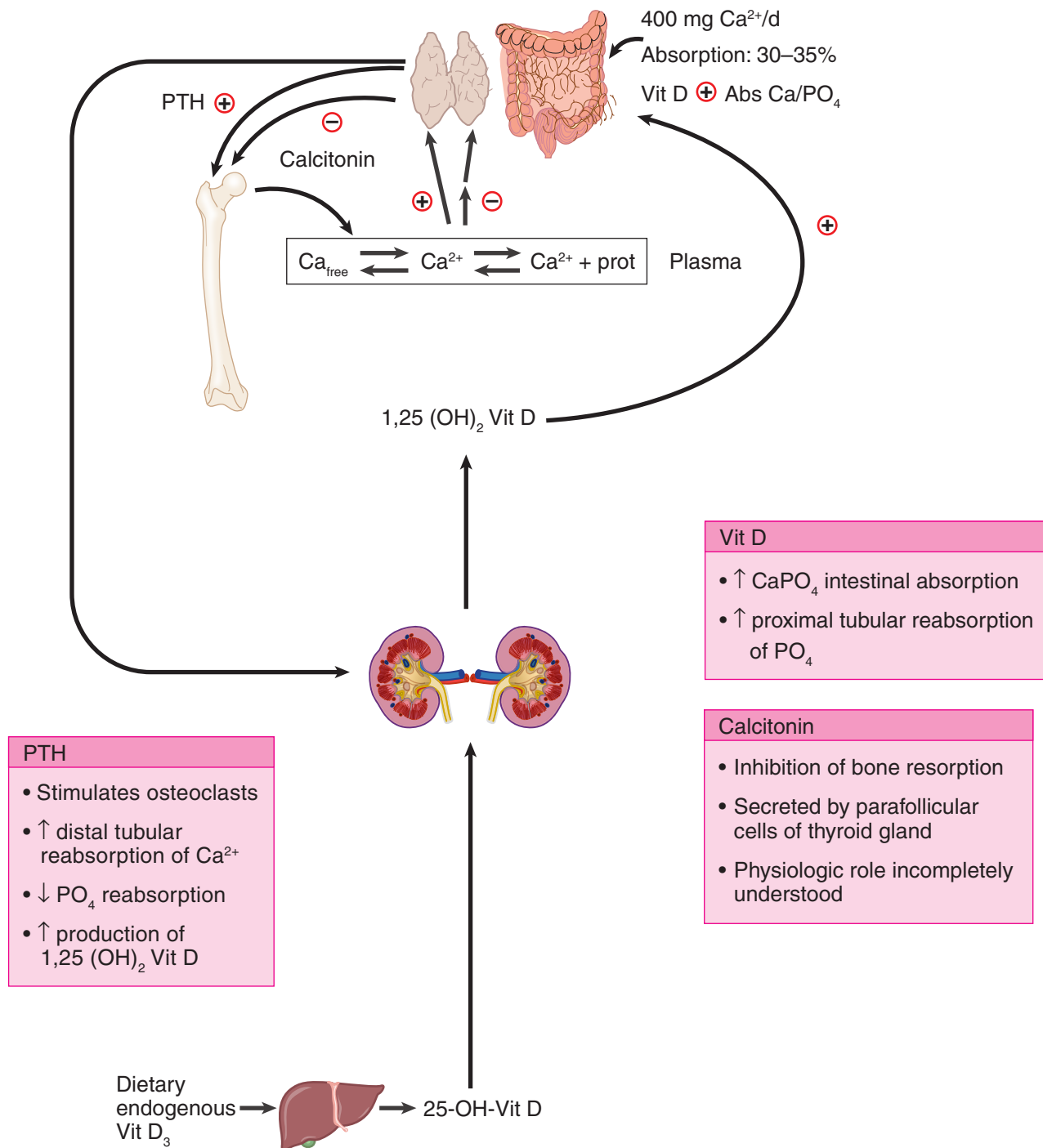


Figure 2-10. Calcium Regulation

Treatment. For severe, life-threatening hypercalcemia, give the following:

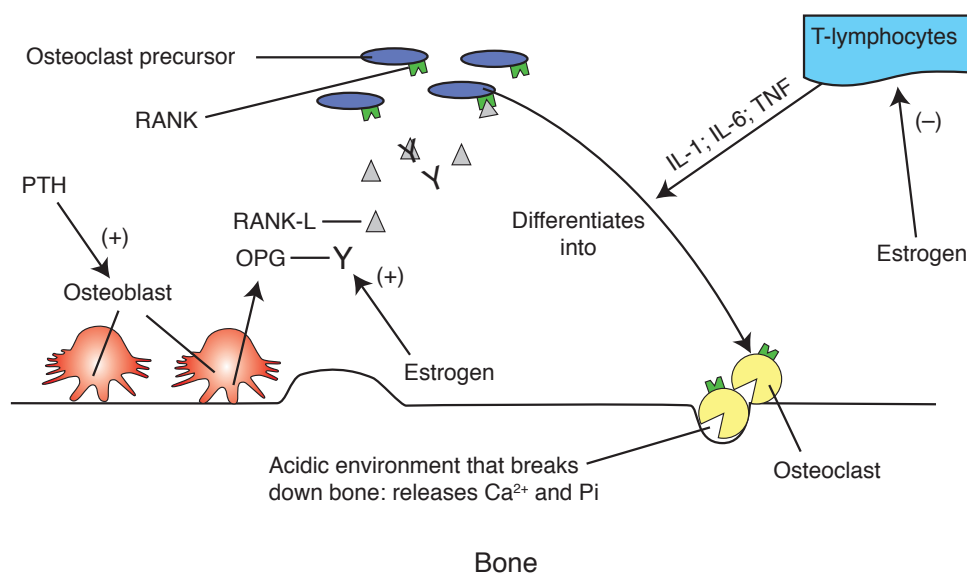
- Vigorous fluid replacement with normal or half-normal saline
- IV bisphosphonate such as zoledronate or pamidronate to inhibit osteoclasts and stimulate osteoblasts (maximum effect takes 2–3 days)
- If fluid replacement and diuretics do not lower the calcium level quickly enough and you cannot wait the 2 days for the bisphosphonates to work, use calcitonin
 - Calcitonin inhibits osteoclasts.
 - After 48 hours, calcitonin can cause tachyphylaxis.
- Prednisone for elevated 1,25-di-hydroxyvitamin D (granulomas or lymphoma), or multiple myeloma
- Hemodialysis for severe hypercalcemia and oliguric renal failure

Loop diuretics are not recommended for hypercalcemia unless the patient has heart failure, renal failure, or volume-overload after aggressive IVFs.

Note

With hypercalcemia:

- Calcitonin is an intermediary measure while waiting for IV bisphosphonate to act.
- Bisphosphonates cannot be used with renal failure.



RANK = receptor activator of nuclear factor kappaB

RANK-L = receptor activator of nuclear factor kappaB ligand

OPG = osteoprotegerin (endogenous blocker of RANK-L)

Pi = phosphate

Figure 2-11. Relationship between Osteoblasts and Osteoclasts



Note

- Think of vitamin D deficiency in cases of low phosphate and low calcium.
- To diagnose, test 25-hydroxy-vitamin D (not 1,25-di-hydroxy-vitamin D) for the following reasons:
 - Most total body stores of vitamin D are in the form of 25-hydroxy-vitamin D (with a very small amount activated).
 - 25-hydroxy-vitamin D has a longer half-life than 1,25-di.

Clinical Correlate

Prolonged vitamin D deficiency can also lead to elevated PTH (seen in intestinal malabsorption and vitamin D-dependent rickets, type II). Symptoms include osteomalacia, bone pain/muscle weakness, and fractures. Calcitriol (activated vitamin D) increases intestinal absorption of calcium and phosphate. To diagnose, test 25-hydroxy-vitamin D (not 1,25-di-hydroxy-vitamin D) because most total body stores of vitamin D are in the form of 25-hydroxy-vitamin D, with a very small amount activated. Also, 25-hydroxy-vitamin D has a longer half-life. Level <30 mg/mL is consistent with deficiency.

Hyperparathyroidism

There are 3 types of hyperparathyroidism.

- **Primary** hyperparathyroidism (**most common condition of mild hypercalcemia**) is caused by a hyperfunction of the parathyroid glands.
 - Most commonly, the oversecretion of PTH is caused by a parathyroid adenoma of one gland (hyperplasia of all 4 glands is a less common cause, and parathyroid cancer is a rare cause).
 - Elevated PTH then causes elevated serum calcium and low serum phosphate.
 - Can be seen with MEN
 - In MEN type I, hyperparathyroidism, pituitary tumors (3 “Ps”), and pancreatic tumors are seen.
 - In MEN type II, hyperparathyroidism, pheochromocytoma, and medullary carcinoma of the thyroid are seen.
- **Secondary** hyperparathyroidism is due to physiologic (i.e., appropriate) secretion of PTH by the parathyroid glands in response to hypocalcemia resulting from vitamin D deficiency or chronic kidney disease.
 - Serum calcium is low (causing the elevated PTH).
 - In the case of chronic kidney failure and anuria, phosphate is elevated (the kidney is unable to ‘trash’ phosphate).
 - Phosphate is low.
 - Prolonged vitamin D deficiency can also lead to elevated PTH (seen in intestinal malabsorption and vitamin D-dependent rickets, type II). Symptoms include osteomalacia, bone pain/muscle weakness, and fractures. Calcitriol (activated vitamin D) increases intestinal absorption of calcium and phosphate. To diagnose, test 25-hydroxy-vitamin D; level <30 mg/mL is consistent with deficiency.
- **Tertiary** hyperparathyroidism is seen with long-term secondary hyperparathyroidism, which can lead to hyperplasia of the parathyroid glands and a loss of response to serum calcium levels.
 - Most commonly seen in patients with chronic renal failure.
 - Is an autonomous activity of the parathyroid glands.
 - Hypercalcemia and hyperphosphatemia will be seen.
 - Treatment is surgical removal.

Clinical Findings. About 50% of patients with hyperparathyroidism are asymptomatic. When symptoms do occur, they include:

- Osteitis fibrosa cystica due to increased rate of osteoclastic bone resorption; will cause bone pain, fractures, swelling, deformity, areas of demineralization, bone cysts, and brown tumors (punched-out lesions producing a salt-and-pepper-like appearance)
- Urinary tract manifestations, including polyuria, polydipsia, stones, and nephrocalcinosis with renal failure (the polyuria and polydipsia are from NDI)
- Neurologic manifestations, including CNS problems, mild personality disturbance, severe psychiatric disorders, mental obtundation or coma, neuromuscular weakness, easy fatigability, and atrophy of muscles

- GI manifestations, including anorexia/weight loss, constipation, nausea/vomiting, thirst, abdominal pain with pancreatitis, and peptic ulcer disease
- Cardiovascular findings, including hypertension and arrhythmias (short QT)

Diagnosis.

- Serum calcium >10.5 mg/dL
- Elevated PTH
- Elevated urine calcium (80%) (but some patients have normal level due to the calcium-reabsorbing action of PTH)
- Low serum phosphate (<2.5 mg/dL)

Imaging studies such as CT, MRI, sonography, and nuclear scan are not used to diagnose hyperparathyroidism. A nuclear parathyroid scan (sestamibi) can be used to localize the adenoma. When combined with a neck sonogram, specificity rises significantly.

Treatment.

Primary hyperparathyroidism.

- Surgery (those age <50)
 - Indications include symptoms of hypercalcemia; serum calcium >1 mg/dL above normal; GFR <60 mL/min; T-score <-2.5; kidney stones; and 24-hour urine calcium >400 mg/day.
 - Before surgery, do sestamibi scan to look for an adenoma; also check 25-hydroxyvitamin D level; if a deficiency exists, correct before surgery, as vitamin D deficiency increases the risk of hungry bone syndrome.
 - Hungry bone syndrome is severe hypocalcemia after parathyroidectomy due to relative hypoparathyroidism and reduced PTH-mediated production of activated vitamin D culminating in rapid influx of calcium into bone.
- If surgery is not needed
 - Calcium, creatinine, and GFR measurement every year
 - BMD measurement every 2 years
- If surgery is contraindicated
 - Medical treatment with bisphosphonates (pamidronate)
 - Reduced dietary calcium to 400 mg/d
 - Oral hydration with 2–3 L of fluid; phosphate supplementation with phospho-soda

Secondary hyperparathyroidism.

- Check for and correct vitamin D
- Correct hyperphosphatemia first with a phosphate-binder such as calcium acetate or sevelamer and lanthanum
- If still no response to PTH level, give calcitriol
 - Activated vitamin D suppresses PTH release by negative feedback inhibition on the parathyroid glands.
 - Phosphate must be <5.5 mg/dL before giving calcitriol because it can increase intestinal absorption of phosphate.

Note

In every other cause of hypercalcemia, the PTH level will be low. In primary hyperparathyroidism, PTH is always elevated.

Note

Calcitonin is an intermediary measure while waiting for IV bisphosphonate to act.

Note

Half of all patients with primary hyperparathyroidism also have vitamin D deficiency, and serum calcium will be even higher after that deficiency is corrected. Check vitamin D in all patients with primary hyperparathyroidism.

**Note**

Hyperparathyroidism can cause pseudogout (look for chondrocalcinosis).

- Cinacalcet, a calcimimetic agent which shuts off the parathyroids, will increase the sensitivity of calcium-sensing receptors to calcium (basolateral membrane potential) on the parathyroid and suppress PTH secretion (side effects include hypocalcemia); it is used only for select circumstances:
 - Patients on hemodialysis
 - Hypercalcemia in patients with parathyroid carcinoma
 - Patients with moderate-to-severe primary hyperparathyroidism unamenable to surgery

Tertiary hyperparathyroidism.

- Parathyroidectomy is usually necessary.

Hypoparathyroidism

See section on *Hypocalcemia*.

Clinical Recall

Which of the following is a clear indication for surgery in a patient with primary hyperparathyroidism?

- A. Calcium level 10.5 mg/dL
- B. Creatinine level 1.0 mg/dL
- C. ECG showing prolonged QT interval
- D. Male gender, age 38
- E. DEXA T-score +1.0

Answer: D

Osteoporosis

Osteoporosis is a disease of decreased bone mass leading to increase fractures. Causes include:

- Estrogen deficiency in women (**most common**)
- Secondary causes (**high yield**)
 - Testosterone deficiency (any man with osteoporosis should have testosterone level checked)
 - Hyperthyroidism
 - Hyperparathyroidism
 - Cushing syndrome
 - Cirrhosis
 - Malabsorption (celiac, Crohn disease)
 - Rheumatoid arthritis
 - CKD

- Vitamin D deficiency
- Medications (steroids, excessive thyroid hormone, phenytoin, phenobarbital, thiazolidinediones, PPI)
- Multiple myeloma

Diagnosis is made with the following:

- BMD test with DEXA scan for women age ≥ 65 and premenopausal women at increased risk (i.e., RA, glucocorticoid use, hyperparathyroidism, malabsorption/celiac sprue).
 - **Osteopenia:** DEXA T-score -1.0 to -2.4
 - **Osteoporosis:** DEXA T-score < -2.5
- History of fragility fracture (fall from standing height or lower)

All patients diagnosed with osteoporosis should have the following checked:

- CBC, TSH, LFTs
- Calcium, phosphorous
- Creatinine
- 25-hydroxy-vitamin D
- tTG antibodies (if celiac is suspected)
- Cushing work-up if there are features of Cushing syndrome

Treatment. Start with smoking cessation, alcohol reduction, resistance exercises, and supplemental calcium/vitamin D. Medical therapy includes:

- Bisphosphonates: alendronate or risedronate (**first-line**)
 - Oral bisphosphonates can lead to pill esophagitis.
 - IV bisphosphonates and denosumab can cause osteonecrosis of the jaw.
- Denosumab (monoclonal antibody that inhibits RANK-L and decreases osteoclast activity) in stage 4 CKD and intolerant/incomplete response to bisphosphonates
- Teriparatide (synthetic PTH) increases bone formation and bone mass
- Calcitonin for pain from fractures
- Teriparatide is associated with osteosarcoma; use for 2 years at most

For osteoporosis, do not use the following:

- Estrogen replacement
- Combination teriparatide + a bisphosphonate
- Combination bisphosphate + CKD (use denosumab instead) and hypocalcemia



Osteomalacia

Osteomalacia is a metabolic bone disease resulting from failure of organic matrix of bone to mineralize because of lack of calcium or phosphorus.

Symptoms and signs include:

- Bone pain, fatigability
- Proximal muscle weakness
- Hypocalcemia and hypophosphatemia
- Elevated alkaline phosphatase

Diagnosis is made with vitamin D testing.

Treatment is high-dose ergocalciferol or cholecalciferol.

Paget Disease of the Bone

Paget is increased bone remodeling, leading to accelerated rates of bone turnover and disruption of the normal architecture of bone and deformities of bone (enlargement of the skull, bowing of the femur). Most patients are asymptomatic and will have incidental x-ray findings or elevated alkaline phosphatase on routine labs.

Symptoms and signs include bone pain; fractures; high-output cardiac failure (**most common cause of death**); cranial nerve compression; and spinal stenosis.

Diagnosis is made with the following:

- Elevated alkaline phosphatase
- X-ray showing focal osteolysis with coarsening of the trabecular pattern (sclerotic bone), cotton wool skull and cortical thickening (bone scan must be ordered to evaluate extent of disease)
- Calcium and PTH are usually normal

Treatment is bisphosphonates if there is bone pain, radiculopathy, or involvement of a weight-bearing bone.

DISORDERS OF THE EXOCRINE PANCREAS

Diabetes Mellitus

Diabetes mellitus (DM) is a disorder of carbohydrate metabolism, affecting 20% of patients age >65 in the United States. Causes include:

- Relative or absolute deficiency of insulin
- Hyperglycemia
- End-organ complications (e.g., nephropathy, retinopathy, neuropathy, accelerated atherosclerosis)

There are 2 types of DM, but **type 2 is far more common**.

- **Type 1 IDDM (insulin-dependent or juvenile onset)** (5–10% of diabetes worldwide, most likely autoimmune)
 - Males = females
 - Age of onset usually age <30
 - Genetically, <10% of first-degree relatives are affected with a 50% occurrence in identical twins
 - Increased prevalence of autoantibodies to islet cells, glutamic acid decarboxylase (GAD), and other tissues with IDDM
 - Associated with HLA-B8, HLA-B15, HLA-DR3, and HLA-DR4
 - Body build usually lean
 - Patients prone to ketosis owing to absent insulin production
 - By the time the condition appears, most of the beta cells in the pancreas destroyed
 - High prevalence of other autoimmune disorders, such as celiac disease, Graves, hypothyroidism, Addison, pernicious anemia, vertigo
 - Think of this diagnosis if age 35–50, BMI <25, acute onset, personal or family history of autoimmune disease
 - Anti-glutamic acid decarboxylase, anti-islet cell, antibodies to tyrosine phosphatase IA-2 will be positive.
 - C-peptide is not helpful in determining type I vs type II because it can be low in DM II also
- **Type 2, or NIDDM (non-insulin-dependent or maturity onset)** (90% of cases)
 - Males > females
 - Age of onset usually age 40
 - Genetically >20% of first-degree relatives are affected with 90–100% occurrence in identical twins
 - No associated autoantibodies
 - Body build usually obese (most are >15% above ideal body weight)
 - Patients are ketosis-resistant, and insulin levels may be high, normal, or low
 - Two clear physiologic defects: abnormal insulin secretion and resistance to insulin action in target tissues
 - Progresses because beta-cells burn out, not because insulin resistance gets worse

Clinical Findings. Symptoms vary by patient, but commonly hyperglycemia, polyuria, polydipsia, polyphagia, ketonuria, and weight loss are seen.

- First event may be an acute metabolic decompensation, resulting in coma (ketoacidosis for IDDM and hyperosmolar coma for NIDDM)
- Occasionally, initial symptom of DM is a degenerative complication like neuropathy

Note

Type 2 diabetes progresses because of loss of beta-cells, not because of worsening insulin-resistance.

**Diagnosis.**

- In **asymptomatic** patients: elevated plasma or urine glucose during routine screening does not establish diagnosis but indicates a need for further evaluation.
- In **symptomatic** patients: polyuria, polydipsia, ketonuria, and weight loss.
 - Plasma glucose >200 mg/dL is sufficient for diagnosis with no further testing needed; random glucose >200 mg/dL is diagnostic
 - Fasting plasma glucose ≥ 126 mg/dL on 2 occasions; DM is diagnosed when plasma glucose ≥ 200 mg/dL at 2 h and on at least one of the earlier samples
 - HbA_{1c} $>6.5\%$ is diagnostic of diabetes

If 2 separate tests are done and one is normal, repeat the abnormal test:

- A1C is falsely low in hemolytic anemia, chronic kidney disease. Use finger sticks for more accurate measurements.
- A1C is falsely high in iron deficiency due to increase proportion of older erythrocytes.

Glycosylated hemoglobin A_{1c} (HbA_{1c}) is produced by nonenzymatic condensation of glucose molecules with free amino groups on the globin component of hemoglobin. It is used both for diagnosis and to follow compliance of the treatment and glucose control in diabetic patients. HbA_{1c} is high in diabetics with chronic hyperglycemia during the preceding 8–12 weeks.

- In young patients, goal A1C is 7%.
- In older patients and young patients with long-term complications (ie, renal failure, blind), goal is 8%.

Treatment. The objectives of diabetic therapy are to control symptoms, prevent acute complications, and limit long-term complications. The goal is HbA_{1c} $<7\%$. Patient education is essential.

- Weight loss, low-fat diet, exercise (up to 25% success rate with this alone): reduction of as little as 4–7% body fat has an enormous effect on peripheral insulin sensitivity and on reduction of postprandial hyperglycemia
- When diet and exercise do not keep HbA_{1c} $<7\%$, medications are introduced.
 - Oral hypoglycemic should be used for all patients with type 2 DM
 - Metformin (**first-line**) and lifestyle intervention should be used for all newly diagnosed patients
 - Metformin is safe and should be used in moderate renal failure (do not use if GFR <30 mL/min and use lower dose if 30–45 mL/min)
 - Does not cause hypoglycemia or weight gain
 - Start at a low dose and slowly increase to avoid GI side effects
 - Side effects include vitamin B12 deficiency and lactic acidosis (very rare)

Note

Oral glucose tolerance test is rarely required in DM.

Clinical Correlate

Exercise lowers glucose level:

- Exercising muscle needs no insulin for glucose to enter.
- Resting muscle needs insulin for glucose entry.

The effects of diet, exercise, and weight loss can last for years.

In all cases, **metformin is the best initial treatment for type 2 DM**. After metformin, add-on drugs include:

- Incretin mimetics (exenatide, liraglutide), direct analogues of GLP-1 except their actions last much longer; given by subcutaneous injection
 - **First-line** for obese patients to promote weight loss; augment the naturally occurring hormones secreted from GI tract in response to food (when food enters the intestine, incretins are released)
 - Proven to reduce A1C up to 2%
 - Slow gastric motility (nausea and vomiting are main side effects); may increase risk of pancreatitis so do not use if history of pancreatitis
 - Increase the release of insulin from the pancreas in a glucose-dependent manner, i.e., only if there is hyperglycemia (very rarely cause hypoglycemia)
 - Inhibit glucagon release
 - Liraglutide significantly reduces cardiovascular death and all-cause mortality; use on anyone with diabetes and cardiovascular disease
- Dipeptidyl peptidase IV (DPP-IV) inhibitors (sitagliptin, saxagliptin, linagliptin, alogliptin): inhibit the metabolism of the incretins GIP and GLP-1; given orally
 - Increase insulin release from the pancreas and slow stomach emptying
 - Weight-neutral
 - Less effective than GLP-1 analogs (GLP-1 analogs are preferred in young, obese patients and those with CAD)
 - Safe in renal failure
- Sodium-glucose co-transporter 2 (SGLT2) inhibitors (canagliflozin, dapagliflozin, empagliflozin, all equal in efficacy) inhibit reabsorption of glucose in the proximal tubules, leading to increased renal excretion of glucose; given orally
 - Cause weight loss 2–3 kg
 - Lower BP and can lead to orthostatic hypotension
 - Use for DM with urine albumin >300 or if GFR >30 ml/minute
 - Side effects include increased risk of genital candida infections, UTI, euglycemic DKA
- Empagliflozin significantly reduces rates of death by CVD, all-cause mortality, and hospitalization for HF (and is FDA-approved for reduction of CV death in adults with type 2 DM and CVD). Also reduces progression of nephropathy (defined as progression to macroalbuminuria, doubling of serum creatinine, initiation of renal replacement therapy, or death from renal disease).
- Canagliflozin is associated with increased risk of amputation (do not use if history of PVD, previous amputations, diabetic ulcer or neuropathy)
- Thiazolidinediones (rosiglitazone, pioglitazone) can worsen CHF. They are thought to act by decreasing the resistance of tissues to insulin. Side effects include weight gain and osteoporosis. Pioglitazone may be linked to bladder cancer.
- Sulfonylureas (glyburide, glipizide, glimepiride) cause insulin secretion from beta-cells. Side effects include weight gain and hypoglycemia. They are used less commonly because of their side effects and lack of proven CVD benefit that is seen in the other agents.

**Note**

If weight loss is desired, use GLP-1 analogs, pramlintide, or SGLT2 inhibitors.

- **Insulin** regimen can be started anytime (will cause weight gain)
 - Start with basal insulin only. If A1C is high but fasting is at goal (80–130), check postprandial 2 hours after a meal. Goal postprandial is <180. Add bolus insulin or meglitinides to control postprandial.
 - Add metformin, GLP-1 analogs, and SGLT2 inhibitors to insulin (leads to better glycemic control and weight loss)
 - When starting insulin, divide 50% into long-acting and 50% into pre-meal short-acting.
 - Usually given as glargine insulin 1×/day injection + 2–3×/day ultra short-acting insulin such as lispro or aspart before meals
 - Glargine causes fewer episodes of hypoglycemia than NPH
 - Levemir is newer, long-acting insulin, lasting 16–18 hours

Table 2-3. Oral Hypoglycemic Drugs

Class	Generic Name
Sulfonylureas	Glyburide, glipizide, glimepiride
Biguanides	Metformin
Thiazolidinediones	Rosiglitazone, pioglitazone
Glucosidase inhibitors	Acarbose, miglitol
Meglitinides	Repaglinide, nateglinide
DPP-IV inhibitors	Sitagliptin, saxagliptin, linagliptin
Subcutaneous agents	
GLP-1	Exenatide, liraglutide
SGLT2 inhibitors	Canagliflozin, dapagliflozin, empagliflozin
Amylin mimetic	Pramlintide (suppresses plasma glucagon secretion; slows gastric emptying and promotes satiety; decreases postprandial glucose rise; and causes weight loss)

Table 2-4. Insulin Preparations

Type	Peak Action (Hours)	Duration of Action (Hours)
Ultra-short-acting		
Insulin lispro	30–60 min	4–6
Insulin aspart	20–30 min	3–5
Rapid (given 5–15 min before meals)		
Regular	2–4	6–8
Semilente	2–6	10–12
Glulisine (given 30 min before meals)		
Intermediate		
NPH	6–12	12–18
Lente	6–12	12–18
Long-acting		
Glargine	2	24
Levemir	18–24	36
Degludec		

Clinical Recall

Which of the following is the best initial drug to start in a patient with newly diagnosed non-insulin-dependent DM?

- A. PO glyburide
- B. PO chlorpropamide
- C. PO acarbose
- D. IM insulin glargine
- E. PO metformin

Answer: E



Bariatric procedures should be considered in obese patients.

There are several important complications that can result from untreated DM.

- **Acute complications**

- **Diabetic ketoacidosis (DKA)** (seen in type 1 DM) is a result of severe insulin insufficiency and may be the presenting manifestation. Precipitating factors include insufficient or interrupted insulin therapy, infection, emotional stress, and excessive alcohol ingestion.
 - Symptoms include anorexia, nausea/vomiting, abdominal pain, rapid breathing (Kussmaul respiration), “fruity” breath odor of acetone, signs of dehydration, and altered consciousness to coma. Acidosis can result in fatal rhythm disturbance.
 - Diagnosis is made with elevated blood glucose, increased serum acetoacetate, acetone, hydroxybutyrate, metabolic acidosis (low serum bicarbonate and low blood pH), and increased anion gap (sodium – [bicarbonate + chloride])
 - Treatment is insulin, fluids, and electrolyte replacement, with normal saline in high volumes. Bolus with 5–10 units of regular insulin.
 - Acutely, DKA is associated with hyperkalemia. The total body level of potassium is depleted because of the urinary loss of potassium. As soon as potassium level falls to ≤ 5 mEq/L, give potassium replacement. Start with IV insulin, then switch to subcutaneous insulin (overlap them both for 6–8 hours) when anion gap normalizes and serum bicarbonate is normal. Add 5% dextrose to the normal saline as blood glucose reaches 200–250 mg/dL and continue IV insulin until the anion gap normalizes. Check potassium before starting IV insulin; if normal (3.3–5.5 mEq/L, start potassium with insulin, but if < 3.3 mEq/L, hold insulin and give potassium first).
 - The “honeymoon” period is an initial episode of ketoacidosis followed by a symptom-free interval during which no treatment is required. Presumably, stress-induced epinephrine release blocks insulin secretion, causing the syndrome. In normal individuals insulin reserve is such that hormone release is adequate even in the face of stress.
 - The **Somogyi effect** is rebound hyperglycemia in the morning because of counterregulatory hormone release after an episode of hypoglycemia during the night.
 - The **dawn phenomenon** is an early morning rise in plasma glucose secondary to a rise in counter-regulatory hormones cortisol, epinephrine, and GH requiring increased amounts of insulin to maintain euglycemia.
 - If someone has morning hyperglycemia, check glucose at 2 AM to determine if the cause is Somogyi effect or dawn phenomenon.
- **Hyperosmolar nonketotic coma (HONK)** (seen in type 2 DM) is characterized by severe hyperglycemia in the absence of significant ketosis. Pathophysiology involved is profound dehydration resulting from a sustained hyperglycemic diuresis. Clinical findings are weakness, polyuria, polydipsia, lethargy, confusion, convulsions, and coma.
 - Precipitating factors include noncompliance of treatment; inability to drink sufficient water to keep up with urinary losses (common in elderly diabetics living in nursing homes); infections; stroke; steroids; immunosuppressant agents; and diuretics.

- Can result after a therapeutic procedure such as peritoneal/hemodialysis, tube feeding of high-protein formulas, or high-carbohydrate infusion.
 - Diagnosis is made with elevated blood glucose (typically ≥ 700 mg/dL) and extremely high serum osmolality (serum osmolality in mOsm/L = $2[\text{sodium}] + [\text{glucose}/18] + [\text{BUN}/2.8]$). High BUN (prerenal azotemia) and mild metabolic acidosis (bicarbonate ~ 20 mEq/L) is also seen without ketosis.
 - Treatment is high-volume fluids, electrolyte replacement, and insulin.
- **Chronic complications**
 - **Microvascular** disease of diabetes includes diabetic nephropathy, neuropathy, and retinopathy (glycemic control shows far greater effect on morbidity and mortality).
 - Diabetic nephropathy
 - Hyperproliferation, proteinuria, and end-stage renal disease can develop.
 - The pathology is commonly diffuse and leads to widening of glomerular basement membrane and mesangial thickening. Nodular pathology can occur and results in hyalinization of afferent glomerular arterioles (Kimmelstiel-Wilson syndrome).
 - Treatment is strict control of diabetes, ACE inhibitors, and dialysis or renal transplantation.
 - Diabetic neuropathy
 - **Peripheral** neuropathy (**most common**) is symmetrical, with symptoms of numbness, paresthesia, and pain. Physical exam reveals absent reflexes and loss of vibratory sense.
 - **Mononeuropathy**—vascular in origin—affects a single nerve or nerve trunk (mononeuritis multiplex); symptoms include sudden foot drop, wrist drop, or paralysis of CN III, IV, or VI.
 - **Autonomic neuropathy** can be devastating; most common symptoms include orthostatic hypotension and syncope. Other symptoms include difficulty swallowing, delayed gastric emptying (gastroparesis), constipation, or diarrhea. Diagnosis of gastroparesis is the gastric emptying scintigraphy study. Bladder dysfunction or paralysis can lead to urinary retention. Impotence and retrograde ejaculation can occur (erectile dysfunction is as high as 50% in patients with 10 years of diabetes).
 - Prevention of neuropathy in diabetes is with tight glycemic control. Treatment once it occurs depends on the type. For **peripheral** neuropathy, use gabapentin, pregabalin, amitriptyline (avoid in CAD, as it increases CVD mortality), venlafaxine, duloxetine, capsaicin cream. For **autonomic** neuropathy, use sildenafil for erectile dysfunction and metoclopramide or erythromycin for gastroparesis.
 - Diabetic retinopathy (**most common cause of blindness in middle-aged patients**)
 - Retina is affected; simple or proliferative (microaneurysms, hemorrhages, exudates, retinal edema), where damage can occur
 - Proliferative retinopathy (PDR) is the presence of vitreous hemorrhages or neovascularization (treatment is laser photocoagulation), while nonproliferative (NPDR), or background retinopathy, can only be prevented with tight glucose control



- Pan retinal laser photocoagulation for PDR and severe NPDR
- Intraocular infection of bevacizumab (VEGF inhibitor) or ranibizumab for PDR or severe NPDR
- **Macrovascular** disease of diabetes (very common) includes CAD, peripheral arterial disease, and stroke (glycemic control shows far less effect on morbidity and mortality).
 - Central pathological mechanism is atherosclerosis, which leads to narrowing of arterial walls throughout the body; atherosclerosis is thought to result from chronic inflammation and injury to the arterial wall in the peripheral or coronary vascular system
 - Lipid management includes lipid testing in those with diabetes at least annually goal BP <130/80 mm Hg, and a statin for all those with DM age >40 (regardless of LDL)
 - Risk for death using ASCVD risk score. For **high risk** (10-year ASCVD score $\geq 7.5\%$), give high intensity statin, i.e., high-dose atorvastatin or rosuvastatin (except for CKD or age >75 due to risk of rhabdomyolysis). For **moderate risk** (10-year ASCVD risk score <7.5%), give moderate intensity statin, i.e., every other statin or low-dose atorvastatin/rosuvastatin.
 - Do coronary artery bypass in a diabetic patient even if there is only 2-vessel coronary disease.

Diabetes

Most common cause of end-stage renal disease in United States

- Screen all diabetics annually for proteinuria (detectable on standard dipstick when >300 mg/24 hrs.
- Microalbuminuria is defined as 30–300 mg.
- All those with proteinuria should receive treatment with an ACE inhibitor or ARB.

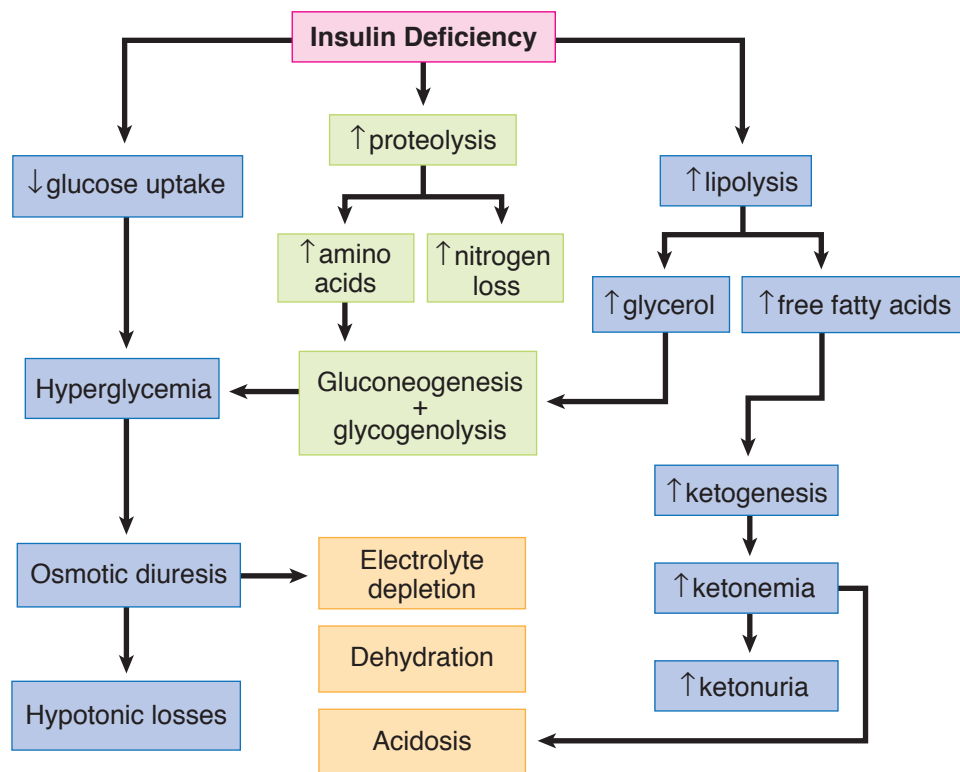


Figure 2-12. Pathophysiology of DKA



Wikimedia, Jonathan Moore

Figure 2-13. Diabetic Foot Ulcer

Note

On the exam, you will be provided with the ASCVD risk score and will not have to calculate.

Note

Macrovascular complications are the most common cause of death in patients with DM. About 75% of deaths result from myocardial infarction, congestive failure, or stroke.

Note

The most common pattern of dyslipidemia in patients with type 2 diabetes is elevated triglyceride and decreased HDL cholesterol.



Hypoglycemia

Glucose is the primary energy source of the brain. Symptoms of low glucose can result from excessive secretion of epinephrine, leading to sweating, tremor, tachycardia, anxiety, and hunger. Hypoglycemia can also result from dysfunction of the CNS, leading to dizziness, headache, clouding vision, blunted mental activity, loss of fine motor skills, convulsions, and loss of consciousness.

There is no uniform correlation between a given level of blood sugar and symptoms. Major symptoms in normal persons may not be seen until blood sugar 20 mg/dL.

- **Postprandial** hypoglycemia (reactive) can be secondary to alimentary hyperinsulinism (after gastrectomy, gastrojejunostomy, pyloroplasty, or vagotomy), idiopathic, and galactosemia.
- **Fasting** hypoglycemia, caused by:
 - Conditions related to the underproduction of glucose, such as hormone deficiencies (panhypopituitarism, adrenal insufficiency), enzyme defects, substrate deficiency (severe malnutrition, late pregnancy), acquired liver disease, or drugs (propanolol, salicylates)
 - Conditions related to overutilization of glucose: hyperinsulinism (which can occur secondary to insulinoma, exogenous insulin, sulfonylureas, drugs [quinine], endotoxic shock, and immune disease with insulin receptor antibodies) and conditions where insulin levels are appropriate, such as extrapancreatic tumors and rare enzyme deficiencies
- **Hypoglycemia caused by insulinoma** (pancreatic B-cell tumor): 90% of these tumors are single and benign. Symptoms include findings of subacute or chronic hypoglycemia, e.g., blurred vision, headache, slurred speech, and weakness. Symptoms occur in the early morning or late afternoon or after fasting or exercise.
 - Factitious hyperinsulinism (common) is caused by self-administration of insulin or ingestion. Most often, patients work in a health profession or have access to drugs through a diabetic family member. A triad of hypoglycemia, high immunoreactivity, insulin, and suppressed plasma C-peptide is pathognomonic of exogenous insulin administration.
 - Ethanol-induced hypoglycemia can occur with prolonged starvation, when glycogen reserves become depleted in 18–24 hours and hepatic glucose output depends completely on gluconeogenesis. Ethanol at a concentration of 45 mg/dL can induce hypoglycemia by blocking gluconeogenesis.

Note

A sulfonylurea screen must be checked before insulinoma can be diagnosed.

Diagnosis is made with serum insulin ≥ 8 mg/mL in the presence of blood glucose < 40 mg/dL (i.e., inappropriately high serum insulin level when glucose is low), noted spontaneously or during a prolonged fast (72 hours). CT scan, U/S, and arteriography may be useful for detecting the tumor(s).

Treatment is surgery, diet, and medical therapy.

Table 2-5. Differential Diagnosis of Insulinoma and Factitious Hyperinsulinism

Test	Insulinoma	Exogenous Insulin	Sulfonylureas
Plasma insulin	High (usually <200 $\mu\text{U/mL}$)	Very high (usually >1,000 $\mu\text{U/mL}$)	High
Proinsulin	Increased	Normal or low	Normal
C peptide (insulin connective peptide) 1:1	Increased	Normal or low	Increased
Insulin antibodies	Absent	+/- Present	Absent
Plasma or urine sulfonylurea	Absent	Absent	Present

Clinical Recall

Which of the following medications is contraindicated in patients with acute pulmonary edema with an ejection fraction of 25%?

- A. Glyburide
- B. Metformin
- C. Rosiglitazone
- D. Exenatide
- E. Sitagliptin

Answer: C

DISEASES OF THE ADRENAL GLAND

The adrenal gland is divided into 2 areas: the cortex and medulla.

- **Cortex**
 - **Outer zone** (glomerulosa), the site of aldosterone synthesis
 - **Central zone** (fasciculata), the site of cortisol synthesis
 - **Inner zone** (reticularis), the site of androgen biosynthesis
- **Medulla**

The disorders of hyperfunction of the gland are associated with specific hormones:

- **Cushing syndrome:** increased cortisol
- **Hyperaldosteronism:** increased aldosterone
- **Virilization in women:** increased adrenal androgens

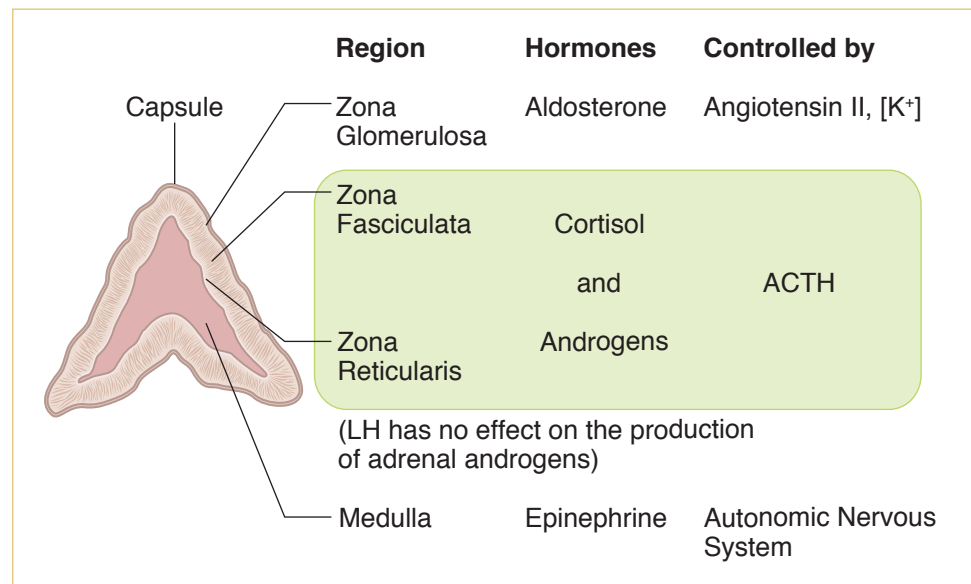


Figure 2-14. Adrenal Cortex Regions

Hyperfunctioning of the Gland

Cushing syndrome

Cushing syndrome results from prolonged exposure to increased cortisol or related corticosteroids. The most common causes are exogenous, iatrogenic, and those secondary to the prolonged use of glucocorticoids. Etiologies include:

- **ACTH-dependent**
 - ACTH-secreting pituitary adenomas (Cushing syndrome)
 - Ectopic ACTH-secreting carcinoma (small cell lung carcinoma, bronchial carcinoid, pheochromocytoma, medullary thyroid carcinoma)
- **ACTH-independent**
 - Adrenal adenoma
 - Adrenal carcinoma

Clinical Findings.

- Deposition of adipose tissue in characteristic sites such as upper fat, moon facies; interscapular buffalo hump; and mesenteric bed, truncal obesity
- Hypertension, muscle weakness, and fatigability related to mobilization of peripheral supportive tissue
- Osteoporosis caused by increased bone catabolism
- Cutaneous striae and easy bruisability

- Acne, hirsutism, oligomenorrhea, and amenorrhea (women) due to increased adrenal androgen secretion
- Glucose intolerance (common, with 20% of patients having diabetes)
- Hypokalemia (due to the mineralocorticoid effect of the steroids; usually not clinically significant) and leukocytosis
- Renal calculi from increased calcium
- Glaucoma
- Increased susceptibility to infections because neutrophils exhibit diminished function as a result of high glucocorticoids

Diagnosis. First-line diagnostic studies include any one of the following tests, but at least 2 of the 3 must be positive.

- **1-mg overnight dexamethasone suppression test** (failure to suppress cortisol to <3)
 - Caution, in this test can produce falsely abnormal or positive tests, due to the following:
 - Drugs which increase the metabolic breakdown of dexamethasone (e.g., phenytoin, carbamazepine), preventing their ability to suppress cortisol
 - Estrogen use, due to increased production of cortisol binding globulin from the liver
 - Stress (as with starvation, anorexia, alcohol use), which increases glucocorticoid levels
 - If cortisol release is suppressed, the etiology is a pituitary adenoma; check intrapituitary sinus sampling for ACTH to confirm the pituitary source.
- **Elevated 24-hour urine cortisol level**
- **Elevated late night salivary cortisol level**

Once Cushing is confirmed, the next step is to order an ACTH.

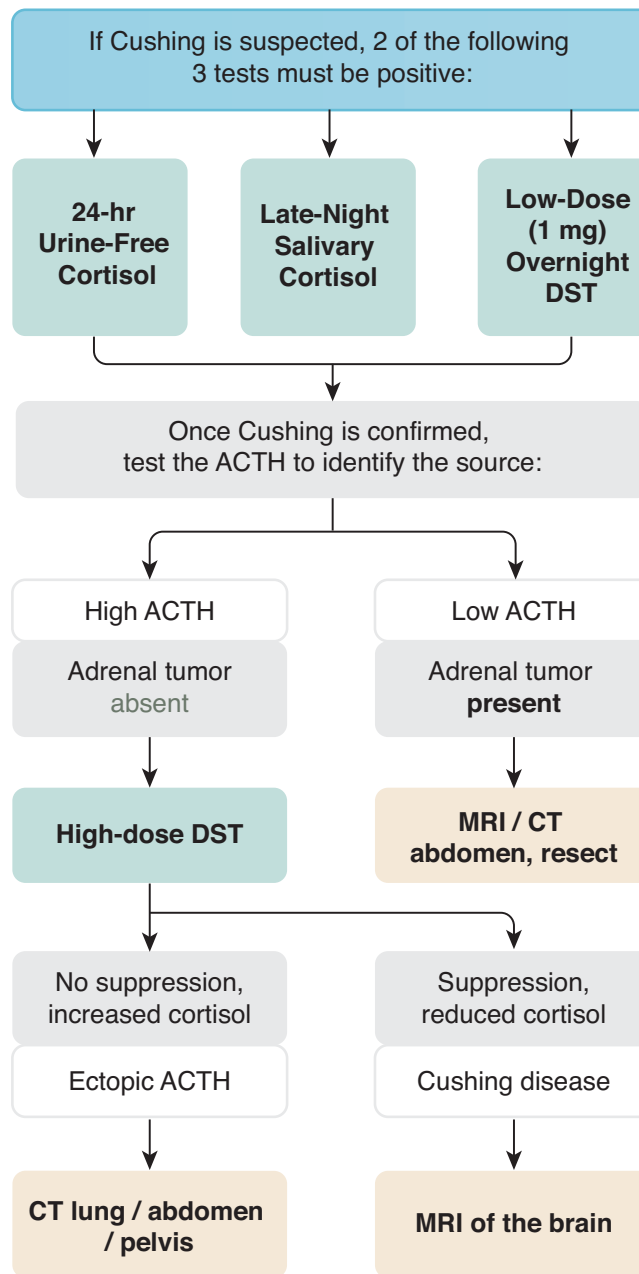
- If ACTH is elevated, it can be a pituitary adenoma or ectopic ACTH-secreting tumor.
 - Confirm the etiology with an MRI of the pituitary. If that is negative, do a high dose dexamethasone suppression test. You give 8 mg of dexamethasone at night and check cortisol in the AM.
 - If high dose does not suppress cortisol production, an ectopic tumor is releasing ACTH.
 - Check chest CT and abdominal CT.
- If ACTH is low, it is an adrenal source, so do an adrenal CT.
 - If ACTH is low, the etiology is most likely from an adrenal tumor (e.g., an adenoma, cancer) or adrenal hyperplasia. When the adrenal gland is the source of increased cortisol production, there is feedback inhibition on the pituitary and the ACTH is suppressed.
 - When ACTH is low, the etiology is confirmed with a CT scan of the adrenals.

Treatment depends on the etiology and can be surgical or medical. Unresectable adrenal tumors are treated with ketoconazole or metyrapone.

Note

A single, random cortisol level is not reliable.

- **High plasma ACTH** suggests a pituitary or ectopic source.
- **Low plasma ACTH** suggests an adrenal tumor or hyperplasia.

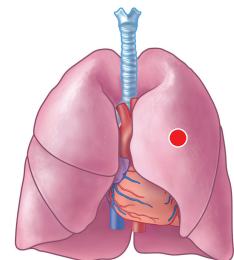


Sources of Cushing Disease:

Anterior Pituitary Adenoma



Ectopic Source



Adrenal Source

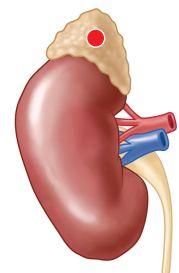


Figure 2-15. Diagnosis and Management for Cushing Syndrome

Hyperaldosteronism

Hyperaldosteronism is associated with hypersecretion of the major adrenal mineralocorticoid, aldosterone. The normal function of aldosterone is to reabsorb sodium and excrete potassium and acid (H^+). There are 2 types of disease:

- **Primary** aldosteronism, in which the stimulus for the excessive aldosterone production is within the adrenal gland
 - Causes include unilateral adrenal adenoma (70% of cases) and bilateral hyperplasia (30%)
 - Excessive black licorice ingestion can mimic this effect, i.e., licorice has aldosterone-like qualities
- **Secondary** aldosteronism, in which the stimulus is extraadrenal
 - Elevated renin level, caused by a low effective circulating volume
 - Seen in renal artery stenosis because there is low blood flow into the JG cells; also seen in cirrhosis and CHF
 - Edema (**high-yield** for the exam)

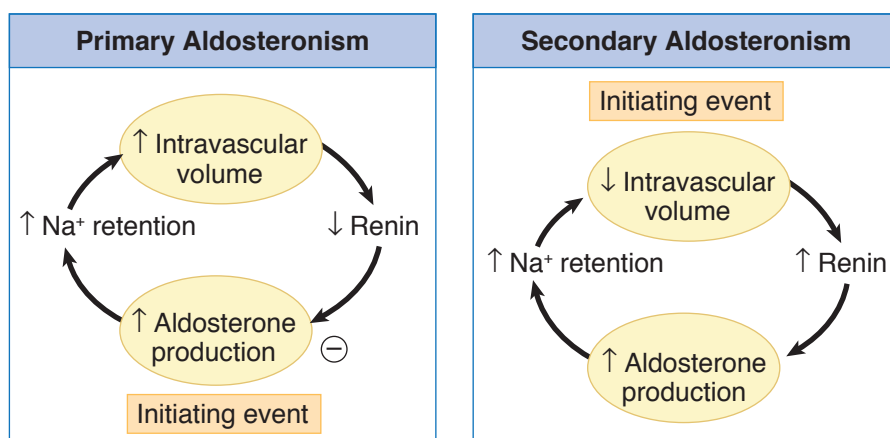


Figure 2-16. Mechanism of Hyperaldosteronism

Clinical Presentation.

- **Primary** hyperaldosteronism
 - Hypertension and low potassium
 - Muscle weakness, polyuria, and polydipsia due to the hypokalemia
 - Metabolic alkalosis due to increased hydrogen ion (H^+) excretion (aldosterone causes alkalosis)
 - Edema (rare because of sodium release into the urine)
- **Secondary** hyperaldosteronism
 - Edema and ascites
 - Volume-overload, but the effective circulating volume is low, leading to elevated secretion of renin

**Table 2-6. Clinical Findings in Primary and Secondary Aldosteronism**

	Primary Aldosteronism	Secondary Aldosteronism
Diastolic hypertension	+	–
Muscle weakness	+	+/–
Polyuria, polydipsia	+	+/–
Edema	–	+/–
Hypokalemia	+	+
Hypernatremia	+	–
Metabolic alkalosis	+	+

Diagnosis.

- Preliminary screen with plasma aldosterone concentration (PAC) and plasma renin activity (PRA): a positive screen is **PAC/PRA ratio >20:1** and **PAC >15 ng/dL**
- Confirmatory screen with an NaCl challenge via normal saline, NaCl tabs, or fludrocortisone: if PAC is still elevated, this confirms the diagnosis
- CT or MRI to evaluate the adrenal glands
- Bilateral adrenal venous sampling (done before surgery even if CT reveals an adrenal mass)
 - Can be an incidental finding, and there may be bilateral adrenal hyperplasia
 - If both adrenal veins have high secretion of aldosterone, do not remove the adrenal mass; the diagnosis is bilateral adrenal hyperplasia and the mass is an incidental finding

Note

Half of patients with primary hyperaldosteronism do not have hypokalemia. Think of this diagnosis when BP is difficult to control or patient is very young.

Note

Testing can be done on patients who are taking any antihypertensive agent, **except for spironolactone and eplerenone**.

Bartter syndrome (a cause of secondary hyperaldosteronism without edema or hypertension) results from a defect in the loop of Henle, in which it loses NaCl. The etiology is a defect in the Na-K-2Cl cotransporter. The result is like having a furosemide-secreting tumor. Symptoms include juxtaglomerular hyperplasia, normal to low BP (but no edema), severe hypokalemic alkalosis, defects in renal conservation of sodium or chloride, and renal loss of sodium—all which stimulate renin secretion and aldosterone production.

Treatment.

- Surgical removal for adenomas
- Spironolactone or eplerenone for bilateral hyperplasia, to block aldosterone

Syndromes of adrenal androgen excess

Syndromes of adrenal androgen excess result from excess production of dehydroepiandrosterone (DHEA) and androstenedione, which are converted to testosterone in extraglandular tissues. The elevated testosterone accounts for most androgenic effects.

Hirsutism, oligomenorrhea, acne, and virilization and common symptoms.

The etiology includes congenital adrenal hyperplasia, adrenal adenomas (rare), and adrenal carcinomas.

Congenital adrenal hyperplasia

Congenital adrenal hyperplasia (CAH) (**most common adrenal disorder of infancy and childhood**) is associated with increased adrenal androgen production due to enzymatic defects. It is the result of autosomal recessive mutations, which produce deficiencies of enzymes needed for cortisol synthesis.

- C-21 hydroxylase deficiency (95% of cases)
- C-11 hydroxylase deficiency: the mineralocorticoid manifestations can be ‘biphasic’
 - In early infancy, despite having excessive mineralocorticoid hormones, patients may present with relative ‘salt-wasting’ (aldosterone deficiency). That is because some infants have inefficient salt conservation as well as immature aldosterone production. During this phase, infants can present with hypotension and hyperkalemia (similar to 21 hydroxylase deficiency).
 - Later in life, there is a better ability to hold onto salt, so patients develop typical C-11 deficiency syndrome (hypertension and hypokalemia).
- C-17 hydroxylase deficiency, characterized by hypogonadism, hypokalemia, and hypertension resulting from increased production of 11-deoxycorticosterone
- Reduced aldosterone secretion (35% of cases)
- Adrenal virilization, with or without an associated salt-losing tendency, owing to aldosterone deficiency, which leads to hyponatremia, hyperkalemia, dehydration, and hypotension

Patients with CAH are female at birth with ambiguous external genitalia (female pseudohermaphroditism), enlarged clitoris, and partial or complete fusion of the labia.

Postnatally, CAH is associated with virilization. Patients may be male at birth with macrogenitosomia; postnatally this is associated with precocious puberty.

Diagnosis. CAH should be considered in all infants exhibiting failure to thrive, especially those with episodes of acute adrenal insufficiency, salt wasting, or hypertension. Testing includes serum testosterone, androstenedione, dehydroepiandrosterone, 17-hydroxyprogesterone, urinary 17-ketosteroid, and pregnanetriol.

Treatment is glucocorticoid (hydrocortisone) replacement.

Clinical Recall

An elderly, obese, diabetic patient presents with LDL 150 mg/dL. Which medication should be given at this time?

- Niacin
- Atorvastatin
- Gemfibrozil
- Lisinopril
- Gabapentin

Answer: B

Note

The ‘biphasic’ presentation is rare. When you think about 11 deficiency, think mineralocorticoid excess (hypertension and hypokalemia) with low cortisol production (remember you need C-11 for the final step in converting to cortisol).

**Note**

Half of patients with autoimmune adrenal insufficiency will have other autoimmune disorders, e.g., type I DM, pernicious anemia, celiac sprue, and vitiligo.

Note

Adrenal crisis may occur in the following situations:

- Previously undiagnosed patient with adrenal insufficiency who has undergone surgery/serious infection/major stress
- Bilateral adrenal infarction or hemorrhage
- Patient who is abruptly withdrawn from chronic glucocorticoid therapy

Adrenal incidentaloma

Adrenal incidentaloma is an incidental adrenal mass found on abdominal CT that has been done for an unrelated reason (e.g., abdominal pain). The first step is to determine if it is malignant:

- Irregular borders
- Size >4 cm
- Hounsfield units >10 (hyper density)

If it appears malignant, treatment is surgical removal. If it is benign (smooth borders, <4 cm, <10 HU), treatment is biochemical testing:

- If BP is normal, do a 1 mg dexamethasone suppression test to evaluate for subclinical Cushing syndrome and a 24-hr urine metanephrine and catecholamine test to evaluate for pheochromocytoma.
- If there is hypertension or hypokalemia, do all of the following tests:
 - Plasma aldosterone-plasma renin ratio (to look for primary hyperaldosteronism)
 - 1 mg dexamethasone suppression test (to look for subclinical Cushing syndrome)
 - 24-hr urine metanephrine and catecholamine (to look for pheochromocytoma)

Hypofunctioning of the Gland**Adrenal insufficiency**

Adrenal insufficiency can be divided into primary adrenocortical insufficiency and secondary failure in the elaboration of ACTH.

- **Primary** adrenocortical insufficiency (Addison disease) is a slow, usually progressive disease due to adrenocorticoid hypofunction. The etiology can be secondary to anatomic destruction of the gland (chronic and acute). Autoimmune destruction accounts for 80% of cases.
 - Idiopathic atrophy is the most common cause of anatomic destruction, and autoimmune mechanisms are probably responsible.
 - Anatomic destruction can also be secondary to surgical removal, infection (TB, fungal, cytomegalovirus), hemorrhagic, trauma, and metastatic invasion.
 - Metabolic failure in hormone production can also lead to Addison disease and can be secondary to CAH, enzyme inhibitors, and cytotoxic agents (mitotane).
- **Secondary** adrenal insufficiency is caused by a lack of ACTH from a pituitary source, most commonly an anterior pituitary adenoma.

Clinical Findings.

- **Primary:** weakness, paresthesias, cramping, intolerance to stress, and personality changes such as irritability and restlessness
 - Chronic disease: small heart; weight loss; sparse axillary hair; hyperpigmentation of the skin (as diffuse brown, tan, or bronze darkening of both exposed and unexposed body parts); arterial hypotension (often orthostatic owing to lack of effect of cortisol on vascular tone); abnormalities of GI function (from mild anorexia with weight loss to vomiting/diarrhea and abdominal pain)
 - Acute disease: fever; hypotension; low sodium with high potassium; mild acidosis

- **Secondary:** similar symptoms to primary, but with the following exceptions
 - No hyperkalemia because ACTH has no control of aldosterone secretion (angiotensin II and serum potassium do)
 - No hyperpigmentation because ACTH levels will be low

In **severe adrenal insufficiency** (adrenal crisis), fever, vomiting, abdominal pain, altered mental status, and vascular collapse may occur.

Diagnosis.

- Rapid ACTH administration and cortisol measurement (obtain cortisol before ACTH)
- WBC count with moderate neutropenia, lymphocytosis, and eosinophilia
- Elevated serum potassium and urea nitrogen
- Low sodium
- Low blood glucose
- Low morning plasma cortisol

Note

A healthy person should show a brisk rise in cortisol level after ACTH administration.

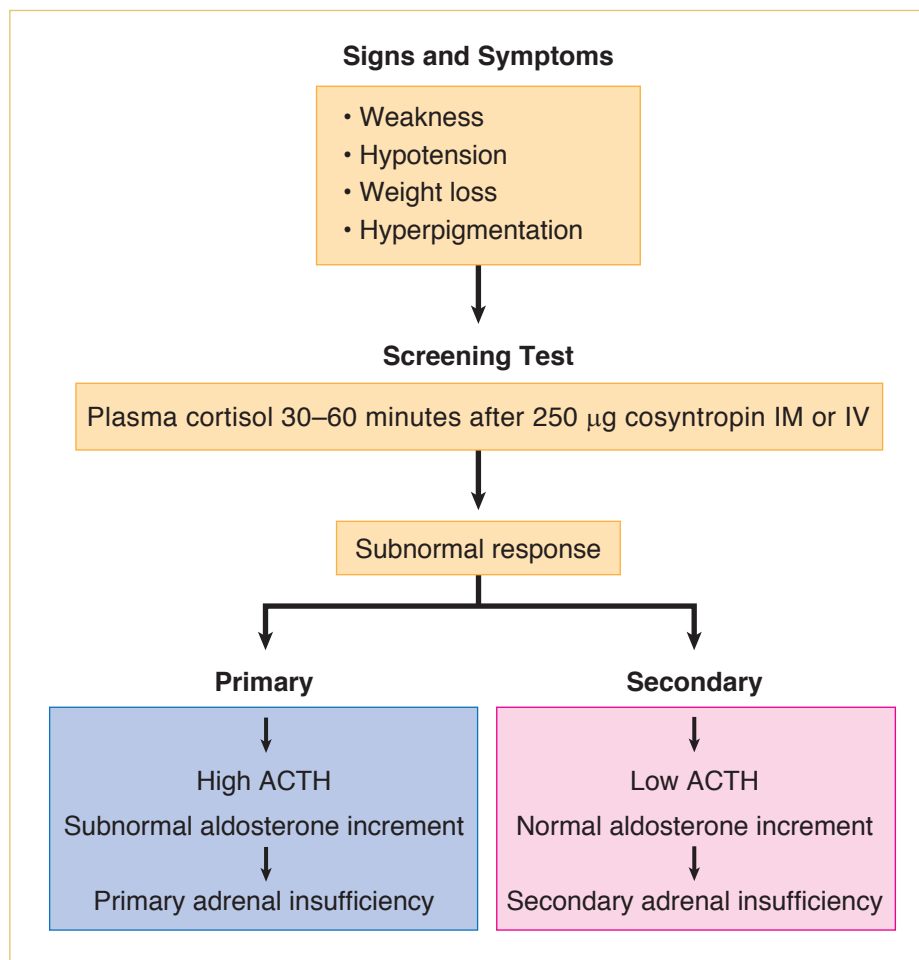


Figure 2-17. Diagnosis of Adrenal Insufficiency



Note

Remember the **rule of 10%** with pheochromocytoma.

- 10% extraadrenal
- 10% malignant
- 10% in children
- 10% bilateral or multiple (> right side)
- 10% not associated with hypertension

Treatment is hydrocortisone to replace glucocorticoids and fludrocortisone to replace mineralocorticoids (only for primary, not secondary). In high stress states such as sepsis and MI, increase the hydrocortisone dose significantly.

With adrenal crisis, get a cortisol level and then rapidly administer fluids and hydrocortisone.

Pheochromocytoma

Pheochromocytoma is a rare, usually benign, tumor that arises from the chromaffin cells of the sympathetic nervous system. It occurs in ~0.1% of the hypertensive population.

- Familial pheochromocytoma (5% of cases) is transmitted as an autosomal dominant trait alone or in combination with MEN type IIa or IIb, von Recklinghausen neurofibromatosis, or von Hippel-Lindau retinal cerebellar hemangioblastomatosis.
- Secretion of dopamine occurs more in familial syndromes and is not associated with hypertension.
- Secretion of epinephrine causes tachycardia, sweating, flushing, and hypertension.
- Norepinephrine is secreted by all extraadrenal tumors.

Clinical Findings.

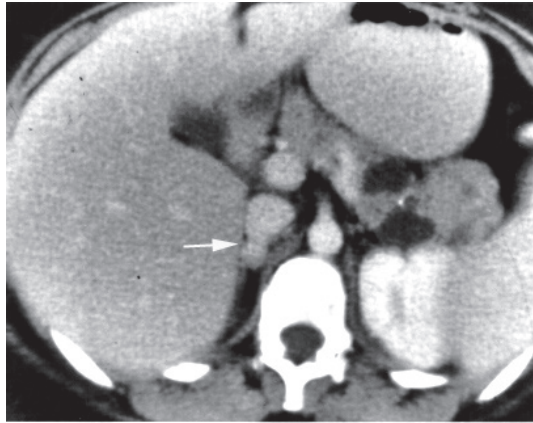
- Paroxysms or crisis (>50% of patients)
- Headache, profuse sweating, palpitations, and apprehension (common)
- Pain in the chest or abdomen, associated with nausea/vomiting
- Elevated BP with tachycardia in crisis (40% of patients have elevated BP only during the attack and 60% have stable hypertension)
- Anxiety, tremor
- Weight loss
- Orthostatic hypotension
- Mild hyperglycemia (30% of patients)
- Death prior to diagnosis, often due to cardiac arrhythmia and stroke (>33% of cases)

Characteristic lesions include:

- **Adults:** unilateral, solitary lesion (80%) with 10% bilateral and 10% extraadrenal
 - Solitary lesions favor the right side.
 - Extraadrenal pheochromocytomas are mostly located within the abdomen and near the celiac, superior mesenteric, and inferior mesenteric ganglia.
- **Children:** 25% bilateral and 25% extraadrenal

Diagnosis is made with the following testing:

- **When pre-test probability is low** (e.g., lack of symptoms or adrenal mass without typical [e.g., vascular] radiographic findings): 24-hour urinary catecholamines, metanephrines, VMA
- **When clinical suspicion is high:** plasma metanephrine (but false-positives are common)
- **Best test overall:** 24-hour urinary metanephrines
- If catecholamines or metanephrines are abnormal, confirm the tumor with CT or MRI; if location of pheochromocytoma is still not revealed, do an MIBG scan



National Institutes of Health

Figure 2-18. Pheochromocytoma

The differential diagnosis of pheochromocytoma includes essential hypertension, anxiety attacks, factitious crisis, intracranial lesions, and autonomic epilepsy.

Treatment.

- Alpha-adrenergic blockade, phentolamine, and/or phenoxybenzamine to control BP and prevent a hypertensive crisis (since high circulating catecholamine levels stimulate alpha receptors on blood vessels and cause vasoconstriction)
- Beta blockers if significant tachycardia occurs after alpha blockade
 - Do not give beta blockers until adequate alpha blockade has been established, since unopposed alpha-adrenergic receptor stimulation can precipitate a hypertensive crisis.
 - Noncardioselective beta blockers (propranolol, nadolol) are the usual choice, though cardioselective agents (atenolol, metoprolol) may be used.
 - Labetalol has been associated with paradoxical episodes of hypertension; thought to be secondary to incomplete alpha blockade.
- Surgical removal of the pheochromocytoma (curative) only after BP has been stabilized; to control BP during surgery, use IV phentolamine—a rapid-acting alpha-adrenergic antagonist.

DISEASES OF THE TESTES

Hypogonadism

In hypogonadism there is decreased function of the testes or ovaries, resulting in the absence or impairment of secondary sexual characteristics and infertility.

- **Primary hypogonadism** (hypergonadotropic: increased LH, FSH) can be caused by:
 - Klinefelter syndrome (small testes, eunuchoid, 47XXY)
 - Anorchia
 - Surgical/accidental castration or radiotherapy
 - Infections (mumps, TB, leprosy)
 - Chemotherapeutic agents (cyclophosphamide)



- **Secondary hypogonadism** (hypogonadotropic: decreased LH, FSH) can be caused by:
 - Hypopituitarism secondary to idiopathic causes or tumors
 - Hypothalamic lesions
 - Kallmann syndrome (hypogonadic hypogonadism, associated with decreased sense of smell)
 - Chronic use of opiates, anabolic steroids, or glucocorticoids
 - Infiltrative diseases (hemochromatosis)
 - Sleep apnea

Clinical Findings.

- Prepubertal hypogonadism, usually caused by a specific gonadotropic deficiency of the pituitary
- Underdeveloped external genitalia, high-pitched voice, beard that does not grow, lack of libido and potency
- Possible gynecomastia
- Possible testes absent from scrotum
- Retarded bone age
- Low to normal urinary 17-ketosteroid and below-normal serum testosterone
- Fatigue, weakness, poor libido, erectile dysfunction (adults)
- Increased risk of osteoporosis (men); treatment is testosterone

Klinefelter syndrome is the most common primary developmental abnormality causing hypogonadism (testicular damage), affecting 1 of every 400–500 males. It is caused by one or more supernumerary X chromosomes.

- 47,XXY karyotype (80% of patients)
- Gynecomastia, with elevated LH and FSH
- Sterility and lack of libido
- Small and thin testes
- Possible intellectual disability
- Low-normal or normal urinary 17-ketosteroids; low to normal serum testosterone; elevated LH and FSH; and elevated serum estradiol
- Affected males have 20× increased risk of breast cancer

Diagnosis.

- Check total testosterone at 8 AM; if it is low, must repeat to confirm
 - Two low AM total testosterone tests are required to diagnose hypogonadism
 - PM total testosterone tests are inaccurate.
- If testosterone is low, check LH next.
 - If **LH is elevated**, it is primary hypogonadism. (Due to negative feedback inhibition, LH must be elevated in primary hypogonadism.)
 - If **LH is low or normal** (abnormally normal), it is secondary hypogonadism. Check prolactin next (prolactin can suppress GnRH, leading to low LH). If prolactin is elevated, do pituitary MRI.

Note

- For diagnosing hypogonadism, neither PM total testosterone nor free testosterone is a correct diagnostic test. (Also, free testosterone has a short half-life.)
- However, free testosterone is the correct diagnostic test (only) for an obese man with 2 low AM total testosterone values. (Obesity has low SHBG, which can produce a false low total testosterone, so check free testosterone to confirm hypogonadism.)

- If patient has arthralgia and elevated liver enzymes, check iron studies for hemochromatosis.

Treatment is testosterone replacement.

- Monitor hematocrit to screen for polycythemia.
- Monitor PSA to screen for prostate cancer.
- Side effects of testosterone replacement are increased risk of venous thromboembolism (due to erythrocytosis) and potential increased risk of cardiovascular disease.

Clinical Recall

Which of the following tests is most specific in the diagnosis of pheochromocytoma?

- A. Urinary-free catecholamines with plasma catecholamine
- B. 24 hour urinary VMA with free catecholamines
- C. Urinary VMA with plasma catecholamine
- D. Plasma catecholamines and VMA with urinary VMA and catecholamine
- E. Plasma metanephrine with 24 hour urinary metanephrine and VMA

Answer: E

Note

If LH is not elevated, it is not primary hypogonadism.

Learning Objectives

- ❑ List the steps for evaluating a patient with arthritis
 - ❑ Differentiate the types of arthritis
 - ❑ Describe the treatment approaches to rheumatoid arthritis, systemic lupus erythematosus, drug-induced lupus, scleroderma, Sjögren syndrome
 - ❑ Describe the treatment approaches to seronegative arthropathies, including ankylosing spondylitis, reactive arthritis, psoriatic arthritis, and enteropathic arthritis
 - ❑ Answer questions about the management of osteoarthritis, crystal-induced arthropathies, and septic arthritis
 - ❑ Describe the diagnosis and management of vasculitis syndromes and inflammatory myopathies
-

TESTS FOR RHEUMATOLOGIC DISEASE

Joint Aspiration (Arthrocentesis)

Fluid in the joint requires immediate analysis. The basic tests to run on the synovial fluid are as follows:

- The 3 Cs (**cell count, crystals, and cultures**)
- The **Gram stain**

Synovial fluid may be stratified according to the number of cells:

- **OA and traumatic arthritis:** 200–2,000 WBCs/mm³ in synovial fluid
- **Inflammatory diseases** (RA, gout): 5,000–50,000 WBC/mm³
- **Septic arthritis:** >50,000 WBC/mm³

**Note**

The white cells counts in the synovial fluid are just a guide. One can see septic joints with $<50,000$ PMNs, and in other cases, crystal-induced arthritis with $>50,000$ PMNs.

Table 3-1. Synovial Fluid Analysis in Rheumatologic Disease

Disease	WBCs	Crystals/Polarization
DJD	$<2,000$	Negative traumatic
Inflammatory	5,000–50,000	- Gout: needle-shaped, negative birefringent - Pseudogout (CPPD): rhomboid-shaped, positive birefringent
Septic	$>50,000$	Negative (Gram stain and culture usually negative for GC but positive in <i>Staph</i> , strep, and gram-negatives)

There are a few exceptions:

- Septic arthritis can be present with $<50,000$ WBC/mm³ in the joint aspirate if antibiotics are given beforehand. Consider it if $>5,000$ WBC/mm³ in the synovial fluid and monoarticular arthritis, but there is an absence of crystals.
- Gout and pseudogout uncommonly present with $>50,000$ WBC/mm³ in the absence of infection. Consider them if there is evidence of crystals in the aspirate.
- Culture of joint fluid is positive in only $\leq 50\%$ of gonococcal arthritis cases.

Antinuclear Antibodies

Antinuclear antibodies (ANAs) are antibodies with the capability to bind to certain structures within a cell nucleus. They are typically found in patients whose immune system is predisposed to generating antibodies against their own body tissues (called *autoimmunity*), such as SLE, Sjögren syndrome, and systemic sclerosis. However, they are also found in $\sim 5\%$ of healthy people (though usually in low titers [$<1:80$]).

The ANA test is performed by exposing the antibodies in the serum of the blood to the laboratory test cells. It is then determined whether there are antibodies that react with various parts of the nucleus.

Subsets of ANAs are associated with specific autoimmune diseases and thus used to further diagnose those diseases. For example, anti ds-DNA and anti-SM antibodies are found in patients with SLE; anti-histone antibodies are found in patients with drug-induced lupus.

Table 3-2. Specific ANAs

Anti-dsDNA (native DNA)	SLE only (60%); an indicator of disease activity and lupus nephritis
Anti-SM	SLE only (25–30%)
Anti-histone	Drug-induced lupus (95%)
Anti-Ro (SSA)	Neonatal lupus, Sjögren and in the 3% of ANA-negative lupus
Anti-LA (SSB)	Sjögren
Anti-centromere	CREST
Anti-RNP	100% mixed connective tissue disease (MCTD)

Rheumatoid Factors

Rheumatoid factors (RFs) are autoantibodies against the Fc portion of IgG.

- Found in ~70% of patients with RA although they are not specific for RA
- Found in 5% of healthy adults (prevalence increases with age, i.e., up to 20% in those age >65)

While RFs are neither sensitive nor specific for the diagnosis of RA, their presence can be of prognostic significance: patients with **high titers** tend to have **more aggressive disease with extraarticular manifestations**.

Antineutrophil Cytoplasmic Antibodies

Antineutrophil cytoplasmic antibodies (ANCA) are antibodies directed against certain proteins in the cytoplasm of neutrophils.

- **Cytoplasmic (c) ANCA** is the diffuse staining pattern observed when serum antibodies bind to indicator neutrophils; it is seen in >90% of patients who have granulomatosis with polyangiitis.
- **Perinuclear (p) ANCA** is a localized staining pattern observed on the indicator neutrophils (the major target of these antibodies is the enzyme myeloperoxidase); it is found in PAN and Churg-Strauss (known as eosinophilic vasculitis) but is a nonspecific test.

Clinical Correlate

Overall, >95% of SLE patients have positive ANA test results, making a negative ANA result a good rule-out test for SLE.

Interpret a positive ANA test in the context of the clinical symptoms:

- Positive ANA with no symptoms or abnormal tests is likely to be a false-positive (5% of population)
- Positive ANA with arthritis, proteinuria, and pleural effusion is likely to be associated with SLE



Antiphospholipid Antibody Syndrome

Antiphospholipid antibody syndrome (lupus anticoagulant or anticardiolipin antibodies) is a hypercoagulable state associated with a group of antibodies that are directed against phospholipids or cardiolipins.

- Etiology unclear, i.e., not clear if the antibodies are directly involved in the etiology of the clotting disorder associated with this syndrome
- The nature of these antibodies causes the common lab abnormalities associated with the syndrome, i.e., elevated PTT and false-positive RPR or VDRL

Clinically, it presents with spontaneous abortion in otherwise healthy women or thromboembolism (pulmonary embolism, DVT) in other patients.

Two first-trimester spontaneous abortions suggest antiphospholipid antibodies.

ARTHRITIS

Initial Evaluation

When a patient presents with joint swelling, a differential diagnosis is generated based on the answers to the following questions:

1. What is the distribution of joint involvement and how many joints are involved?

- Polyarticular symmetric involvement is seen with RA, SLE, parvovirus B19, hepatitis B, and vasculitis.
- Monoarticular arthritis is consistent with OA, crystal-induced arthritis (gout, pseudogout), septic arthritis (gonococcus), trauma, and hemarthrosis.
- Migratory arthropathy (inflammation and pain migrate from joint to joint while the previous involved joints improve) is caused by rheumatic fever, disseminated gonococcal infection, and Lyme disease.
- Oligoarticular asymmetric arthritis is common with the spondyloarthropathies (ankylosing spondylitis) and OA involving the small joint of the upper extremities; it is rarely in the presentation of polyarticular gout.

2. Are the symptoms acute or chronic?

- OA is a chronic disease; patients have symptoms for months to years.
- With septic arthritis or crystal-induced arthropathy, patients have short-lived symptoms, i.e., only a few days.

3. Does the patient have systemic symptoms (beyond the arthritis)?

- SLE presents with lung (pleural effusions), kidney (proteinuria and renal failure), CNS (vasculitis, strokes, and change in personality), skin (malar and photosensitivity rash), and hematologic (immune-mediated anemia, thrombocytopenia) manifestations.
- Sjögren syndrome has keratoconjunctivitis sicca (dry eyes/mouth) and parotid enlargement.
- Systemic sclerosis has skin involvement and Raynaud phenomenon.

Note

Do not go further into a history unless these questions have been answered.

- Wegener granulomatosis presents with upper respiratory (sinusitis and rhinitis), lower respiratory (lung nodules and hemoptysis), and renal (necrotizing glomerulonephritis) involvement.
- OA has no systemic symptoms.

4. Is there evidence of joint inflammation?

- Evidence of joint inflammation includes joint stiffness in the AM >1 hour, joint erythema and warmth, and elevated ESR and C-reactive protein.
- RA would produce inflammation, while OA would not.

Examples of patients presenting with joint swelling include:

- A 62-year-old man presents with right knee pain
- A 24-year-old woman presents with bilateral wrist, MCP, PIP joint swelling, and pain
- A 32-year-old man returns to your office with knee swelling after being seen a week ago for left wrist pain and swelling, which has now resolved
- A 29-year-old man has right knee pain and swelling and left hip pain

Rheumatoid Arthritis

A 26-year-old woman with no prior medical history presents with a 3-week history of joint swelling and stiffness. Every morning she has stiffness for about 2 h, but that improves as the day progresses. She denies back stiffness or back pain. She has fatigue and low-grade fever. On examination of the wrist, MCPs and PIPs are red and swollen on both hands. The DIPs are not involved. There is fluid in the wrist joints. Otherwise the examination is normal.

Rheumatoid arthritis (RA) is a chronic inflammatory multisystemic disease with the main target being the synovium.

- Women > men by 3:1
- Onset is most commonly age 35–50
- Etiology is unknown
 - RA may be triggered as a reaction to an infectious agent (mycoplasma, parvovirus) in a susceptible host.
 - Of the environmental factors, only cigarette smoking seems to be associated with RA.

Symptoms include:

- Inflammatory synovitis (**hallmark of RA**), presenting in a symmetric distribution
 - First, an initiation phase of nonspecific inflammation
 - Next, an amplification phase, resulting from T-cell activation
 - Last, the chronic inflammation and tissue injury phase
- Intense joint inflammation, with the potential to destroy cartilage, cause bone erosions, and eventually deform the joint
- Positive anti-CCP (cyclic citrullinated peptide) (**very high specificity**)



Note

DIPs and joints of the lower back are never involved in RA.

Note

In 2010, new criteria for RA were proposed by the American College of Rheumatology and European League against Rheumatism focusing more on serology, acute phase reactants, number of joints involved, and duration of joint involvement over 6 weeks. This leads to a point system.

For the moment, the 1987 criteria are not obsolete.

Note

RF can cause elevated an cryoglobulin level.

The predominant infiltrating cell is the T lymphocyte. Diseases such as HIV, where T cells are decreased, will characteristically improve preexisting RA; this also explains why RA is very rare in patients with HIV.

Clinical Presentation. Required for a diagnosis of RA are 4 of the following diagnostic criteria:

- Morning stiffness (>1 h) for 6 weeks
- Swelling of wrists, MCPs, PIPs for 6 weeks
- Swelling of 3 joints for 6 weeks
- Symmetric joint swelling for 6 weeks
- RF positive or anti-cyclic citrullinated peptide
- CRP or ESR

X-ray abnormalities and nodules are not needed for diagnosis.

Criteria. RA is a chronic inflammatory symmetric arthropathy. There needs to be involvement of multiple joints, but some joints are **never** involved in RA:

- DIPs
- Joints of the lower back

Because RA is a systemic disease, ~70% of patients present with constitutional symptoms—fatigue, anorexia, weight loss, generalized weakness—before the onset of the arthritis.

- Damage to the ligaments and tendons
 - Radial deviation of the wrist with ulnar deviation of the digits
 - Boutonnière deformity
 - Swan-neck deformity
- Rheumatoid nodules
 - Initial event caused by focal vasculitis
 - 20–30% of patients with RA; usually occur in areas of mechanical stress (olecranon, occiput, Achilles tendon)
 - Methotrexate may flare this process
- Felty syndrome (RA + splenomegaly + neutropenia)
- Caplan syndrome (RA + pneumoconiosis)
- RF or anti-CCP
- Anemia
- ESR or C-reactive protein
- Synovial fluid analysis

Diagnosis. Diagnosis is clinical; there is no single test that will diagnose RA.

Anti-CCP is more specific than RF.

Treatment.

- NSAIDs
 - In RA, NSAIDs are not “better” than aspirin but they have fewer GI side effects
 - All NSAIDs are equally effective, even the newer ones
 - Cyclooxygenase 2 (COX-2) inhibitors have fewer side effects (less GI disturbance)
 - Do not use NSAIDs with steroids
- Hydroxychloroquine and sulfasalazine for early, mild disease
- Glucocorticoids (short courses only, while waiting for methotrexate to work)
- **Disease-modifying agents**
 - Methotrexate (MTX) (**gold-standard**)
 - If MTX does not control disease, add an anti-TNF medication
 - Tumor necrosis factor (TNF) receptor inhibitors
 - Infliximab, a monoclonal antibody to TNF- α that binds to TNF- α in the joint and circulation. The combination of infliximab + methotrexate is very effective in reducing clinical manifestations of disease. Infliximab is given as an IV infusion.
 - Adalimumab, an anti-TNF mAb that differs from infliximab in that its sequences are entirely human
 - Etanercept, a human fusion protein that is entirely human; anti-etanercept antibodies are relatively uncommon
 - Newer biologics
 - Side effects include sepsis, disseminated TB (always assess for TB beforehand), and other opportunistic infections
 - Antimalarials
 - Gold
 - Sulfasalazine

Note

Recent studies have shown that excessive amounts of the pro-inflammatory cytokines, TNF- α , IL-1, and IL-6, mediate most of the pathogenic features of RA. This underscores the focus of new treatment modalities on inhibiting these cytokines.

Clinical Correlate

COX-2 inhibitors are a type of NSAID which selectively block the COX-2 enzyme at the site of inflammation. Their benefit is that they do not inhibit COX-1 (an enzyme that helps with the production of the protective stomach lining). Traditional NSAIDs block both COX-1 and -2, which can lead to increased risk of GI side effects.

Note

- Tumor necrosis factor alpha (TNF- α) is a pro-inflammatory cytokine produced by macrophages and lymphocytes. It is found in large quantities in the rheumatoid joint and is produced locally in the joint by synovial macrophages and lymphocytes infiltrating the joint synovium.
- TNF inhibitors relieve the signs/symptoms of RA, slow/halt radiographic damage, and are proven effective for those who are resistant to MTX.

Table 3-3. Side Effects of DMARD

Drug	Profile/Side Effects	Screening Tests for Toxicity
Hydroxychloroquine	Retinopathy	Regular eye examination
MTX (methotrexate; most utilized agent and mainstay of treatment)	Rapid onset of action; hepatitis and hepatic fibrosis; pneumonitis; may flare rheumatoid nodules	CBC and liver enzymes every 4–8 weeks

**Note**

Because of the increased risk of MI, both rofecoxib and valdecoxib have been recalled; currently only celecoxib is available.

Note

Screen for TB before using TNF inhibitors.

Clinical Pearl

Consider atlantoaxial subluxation in patients with RA who complain of occipital headaches and upper extremity tingling and numbness.

Always rule out subclinical subluxation in patients with RA who are undergoing surgery and intubation electively.

Aggressive disease is likely to occur with the following features: high titers of RF, diffuse rheumatoid nodules, early joint erosions, late age of onset, and certain subtypes of the HLA-DR4.

Complications of RA include:

- Atlantoaxial subluxation may occur with excessive movement at the junction between the atlas (C1) and axis (C2), due to a bony or ligamentous abnormality. (In RA, the incidence of cervical involvement is 25–80% and results from pannus formation at the synovial joints between C1 and C2.)
- Neurologic symptoms may occur when the spinal cord is involved (paraplegia, quadriplegia). Commonly, patients have subtle symptoms, i.e., neck pain (occipital), C2 radicular pain (paresthesias of the hands and feet), and myelopathy. Consider this diagnosis in patients who have RA and neck pain, paresthesias, etc. The first diagnostic test is x-ray of the cervical spine (multiple views, including an open-mouth view), and possibly CT scan or MRI. If radiologic testing is positive, refer to a spine surgeon. Before any intubation or anesthesia, use x-ray to screen all RA patients for C1–C2 subluxation.
- A swollen painful calf may occur, as a possible ruptured Baker cyst. Baker cyst is the extension of inflamed synovium into the popliteal space.

Clinical Recall

A 39-year-old woman presents with pain and stiffness in her hands and wrists for 6 weeks. She is diagnosed with rheumatoid arthritis, although there is no evidence of erosion on x-ray. Which of the following is the best management at this time?

- A. NSAID alone
- B. NSAID and corticosteroids
- C. Corticosteroids alone
- D. Corticosteroids and methotrexate

Answer: A

Osteoarthritis

A 64-year-old man presents with knee pain. He tells you that he has had right knee pain for many years but it has recently gotten worse. He denies constitutional symptoms and other joint pain except for his left second and third DIPs. He has not noticed stiffness in the morning. On examination crepitations are heard as you move the right knee, but otherwise there is no evidence of swelling, warmth, or erythema of the knee. Laboratory testing is unremarkable.

Osteoarthritis (OA) is the most common joint disease in humans; the target tissue is articular cartilage. There is destruction of cartilage along with secondary remodeling and hypertrophy of the bone.

Unlike RA, OA is not an inflammatory disease.

- Knee OA is the leading cause of chronic disability in the elderly.
- Major risk factors for OA include age, female sex, genetic factors, major joint trauma, repetitive stress, and obesity.
- Classification: **idiopathic** (most common form) where no predisposing factor is evident, and **secondary**, where there is an underlying cause, e.g., another arthropathies (gout), endocrine disease (DM, acromegaly), deposition diseases (hemochromatosis), and mechanical factors (valgus or varus deformity, unequal lower extremity length).
 - Any disease that causes stress or trauma to a joint may eventually cause secondary OA.
 - Idiopathic OA and secondary OA are pathologically indistinguishable.

The most common joint affected by OA is the knee, and the second most common is the base of the thumb.

Clinical Presentation. The major joints involved in OA are the weight-bearing joints (hip and knee) and the small joints of the fingers (PIPs and DIPs). These joints are affected in an oligoarticular-asymmetric or monoarticular pattern. The joint involvement is very slow, progressive, and irreversible. Because the cartilage fails and there is increased pressure on articular bone, joint pain increases with exercise and is relieved by rest. Morning stiffness is always <20–30 min. Crepitations may be noted with movement of the joint. There are no systemic manifestations in OA.

- Lab tests are always normal, especially indices of inflammation.
- Thus, ESR and C-reactive protein are always normal. (If ESR is elevated, some other process is complicating OA, e.g., septic joint, or it is not OA.)
- X-ray findings include osteophytes and unequal joint space.
- Osteophytes (spurs) are the reparative efforts by the bone; when these occur in the PIPs they are called Bouchard's nodes, whereas similar changes occurring in the DIPs are called Heberden's nodes.

Diagnosis is made with clinical and x-ray findings.

Treatment. There is no cure for OA, so focus on maintaining mobility and reducing pain. Therapy is palliative because no agent has been shown to change the natural course of the disease.

- Reduce joint loading with correction of poor posture and weight loss.
- Design physical therapy and exercise programs which maintain range of motion, strengthen periarticular muscles, and improve physical fitness.
- Use NSAIDs only to alleviate pain (chondroprotective effect of certain NSAIDs has not been proven). In double-blinded placebo trials, there was no difference in relief of joint pain among acetaminophen (4,000 mg/d), analgesic doses of ibuprofen (1,200 mg/d), and antiinflammatory doses of ibuprofen (2,400 mg/d).

Note

Acetaminophen is effective if given as a standing medication.

- Do not exceed 4 grams per day (3 grams in the elderly).
- Do not exceed 2 grams per day in those with liver dysfunction.



- Use acetaminophen as the first drug to use for pain in OA. However, it is reasonable to add analgesic doses of NSAIDs if there is no relief. Use cautious dosing with the elderly because they are at highest risk for the side effects associated with NSAIDs, especially GI (ulcers, hemorrhage, etc.). Consider COX-2 inhibitors for those at high risk for GI complications (only available agent is celecoxib).
- Use capsaicin cream, which depletes local sensory nerve endings of substance P. Some patients do feel local burning.
- Perform orthopedic surgery and joint arthroplasty only when aggressive medical treatment has been unsatisfactory, especially if the patient's quality of life has been decreased.
- Intraarticular injection of hyaluronic acid has been approved for treatment of knee OA that hasn't responded to pharmacologic treatment. However, its effectiveness has been questioned since a large clinical trial failed to demonstrate superiority over intraarticular injections of saline. Similarly, glucosamine and chondroitin sulfate are not routinely used for OA since they have not been shown to be more effective than placebo. There is ongoing research to examine whether glucosamine is chondroprotective.

Note

There are rare cases of erosive OA, polyarticular OA, and OA with inflammatory features. You will not need to know them for the exam.

Clinical Recall

Which of the following is a major risk for osteoarthritis?

- A. Onset at early age
- B. Male gender
- C. Long-term steroid use
- D. Low BMI
- E. Trauma

Answer: E

SYSTEMIC LUPUS ERYTHEMATOSUS

A 35-year-old woman is brought for the evaluation of confusion lasting 1 day. Her friends and family inform you that "she did not know how to come home from work" and that lately "she has not been herself." You find that the patient has elevated blood pressure, decreased air entry on the right lung base with dullness to percussion, and symmetrical joint swelling of the wrists and MCPs. Chemistry profile shows elevated creatinine 2.4 mg/dL and protein in the urine on the urinalysis.

Systemic lupus erythematosus (SLE) is a systemic disease in which tissues and multiple organs are damaged by pathogenic autoantibodies and immune complexes. Etiology is unknown.

- 90% of cases are women.
- The abnormal immune response probably depends on interactions between a susceptible host and environmental factors. **Ultraviolet (UV)-B light** is the only environmental factor known to cause flares.

Clinical Presentation. Required for a diagnosis of SLE are 4 of the following diagnostic criteria:

- Malar rash
- Discoid rash
- Photosensitivity
- Oral ulcers
- Arthritis
- Serositis (pleuritis or pericarditis)
- Renal involvement
- Neurologic disorder (seizures or psychosis)
- Hematologic disorder (hemolytic anemia, leukopenia, thrombocytopenia)
- Immunologic disorder (anti-dsDNA, anti-SM, and other ANAs)

Summary of Criteria

- Arthritis is identical to that of RA except that it is non-erosive.
- Both the malar rash and photosensitivity rash (diffuse, maculopapular) flare with exposure to UV-B light (thus are considered photosensitive) and resolve with no scarring of the skin. The discoid lupus (DLE) is a circular rash with a raised rim that occurs over the scalp and face; it can be disfiguring because of central atrophy and scarring. Only 5% of patients with DLE will go on to develop SLE.
- All patients with renal involvement must undergo renal biopsy before treatment is initiated.
- Change of personality and psychosis may be manifestations of CNS lupus. Seizures, paralysis, and aphasia may follow.
- Libman-Sacks endocarditis is a noninfectious endocarditis that is occasionally seen in lupus patients.

Diagnosis. A positive ANA supports the diagnosis but is not specific for SLE. Complement levels (C3, C4) are decreased in those with active lupus, as are elevated levels of ds-DNA antibodies.

Treatment. There is no cure; treat to control symptoms.

- NSAIDs to treat arthritis and pleurisy
- Corticosteroid creams to treat skin rash; antimalaria drugs (hydroxychloroquine) and oral corticosteroids for skin and arthritic symptoms



- Cytotoxic drugs (azathioprine, cyclophosphamide, and mycophenolate) for severe symptoms (lupus nephritis, heart and lung involvement, hemolytic anemia, CNS involvement), along with corticosteroids
- Mycophenolate to treat lupus nephritis

All patients should be advised to wear protective clothing, sunglasses, and sunscreen when in the sun. Belimumab is an inhibitor of B-cell activation; it is an IgG monoclonal antibody given intravenously to prevent B-cell activation.

Prognosis. The prognosis of patients with SLE has improved significantly in recent years with a 10-year survival rate >85%. People with severe involvement of the CNS, kidney, heart, and lungs have a worse prognosis in terms of overall survival and disability. Lupus nephritis is probably the most common cause of disability in patients with SLE.

Note the following with respect to **SLE** and **pregnancy**:

- Fertility rates are normal in patients with SLE, but spontaneous abortion and stillbirth are more common when compared with healthy patients; one reason for the spontaneous abortion may be anti-phospholipid antibodies, which cause placental infarcts. This is treated with low-molecular weight heparin during pregnancy.
- It is unclear whether lupus worsens with pregnancy. In the case of a lupus flare during pregnancy, steroids may be used safely to suppress the disease.
- All pregnant patients with lupus need to be screened for SSA/anti-Ro antibodies. These antibodies cross the placenta and are passively transferred to the fetus, causing neonatal lupus and heart block.

DRUG-INDUCED LUPUS

Drug-induced lupus erythematosus is a side effect of certain medications. Over 40 drugs have been implicated, but the most common are hydralazine, isoniazid, procainamide, and quinidine.

Symptoms typically include arthritis, fatigue, fever, and pleurisy (rare).

- Acute onset SLE is usually not confused with drug-induced lupus, due to the lack of skin disease, kidney disease, and milder symptoms seen in the latter. Also, photosensitivity, hair loss, and CNS disease are uncommon in drug-induced lupus.
- Patients with drug-induced lupus develop ANAs, although those with drug-induced lupus related to quinidine often are ANA-negative. The ANAs in drug-induced lupus are autoantibodies that react with a histone-DNA complex, which is the major component of the nucleus (anti-histone antibodies).

Diagnosis is anti-histone antibody testing, a sensitive marker for this disease. (Hydralazine is the exception, as only 35% of patients will have positive anti-histone antibodies.)

Treatment is to stop the suspected medication. Resolution of symptoms in 1–2 weeks will confirm the diagnosis.

Note

Drug-induced lupus usually spares the visceral organs (kidney, CNS and heart).

SCLERODERMA

A 36-year-old woman presents with skin tightness and painful fingertips with exposure to cold for >1 year. Physical examination reveals blood pressure 165/100 mm Hg and diffuse shiny, thickened skin. Lab tests reveal elevated serum creatinine. The examination is otherwise normal.

Systemic sclerosis (SSc) (or scleroderma) is a chronic multisystem disease characterized by a thickening of the skin caused by accumulation of connective tissue and by involvement of visceral organs (GI, lungs, kidneys).

SSc comes in diffuse and limited forms. Diffuse scleroderma is more likely to affect internal organs. Limited scleroderma affects part of the body and a slower progression.

Clinical Presentation. All patients with SSc have the following symptoms, but there are differences in the severity and distribution of the disease.

- Skin thickening
- Esophageal disease
- Lung disease
- **Raynaud phenomenon**, episodes of pallor or cyanosis in response to cold or emotional stimuli, as a result of vascular damage and diminished blood flow to the extremities; after rewarming the hands, the blood flow will rebound (hyperemia) and the skin will appear reddened or blushed
 - Pallor is caused by vasoconstriction of blood vessels (arteries and arterioles) that results in reduced blood flow
 - Cyanosis is created by deoxygenation of slow-flowing blood
 - Patients complain of cold sensitivity and involvement of other areas of the skin, including the ears, nose, and lower extremities
 - Episodes come as sudden attacks and are often triggered by rapid changes in ambient temperature; attacks may begin in 1 or 2 fingers but typically involve all fingers and/or toes symmetrically and bilaterally
 - In **primary Raynaud phenomenon** (Raynaud disease), the patient has no associated underlying disease, while in **secondary Raynaud phenomenon**, the patient has a defined secondary or associated disease (e.g., scleroderma).
 - To differentiate them, do a nailfold capillaroscopy test (place a drop of oil on patient's nailfold at the base of the fingernail).
 - Examine that area under a microscope for any capillary changes.
 - Enlarged, dilated, or absent nailfold capillaries are noted among patients with scleroderma and other autoimmune diseases.
- Positive ANA testing

Note

Raynaud phenomenon

- Seen in 5% of the general population, especially young women
- About 30% have a first-degree relative with Raynaud
- Most patients have primary Raynaud phenomenon without any defined cause or associated systemic disease



Note

Pulmonary involvement is now the leading cause of death in SSc.

Limited scleroderma was previously called **CREST syndrome**. The acronym CREST represents the hallmarks of the disease:

- Calcinosis (calcium deposits in soft tissues—usually fingers, especially PIP joints), knees, elbows; deposits occur near skin surface and may ulcerate and become infected)
- Raynaud
- Esophageal dysfunction
- Sclerodactyly (skin thickening, primarily on fingers and toes)
- Telangiectasias

Additional symptoms of the **diffuse form** include:

- GI: esophageal dysmotility; hypomotility of small intestine with bacterial overgrowth and malabsorption; dilatation of large intestine with formation of large diverticula
- Pulmonary: pulmonary fibrosis with restrictive lung disease, pulmonary hypertension, alveolitis, and cor pulmonale
- Renal: scleroderma renal crisis in which malignant hypertension develops and causes acute renal failure (had been leading cause of death but is now easily treated with ACE inhibitors)
- Cardiac: myocardial fibrosis, pericarditis, valve disease, arrhythmias due to fibrosis of the conducting system

Additional symptoms of the **limited form** include:

- Skin involvement that does not extend above the elbow or above the knee (rarely, the face may be affected)
- Pulmonary arterial hypertension is more common than interstitial fibrosis
- Positive ANA test, showing a pattern of anticentromere antibodies (up to 90% of patients)
- Negative antibodies to Scl-70, as compared with positive antibodies to Scl-70 with diffuse scleroderma

An important complication of SSc is **scleroderma renal crisis**, when malignant hypertension occurs over days to weeks. It is associated with acute renal failure (rapid rise in creatinine and proteinuria). Treatment is ACE inhibitors (enalapril, lisinopril), initiated immediately.



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Figure 3-1. Shiny Skin of Scleroderma

Treatment. There is no cure for SSc.

- For skin manifestations, use D-penicillamine.
- For severe Raynaud phenomenon, use CCBs, specifically nifedipine.
- For hypertension, use ACE inhibitors.
- For severe systemic skin manifestations, use immunomodulating agents such as mycophenolate, rituximab, and short courses of systemic corticosteroids. Hydroxy-chloroquine may be used as well.

SJÖGREN SYNDROME

A 42-year-old woman presents with some peculiar symptoms lasting 1 year. She feels there is constantly something in her eyes—like dust or sand—and that dry and solid foods are painful to swallow. You are perplexed by her complaints but decide to examine her and find that she has bilateral parotid enlargement. Physical examination is otherwise normal. ANA test is positive.

Sjögren syndrome is a chronic autoimmune disease characterized by lymphocytic infiltration of the exocrine glands, resulting in xerostomia and dry eyes. It may be primary or secondary to another autoimmune disease, such as RA, primary biliary cirrhosis, or SLE.

As the syndrome progresses, it becomes a systemic disease involving major organs (lungs, kidneys, etc.), and may eventually evolve into a lymphoproliferative disease—malignant lymphoma.

Clinical Presentation.

- Itchy eyes, with a “sandy feeling” under the eyes due to reduced lacrimal production and destruction of the corneal epithelium—keratoconjunctivitis sicca
- Difficulty swallowing food
- Possible increase in dental caries
- Possible parotid enlargement
- Schirmer’s test will show decreased tear production, and rose bengal stain will document corneal ulcerations
- ANAs will be positive and specifically anti-Ro (SSA) and anti-La (SSB)
- Lymphocytic infiltration of the salivary glands will be noted on biopsy

Treatment. Treatment is symptomatic only. Use artificial tears. Pilocarpine and cevimeline increase acetylcholine and increase tear and saliva production. Visceral organ involvement usually requires corticosteroids or other immunosuppressive agents.

Note

All of the diseases we just reviewed have an arthritis that is symmetric and polyarticular. RA is a disease that involves mostly the joints; the others (SLE, SSc, and Sjögren) usually have arthritis plus multiple organ involvement.

(Note that parvovirus B19 and hepatitis B may also cause symmetrical polyarthropathy.)

**Clinical Recall**

A 24-year-old woman is recently diagnosed with systemic lupus erythematosus. Which of the following would be appropriate counseling at the time of diagnosis?

- A. The disease has no cure
- B. Use sunscreen whenever outdoors to avoid flare-ups
- C. You have a higher than normal chance of spontaneous abortion if you become pregnant
- D. Prognosis is based on the severity and evolution of the disease
- E. All of the above

Answer: E

ARTHROPATHIES**Seronegative Arthropathies, Spondyloarthropathies**

A 27-year-old man presents with complaints of severe lower back stiffness and pain that have been bothering him for the past 5 years. The stiffness is most apparent in the morning when he wakes up, lasting sometimes >2 h. The only thing improving these problems is exercise. On examination there is 2/6 murmur over the second right intercostal space and decreased range-of-motion of the lumbar spine.

The spondyloarthropathies are a group of disorders that share certain clinical features and an association with the B-27 allele. Their similarities suggest that these disorders share pathogenic mechanisms.

There are 4 diseases that have similar clinical and laboratory characteristics:

Table 3-4. Seronegative Arthropathies

Disease	Characteristics
Ankylosing spondylitis	• Seronegative (ANA negative, RF negative)
Reactive arthritis	• Involve lower back and sacroiliac joints
Psoriatic arthritis	• HLA-B27
Enteropathic arthropathy	• Extraarticular manifestations

All of the diseases have most of the 4 characteristics, plus a few others that are disease-specific.

Ankylosing Spondylitis

Ankylosing spondylitis (AS) is an inflammatory disorder that affects primarily the axial skeleton and peripheral joints. Etiology is unknown.

- Usually starts by decade 2 or 3 of life (very rare age >40)
- Men > women by 3–4× (this is one of the few collagen vascular diseases that affects men more than women)
- 90% of patients are positive for HLA B-27

Clinical Presentation. AS will usually present with **chronic lower back pain** in a young man (in his late twenties to early thirties). The giveaway is the **morning stiffness** lasting at least **1 h** that **improves with exercise**.

- Extraarticular manifestations (common): anterior uveitis, aortic insufficiency sometimes leading to CHF, and third-degree heart block
- Evidence of decreased spine mobility on examination: positive Schober test (measures spine flexion) and possible obliteration of the lumbar lordosis
 - Because of this, spine fracture can be seen in AS patients after minimal trauma (know that spine fractures occur with insignificant stress in older people with osteoporosis and young people with long-standing inflammatory disease of the spine, e.g., AS)
- Cervical spine is rarely, if ever, affected and only late in the disease
- X-ray shows evidence of sacroiliitis (**earliest finding**) and eventual fusing of the sacroiliac joint; chronic spine inflammation will eventually cause bamboo spine and squaring of vertebral bodies

Diagnosis is based on clinical and x-ray findings. The HLA-B27 is not commonly used as a diagnostic test.



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Figure 3-2. X-ray of Pelvis in AS Demonstrating Sacroiliitis



Treatment. Treat with NSAIDs, physical therapy, and exercise. The most promising medications for AS and other spondyloarthropathies are the TNF blockers (infliximab, adalimumab, etanercept). These biologic agents are recommended for axial disease.

Unlike RA, anti-TNF medications are used first and methotrexate used later. Anti-TNF drugs work better for axial disease.

Reactive Arthritis

Reactive arthritis (ReA) is a seronegative arthropathy that occurs as a complication from an infection somewhere in the body. There are 2 types of infections causing different syndromes.

- One (Reiter syndrome) occurs after a nongonococcal urethritis (chlamydia, ureaplasma). These patients have distinct mucocutaneous manifestations: keratoderma blennorrhagica, circinate balanitis, oral or genital ulcers, conjunctivitis, and arthritis.
- The other ReA occurs after an infectious diarrhea caused by *Campylobacter*, *Shigella*, or *Salmonella* organisms (think of the organisms that cause enteroinvasive diarrheas; these are the same ones that cause ReA). The most common is *Campylobacter*.

Diagnosis is based on clinical criteria. X-ray findings will be consistent with a seronegative spondyloarthropathy.

Treatment. Treatment is the same as for AS. There are studies that support an accelerated recovery of Reiter syndrome caused by a chlamydial infection from prolonged tetracycline use (~3 weeks' duration). There are also studies to support the notion that prompt antibiotic use in urethritis will decrease the chance of Reiter syndrome (this is the only exception to the rule that the seronegative arthropathies are untreatable diseases).

A severe form of Reiter syndrome and reactive arthritis has been described in HIV patients. The skin manifestations are particularly aggressive in these patients and improve with antiretroviral medications.



phil.cdc.gov

Figure 3-3. Keratoderma Blennorrhagica Seen with Reiter Syndrome

Psoriatic Arthritis

Psoriatic arthritis commonly involves the DIP joints when associated with psoriatic nail disease (pitting of the nails); this involvement may sometimes cause the characteristic sausage-shaped digit. Here, the peripheral arthritis is deforming. The psoriasis may be especially diffuse, often requiring systemic therapy.

Enteropathic Arthropathy

Enteropathic arthropathy occurs with UC and Crohn disease; sometimes the arthritis occurs with flares of the IBD. Patients may develop characteristic skin lesions: pyoderma gangrenosum and erythema nodosum. (However, neither of these skin manifestations is specific for IBD.)



Wikipedia, James Heilman, MD

Figure 3-4. Erythema Nodosum, Characteristic of Some Rheumatic Disorders

Crystal-Induced Arthropathies

The crystal-induced arthropathies—monosodium urate (MSU), calcium pyrophosphate (CPPD), calcium oxalate (CaOx), and calcium hydroxyapatite (HA)—are caused by microcrystal deposition in joints. In spite of differences in crystal morphology, they have identical clinical presentations and can be distinguished only by synovial fluid analysis.

Gout

Gout is a type of inflammatory arthritis caused by elevated uric acid in the blood. It affects mostly middle-aged men (85%), but women become increasingly susceptible to gout after menopause.

Gout most commonly presents with acute monoarthritis. As it becomes chronic, multiple joints may be involved, and deposition of urate crystals in connective tissue (tophi) and kidneys may occur.

- Metatarsophalangeal joint of the first toe is commonly affected (podagra), but other joints such as the knee, ankle, PIPs, or DIPs may be initially involved
- First episode often occurs at night, with severe joint pain waking the patient from sleep; the joint rapidly becomes warm, red, and tender (it looks exactly like cellulitis)
- Without treatment the joint pain goes away spontaneously within 3–14 days

**Note**

Gout can be very inflammatory, thus the WBCs in the synovial fluid can easily >50,000 cells at times.

Note

- For acute gout, do not initiate allopurinol. (However, if a patient has already been taking allopurinol, do not discontinue.)
- For chronic gout, allopurinol is first-line (to prevent attacks).

Note

Today, patients with gout are not assessed about being overproducers or underexcretors. Therefore, probenecid is no longer used.

Certain events can precipitate gout: excessive alcohol ingestion, red meat intake, trauma, surgery, infection, steroid withdrawal, drugs (diuretics such as hydrochlorothiazide and furosemide; anti-TB medications such as pyrazinamide and ethambutol), or serious medical illness.

MSU deposition causes an intense inflammatory process—red, warm joint.

Diagnosis. Serum uric acid level is of no value in the diagnosis of acute urate arthropathy. During an acute attack, serum uric acid may be normal or low, but many people with elevated serum uric acid never develop gout. Diagnosis is made by analysis of synovial fluid instead. On synovial fluid analysis, the MSU crystals are negative birefringent and needle-shaped. WBCs will range 5000–50,000. X-ray of a joint that has been involved in multiple gouty attacks will show erosive calcifications.

Treatment. With **acute gouty arthritis**, the goal is to decrease inflammation and thus prevent erosion and joint destruction; also in this stage it is very important to avoid fluctuations in serum uric acid level.

- NSAIDs
- Steroids oral (rarely intraarticular) in elderly patients who cannot tolerate NSAIDs/colchicine or in patients with renal impairment
- Colchicine is rarely to be used in acute gout but is still available

With **chronic hyperuricemic gout**, the goal is to decrease uric acid levels. This is usually required for life and initiated in those whose recurrent gouty attacks cannot be corrected by low-purine diet, alcohol limitation, avoiding diuretics, etc. Unlike acute gout, the uric acid level here may help the physician to follow the effect of hypouricemic treatment.

- Allopurinol can be used in overproducers, undersecretors, or patients with renal failure or kidney stones
- Febuxostat is used in those intolerant of allopurinol
- Pegloticase dissolves uric acid: used in refractory disease

Consider the following scenario.

A 32-year-old man comes with a history of right ankle swelling that occurred the night before. He has noticed that his ankle has been red, warm, and very painful. He occasionally drinks alcohol. On examination a red swollen ankle is noted with evidence of an effusion. Range of motion is restricted.

The first step with this patient is **aspiration**. After confirming the diagnosis, treat with **NSAIDs**.

Six months later, the patient returns with left knee swelling. On examination a red warm knee is noted.

The first step now is **aspiration**. After confirming the diagnosis, treat with **NSAIDs**.

On a routine visit the same patient has had 4 documented episodes of gout, despite limiting alcohol and diet.

Now the next step is to consider **allopurinol** or **probenecid**.

You decide to place the patient on allopurinol. He does very well for 2 years with no gouty attacks. After that he experiences another episode of right ankle swelling.

Pseudogout

CPPD crystal deposition is more common in elderly and in those with preexisting joint damage. A small percentage of the patients have metabolic abnormalities that are associated with CPPD deposition (secondary).

Remember the 4 Hs. The presence of pseudogout in a patient age <50 should raise suspicions about one of these metabolic abnormalities.

- Hyperparathyroidism
- Hemochromatosis
- Hypophosphatemia
- Hypomagnesemia

Clinical Presentation.

- Possible acute presentation like gout, or possible asymptomatic and chronic form
- Knee is most commonly affected joint; other joints commonly affected are the wrist, shoulder, and ankle

Definitive diagnosis requires the typical rectangular, rhomboid, positive birefringent crystals on synovial fluid evaluation. X-ray may reveal linear radiodense deposits in joint menisci or articular cartilage (chondrocalcinosis).

Treatment. Treat as you would treat gout. Low doses of colchicine may be considered to prevent frequent recurrences.

SEPTIC ARTHRITIS

A 67-year-old woman with history of RA for many years presents with right shoulder pain and swelling for 2 days. She has low-grade fever. Examination reveals decreased passive and active range of motion of the right shoulder joint, as well as erythema. She asks you if this is related to an RA flare and if she should start steroids to decrease the pain.

The most common cause of infectious arthritis is gonorrhea (70% of episodes in patients age <40). Women are at greater risk during menses and pregnancy, and women are 2–3× more likely than men to develop disseminated arthritis.

Clinical Pearl

Always investigate patients with pseudogout for systemic disease, especially hemochromatosis.



In older patients, *Staphylococcus aureus* is a common cause of infectious arthritis and occurs in patients with preexisting joint destruction from other rheumatic diseases. Patients with RA have the highest risk because of chronic inflamed or destroyed joints, steroid therapy, and frequent skin breakdown over deformed joints.

Diagnosis. Acute bacterial infection may cause rapid cartilage destruction, so a patient presenting with monoarticular arthritis needs prompt diagnosis. This is done with arthrocentesis.

Further, *Staph* or *Strep* must be cleaned out of the joint space by arthrocentesis or arthroscopy.

Remember that most infected joints with gonococcal will not have positive cultures, and the Gram stain will be negative. Do *Neisseria gonorrhoeae* cultures of the throat, penis, vagina and rectum when GC is in differential.

Treatment focuses on the likely etiology. A 30-year-old woman with acute monoarticular arthritis and >50,000 WBCs in the synovial fluid without crystals should be treated with ceftriaxone. A 72-year-old man with RA with the same findings should be treated with nafcillin or vancomycin.

This disease is discussed further in the Infectious Diseases chapter.

VASCULITIS SYNDROMES

Vasculitis is an inflammatory process involving the blood vessels, resulting in a decrease of the lumen diameter and eventual ischemia of the tissues supplied. The vasculitis syndromes are stratified according to the types of vessels involved.

Granulomatosis with Polyangiitis

Granulomatosis with polyangiitis (GPA) (formerly called Wegener granulomatosis) is a small vessel vasculitis. It typically affects the respiratory tract (sinuses, nose, trachea, and lungs) and kidneys, but can involve any organ system.

Symptoms include:

- Involvement of the upper respiratory tract (**most common sign**): rhinitis, sinusitis, subglottic stenosis, and nasal ulcers (rare)
- Chronic rhinitis (common) that is unresponsive to standard treatment and that becomes increasingly worse
- Despite lack of symptoms, lungs are affected in most people; if symptoms are present, they include cough, hemoptysis, and dyspnea
- Kidney involvement (>80% of patients) (major cause of morbidity and mortality)
- Arthritis (60% of patients)
- Presence of antineutrophil cytoplasmic antibodies (C-ANCA)
 - Although a positive ANCA test is useful to support a suspected diagnosis of GPA, it is never diagnostic.
 - The C-ANCA test may be negative in some people with active Wegener. The only way to confirm the diagnosis is with a biopsy of an involved organ (usually nasal septum), demonstrating the presence of vasculitis and granulomas.

Treatment is a combination of a glucocorticoid plus an immunosuppressive agent (cyclophosphamide). This has proven by the National Institutes of Health (NIH) to be very effective for long-term survival.

Polyarteritis Nodosa

Polyarteritis nodosa (PAN) is a multisystem disease which presents with nonspecific complaints such as fever, malaise, weight loss, anorexia, and abdominal pain. The disease can affect nearly any site in the body except the lungs. It has a predisposition for organs such as the skin, kidney, nerves, and GI tract.

- Peripheral neuropathies (**very common**): tingling, numbness, and/or pain in hands, arms, feet, and legs
- Mononeuritis (e.g., foot drop)
- GI manifestations (common): abdominal pain and GI bleed (occasionally mistaken for IBD)
- Active hepatitis B infection (uncommon)
- Severe hypertension
- Testicular pain due to infarction
- Glomerulonephritis (rare)

Diagnosis.

- Biopsy of involved organs (most commonly taken from skin, symptomatic nerves, or muscle); biopsy will show pathologic changes in medium-size arteries
- Angiogram of the abdominal vessels may be helpful, since aneurysms affecting the arteries of the kidneys and/or GI tract are found

Treatment is high doses of corticosteroids and immunosuppressive drugs (cyclophosphamide).

Eosinophilic Vasculitis

Eosinophilic vasculitis (formerly called Churg-Strauss syndrome) shares many of the clinical and pathologic features of PAN; both involve the small- and medium-sized arteries. Any organ can be involved.

The cardinal manifestations are asthma, peripheral eosinophilia, and lung involvement.

The typical patient is middle-aged, with new-onset asthma. Asthma symptoms may begin long before the onset of vasculitis. Other symptoms include mononeuropathy (mononeuritis multiplex similar to PAN), transient pulmonary infiltrates on chest x-ray, paranasal sinus abnormalities, nasal polyps, and allergic rhinitis.

Diagnosis is made by biopsy. Treatment is similar to PAN (combination of prednisone and cytotoxic agent).

Note

Recently, data has emerged on the use of rituximab in lieu of cyclophosphamide. For now, cyclophosphamide is a good first-line agent.

Clinical Pearl

In patients with PAN, exclude co-existing chronic active viral hepatitis.

Note

Years ago, untreated PAN was usually fatal within weeks to months. Most deaths occurred from kidney failure, or heart or GI complications.

Note

To help remember eosinophilic vasculitis, think of it as PAN in an asthmatic patient.



Temporal Arteritis

A 72-year-old woman presents with a right-sided headache for the past 4 weeks. She has never had migraine headaches and denies blurry vision, nausea, or vomiting. The headache does not get worse at any specific time of day. She has noticed a feverish feeling and hip stiffness along with the headache.

Temporal arteritis (TA) (also known as giant cell arteritis), is a vasculitis affecting the large arteries that supply the head, eyes, and optic nerves. New-onset headache in any patient age >50 prompts consideration of this diagnosis, which if left untreated may result in permanent vision loss. Symptoms include:

- Headache and pain in one or both temples (most common symptoms)
- Scalp tenderness (pain when combing hair)
- Jaw claudication (jaw pain when chewing)
- Decreased vision or blurry vision
- Tongue numbness
- Sudden loss of vision (rare)
- Proximal stiffness (neck, arms, hips) due to polymyalgia rheumatica, a coexisting condition (seen in >25% of patients with TA) (polymyalgia rheumatic is not a myositis, so CPK will be normal)

Clinical Pearl

Always consider TA in patients with new-onset headache who are age >50–60.

Diagnosis.

- Elevated ESR (hallmark, 100% sensitive)
- Biopsy of the temporal arteries (to confirm diagnosis) will demonstrate the characteristic giant cells

Treatment. When TA is suspected and ESR is elevated, start corticosteroids immediately, before the temporal artery biopsy is performed. Do not withhold treatment.

Takayasu Arteritis

Takayasu arteritis is the other large artery vasculitis, and like temporal arteritis, involves branches off the aorta such as the renal arteries, subclavian arteries, mesenteric system and coronaries.

Patients are commonly age <50.

Clinical Presentation. Symptoms include:

- Fever, chills
- Weight loss
- Elevated ESR and CRP
- Hypertension
- GI manifestations
- Angina
- CHF in extreme cases
- Weak (even absent) peripheral pulses

Diagnosis requires angiographic imaging with MR or CT that demonstrates 3 large artery occlusions. The subclavian is usually involved.

Treatment is corticosteroids at high doses. Add a steroid-sparing agent such as mycophenolate, azathioprine, methotrexate or cyclophosphamide to help taper the steroid dose.

INFLAMMATORY MYOPATHIES

A 42-year-old woman is admitted to your service with severe proximal weakness for 2 months. Examination shows a diffuse lilac rash over the sun-exposed areas. Motor strength is 3/5 in the upper and lower proximal muscle groups.

The inflammatory myopathies are inflammatory muscle diseases that present with progressive muscle weakness. They include **polymyositis**, **dermatomyositis**, and **inclusion body myositis**.

- Patients report difficulty with tasks that involve the proximal muscles: lifting objects, combing hair, getting up from a chair.
- Fine-motor tasks that involve the distal muscles, e.g., writing, are affected only late in the disease.
- Ocular muscles are never involved (this feature **differentiates the inflammatory myopathies from myasthenia gravis and Eaton-Lambert syndrome**).

Dermatomyositis will also have skin involvement; the heliotrope rash is a purple-lilac discoloration of the face, eyelids, and sun-exposed areas of the body. Gottron's papules are the scaly lesions seen sometimes over the knuckles.

Laboratory Findings. The inflammatory destruction of muscles causes elevated muscle enzymes (sometimes up to 50-fold), CPK, and aldolase. These are the most sensitive tests to perform in patients suspected of an inflammatory myopathy.

Autoantibodies (anti-Jo-1) occur in patients with inflammatory myopathies, supporting a possible autoimmune origin.

Diagnosis. Electromyography shows evidence of myopathic potentials characterized by short-duration, low-amplitude units. Diagnosis is confirmed by muscle biopsy.

Treatment. For polymyositis and dermatomyositis, steroids are useful. Inclusion body myositis is resistant to immunosuppressive therapy.

Clinical Recall

A 55-year-old man presents with complaints of right toe pain for 8 hours. He is diagnosed with acute gouty arthritis. Which of the following is the recommended drug?

- Allopurinol
- Indomethacin
- Corticosteroids
- Methotrexate

Note

Autoimmune necrotizing myositis is a very rare inflammatory myositis associated with use of HMG-CoA inhibitors. Treatment is to stop the HMG-CoA inhibitor and administer an immunosuppressive agent.

Answer: B

Learning Objectives

- ❑ List diseases that should be considered for presenting complaints of epigastric pain, diarrhea, or constipation
- ❑ Describe the presentation and management of a patient with GI bleed
- ❑ Describe the epidemiology and management of diseases of the esophagus, liver, pancreas, and colon including cirrhosis, acute pancreatitis, and colon cancer
- ❑ Describe the types of malabsorption syndrome, their causes, and treatment
- ❑ Differentiate diverticular disease and different forms of IBD in terms of their presentation and treatment



DISEASES OF THE ESOPHAGUS

Most diseases of the esophagus will result in dysphagia (difficulty swallowing), yet only a few of them will result in pain on swallowing (odynophagia). Both dysphagia and odynophagia will cause weight loss if symptoms persist for more than a few days.

Dysphagia can be classified as oropharyngeal or esophageal. **Oropharyngeal dysphagia** is caused by muscular and neurologic disorders, such as stroke, Parkinson, ALS, NG, muscular dystrophy, or Zenker's diverticulum. Evaluation includes select videofluoroscopy (modified barium swallow); the patient swallows food under fluoroscopy and the upper esophageal sphincter is evaluated as the initial swallow is made. Patients with this condition present with:

- Coughing with swallowing
- Choking
- Nasal regurgitation with fluids
- Aspiration while swallowing

Patients with **esophageal dysphagia** report food “sticking” or discomfort in the retrosternal region.



Achalasia

A 32-year-old woman with no past medical history presents with “difficulty swallowing” foods for almost 1 year. She reports that food “sticks” in her chest. It is most difficult to eat solids. Her symptoms have not worsened at all over the course of the year, and her weight has been stable. Physical examination is unremarkable.

Achalasia is caused by degeneration of the myenteric plexus with loss of the normal inhibitory neural structure of the lower esophageal sphincter (LES). The LES fails to relax and there is decreased peristalsis. The LES is usually contracted to prevent the acidic gastric contents from refluxing backward into the esophagus.

The vast majority of cases are of unknown etiology. A very small number can be from Chagas disease, gastric carcinoma, or a disease that can infiltrate into the area such as lymphoma.

Clinical Presentation. Achalasia presents with progressive dysphagia to both solids and liquids simultaneously and can have regurgitation several hours after eating. The patient complains of esophageal dysphagia with possible weight loss.

Diagnosis. Heme-positive stools, symptoms >6 months, and weight loss will confirm diagnosis. Diagnostic testing should be done in the following order:

1. Barium swallow (very accurate) will show dilation of the esophagus, which narrows into a “bird’s beak” at distal end
2. Esophageal manometry (**gold standard, mandatory to confirm diagnosis**) will show increased lower esophageal (LES) resting pressure and the absence of peristalsis
3. Upper endoscopy with endoscopic U/S (to rule out adenocarcinoma [pseudoachalasia]) if there is concern for malignancy:
 - Rapid onset/progression of symptoms in <6 months
 - Rapid and significant weight loss
 - Age >50–60

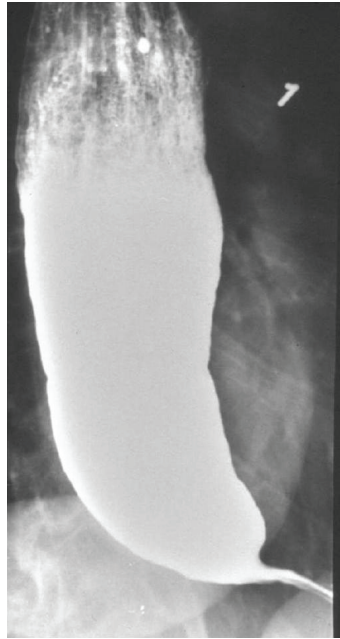
Primary achalasia typically has a more insidious onset over several years and only a mild weight loss.

Treatment. The best initial treatment is pneumatic dilation or laparoscopic surgical myotomy.

- Pneumatic dilation (effective in 80–85% of patients, with 3–5% risk of perforation)
- Botulinum toxin injection into the LES (second-line) for relief of symptoms >6 months and for those who are poor surgical candidates, e.g., elderly with comorbid conditions
- CCBs and nitrates (third-line)

Note

Achalasia has no relationship with alcohol or tobacco use. This is different from esophageal cancer, which not only presents with dysphagia to solid foods and progresses to difficulty swallowing liquids, but also is more common in older patients with a long history of alcohol/tobacco use.



Wikimedia, Farnoosh Farrokhi
and Michael F. Vaezi

Figure 4-1. Achalasia

Esophageal Cancer

A 62-year-old man comes for evaluation of progressive “difficulty swallowing solids and, recently, semisolids” for 4 months. He has noticed a 20-lb weight loss. His past medical history is significant for reflux esophagitis for 15 years and a 40-pack-year smoking history. On physical examination a 1.5-cm, left supraclavicular lymph node is found. The remainder of the physical examination is unremarkable.

Esophageal cancer is linked to the synergistic, carcinogenic effect of alcohol and tobacco use for cases of squamous cell cancer in the proximal two-thirds of the esophagus. Adenocarcinoma is found in the distal third of the esophagus and is associated with long-standing GERD and Barrett esophagus. The rate of development of cancer from Barrett esophagus is 0.4–0.8% per year. Squamous and adenocarcinoma are now of equal frequency.

Clinical Presentation. Esophageal cancer presents with progressive dysphagia first for solid food, then for liquids. Weight loss is prominent. Rarely, halitosis, regurgitation, and hoarseness occur. Hypercalcemia may arise, as it can with most cancers. Diagnostic testing includes:

- Barium swallow first
- Endoscopy (**mandatory**) second because this is a diagnosis which requires a tissue biopsy
- CT scan to detect the degree of local spread
- Bronchoscopy to detect asymptomatic spread into the bronchi
- Endoscopic U/S to stage



Treatment is surgical resection if the disease is sufficiently localized to the esophagus. Only 25% of patients are found to be operable. Five-year survival is 5–20%.

Chemotherapy with a 5-fluorouracil-based chemotherapy is combined with radiation to control locally metastatic disease.

Scleroderma (Progressive Systemic Sclerosis)

As many as 80–90% of patients with scleroderma will develop diminished esophageal peristalsis from the atrophy and fibrosis of the esophageal smooth muscle.

Clinical Presentation. Although there is dysphagia, the main clue to the diagnosis is simply the presence of gastroesophageal reflux symptoms in a person with a history of scleroderma. The LES will neither contract nor relax and basically assumes the role of an immobile open tube.

The most accurate diagnostic test is a motility study. Barium studies are generally unnecessary.

Treatment is a PPI e.g., omeprazole. Metoclopramide, a promotility agent, has a modest effect.

Diffuse Esophageal Spasm and Nutcracker Esophagus

A 34-year-old man complains of “crushing” chest discomfort for 1 hour. He has no significant medical history. The ECG is normal. He is given sublingual nitroglycerin in the emergency room that improves his chest pain almost immediately.

Esophageal spastic disorders are idiopathic abnormalities of the neural processes of the esophagus. Fundamentally, diffuse esophageal spasm and nutcracker esophagus are the same disease; the only difference may be in the manometric pattern.

Clinical Presentation. Patients present with intermittent chest pain and dysphagia. The pain can simulate that of a myocardial infarction, but it bears no relationship with exertion. There is no relationship with eating, ruling out odynophagia. The pain can be precipitated by drinking cold liquids.

Barium study may show a “corkscrew” pattern at the time of the spasm. The most accurate test for diagnosis is a manometric study, which will show high-intensity, disorganized contractions. Because the contractions are disorganized, they do not lead to the forward flow of food and peristalsis.

Treatment is a CCB, e.g., nifedipine, for dysphagia. Trazadone plus imipramine or sildenafil can relieve chest pain.

Rings and Webs

Schatzki's ring and Plummer-Vinson syndrome (PVS) reveal thin, epithelial membranes made out of squamous epithelial cells. Neither is progressive in nature, distinguishing them from achalasia.

- Schatzki's ring (**more common**) leads to intermittent dysphagia and is not associated with pain. It is more distal and located at the squamocolumnar junction proximal to the lower esophageal sphincter.
- PVS is more proximal and is located in the hypopharynx. It is typically seen in middle-aged women. PVS is associated with iron-deficiency anemia and squamous cell cancer.

Both disorders are diagnosed with a barium swallow or barium esophagogram.

Treatment is dilation procedures for both disorders. PVS may respond to treatment for the iron deficiency.

Esophagitis

Esophagitis refers to infection or inflammation of the esophagus.

- **Infection:** *Candida albicans* (**most common**), seen with
 - HIV-positive patients with CD4 count $<200/\text{mm}^3$ (**most often**)
 - DM
 - Herpes simplex, cytomegalovirus, and aphthous ulcers (rarely)
- **Inflammation**

Esophagitis pain is simply from the mechanical rubbing of food against an inflamed esophagus as it passes by. It can also result from ingestion of medication and caustic substances; the direct effect of contact between the mucosa and the pill causes inflammation rather than infection.

As with most other toxin-mediated damage to an organ, diagnosis is based on the presentation and identification of the toxin in the history. The most common pills causing esophagitis are alendronate, quinine, risedronate, vitamin C, potassium chloride, doxycycline, NSAIDs, and iron sulfate. Consider pill esophagitis in a young patient who takes acne medication and who has an acute onset of odynophagia.

Symptoms include:

- Progressive odynophagia
- Painful swallowing, but food is still able to pass (until disease is extremely advanced)
- Oral thrush (70% of patients)

If there is severe pain and fever, but no thrush in a patient with CD4 count <50 , think CMV esophagitis and get an endoscopy.

Treatment. If the patient is HIV-positive, assume *Candida* esophagitis and start fluconazole; improved symptoms will confirm the diagnosis. If symptoms do not improve, perform endoscopy and biopsy to exclude other causes such as HSV and CMV.

Note

The pain in esophagitis is only on swallowing, while the pain in spastic disorders is intermittent without even needing to swallow.

Clinical Correlate

Barium swallow is the incorrect test for esophagitis. It is always the correct first test for dysphagia.



Treatment for *Candida* **must be fluconazole**. Nystatin swish and swallow will not work (and is a common incorrect answer on the exam).

- 30% of patients with *Candida* esophagitis will not have oral thrush (an absence of oral candida does not rule out esophageal candida)
- Because esophagitis can also result from ingestion of medication and caustic substances, the direct effect of contact between the mucosa and the pill causes inflammation rather than infection. As with most other toxin-mediated damage to an organ, diagnosis is based on the presentation and identification of the toxin in the history. The most common pills causing esophagitis are alendronate, quinine, risedronate, vitamin C, potassium chloride, doxycycline, NSAIDs, and iron sulfate. Consider pill esophagitis in a young patient who takes acne medication and who has an acute onset of odynophagia.

Pill esophagitis is prevented by simply swallowing pills in the upright position and drinking enough water to flush them into the stomach.

Eosinophilic Esophagitis

A young man with a history of allergies, asthma, or eczema presents with extreme solid food dysphagia. Upper endoscopy shows stacked circular rings and mucosal furrowing.

Biopsy shows marked infiltration with ≥ 15 eosinophils/hpf. Endoscopic findings include rings, longitudinal furrows, luminal narrowing and white exudate and plaques.

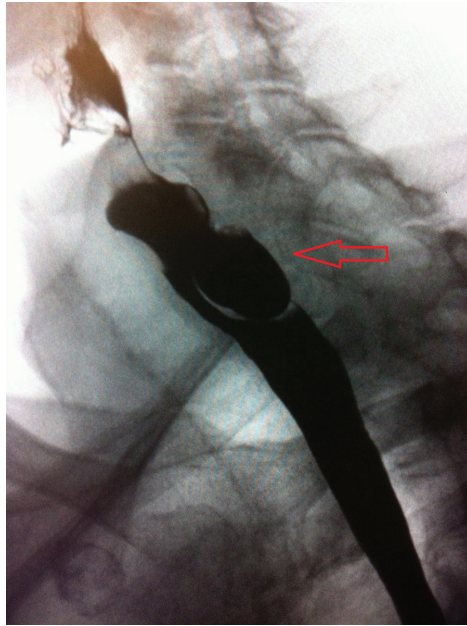
GERD can also cause esophageal eosinophilia (EE) and can mimic it, and there is commonly a crossover with both. Proximal esophageal involvement; large numbers of intraepithelial eosinophils on histologic examination; younger age; male sex; presence of dysphagia and food allergies; presence of esophageal rings, furrows, and plaques; and lack of a hiatal hernia make it more likely to be EE than GERD.

Treatment. Treat with swallowed fluticasone/budesonide or PPIs. For esophageal stricture that does not respond to medical therapy, do endoscopic dilation.

Zenker Diverticulum

A 25-year-old medical student seeks your help because he thinks he “has bad breath.” This past weekend, a most disturbing event occurred while he was watching a football game: He coughed up the chicken teriyaki he ate 2 days earlier. He claims to brush his teeth every night. The physical examination is normal. What is the next step in evaluation?

Zenker diverticulum is the outpocketing of the posterior pharyngeal constrictor muscles at the back of the pharynx.



Wikipedia, James Heilman, MD

Figure 4-2. Zenker Diverticulum

Clinical Presentation. Zenker diverticulum is a very slowly developing problem that occurs in older patients.

- Bad breath
- Difficulty initiating swallowing (due to such a proximal lesion)
- Need to repeatedly clear the throat
- Waking up with undigested, regurgitated food on the pillow (food from perhaps several days ago)

Barium study will confirm diagnosis.

Treatment. Treat with surgical resection. Endoscopy and the placement of nasogastric tubes are contraindicated because they could perforate the pharynx.

Mallory-Weiss Syndrome

Mallory-Weiss syndrome is a nontransmural tear of the lower esophagus that is related to repeated episodes of retching and vomiting.

Clinical Presentation. Although Mallory-Weiss syndrome is an esophageal disorder, the presentation is markedly different from the other problems described.

- No dysphagia or odynophagia, but rather, painless upper GI bleed
- Black stool from melena if volume of bleed >100 mL or with hematemesis if there is continued vomiting

Diagnosis is made with direct visualization on upper endoscopy.

Treatment. Typically, Mallory-Weiss tears will resolve spontaneously. It may be necessary to inject the tear with epinephrine or perform cauterization.



Clinical Recall

A 58-year-old patient presents with non-painful, progressive difficulty in swallowing solid foods for the past 6 weeks. Which of the following is the best initial test?

- A. Barium swallow
- B. Contrast CT of the chest
- C. Endoscopy
- D. Endoscopic ultrasound
- E. Esophageal manometry

Answer: A

EPIGASTRIC PAIN

In most cases, there is no definite way to determine the etiology of epigastric discomfort or pain simply by examining the patient's history. Epigastric pain can be caused by the following:

- Pancreatitis (most common reason for epigastric tenderness and pain)
- Ulcer disease (associated with epigastric tenderness in <20% of patients)
- GERD
- Gastritis
- Gastric cancer (rare)

Helicobacter pylori is most strongly associated with the development of duodenal ulcers, gastric ulcers, and gastritis.

Despite these diagnostic possibilities, the most common etiology of epigastric pain is, in fact, never truly determined. This is referred to as nonulcer dyspepsia, a functional disorder in which there is persistent pain in the epigastric area but all tests are found to be normal.

Guidelines recommend upper endoscopy for patients with dyspepsia and alarm features, so the first step is to look for those. Alarm features include the following:

- Onset age >60
- Anemia
- Dysphagia
- Odynophagia
- Vomiting
- Weight loss
- Family history of upper GI malignancy
- Abdominal mass or lymphadenopathy on examination

Any alarm feature requires upper endoscopy. Endoscopy is also indicated if symptoms have not resolved with antisecretory therapy, such as PPIs.

If there are no alarm features in a patient age <60, use a noninvasive test-and-treat approach for *H. pylori*, such as a urea breath test or stool antigen test.

Treatment. Although endoscopy is the most accurate way to diagnose an ulcer, one can empirically treat ulcers, reflux disease, and gastritis.

- Start by testing for *H. pylori*. If positive, treat. If negative, give a PPI.

Gastroesophageal Reflux Disease

A 32-year-old man comes to the ED for substernal chest pain of 2 hours' duration. He says that he sometimes gets this pain while lying in bed at night. He is otherwise free of symptoms, except for a nonproductive cough that he has had for the past month. Physical examination is unremarkable. ECG is normal. He is given sublingual nitroglycerin and notes that his chest discomfort is worsened.

Gastroesophageal reflux disease (GERD) is caused by the abnormal flow of the acid gastric contents backward from the stomach up into the esophagus (the lower esophageal sphincter).

A number of factors can cause decreased tone or loosening of the sphincter.

- Nicotine, alcohol, caffeine
- Peppermint, chocolate
- Anticholinergics
- CCBs
- Nitrates

When the tone of the lower esophageal sphincter decreases, acid is more likely to reflux backward into the esophagus, particularly when the patient is lying flat. GERD can still occur in the absence of these precipitating factors and can often simply be idiopathic in origin.

Clinical Presentation. GERD will present with heartburn (burning substernal pain); sore throat; a metal-like taste in the mouth; hoarseness; cough and wheezing. In addition, it is often associated with pain in the substernal area. Symptoms are worse after a meal or while lying flat.

The most accurate diagnostic test is a 24-hour pH monitor; an electrode is placed several centimeters above the gastroesophageal junction, and a determination is made of what the average pH is in that area. Normal endoscopy does not exclude reflux disease.

Note the following order when working up GERD:

- Initiate PPI; if no improvement after 4–8 weeks, increase PPI to 2×/day (before EGD) for 4–8 weeks and make sure patient is taking properly (30–60 min before meals)
- If no improvement, do EGD: If EGD shows esophagitis, that confirms GERD and 24-hour pH monitoring is not needed. If EGD is normal, do ambulatory 24-hour pH monitoring (while off the PPI) and if results are consistent with GERD, do Nissen fundoplication.

Note

Any alarm features such as bleeding, weight loss, or difficulty swallowing requires upper endoscopy.

Note

There is no point in treating *H. pylori* without evidence of disease such as gastritis or ulcer disease.

Note

The lower esophageal sphincter is not a true anatomic sphincter (it cannot be found in a cadaver); it is created by the different responses of the smooth muscle cells in the distal esophagus.

**Note**

For the exam, make sure you know the side effects of PPIs.

Note

In patients with chronic cough (≥ 8 weeks), symptoms typical of GERD (heartburn, cough that is worse after a large meal), and negative chest x-ray, initiate a PPI as the next most appropriate step.

In clear cases of epigastric pain going under the sternum and associated with a respiratory complaint or bad taste in the mouth, **initiate therapy immediately** with antisecretory medications such as PPIs.

Treatment starts with lifestyle modification: avoid nicotine/alcohol/caffeine/chocolate/late-night meals and elevate the head of the bed 6–8 inches with blocks to keep acid in the stomach.

Next, give a PPI to increase the pH of the gastric contents to >4.0 .

- Omeprazole, esomeprazole, lansoprazole, pantoprazole, or rabeprazole (**all equally effective**)
- Side effects of PPIs include:
 - Increased risk of *C. difficile* infection
 - Aspiration pneumonia
 - Osteoporosis
 - Microscopic colitis
 - Hypomagnesia
 - Vitamin B12 deficiency
 - Interstitial nephritis
 - Hip fracture
- If no response to PPIs ($<5\%$ of patients) or there are refractory side effects (headaches, diarrhea): surgery to tighten the sphincter (traditionally, a Nissen fundoplication is done laparoscopically) (do a motility study beforehand to avoid iatrogenic dysphagia)
- H2 blockers only for very mild, intermittent symptoms (less effective than PPIs)

Barrett Esophagus

Barrett esophagus is a complication of long-standing reflux disease. After several years of GERD, the epithelium of the lower esophagus undergoes histologic change from a normal squamous epithelium to a columnar epithelium.

Men age ≥ 50 with chronic GERD (5+ years) and additional risk factors (nocturnal symptoms, hiatal hernia, obese, smokers) should be screened.

Patients with Barrett esophagus should have repeat endoscopy every 3–5 years to see whether dysplasia or esophageal cancer has developed:

- If low-grade dysplasia, treat endoscopically or repeat endoscopy in 6–12 months
- If high-grade dysplasia, do radiofrequency ablation, photodynamic therapy, or endoscopic mucosal resection
- The usual rate of progression to cancer is about 0.5% per year.

Do not check barium swallow, as it will be normal.

Treatment. PPIs for all patients

Peptic Ulcer Disease

(PUD) includes both duodenal and gastric ulcers. The most common causes of ulcer disease are *H. pylori* (80–90% of duodenal ulcers and 70–80% of gastric ulcers) and NSAIDs.

About 10–20% of ulcers are idiopathic, with no clear etiology.

- NSAIDs can cause ulcer formation because they decrease the normal production of the mucous barrier protecting the epithelial cells of the gastric mucosa. Prostaglandins, the major stimulant for mucous production that forms this protective barrier, are inhibited by NSAIDs and hence diminish the protective barrier of the stomach lining. Screen all patients with PUD for *H. pylori*, regardless of NSAID use.
- Steroid use by itself does not cause PUD and is therefore not a routine indication for stress ulcer prophylaxis.
- Smoking and alcohol use do not cause PUD, but they can delay healing and are associated with the development of gastritis.

Parietal cells in the stomach produce acid. The 3 stimulants to the production of acid from the parietal cells are gastrin, acetylcholine, and histamine.

- Gastrin is produced by G cells in the stomach, and its release is stimulated by distention of the stomach, the presence of amino acids, and vagal stimulation. Vagal stimulation also releases acetylcholine and gastrin-releasing peptide. However, the single most important stimulant to gastrin release is distention of the stomach.
- Histamine is released by enterochromaffin-like cells present in the same glandular elements of the stomach that have the parietal and chief cells. Chief cells release pepsinogen, which is converted to pepsin by the acid environment of the gastric lumen. Histamine directly stimulates the parietal cells to both release acid and potentiate the effects of acetylcholine and gastrin on the parietal cells. This is why H₂ blockers such as cimetidine, famotidine, and ranitidine inhibit acid release.

Zollinger-Ellison syndrome is the excessive production and release of gastrin from the pancreas. Somatostatin is the counterbalance to this system, inhibiting the release of gastrin and histamine, as well as having a direct inhibitory effect on the production of acid from the parietal cells. Secretin is released from the S cells of the duodenal lining. The main stimulant to the release of secretin is the presence of acid in the duodenum. Secretin inhibits the production of gastrin, as well as stimulates pancreatic and biliary bicarbonate production and release.

Clinical Presentation. The most common presentation of ulcer disease is midepigastria pain. There is no definite way to distinguish between duodenal and gastric ulcer simply by symptoms. Gastric ulcer is often associated with pain on eating (frequently leading to weight loss), while duodenal ulcer is thought to be relieved by eating. However, these associations are only rough approximations, and endoscopy is still required for a definite diagnosis.

Tenderness of the abdomen is unusual with ulcer disease. More than 80% of cases are not associated with abdominal tenderness in the absence of a perforation. Nausea and vomiting are occasionally found with both of them.

Note

For burn victims >30% BSA and intubated patients, the correct answer is stress ulcer prophylaxis is.

**Note**

H. pylori can be associated with ITP.

Note

Gastric ulcers must be biopsied to exclude cancer.

Diagnosis. Ulcer disease is best diagnosed with upper endoscopy. Barium studies are inferior.

- If patient age <60 and has no alarm symptoms, use non-invasive testing and treat for *H. pylori*. If *H. pylori* is negative, give trial of PPIs. If symptoms persist, perform endoscopy.
- If patient age >60 or has alarm symptoms (weight loss, anemia, heme-positive stools, or dysphagia), perform endoscopy.

Diagnosis of *H. pylori* is based on urea breath testing, stool antigen testing, or biopsy with histology or rapid urease testing. The first 2 tests are non-invasive.

- Before testing for *H. pylori*, patient must be off PPIs for 2 weeks and antibiotics for 4–8 weeks (can cause false-negatives).
- Biopsy with histology can be done on treatment.
- Biopsy with rapid urease testing can be false-negative on treatment. Bleeding ulcers can cause a false-negative biopsy result, so if there is a bleeding ulcer on the endoscopy, send another test for *H. pylori*, like urea breath test or stool antigen.

Do not check serum antibodies as they will not indicate whether this is a past or present infection.

Treatment centers around treatment for *H. pylori*.

- PPI plus antibiotics (effective in >90% of patients) for 10–14 days (the PPI may be continued to heal the gastric mucosa)
 - The PPIs omeprazole, lansoprazole, pantoprazole, rabeprazole, and esomeprazole are all equal in efficacy
 - *H. pylori* resistance to clarithromycin has increased in recent years
 - If local resistance rates >15%, previous treatment with a macrolide, or eradication rates with clarithromycin-based triple therapy <85%, use metronidazole, tetracycline, bismuth, or a PPI; another alternative is a PPI + levofloxacin + amoxicillin
 - If triple therapy fails, use another regimen
- Repeat endoscopy for gastric ulcer is needed only if symptoms persist or if biopsy was not done the first time. Follow-up endoscopy for duodenal ulcer is not needed.

Wait 4–8 weeks post-treatment to check for eradication with urea breath test or fecal antigen test. This should be done in all cases after treatment because of risk of PUD and gastric malignancy.

- If **organism was not eradicated**: repeat treatment with different antibiotics, plus bismuth subsalicylate. Explore sensitivity testing for the organism.
- If **organism was eradicated** but ulcer persists/worsens: consider Zollinger-Ellison syndrome.

Ordinary ulcer not related to *Helicobacter* can be treated with PPIs alone. Stop NSAIDs. If unable to stop aspirin or NSAIDs, give COX-2 inhibitor + PPI. Sucralfate does not help and should not be used.

Give PPI for prophylaxis if patient is high risk. Risk factors include:

- History of PUD or GI bleed
- Age 65 years or older
- Chronic comorbid illness
- High-dose NSAID use
- Concomitant use of aspirin (of any dose), anticoagulants, other NSAIDs, or glucocorticoids

Indications for surgery in PUD:

- UGI bleed not amenable to endoscopic procedures
- Perforation
- Refractory ulcers
- Gastric outlet obstruction (can change endoscopic dilation)

Gastritis

Gastritis is inflammation, erosion, or damage of the gastric lining that has not developed into an ulcer.

- **Type B** gastritis (most common) caused by:
 - Alcohol, NSAIDs, *Helicobacter*, head trauma, burns, and mechanical ventilation
 - **Increased gastric acid production**
- **Type A** gastritis caused by:
 - Atrophy of the gastric mucosa
 - Associations include vitamin B12 deficiency (autoimmune), **diminished gastric acid production** and achlorhydria (patients with achlorhydria will have markedly elevated gastrin because acid inhibits gastrin release from G cells)
 - MALT leads to metaplasia (and possible dysplasia) and then to gastric cancer

Clinical Presentation. Patients typically present with asymptomatic bleeding (as hematemesis or melena). Nausea and vomiting may occur.

When the gastritis is severe and erosive, abdominal pain will occur in the same area that patients with ulcer disease feel theirs.

Diagnosis and Treatment.

- Diagnosis and treatment of *Helicobacter* are the same as that for gastritis (described for ulcer disease).
- Diagnosis of vitamin B12 deficiency and pernicious anemia are made initially with low B12 and increased methylmalonic acid.
- Pernicious anemia is confirmed with the presence of antiparietal cell antibodies and anti-intrinsic factor antibodies; treatment is B12 replacement, as with all cases of B12 deficiency.
- Evaluate all patients who have pernicious anemia for gastric adenocarcinoma with upper endoscopy and biopsy.



Zollinger-Ellison Syndrome

A 42-year-old woman presents with complaints of diarrhea for 6 months. She has stopped all dairy products but there has been no improvement. There is no blood or pus with the stools. She takes maximum doses of omeprazole daily, along with famotidine, and still has ulcer symptoms. She has a mild hypercalcemia.

Zollinger-Ellison syndrome (ZES) is hypergastrinemia caused by cancer of the gastrin-producing cells. There is no known cause.

- 50% are located in the duodenum
- 25% are located in the pancreas
- <20% are associated with MEN type 1, or a parathyroid/pituitary/pancreatic tumor

More than 95% of patients with ZES present with ulcer disease. Of those, <1% have an underlying ZES or gastrinoma. Symptoms include:

- Ulcers that are recurrent after therapy, multiple in number, occur in the distal portion of the duodenum, or are resistant to routine therapy
- Diarrhea (70% of patients), i.e., ordinary watery diarrhea or steatorrhea (due to inactivated lipase from large volume of acid passed into the duodenum)
- Metastatic disease (evident in 30% of patients, with an additional 20% developing it later)

Diagnosis. An elevated gastrin level is indicative of ZES, but testing must occur after the patient has been off antisecretory therapy for several days.

Diagnosis is the combination of elevated gastrin and increased gastric acidity (must check gastric pH to make diagnosis; if pH >4, it is not a gastrinoma). The secretin stimulation test is positive (abnormal) if there is a rise in gastrin level after the injection of secretin (normally, secretin should suppress gastrin release).

Other causes of increased gastrin include:

- Pernicious anemia
- Chronic gastritis
- Renal failure
- Hyperthyroidism

After confirming a diagnosis of gastrinoma, the most important step is to determine if the lesion is localized or metastatic.

- Localized lesions can be surgically removed.
- Metastatic disease can be suppressed only with PPIs
 - U/S, CT, and MRI (60–80% sensitive to detect metastatic disease)—specific enough to prove the presence of tumor if positive but not sensitive enough to safely exclude disease if negative
 - Endoscopic U/S (**most sensitive test**)
 - Nuclear test, somatostatin-receptor scintigraphy (90% sensitive to detect metastatic disease)

Note

The presence of hypercalcemia is the clue to detecting MEN-1. This is because of the hyperparathyroidism.

Note

All patients on an H2 blocker or PPI will have elevated gastrin. (The main stimulus to the suppression of gastrin release is acid, so if acid production is suppressed, then gastrin goes up.) So to diagnose ZES, the patient must have stopped the medication several days prior.

Treatment. Localized disease is surgically resected and metastatic disease is treated with the long-term administration of PPIs simply to block acid production.

Gastroparesis

Gastroparesis, or delayed gastric emptying, results in delayed movement of food from the stomach to the small intestine. The most common association is diabetes. Electrolyte problems with potassium, magnesium, and calcium can also weaken the musculature of the bowel wall.

Clinical Presentation. Patients with gastroparesis present with early satiety, postprandial nausea, and a general sense of increased abdominal fullness due to decreased motility of the stomach and the accumulation of food there. Gastroparesis generally occurs in those presenting with abdominal pain and bloating and those with a long-standing history of diabetes, a long-standing history of poor glycemic control, retinopathy, neuropathy, and nephropathy. It can accompany scleroderma, hypothyroidism, anti-cholinergic use, and narcotic use.

Diagnosis. The first test should be endoscopy. Then, do the gastric-emptying study, where radioisotope-labeled food is ingested to measure transit time through the stomach. In a long-term diabetic, a diagnosis of diabetic gastroparesis is generally obvious as the cause of bloating, vomiting, and nausea, after endoscopy excludes other diseases. **Make sure blood glucose <275 mg/dL before testing** because severe hyperglycemia can impair gastric emptying.

Treatment. Treatment is agents that will increase motility of the stomach, such as erythromycin or metoclopramide. Also, smaller, more frequent portions of food are recommended, since emptying from the stomach is faster when there is less food.

Metoclopramide can cause tardive dyskinesia, Parkinsonism, and dystonia. If patients develop extrapyramidal symptoms, use promethazine.

Dumping Syndrome

Dumping syndrome is an increasingly rare disorder because surgery is so infrequently needed anymore for ulcer disease. It was far more common in the past, when vagotomy and gastric resection were performed to treat severe ulcer disease.

Dumping syndrome is caused by 2 phenomena.

- First, there is the rapid release of hypertonic chyme into the duodenum, which acts as an osmotic draw into the duodenum, causing intravascular volume depletion.
- Next, there is a sudden peak in glucose levels in the blood because of the rapid release of food into the small intestine. This is followed by the rapid release of insulin in response to this high glucose level, which then causes hypoglycemia to develop.

Patients present with sweating, shaking, palpitations, and lightheadedness shortly after a meal.

Treatment. Treatment is supportive. Eat multiple, small meals.

Nonulcer Dyspepsia

When all the causes of epigastric pain have been excluded and there is still pain, fullness, or burning sensation, the diagnosis is nonulcer (or functional) dyspepsia. The cause of nonulcer dyspepsia is unknown.



Treatment is symptomatic, with antacids, H₂ blockers, PPIs,

- If there are no alarm symptoms, test and treat *H. pylori*. If negative, treat with PPI.
- If there are alarm symptoms or refractory symptoms, do endoscopy.
- Try a low-dose tricyclic antidepressant if symptoms do not respond to PPI or H₂-blocker therapy.

Clinical Recall

A 36-year-old man complains of intermittent, worsening epigastric pain radiating to the back for the past 3 months. He claims to drink alcohol only during business trips but admits to blacking out several times from too much alcohol. Which of the following is the most likely cause of his symptoms?

- A. Barrett's esophagus
- B. Candida esophagitis
- C. Gastritis
- D. GERD
- E. Pancreatitis

Answer: E

INFLAMMATORY BOWEL DISEASE

Inflammatory bowel disease (IBD) describes 2 disease entities: **Crohn disease** (CD) and **ulcerative colitis** (UC). They can be discussed simultaneously because of the large degree of overlap in terms of presentation, testing, and treatment.

- Idiopathic disorders of the bowel associated with diarrhea, bleeding, weight loss, fever, and abdominal pain
- Most accurately diagnosed with endoscopy and sometimes barium study, "string sign" on small bowel follow through after barium meal in CD
- Treat with anti-inflammatory medications such as mesalamine, azathioprine, and 6-mercaptopurine (6MP); steroids are reserved for acute exacerbations

Clinical Presentation. IBD presents with fever, diarrhea, weight loss, and, occasionally, abdominal pain and bleeding. The extraintestinal manifestations of IBD are episcleritis, scleritis and iritis, sclerosing cholangitis, joint pains, and skin manifestations such as pyoderma gangrenosum or erythema nodosum.

Table 4-1. CD versus UC

Crohn Disease	Ulcerative Colitis
Linear, stellate deep ulcerations with skip lesions involving entire GI tract	Mucosal edema, erythema, friability, ulceration
Granulomas, transmural involvement	Bloody diarrhea common; diarrhea prominent, tenesmus, urgency, hematochezia
Abdominal pain prominent; inflammatory masses	Altered crypt architecture with shortened branched crypts and crypt abscesses
Smoking is risk factor	Smoking alleviates
Rectal sparing	Rectum always involved
Cobblestone appearance	Limited to large bowel
Strictures and fistulas	No skip lesions, anal involvement, or fistulas
Complications include diarrhea, calcium oxalate kidney stones, and cholesterol gallstones	

Diagnosis. IBD is diagnosed with endoscopy and sometimes barium study. (CD can cause deficiency of B12, K, calcium, and iron because of malabsorption.)

- **Anti-*Saccharomyces cerevisiae* antibodies (ASCA)** are associated with CD, while **antineutrophil cytoplasmic antibody (ANCA)** is associated with UC.
- If a patient is **ASCA-positive and ANCA-negative**, he has a **>90% chance of having CD**.
- If a patient is **ASCA-negative and ANCA-positive**, he has a **>90% chance of having UC**.
- With CD, prothrombin time may be prolonged because of vitamin K malabsorption. Also, kidney stones are more often seen because the fat malabsorption causes reduced calcium and increased absorption of oxalate. Use cholestyramine to treat calcium oxalate stones.

Treatment. Therapy is divided into active and maintenance.

Note

Sclerosing cholangitis does not correlate to disease activity.

Note

Always check stool studies, especially *C. difficile* toxin during a flare.

**Note**

- Check thiopurine methyltransferase level before starting azathioprine and 6-mercaptopurine, as they are contraindicated in 1 in 300 patients who lack this enzyme and are at high risk for drug toxicity.
- Do not give allopurinol or febuxostat with these drugs (they are also metabolized by xanthine oxidase).

Clinical Correlate

Patients with UC are hypercoagulable.

Note

For Crohn disease, 5-ASAs have recently been proven to have little efficacy. **TNF-alpha inhibitors are now the most common treatment for Crohn.**

Note

Check PPD, HBV, HCV prior to initiating anti-TNF agent.

Table 4-2. Treatment of CD versus UC

Crohn Disease	Ulcerative Colitis
5-ASAs are often ineffective	Depends on severity of disease
Mild: For active disease prednisone or budesonide For maintenance azathioprine and 6-mercaptopurine	Mild: 4 bowel movements/day, mild bleeding, normal labs Mesalamine or sulfasalazine (causes reversible infertility in men and leukopenia by its sulfapyridine group)
Moderate: fever, weight loss, anemia, abdominal pain, nausea/vomiting For active steroids For maintenance azathioprine and 6-mercaptopurine or methotrexate For remission anti-TNF antibodies	Moderate: 4–6 bowel movements/day For active disease prednisone For remission budesonide For long-term maintenance azathioprine and 6-mercaptopurine (associated with drug-induced pancreatitis) to try to keep patients off steroids
Severe to fulminant: high fever, vomiting, rebound, obstruction For acute exacerbations, IV steroids or anti-TNF (better choice), possible surgery	Severe: >6 bowel movements/day, bleeding, fever, tachycardia, ESR >30 mm/h, anemia For acute exacerbations that fail steroids and for maintenance if azathioprine and 6-mercaptopurine fail or are contraindicated, IV steroids followed by anti-TNF-alpha (infliximab, adalimumab, golimumab)
Fistula: anti-TNF For induction and maintenance anti-TNF antibodies (infliximab, adalimumab, certolizumab); if anti-TNF fails, use natalizumab (a monoclonal antibody to integrin-alfa-4 on leukocytes) (can cause PML so check JC virus antibodies first)	
For those with perianal disease ciprofloxacin and metronidazole For those who form fistulae or have disease refractory to other therapies infliximab	
Surgery is not very effective; disease tends to reoccur at the site of anastomosis	Surgery is curative; almost 60% of patients will require surgery within 5 years after diagnosis due to refractory symptoms or severe disease

For both, start screening colonoscopy 8–10 years after diagnosis and repeat every 1–2 years.

DIARRHEA

Diarrhea is increased frequency or volume of stool per day (alternatively, it can be defined as few stools per day but with watery consistency). The most common causes include an infectious, antibiotic-associated, or lactose-intolerance etiology, irritable bowel syndrome, and carcinoid syndrome.

The patient is often hypotensive, febrile, and experiencing abdominal pain.

Diagnosis. The first step in the evaluation of diarrhea is to see if there is hypovolemia as defined as hypotension or orthostasis. This is more important than determining specific etiology because the patient could die while waiting for the results to come back.

Treatment. No matter the etiology, if the patient is hypotensive, febrile, and having abdominal pain, admit as inpatient and give IV fluids and antibiotics. Blood in the stool is especially serious and is probably the single strongest indication for the use of antibiotics, such as ciprofloxacin.

Infectious Diarrhea

The majority of acute diarrhea is viral and self-limited. *Clostridium difficile* toxin and stool *Giardia*-antigen testing are done when there are clues to these diagnoses in the history.

With bacterial diarrhea, the most common causes are *Campylobacter* and *Salmonella*, especially in patients with sickle cell and achlorhydria. A definitive determination of the etiology can only be made with a stool culture.

Note

With management of diarrhea, determine **when to admit** the patient and **when to use IV fluids and antibiotics**. That is more important than determining the precise causative agent.

**Table 4-3. Clues to the Diagnosis of Infectious Diarrhea Prior to Results of Culture**

Causative Agent	Patient Symptoms or History	Additional Comments
<i>Bacillus cereus</i>	- Ingestion of refried Chinese food and the spores from <i>Bacillus</i> that it contains - Vomiting is prominent - Blood is never present	Short incubation period (1–6 hours)
<i>Campylobacter</i>	Reactive arthritis, Guillain-Barré syndrome	Most common cause of bacterial gastroenteritis
<i>Cryptosporidia</i> , <i>Isospora</i>	Found in HIV-positive patients with $<100/\text{mm}^3$ CD4 cells	—
<i>E. coli</i> 0157:H7	Ingestion of contaminated hamburger meat; the organism can release a Shiga toxin, provoking hemolytic uremic syndrome	Hemolytic uremic syndrome happens when organism dies; that is why antibiotics are contraindicated. Platelet transfusion is also contraindicated, even if platelet count is low because new platelets may only make it worse.
<i>Giardia</i>	- Ingestion of unfiltered water, as on a camping trip in mountains or lake - Blood is never present - Abdominal fullness, bloating, and gas	If not eradicated, can simulate celiac disease in terms of causing fat and vitamin malabsorption
<i>Salmonella</i>	Ingestion of chicken and eggs, dairy products	—
Scombroid	Ingestion of contaminated fish; almost immediate vomiting, diarrhea, flushing, and wheezing	Organisms invade, producing and then releasing histamine into the flesh of fish, such as tuna, mahi mahi, and mackerel
<i>Shigella</i> , <i>Yersinia</i>	No clues strong enough to point to etiology until the results of stool culture are known	<i>Yersinia</i> can mimic appendicitis. Also common in people with iron overload, e.g., hemochromatosis.
<i>Vibrio parahaemolyticus</i>	Ingestion of raw shellfish, such as mussels clams	Typically presents as severe systemic gastroenteritis in patients with underlying disease (esp. chronic liver disease)
<i>Vibrio vulnificus</i>	- Ingestion of raw shellfish (particularly affects those with underlying liver disease) - Skin bullae	Typically presents as severe systemic gastroenteritis in patients with underlying disease (esp. chronic liver disease or disorders of iron metabolism)
Viral	Children in day-care centers; absence of blood and white cells	No systemic manifestation
<i>Staphylococcus aureus</i>	- Ingestion of dairy products, eggs, salads - Upper GI symptoms (nausea/vomiting) predominate; rarely diarrhea	Short incubation period (1–6 hours)
<i>Ciguatera</i> -toxin	Ingestion of large reef fish (grouper, red snapper, barracuda); 2–6 hours after ingestion, neurological symptoms leading to paresthesia, weakness, reversal of hot/cold	—

Diagnosis. Only send stool studies if condition does not resolve in 1 week. Invasive organisms need 24–36 hours to produce their effect and never produce blood in the stool within the first few hours of ingestion (except the protozoan *Entamoeba histolytica*, which can give blood or white cells in stool). The most definitive test for these bacterial organisms is stool culture.

The invasive organisms are:

- *Salmonella*
- *Shigella*
- *Campylobacter*
- *Vibrio parahaemolyticus*
- *Yersinia*
- *E. coli*
- *Vibrio vulnificus* (think fishermen exposed to sea water or eating raw oysters)

Cryptosporidiosis diagnosis requires a unique test—a modified acid-fast test; it cannot be detected reliably by the routine ova and parasite exam.

Giardia diagnosis is best made with an ELISA stool antigen test (a single test has 90% sensitivity, whereas 3 stool ova and parasite exams have only 80% sensitivity). Consider this for chronic diarrhea in patients exposed to young children or who drank water from a lake or stream.

Treatment. Most cases of food poisoning and infectious diarrhea will resolve spontaneously and will not need antimicrobial therapy. Even when they cause severe disease, as defined by high-volume stools with dehydration, antibiotics generally do not help. Use antibiotics if there is abdominal pain, blood in the stool, and fever >7 days.

The decision to use antibiotics is always made prior to knowing the result of the stool culture, so the treatment is always empiric and then modified when the culture results are known. The best empiric therapy for infectious diarrhea is ciprofloxacin or the other fluoroquinolones ± metronidazole. Macrolides are preferred for *Campylobacter* when indicated because of increasing resistance to fluoroquinolones.

Do not give antibiotics for *E. coli* 0157:H7, as that precipitate HUS.

Scombroid poisoning is treated with antihistamines, such as diphenhydramine. *Giardia* is still treated primarily with metronidazole. A newer agent for *Giardia* is tinidazole, which is effective in a single dose. Cryptosporidiosis is treated with nitazoxanide, although it has limited efficacy. The truly effective therapy for cryptosporidiosis is to raise the CD4 count to >100/mm³ with antiretrovirals. Nitazoxanide is superior to paromomycin for cryptosporidium.

There is no specific therapy for viral diarrhea. Patients are managed with fluid and electrolyte support until the infection resolves.

For chronic diarrhea (>4 weeks), think of the following:

- Use of artificial sweeteners (get diet history)
- *Giardia* if camping or exposed to children (daycare worker)
- If bloating and discomfort are relieved by bowel movement with no weight loss: **IBS, test for celiac**

Note

- TMP/SMX for *Isospora*
- Doxycycline for *Vibrio vulnificus*
- Rifaximin for travelers' diarrhea

Note

Prophylactic antibiotics for traveler's diarrhea is never a correct approach.



- If woman age 45–60, unrelated to food (nocturnal diarrhea), no abdominal pain or weight loss, and normal colonoscopy, think microscopic colitis; biopsy must be done to diagnose (will see collagenous or lymphocytic colitis); associated with NSAIDs, SSRIs, and PPIs; treat with loperamide, bismuth, or budesonide for severe cases (stop NSAIDs, SSRIs, PPIs)
- Small intestinal bacterial overgrowth: nocturnal diarrhea due to overgrowth of bacteria in the small bowel; think of this in patient with poorly controlled diabetes, scleroderma, or history of gastric bypass surgery; there will be B12 deficiency with elevated folate (bacteria produce folate); check glucose hydrogen breath test or empiric antibiotics (usually rifaximin)
- Flushing and wheezing: carcinoid syndrome; check urine 5-HIAA

Antibiotic- and *C. difficile*-Associated Diarrhea

Antibiotic-associated diarrhea (AAD) is a benign, self-limited diarrhea following the use of antimicrobials. Typically, no pathogens are identified; the diarrhea is caused by changes in the composition and function of the intestinal flora, as well as increased motility (common with agents like erythromycin). Most patients respond to supportive measures and discontinuation of antibiotics.

Clostridium difficile-associated diarrhea (*C. diff*) refers to a spectrum of diarrheal illnesses caused by the toxins produced by *C. diff*, including severe colitis with or without the presence of pseudomembranes. (For exam purposes, this discussion will focus on *C. diff*.)

Pathogenesis. Any antibiotic can lead to diarrhea with *C. diff*, although antibiotics that are broad spectrum are more likely to do so. Clindamycin may have one of the highest frequencies of association, as do fluoroquinolones and cephalosporins.

C. diff diarrhea is largely a nosocomial disease and is the most frequent cause of diarrhea in hospitalized patients. It occurs infrequently in the outpatient setting, other than in patients confined to nursing homes. Research suggests a significant association between *C. difficile* and the use of PPIs.

Clinical Presentation and Diagnosis. The clinical manifestations of *C. diff* may vary from mild diarrhea to fulminant colitis. If a patient develops diarrhea several days to weeks (even up to 8 weeks) after using antibiotics, evaluate for *C. diff*. Marked leukocytosis and systemic symptoms are evident in severe cases.

- Until a few years ago, the diagnostic method of choice for *C. difficile* colitis was the enzyme-linked immunosorbent assay (ELISA), based on toxin detection in the stool. While ELISA is fast, inexpensive, and has excellent specificity, its sensitivity is variable (75–85%).
- The newer preferred method of diagnosis is the nucleic acid amplification (LAMP, loop-mediated isothermal amplification) assay, which may include the real-time polymerase chain reaction (PCR) or loop-mediated isothermal amplification test (both of which detect the toxin A and B genes responsible for the production of toxins). LAMP has specificity 94–100% and sensitivity 90–100%. There is no benefit to testing multiple stool specimens or repeat testing following a positive test.

Treatment.

- **Severe *C. diff*** (WBC >15,000 or increased serum creatinine >1.5 × normal): oral vancomycin, not fidaxomicin
- **Initial infections:** oral vancomycin or fidaxomicin
- **Fulminant infections** (ileus, hypotension, shock, toxic megacolon): oral vancomycin + IV metronidazole. (IV vancomycin will have no effect in the bowel because it does not pass bowel wall. Similarly, oral vancomycin will have no systemic effect.)

If there is a second recurrence, use a tapered and pulsed course of oral vancomycin (6–8 weeks). It must be 6 weeks to be effective and it must be tapered.

- If vancomycin was used for the initial episode, try fidaxomicin, which seems to reduce the number of episodes of recurrent *C. difficile* colitis.
- Alternatively, consider fecal transplant (after 2 recurrences treated with the appropriate antibiotics).

Lactose Intolerance

Lactose intolerance is perhaps the single most common potential cause of diarrhea because of the enormously high prevalence of lactase deficiency. This is a disorder so common that the testing and treatment are generally empiric.

The diarrhea produced is associated with gas and bloating, but never contains blood or leukocytes. Despite the malabsorption of lactose, weight loss does not occur.

Diagnosis can be confirmed with increased stool osmolality and increased osmolar gap.

- Osmolar gap means that the difference between the osmolality measure in the stool and the osmolality calculated from the sodium and potassium levels is >50 mOsm/kg.
- Therefore, the measured stool osmolality is greater than would be expected just by the level of sodium and potassium. The extra osmoles are from lactose.
- Other causes of an increased stool osmolar gap are magnesium and polyethylene glycol in the stool, or nutrient malabsorption leading to pancreatic insufficiency, celiac sprue, and bacterial overgrowth.

The routine way to diagnose lactose intolerance is simply to remove milk, cheese, ice cream, and other dairy products (except yogurt) from the diet and observe for resolution of symptoms, which should occur within 24–36 hours. (This differs from celiac disease, where resolution of diarrheal symptoms make take weeks after stopping the ingestion of gluten-containing foods.) If resolution of symptoms does occur, then dietary changes are the best therapy. The patient can use lactase supplements.

Irritable Bowel Syndrome

Although it is often described at the same time as diarrheal illnesses, irritable bowel syndrome (IBS) is predominantly an abdominal pain syndrome with altered bowel habits. The etiology is unknown.

Note

Effective 2018, metronidazole is no longer considered first-line treatment for *C. difficile*.

PO vancomycin or fidaxomicin is now considered first-line treatment.



IBS is an idiopathic disorder in which there is increased frequency of the normal peristaltic and segmentation contractions of the bowel. Pain is often relieved by a bowel movement.

- 20% of patients have constipation only, while a large percentage have diarrhea alone or diarrhea alternating with constipation.
- Everyone has pain.
- There are no nocturnal symptoms.
- There are no constitutional signs or symptoms, e.g., fever, weight loss, anorexia, or anemia.

Diagnosis. There is no specific diagnostic test for IBS. The first step is to exclude lactose intolerance, IBD, celiac disease, carcinoid, *Giardia* infection, and anatomic defects of the bowel as the cause.

The diagnostic criteria, called Rome criteria, must occur for at least 3 months:

- Pain relieved by a bowel movement or by a change in bowel habit (e.g., when you develop diarrhea, the pain goes away)
- Fewer symptoms at night
- Diarrhea alternating with constipation

Colonoscopy is not needed for diagnosis, but a **work up for celiac sprue must be done if diarrhea is predominant.**

Treatment.

- High-fiber diet to increase bulk of the stool
- Antidiarrheal agent such as loperamide or diphenoxylate for diarrhea-predominant disease
- Hyoscyamine or dicyclomine for abdominal pain
 - Tricyclic antidepressant for IBS-D
 - SSRI for IBS-C
- Osmotic laxative polyethylene glycol for IBD-C; lubiprostone (women) and linaclotide for IBD-C unresponsive to PEG; eluxadoline for abdominal pain and stool consistency in IBS-D; rifaximin for IBS-D

Do not use alosetron due to risk of ischemic colitis.

Carcinoid Syndrome

Carcinoid syndrome describes tumors of the neuroendocrine system. They are most often located in the appendix and ileum. By definition carcinoid syndrome implies metastatic disease (except for bronchial carcinoids). Until there is an enormous tumor burden, the liver is able to neutralize all of the serotonin released by the carcinoid in the bowel. This usually does not happen until the metabolic capacity of the liver has been overwhelmed by metastatic disease.

Bronchial carcinoids are rare but highly symptomatic because the serotonin produced is released directly into the circulation without being detoxified in the liver.

Clinical Presentation. Carcinoid syndrome presents with diarrhea, flushing, tachycardia, and hypotension. A rash may develop from niacin deficiency, a direct result of the carcinoid. Serotonin and niacin are both produced from tryptophan, so if there is an overproduction of serotonin, a tryptophan deficiency (and thus a niacin deficiency) will result. Endocardial fibrosis also occurs because of a constant exposure of the right side of the heart to the serotonin. This leads to tricuspid insufficiency and pulmonic stenosis.

Diagnosis. The diagnosis is confirmed with urinary 5-hydroxyindolacetic acid level (5-HIAA).

Treatment. Therapy is generally based on controlling the diarrhea with octreotide, a somatostatin analog. Very few carcinoids are sufficiently localized to be amenable to surgical resection. If a tumor does happen to be localized, then it should be resected. This is most often possible with bronchial carcinoid. Surgery is also used to relieve obstruction of the bowel.

MALABSORPTION SYNDROMES

The major causes of fat malabsorption are celiac disease and chronic pancreatitis, although in extremely rare cases it is caused by tropical sprue or Whipple disease. What they all have in common is the production of diarrhea characterized as greasy, oily, floating, and fatty, with a particularly foul smell, as if fat were fermenting. This type of diarrhea with fat is called *steatorrhea*.

All malabsorption syndromes are characterized by weight loss because fat has the highest caloric content of all the foods. In addition, there is malabsorption of the fat-soluble vitamins A, D, E, and K.

- Vitamin A deficiency: night blindness (early), complete blindness
- Vitamin D deficiency: hypocalcemia hypophosphatemia, osteomalacia
- Vitamin E deficiency: neuromuscular disorders, hemolysis
- Vitamin K deficiency: prolongation of prothrombin time and easy bruising

Iron malabsorption occurs if there is involvement of the duodenum where iron is normally absorbed. Iron deficiency anemia is evident in all patients with celiac sprue. Macrocytic anemia occurs if folate is malabsorbed. **Vitamin B12 malabsorption** occurs from damage or loss of the mucosal surface of the terminal ileum.

Clinical Presentation. All malabsorption syndromes present with chronic diarrhea. The only unique feature of celiac disease is dermatitis herpetiformis, a vesicular skin rash on the extensor surfaces of the body (10% of patients). Even without dermatitis herpetiformis, celiac disease is the most likely etiology of fat malabsorption because it is the most common.

Chronic Pancreatitis

Chronic pancreatitis is diagnosed with the following:

- History of pain, recurrent attacks of acute pancreatitis, weight loss
- Pancreatic calcifications on imaging
- Exocrine pancreatic insufficiency (steatorrhea)
- Diabetes
- Chronic alcohol abuse (most common cause)

Clinical Pearl

Antibodies Seen in Celiac Disease

- IgA endomysial antibody
- IgA tissue transglutaminase antibody
- IgG tissue transglutaminase antibody

Anti-tissue transglutaminase antibody (IgA) is the most sensitive and specific. In patients with **IgA deficiency**, IgA endomysial and transglutaminase antibodies are **falsely normal**.

Note

In chronic pancreatitis, lipase and amylase are usually normal due to a burnt out pancreas.



Clinical Correlate

Do not let an absence of diarrhea and weight loss keep you from considering celiac. Test for celiac in anyone with unexplained elevation in LFTs or multiple vitamin deficiencies.

If CT does not show calcifications, get MRCP to detect abnormal pancreatic ducts.

For young adults with chronic pancreatitis, work up for cystic fibrosis (especially if there is recurrent pneumonia, sinusitis, and infertility).

Suspect tropical sprue when there is a history of being in a tropical country, and Whipple disease (very rare) if there is dementia (10%) or arthralgia (80%).

Treatment is pancreatic enzymes; pain control with NSAID/acetaminophen, tramadol (may cause hypoglycemia), tricyclic antidepressant, gabapentin, or pregabalin; insulin (required for diabetics, as it mimics type 1 diabetes due to destruction of beta cells).

Do not use narcotics for pain control.

Celiac Sprue

Celiac sprue is secondary to ingestion of wheat, gluten, or related rye and barley proteins. Patients present with the following:

- Chronic diarrhea or steatorrhea
- Bloating, weight loss, abdominal pain
- Pruritic papulovesicular rash on extensor surfaces (dermatitis herpetiformis)
- Isolated abnormalities in liver chemistry tests
- Unexplained iron deficiency anemia (after a negative work up for GI bleed)
- Fat-soluble vitamin deficiencies
- Early onset osteoporosis
- Strong association with type 1 diabetes (should be screened)
- Malabsorption of thyroid hormone in patient with thyroiditis
- IBS-D

The antibodies seen in celiac disease include IgA endomysial antibody, IgA tissue transglutaminase antibody, IgG tissue transglutaminase antibody. **Anti-tissue transglutaminase antibody (IgA)** is the most sensitive and specific. In patients with IgA deficiency, IgA endomysial and transglutaminase antibodies are falsely normal. Check IgG anti-tTG.

Work up celiac in a patient with thyroiditis who is not responding to high doses of levothyroxine.

Diagnosis. Just removing gluten (wheat, rye, oats) from the diet is not an accurate way to establish the diagnosis, because circulating antibodies will be present for weeks after the gluten has stopped.

- First, test for the presence of antiendomysial and anti-transglutaminase antibodies
- Then, small bowel biopsy (**most accurate test**) will show flattening of villi
- Even if antibodies are elevated, do a bowel biopsy to confirm diagnosis and exclude small bowel lymphoma.
- Adherent patients with recurrent malabsorption should be evaluated for intestinal lymphoma.
- Bone mineral testing (for all patients)

An association with IgA deficiency can lead to false-negative IgA-based tests. In patients with IgA deficiency, check IgG-tTG.

Tropical sprue and Whipple disease are diagnosed by finding organisms on a bowel-wall biopsy. The single most sensitive test for Whipple disease is a polymerase chain reaction (PCR) of the bowel biopsy. A positive *Tropheryma whippelii* biopsy shows foamy macrophages that are PAS positive.

Treatment. Celiac disease is managed by adhering to a gluten-free diet (no wheat, oats, rye, or barley); nonadherence is the most common reason for failure. Use dapsone when celiac patients have dermatitis herpetiformis.

- Trimethoprim/sulfamethoxazole or doxycycline × 6 months (for tropical sprue)
- Trimethoprim/sulfamethoxazole, doxycycline, or ceftriaxone × 1 year (for Whipple disease)

Although all malabsorption syndromes are associated with multiple deficiencies, note some complications:

- Celiac disease is associated with GI lymphoma and adenocarcinoma; there is also high risk for osteoporosis (do a DEXA scan) and streptococcus (give pneumococcal vaccine)
- Celiac sprue is associated with lymphoma (enteropathy-associated T cell lymphoma) (10-15% of cases); unclear whether therapy with gluten-free diet reduces incidence of lymphoma

Clinical Recall

A 22-year-old woman complains of intermittent bloating and diarrhea for the past 3 months. Her symptoms are relieved when she avoids her morning coffee and ice cream. On diagnostic testing, her blood and stool tests are within normal limits except for a mild elevation in stool osmolality. What is the most likely cause of her symptoms?

- Celiac sprue
- Carcinoid syndrome
- Irritable bowel syndrome
- Lactose intolerance
- Whipple disease

Answer: D

Note

Celiac patients are at risk for adenocarcinoma of the intestine.



DIVERTICULAR DISEASE

In diverticular disease, small bulges or pockets develop in the lining of the intestine. They often develop where the muscles are weakest, e.g., where penetrating vessels cross through muscle.

Diverticulosis

Diverticulosis is so common in older populations throughout the Western world (50% of persons age >50, with higher rates in older populations) that it is almost considered a normal part of aging. The cause of diverticulosis is believed to a lack of fiber in the diet to give bulk to stool. There is a subsequent rise in intracolonic pressure, leading to outpocketing of the colon.

Clinical Presentation. Most of the time, patients are asymptomatic. When symptoms do exist, they are typically left lower quadrant abdominal pain that is colicky in nature.

Diverticulosis is diagnosed with colonoscopy. Endoscopy is superior to barium study, particularly when bleeding is present. Diverticula are more common on the left in the sigmoid, but bleeding occurs more often from diverticula on the right because of thinner mucosa and more fragile blood vessels. When bleeding occurs from diverticula, it is painless.

Treatment. Treatment is an increased-fiber diet as is found in bran, bulking agents such as psyllium husks, and soluble fiber supplements.

Diverticulitis

Diverticulitis occurs when one of the bulges or pockets (diverticula) becomes infected. This can occur when the diverticular entrance in the colon becomes blocked, perhaps by nuts or corn.

Diverticulitis is distinguished from uninfected diverticula by the presence of fever, tenderness, more intense pain, and elevated white blood cell count.

Diagnosis is confirmed with CT scan. Barium study and endoscopy are contraindicated because there is a slightly higher risk of perforation.

Treatment is antibiotics such as ciprofloxacin and metronidazole. Alternatives are ampicillin/sulbactam, piperacillin/tazobactam, or ertapenem. For mild disease, an oral antibiotic, e.g., amoxicillin/clavulanic acid, can be used. Do colonoscopy 1–2 months after recovery to evaluate.

CONSTIPATION

A 72-year-old woman has a history of upper GI tract bleed and iron-deficiency anemia, for which she has recently been started on oral ferrous sulfate iron replacement. She also has a history of diabetes with peripheral neuropathy, for which she takes amitriptyline. She has untreated hypothyroidism, but is treated for hypertension with nifedipine. Currently, she has constipation, and when the stool does pass it is very dark in color, almost black.

The most common cause of constipation is lack of dietary fiber and insufficient fluid intake. CCBs, oral ferrous sulfate, hypothyroidism, opiate analgesics, and medications with anticholinergic effects such as the tricyclic antidepressants all cause constipation. In the patient, the most likely cause of the constipation is the ferrous sulfate.

- Very dark stool, as in this patient, occurs only with bleeding, bismuth subsalicylate ingestion, and iron replacement.
- However, GI bleed produces diarrhea—not constipation—because blood acts as a cathartic.
- Blood causes diarrhea, and iron tablets cause constipation.

Treatment. Stop all medications that cause constipation; then make sure the patient stays well-hydrated and consumes 20–30 grams of daily fiber.

- Bulking agents, such as those used to manage diverticular diseases
- Drug treatment: milk of magnesia, cascara, bisacodyl, docusate
- Enema (acute and serious constipation)
- Lactulose and polyethylene glycol

COLON CANCER

The lifetime risk of colon cancer is >6%. Most cases occur sporadically, which is to say there is no clearly identified etiology.

A diet high in red meat and fat leads to an increased risk, as does smoking.

- When the cancer is in the right side of the colon, patients present with heme-positive brown stool and chronic anemia.
- When the cancer is in the left side or in the sigmoid colon, patients present with obstruction and narrowing of stool caliber; that is because the right side of the colon is wider than the left, and the stool is more liquid in that part of the bowel, making obstruction less likely on the right.
- Endocarditis by *Streptococcus bovis* and *Clostridium septicum* have a strong association with colon cancer. Anyone presenting with endocarditis due to one of these organisms requires a GI work-up.

Diagnosis. Colonoscopy is the most accurate diagnostic test. Sigmoidoscopy will reach the lesion only within the distal 60 cm of the colon. If the lesion is in the distal area then the sigmoidoscopy will be equally sensitive as colonoscopy, but only 60% of cancers occur there. Barium study is not as accurate as colonoscopy, nor can you biopsy.

Treatment. Treatment depends on the stage of disease and extent of its spread.

- Single liver metastatic lesion: surgical resection
- Cancer localized to the mucosa, submucosa, and muscularis layers: surgical resection; curable
- Cancer penetrated to the serosa and spread into surrounding tissue and lymph nodes: surgical resection not effective in eradicating disease
- Widespread disease: chemotherapy (mainstay of chemotherapy for GI malignancies such as colon cancer is 5-fluorouracil [5FU])



Screening should occur in the general population after age 50, as per the following recommendations.

- High-sensitivity fecal occult blood testing (FOBT) or fecal immunochemical test (FIT) every year
- Flexible sigmoidoscopy every 5 years
- Flexible sigmoidoscopy every 10 years with annual FIT **or** colonoscopy every 10 years
- CT colonography every 5 years

If adenomatous polyps were found on previous colonoscopy, repeat colonoscopy in 3–5 years. In cases of family history of colon cancer, begin screening at age 40 or 10 years earlier than the family member got cancer, whichever is younger (also see Preventive Medicine chapter).

After polypectomy, intervals for follow-up colonoscopy are as follows:

- **Small rectal hyperplastic polyp:** every 10 years
- **1–2 small (<1 cm) tubular adenomas:** every 5 years
- **3–10 adenomas, any adenoma >1 cm, or adenoma with high-grade dysplasia or villous:** every 3 years
- **>10 adenomas:** every <3 years (consider familial syndromes)
- **Large (>2 cm) (size does matter) sessile polyp removed by piecemeal excision:** every 2–6 months
- **Polyp with adenocarcinoma** (minimal invasion and >2 mm margin): every 2–3 months

Hereditary Nonpolyposis Syndrome (Lynch Syndrome)

Certain families carry a genetic defect with a high degree of penetrance for colon cancer. The genetic defect does not cause polyps, however. By definition, the syndrome is defined as:

- Three family members in at least 2 generations with colon cancer
- One of these cases should be premature, i.e., occurred in someone age <50

Patients with this syndrome are also at increased risk for ovarian and endometrial cancer (up to 30%).

Screening. Start screening at age 25 and undergo colonoscopy every 1–2 years.

Hereditary Polyposis Syndromes

Familial adenomatous polyposis has a very clear genetic defect. The adenomatous polyposis coli gene (APC) confers 100% penetrance for the development of adenoma by age 35 and of colon cancer by age 50. Polyps can be found as early as age 25.

- Start screening at age 10–12 and do flexible sigmoidoscopy every 1–2 years.
- As soon as polyps are found, perform a colectomy; a new rectum should be made from the terminal ileum.
- Do upper endoscopy screening for duodenal cancer at the onset of colonic polyposis or age 25–30, whichever comes first.

By contrast, **juvenile polyposis syndrome** confers about a 10% risk of colon cancer. There are only a few dozen polyps, as opposed to the thousands of polyps found in those with familial polyposis. In addition, the polyps of the juvenile polyposis syndrome are hamartomas, not adenomas. Hamartomas confer very little risk of developing into cancer. There is no specific recommendation for screening.

Cowden syndrome is another polyposis syndrome with hamartomas that gives only a slightly increased risk of cancer compared with the general population. These polyposis syndromes can present with rectal bleeding in a child.

Other Polyposis and Colon Cancer Syndromes

Gardner syndrome is the association of colon cancer with multiple, soft-tissue tumors, such as osteomas, lipomas, cysts, and fibrosarcomas. Osteomas are frequently found on the mandible. If osteomas are found as an incidental finding on x-ray, do a colonoscopy.

Peutz-Jeghers syndrome is the association of hamartomatous polyps in the large and small intestine with hyperpigmented spots. These are melanotic spots on the lips, buccal mucosa, and skin. The risk of cancer is slightly increased above the general population. Most common presentation is with abdominal pain due to intussusception/bowel obstruction.

Turcot syndrome is simply the association of colon cancer with CNS malignancies.

Screening. There is no recommendation for increased cancer screening for any of these syndromes; they are not common enough to warrant a clear recommendation for uniform early screening. There is an association of endocarditis from *Streptococcus bovis* with colon cancer, so if a patient has endocarditis from *S. bovis*, colonoscopy should be performed.

GASTROINTESTINAL BLEEDING

A 72-year-old man with a history of aortic stenosis is brought to the ED with red/black stool several times today. His blood pressure is 94/60 mm Hg and pulse 110/min.

With GI bleed, **treat before you investigate the etiology.**

- **Upper GI bleed** causes include:
 - Ulcer disease
 - Gastritis
 - Mallory-Weiss syndrome
 - Esophagitis
 - Gastric cancer
 - Aortoenteric fistula (consider if there is a history of abdominal aortic aneurysm repair in past 6–12 months)
 - Variceal bleed, common in those with portal hypertension from cirrhosis

Note

If osteomas are seen as an incidental finding on x-ray, perform a colonoscopy.

Note

Upper GI bleed is defined as bleeding occurring proximal to the ligament of Treitz, which anatomically separates the duodenum from the jejunum.

**Note**

Orthostasis is defined as a >10-point rise in pulse when patient goes from supine to standing or sitting OR a >20-point drop in systolic BP on a change in position.

- At least 1 minute must pass between the position change and the measurement of pulse/BP, to allow the normal autonomic discharge to accommodate to the position change.
- In the vignette described here, the measurement of orthostatic changes is not necessary because pulse >100/min or systolic BP <100/min already indicates a >30% blood loss.

Note

- Occult blood—positive brown stool can occur with as little as 5–10 mL of blood loss.
- Melena can occur with ≥ 100 mL of blood loss.

Note

Virtual endoscopy is a CT scan used to try to detect cancer without the need of endoscopy. It lacks both sensitivity and specificity to detect causes of GI bleed.

Do not use for this purpose.

- **Lower GI bleed** causes include:

- Diverticulosis
- Angiodysplasia (also known as AVM or vascular ectasia)
- Hemorrhoids
- Cancer
- IBD
- Iron deficiency (slow and chronic bleeding)

Clinical Presentation.

- **Upper GI bleed:** generally black stool or melena
 - Bright red blood per rectum in 10% of cases
 - Elevated BUN/creatinine ratio if volume of bleeding is very high (so high that it is rapidly transported to the bowel without time to oxidize and turn black)
 - Orthostasis (pulse or drop in BP persists after one's position has changed), which indicates a 15–20% blood loss
- **Lower GI bleed** more commonly presents with red blood in the stool

Diagnosis.

- Endoscopy (**most accurate test to determine etiology**); occasionally, endoscopy will not reveal the etiology of lower GI bleeding, even during an active bleed
- Barium study (less accurate)
- Biopsy if needed, but do endoscopy first
- Nuclear bleeding scan for low volume bleeds 0.1–0.5 mL/min; RBCs from the patient are tagged with technetium, reinjected back, and then detected to determine the site of bleeding
- Angiography
 - Requires a higher volume of blood loss >0.5 mL/min compared with the nuclear scan
 - Used in extremely high-volume bleeding when so much blood is coming out that endoscopy cannot see the source
 - May then be used prior to embolization of the site of the bleeding or hemicolectomy
 - Can help guide the occasional use of a local vasopressin injection in the control of severe lower GI bleeding

Obscure GI bleeding is recurrent blood loss without an identified source. It could be a tumor, Crohn disease, or angiodysplasia (40%). Patients may have melena or hematochezia or positive FOBT.

- The first step is to repeat the upper endoscopy and/or colonoscopy (diagnostic in 25%). (This should be done before capsule endoscopy.)
- For active obscure GI bleeding, perform nuclear studies followed by angiography. If unrevealing, perform push enteroscopy or balloon-assisted enteroscopy.
- The newest modality to visualize the small bowel with occult bleeding is capsule endoscopy; the patient swallows a capsule containing an electronic camera which then transmits thousands of images to a nearby receiver and allows anatomic localization of the lesion.

Treatment must start with fluid resuscitation using normal saline or Ringer's lactate. Complete blood count, prothrombin time, and type and crossmatch should be done, but if the patient is having a high volume bleed, do not wait for the test results to begin fluid resuscitation.

- Prothrombin concentrate complex if prothrombin time is elevated
- IV vitamin K if on warfarin, to replace fresh frozen plasma
- Platelet transfusion if platelets $<50,000/\text{mm}^3$ and patient is actively bleeding
- IVFs to keep HR $<100/\text{min}$ and systolic BP >100 mm Hg
- Blood transfusion if there is hemodynamic instability or hemoglobin <7 g/dL
- IV PPI
- Upper endoscopy within 24 hours (within 12 hours for variceal bleeding)
- Do not use a nasogastric tube

For **acute bleeding**, additional treatment is as follows:

- Octreotide to lower portal pressure
- Antibiotics (ceftriaxone or ciprofloxacin) to prevent systolic BP rise, even if there is not ascites (**high yield for the exam**)
- If banding is not effective in stopping an acutely bleeding esophageal varix, then perform TIPS (transjugular intrahepatic portosystemic shunting); the most common long-term complication of TIPS is worsening of hepatic encephalopathy
- Blakemore tube to tamponade the site of bleeding in the stomach or esophagus (rarely used) is only a temporary bridge to surgery

Propranolol is a nonselective beta-blocker used in the long-term management of portal hypertension to decrease the frequency of bleeding. Everyone with varices from portal hypertension and cirrhosis should be on a beta-blocker.

Low risk ulcers are clean-based or have nonprotuberant pigmented spots; treat with oral PPIs, full diet and early hospital discharge (12 hours).

High risk ulcers have active arterial spurting or nonbleeding visible vessel or adherent clot. Treat endoscopically with hemo-clips, thermal therapy, or epinephrine injection; clear diet for 48 hours; and IV PPI infusion for 72 hours.

Clinical Recall

Which of the following colonic conditions requires additional colonoscopy screening?

- Cowden syndrome
- Gardner syndrome
- Juvenile polyposis syndrome
- None of the above

Answer: D

Note

H2 blockers are not helpful with GI bleed.

Note

In the TIPS procedure, a catheter is placed into the jugular vein and guided radiographically through the liver. The goal is to form a shunt between the systemic circulation in the hepatic vein and the portal circulation through the portal vein.

TIPS has largely replaced the need to surgically place the shunt.

Note

Lower GI bleeding presents with red blood in the stool, whereas **upper GI** bleeding usually presents with black stool.



Clinical Pearl

Always consider gallstone pancreatitis and rule it out by U/S, even in patients with history of alcohol use.

Note

Signs of Severe Necrotizing Pancreatitis

Cullen sign: blue discoloration around umbilicus → due to hemoperitoneum

Turner's sign: bluish purple discoloration of the flanks → tissue catabolism of Hb

Note

CT is more accurate than sonogram for detecting inflammation, necrosis, pseudo-cysts, abscesses, and ductal stones.

PANCREATITIS

Acute Pancreatitis

Acute pancreatitis is inflammation of the pancreas due to premature activation of trypsinogen into trypsin while still in the pancreas (common pathway of most causes of pancreatitis). This results in autodigestion of the pancreas. Circulating cytokines can lead to many complications.

Most cases of pancreatitis are caused by alcoholism and gallstones. Other causes include:

- Medications such as valproate, pentamidine, didanosine, azathioprine, and sulfa derivatives, e.g., sulfamethoxazole/trimethoprim and thiazide diuretics
- Hypercalcemia
- Hypertriglyceridemia, where elevated triglycerides are broken down to fatty acids, causing inflammation of the biliary tract and eventual pancreatitis
- ERCP, presumably because of back pressure from injection of the contrast material into the ductal system; most patients who have pancreatic injury from ERCP have just an asymptomatic increase in amylase
- Trauma and various viruses, such as mumps

Clinical Presentation. Midpigastirc pain with tenderness and nausea/vomiting. The pain typically radiates straight through to the back.

When extremely severe, pancreatitis can mimic many of the features of septic shock, with fever, hypotension, respiratory distress from ARDS, elevated WBCs, and a rigid abdomen.

Diagnosis. To diagnose, 2 of the following 3 features must be present:

- Acute onset of upper abdominal pain
- Amylase or lipase $>3\times$ the upper limit of normal
- Evidence on imaging

The initial tests remain as amylase and lipase (lipase is more specific to the pancreas than amylase). CT scan should not be given routinely; only do if pancreatitis is severe, lasts longer than 48 hours, or complications are suspected.

Hypertriglyceridemia can give falsely normal amylase and lipase levels.

The most important sign of severe pancreatitis and poor prognosis is elevated or rising BUN.

- **CT scan:** most accurate test for determining severity; the APACHE score is also used to stratify acute pancreatitis
- **ERCP:** most accurate test for detecting biliary and pancreatic ductal pathology

Treatment is aggressive IV fluids (250–500 mL/hr), bowel rest, and pain medication. Use morphine, as it does not constrict the sphincter of Oddi, and never use meperidine (can cause seizures).

- Aggressive IV fluids are most beneficial in first 12–24 hours and may be harmful after that time; reduce after 24 hours (Lactated Ringer's is preferred over normal saline based on clinical data).
- Resume oral feeding as soon as pain and nausea resolve; no need to wait.

- Administer antibiotics only if evidence of infected necrosis based on biopsy; do not give antibiotics for necrosis without infection.
- Do ERCP only if ascending cholangitis or nonresolving biliary obstruction, as it can otherwise worsen pancreatitis.

For gallstone pancreatitis, do cholecystectomy prior to discharge.

For severe acute pancreatitis that does not resolve within 72 hours, give enteral feeding via NGT or nasojejunal feeds, not total parental nutrition. Data shows that enteral feeding improves mortality (vs parental). Do not keep patient NPO after 72 hours, as that leads to increased risk for sepsis and death.

- When pancreatitis is very severe, e.g., >30% necrosis visible on CT, the risk of infected and hemorrhagic pancreatitis markedly increases.
- Severe necrosis, particularly when there is persistent fever, is also an indication to perform a percutaneous needle biopsy of the pancreas. If infection of the pancreas accompanies the necrosis, imipenem and urgent surgical debridement are indicated.
- Antibiotics should not be routinely given for pancreatic necrosis; they should be reserved for those with proven infection.
- If patient does not improve or deteriorates 7–10 days after presentation, perform CT-guided fine-needle aspiration.
- In stable patients with infected necrosis, the preferred approach is to initiate antibiotics and to ideally delay drainage procedures for at least 4 weeks to allow the collection to become encapsulated, which facilitates drainage.
- Pseudocysts develop only 2–4 weeks after the episode of pancreatitis; drain them if there is pain, fistula formation, or rupture (asymptomatic pseudocysts need not be drained).

Note

Other complications of pancreatitis include:

- Ascites (high in amylase)
- Pleural effusion (transudate, increased amylase)
- Splenic vein thrombosis (think when there are gastric varices but no esophageal varices)



Wikipedia, James Heilman, MD

Figure 4-3. Pancreatic Pseudocyst



Autoimmune Pancreatitis

Autoimmune pancreatitis is an autoimmune condition involving the pancreas and bile duct. Men > women.

Type I presents with painless jaundice or acute pancreatitis (rare).

- ‘Sausage-shaped’ pancreas on CT
- Older man
- Elevated IgG4

IgG4-related disease (IgG4-RD) is a chronic inflammatory condition characterized by tissue infiltration with lymphocytes and IgG4-secreting plasma cells causing various degrees of fibrosis (scarring) involving multiple organs.

Multiple autoimmune conditions are seen, including Sjögren syndrome, primary sclerosing cholangitis, hepatomegaly interstitial nephritis (enlarged kidneys), and inflammatory bowel disease.

Type II presents with chronic pancreatitis.

- No systemic disease
- Normal IgG4
- Need biopsy to diagnose

Treatment is steroids.

Note

While alcohol is the most common cause of cirrhosis in the United States, the most common reason to need a liver transplant is chronic hepatitis C.

Note

- All of the clotting factors are made in the liver—except for factor VIII and von Willebrand factor, made by endothelial cells.
- If factor VIII is low in addition to other factors, it is not liver disease—think disseminated intravascular coagulation (DIC).

LIVER DISEASE AND CIRRHOSIS

Cirrhosis develops when there is chronic and severe inflammation of the liver for an extended period of time. The regenerative capacity of the liver is enormous; however, over a long time, fibrosis will develop. And when at least 70–80% of liver function has been lost, the synthetic capacity of the liver is diminished.

In the United States the most common cause of cirrhosis is alcohol. Other causes include primary biliary cirrhosis, sclerosing cholangitis, alpha-1 antitrypsin deficiency, hemochromatosis, and Wilson disease.

The complications of cirrhosis are due to portal hypertension. Portal hypertension develops because of mechanical factors of fibrosis and regenerative liver nodules, as well as increased intrahepatic vascular resistance in increased portal inflow. The high pressure in the portal vein is decompressed through collateral portosystemic shunts that occur in the esophagus and the stomach.

Clinical Presentation. Despite the etiology, all forms of cirrhosis have the following features:

- Low albumin
- Portal hypertension
- Esophageal varices
- Ascites (the result of portal hypertension)
- Peripheral edema

- Elevated prothrombin time (prolonged due to loss of ability to synthesize clotting factors)
- Splenomegaly
- Thrombocytopenia
- Spider angiomas
- Palmar erythema
- Asterixis
- Encephalopathy (possible)
- Jaundice (possible)

A paracentesis is a sample of the ascitic fluid obtained by needle through the anterior abdominal wall. A paracentesis is used to exclude infection, as well as to determine the etiology of the ascites if it is not clear from the history.

Spontaneous bacterial peritonitis (SBP) is an idiopathic infection of ascites. The Gram stain is rarely positive because the density of microorganisms is so low. Although culture of the fluid is the most specific test, do not wait for the results to make a decision as to whether to give antibiotics.

- Neutrophils $>250/\text{mm}^3$ are the criteria for the presence of infection
- Treatment is cefotaxime or ceftriaxone; albumin infusion can help to reduce the risk of hepatorenal syndrome
- Once a patient has SBP, the risk of recurrence is 70% per year; give norfloxacin or ciprofloxacin daily (indefinitely) to prevent recurrence
- Stop all beta-blockers due to increased mortality

Serum-Ascites Albumin Gradient. Normally, the ascitic fluid albumin level is less than the serum level. The **difference between them** is referred to as the serum-ascites albumin gradient (SAAG). Total protein in the ascites fluid must also be checked.

When $\text{SAAG} \geq 1.1$, portal hypertension, the cause of ascites is increased hydrostatic pressure. The ascites total protein will tell you the cause of the elevated hydrostatic pressure.

- When $\text{SAAG} \geq 1.1$ and total protein <2.5 g/dL, the portal hypertension is due to cirrhosis (liver produces less protein due to decreased function).
- When $\text{SAAG} \geq 1.1$ and total protein >2.5 g/dL, heart failure, Budd-Chiari (check JAK2 to work up P. vera).

When $\text{SAAG} < 1.1$, it means the ascitic fluid albumin level is high. Cancer and infections generally produce $\text{SAAG} < 1.1$.

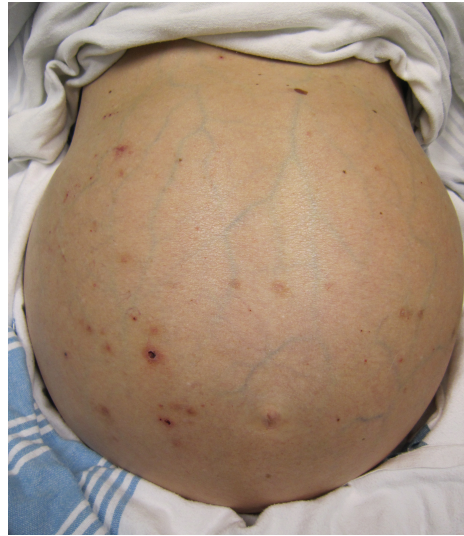
- When $\text{SAAG} < 1.1$ and total protein <2.5 g/dL, there is nephrotic syndrome (protein is lost in urine).
- When $\text{SAAG} < 1.1$ and total protein >2.5 g/dL, there is carcinomatosis (think ovarian), Tb (do peritoneum biopsy, which will have high lymphocytes in ascites, too)

Note

Although a culture of the ascitic fluid is the most specific test for SBP, do not wait for culture results when considering antibiotics.

Clinical Pearl

Remember to subtract the lower number (ascites albumin) from the higher number (serum albumin) when calculating SAAG.



Wikipedia, James Heilman, MD

Figure 4-4. Ascites

Note

For HCC, do U/S screening every 6 months.

Treatment. There is no specific therapy to reverse cirrhosis; one can only manage the complications and treat the underlying causes. (A complication to consider is hepatocellular carcinoma.) Edema and fluid overload in third spaces, such as ascites, are managed with diuretics (spironolactone most useful in cirrhosis). That is because cirrhotics have intravascular volume depletion, producing a high aldosterone state (secondary hyperaldosteronism). Furosemide is commonly added after spironolactone to increase volume removal. Giving furosemide without spironolactone will lead to hypokalemia, which can cause encephalopathy.

Propranolol is used to prevent bleeding in portal hypertension and varices. Discontinue after SBP, refractory ascites, or hypotension.

Encephalopathy is managed with lactulose, a nonabsorbed disaccharide that bacteria metabolize in the colon, making it more acidic. This converts the NH_3 to NH_4^+ , or ammonia to ammonium. Ammonium is not absorbed very well, and that leads to an overall increased excretion of ammonia from the body.

If patient is not responsive, add rifaximin, an RNA polymerase blocker not absorbed which changes the flora of the GI tract. Neomycin is not used for encephalopathy due to renal toxicity.

Note

Give octreotide during a bleed, then band. Give propranolol after the bleed to prevent another bleed.

Hepatorenal syndrome is diagnosed by the following:

- Increased creatinine >1.5 mg/dL over days to weeks
- Lack of response to albumin infusion for 48 hours (stop diuretics, too)
- Exclusion of other causes of AKI (sepsis); must have normal urine (no blood or protein)
- Type 1 is more severe with doubling of creatinine in 2 weeks.
- Type 2 is less severe with more gradual increase in creatinine.

Treat with midodrine, octreotide and albumin (must give for 48 hours first to rule out pre-renal). If it fails, perform liver transplant.

Although vitamin K is often given because of the elevated prothrombin time, it is not effective because the liver is unable to synthesize clotting factors regardless of how much vitamin K is present.

Primary Biliary Cirrhosis

Primary biliary cirrhosis is an idiopathic autoimmune disorder that is often seen in middle-aged women. Bilirubin does not elevate until the disease is extremely far advanced (5–10 years). There is a strong association with other autoimmune diseases, such as Sjögren syndrome, rheumatoid arthritis, and scleroderma.

Clinical Presentation. The most common symptoms are fatigue and pruritus. At least 30% of patients are asymptomatic but are found to have an elevated alkaline phosphatase when measured for other reasons. Osteoporosis and hypothyroidism are found in 20–30% of patients.

Diagnosis. The transaminases are often normal. The most common abnormality is elevated alkaline phosphatase and gamma glutamyl transpeptidase (GGTP). Total IgM levels are also elevated. The most specific blood test is the antimitochondrial antibody.

Biopsy is always the best way to diagnose liver disease. It is the only test more specific than antimitochondrial antibodies.

Treatment. There is no specific therapy for primary biliary cirrhosis. Steroids will not help. Ursodeoxycholic acid is primary treatment. Cholestyramine will help with the pruritus, as will ultraviolet light. Liver transplant for late stage PBC may also be considered.

Primary Sclerosis Cholangitis

Primary sclerosis cholangitis is an idiopathic disorder of the biliary system most commonly associated with IBD. Although it is more often found with ulcerative colitis, it can also occur with Crohn disease. Cancer of the biliary system can develop in 15% of patients from the chronic inflammation.

Clinical Presentation and Diagnosis. The presentation and general lab tests are typically the same as those for primary biliary cirrhosis, except that the antimitochondrial antibody test will be negative. The most specific test for primary sclerosis cholangitis is ERCP or MRCP: “string of beads of MRCP or ERCP.” This is the only chronic liver disease in which a liver biopsy is not the most accurate test.

Treatment. Treat with endoscopic therapy for strictures; cholestyramine for itching.

Hemochromatosis

Hemochromatosis is one of the most common inherited genetic diseases. There is an overabsorption of iron in the duodenum, leading to iron buildup in tissue throughout the body, thus resulting in chronic hepatic inflammation and fibrosis. Presentation includes the following:

- Cirrhosis (most common finding)
- Hepatocellular cancer (15–20% of patients)
- Restrictive cardiomyopathy (15% of patients)

Note

In a patient with ascites, stop ACE-I, ARBs, and NSAIDs.

Note

Primary sclerosis cholangitis is the only chronic liver disease in which a **liver biopsy is not the most accurate test**.



Note

Ferritin is elevated in liver disease and alcoholics.

Transferrin saturation is the best screening test; if it is **negative, diagnosis is not hemochromatosis**.

- Arthralgias, **osteoarthritis in the MPC joints, osteophytes on x-ray**, skin hyperpigmentation, diabetes, and secondary hypogonadism (decreased libido and impotence)
- *Vibrio vulnificus* and *Yersinia* infections occur with increased frequency because of their avidity for iron.

Screening for hemochromatosis is made with elevated transferrin saturation >55%. Ferritin is also elevated. C282Y homozygous and C282Y/H63D are diagnostic of hemochromatosis and do need a liver biopsy for diagnosis.

The most accurate test is a liver biopsy.

Treatment. Phlebotomy is used to remove large amounts of iron from the body—it removes far more iron than do the chelating agents deferoxamine and deferasirox. Deferoxamine and deferasirox are used only for those who cannot undergo phlebotomy.

Wilson Disease

Wilson disease is an autosomal recessive disorder leading to a diminished ability to excrete copper from the body. There is also increased copper absorption from the small intestine.

- Copper builds up in the liver, brain, and cornea.
- Basal ganglia dysfunction contributes to the movement disorder which develops.
- Psychiatric disturbance is seen in 10% of patients.
- Kayser-Fleischer rings are found in the eye on slit-lamp examination.
- Tremor and Parkinson result in 35% of patients.
- Fanconi syndrome and type II proximal renal tubular acidosis develop due to copper deposition in the kidney.
- Hemolytic anemia may be present (copper destabilizes the RBC membranes).

The most specific blood test for diagnosis is decreased ceruloplasmin but that alone is not enough. There is also increased urinary copper. The single most specific test is liver biopsy, which will demonstrate increased copper deposition in the liver. Occasionally, hemolytic anemia is seen when copper levels go high and are toxic to the red cells.

Treatment. Penicillamine and trientine are copper chelators. Oral zinc interferes with copper absorption. Steroids will not help. Liver transplantation is curative.

Alpha-1 Antitrypsin Deficiency

Alpha-1 antitrypsin deficiency (AATD) is an autosomal recessive condition which causes a low level (or no level) of alpha-1 antitrypsin (AAT) in the blood. The condition is found in all ethnic groups but occurs most often in whites of European ancestry. AAT protects the lungs so they can have normal function. AAT is made in the liver; without enough of it, the lungs become damaged, leading to emphysema.

- Everyone has 2 copies of the gene for AAT and receives 1 copy of the gene from each parent.

Note

A patient presenting with choreoathetoid movements and psychosis gives the clue to perform the slit-lamp examination. Kayser-Fleischer rings are then found, confirming the diagnosis of Wilson disease.

- Patients with AATD have 1 normal copy and 1 damaged copy, or they have 2 damaged copies.
 - Most patients with 1 normal gene can produce enough AAT to live healthy lives, especially if they do not smoke.
 - Those with 2 damaged copies of the gene are generally not able to produce enough AAT, leading them to have more severe symptoms.

The most prominent finding is emphysema developing at a young age in a nonsmoker. Approximately 15% of those with AATD develop cirrhosis. Large amounts of abnormal AAT are made in the liver; nearly 85% of this protein accumulates in the liver causing inflammation and eventually, fibrosis.

Diagnosis. Testing for AATD using a blood sample from the individual is simple, quick and highly accurate. Three types of tests are usually done on the serum sample:

- Alpha-1 genotyping, which examines a person's genes and determines his genotype
- AAT PI type of phenotype test, which determines the type of AAT protein a person has
- AAT level test, which determines the amount of AAT in a person's blood

Treatment. There is no specific therapy for the liver disease. Those with emphysema should receive replacement of the enzyme and stop smoking.

Chronic Hepatitis B and C

Hepatitis B and C are transmitted by blood products, needlestick injury, and sexual contact. Injection drug use is also strongly associated with both viruses.

- Hepatitis C virus causes 60–70% of cases of chronic hepatitis; at least 80% of acute hepatitis C cases become chronic
- About 10% of hepatitis B cases, sometimes with hepatitis D coinfection, become chronic; hepatitis D does not occur by itself but rather only as a coinfection with hepatitis B
- Rarely, hepatitis E virus causes chronic hepatitis in those with weakened immune systems (organ transplant treatment, chemotherapy for cancer, HIV infection)
- Hepatitis A virus does not cause chronic hepatitis

Hepatitis C is the most common cause of chronic hepatitis in the United States; it is also the most common cause of cirrhosis and hepatocellular carcinoma.

Most patients are asymptomatic until the disease is very far advanced.

Diagnosis.

- To **confirm hepatitis B**: persistence of hepatitis B surface antigen >6 months (though it takes years for cirrhosis to develop)
 - Remember, in **chronic hepatitis B, the hep B surface antibody is negative.**
- To confirm hepatitis C: finding an antibody to hepatitis C, and then finding an elevation of the viral load by PCR methods
 - Single most accurate test to diagnose the extent of liver disease is liver biopsy



Treatment. Chronic hepatitis B is treated with interferon, lamivudine, entecavir, telbivudine, or adefovir. Combining these agents does not lead to increased efficacy.

Chronic hepatitis C is now cured with the new combination antiviral drugs. The most commonly used is **ledipasvir/sofosbuvir** (trade name **Harvoni**), a 2-drug combination. It is administered as a 1×/daily pill containing the viral NS5A inhibitor ledipasvir and a nucleotide inhibitor of the viral RNA polymerase, sofosbuvir. Taken daily for 8–12 weeks, it provides cure rates of 94–99% in those infected with genotype 1 (the most common form of hepatitis C in the United States and some European countries), irrespective of the presence or absence of liver cirrhosis or prior unsuccessful treatment. It has also been evaluated for the treatment of infection with other hepatitis C genotypes and has shown promising results in genotypes 3 and 4.

Clinical Recall

Which of the following is not a cause of cirrhosis?

- A. Alpha-1 antitrypsin deficiency
- B. Budd-Chiari syndrome
- C. Hepatitis A
- D. Hemochromatosis
- E. Primary biliary cirrhosis

Answer: C

Learning Objectives

- ❑ Outline a differential diagnosis and diagnostic plan for patients with acute chest pain or chest discomfort
 - ❑ List the causes of and treatment for heart rate and rhythm disturbance
 - ❑ Describe the physiology of valvular disease and CHF, and describe the mechanism of action of appropriate treatments
 - ❑ Give an overview of presentation, epidemiology, and management of ischemic heart disease, acute coronary syndrome, myocardial disease, and pericardial disease
 - ❑ Describe the most common medications used to treat cardiovascular disease and their most serious or common side effects
-

ACUTE CHEST PAIN

Chest pain or discomfort is one of the most common complaints that brings patients to the physician's office or ED. Patients presenting with this symptom may have an underlying cause that is benign and requires only moderate analgesic medication or is life-threatening (e.g., acute myocardial ischemia or aortic dissection) which mandates prompt diagnosis and treatment.

In the evaluation of chest pain, the focus should be on **excluding the more serious conditions**.

History

Assessing the setting in which the chest pain occurs is one of the most important aspects of the evaluation. The healthy 26-year-old medical resident with chest pain that occurred after on-call is unlikely to have cardiovascular disease, no matter the quality or duration of chest pain. The 58-year-old man who has type 2 diabetes and dyslipidemia with chest discomfort of any type has a much higher probability for cardiac-related chest pain.

Overall, the **chest pain history is more useful than the physical examination**. Important aspects of the history include duration, quality, location, radiation, frequency, alleviating or precipitating factors (especially exercise), and associated symptoms.



- For both stable angina and acute coronary syndromes, the quality of chest pain is described by the patient as “tightness,” “heaviness,” or “pressure,” but symptoms resembling acute abdomen (pain in upper abdomen, nausea) are not uncommon. Nausea and vomiting are sometimes the main symptoms in inferior wall ischemia (also, vagal reflexes may cause bradycardia and hypotension, presenting as dizziness or fainting).
- “Sharp” or “knife-like” chest pain and pain which the patient can pinpoint to an “exact area” are less likely to be related to ischemia or infarction, especially if the chest pain is reproduced by changes in position or palpation.
- Myocardial infarction (MI) is associated with pain that lasts >20–30 minutes in duration.
- Response of chest pain to nitroglycerin (within a few minutes) is most consistent with transient ischemia or esophageal spasm. Chest pain that worsens with nitroglycerin sometimes occurs with gastroesophageal reflux disease. The response to nitroglycerin is not enough to confirm coronary disease as the cause of chest pain.
- Acute coronary syndromes in women often present without “classic” symptoms: instead, they may have dyspnea, shortness of breath, fatigue.

Physical Examination

One of the most important parts in a chest pain examination is the “initial impression.”

- Diaphoresis, tachypnea, and anxious expression should alert you to a potentially life-threatening process.
- Tachycardia and tachypnea are both nonspecific but occur in almost all cases of pulmonary embolism.
- Check BP in both arms: a difference >20 mm Hg systolic suggests aortic dissection (present in ~70% of cases).
- Hypotension may suggest massive pulmonary embolism or cardiac shock.
- Fever may suggest pneumonia or mediastinitis (esophageal rupture) as the cause of chest pain.
- Evidence of atherosclerosis (corneal lipid rings, narrowed retinal arteries, and pigment and hair changes in the legs) is commonly seen in patients with coronary syndromes.

Inspect the chest wall for tender areas, respiratory motion, respiratory retractions, or accessory muscle use. If the tender area corresponds to the location of the patient’s pain and palpation exactly reproduces the pain, consider musculoskeletal chest pain as the cause of chest pain.

Abnormal heart sounds and new murmurs are commonly found in certain chest pain syndromes.

- Wide physiologic splitting of the second heart sound (splitting wider with inspiration) can be found in right bundle branch block or in right ventricular infarction.
- New paradoxical splitting is most often due to left bundle branch block (LBBB), or anterior or lateral infarction.
- A new fourth heart sound can occur with angina or infarction. An S3 is more likely due to underlying heart failure.
- A new murmur may be significant: aortic regurgitation occurs in over half of patients with aortic dissection, while mitral regurgitation can occur in patients with angina or infarction and is due to papillary muscle dysfunction.

The lungs should be auscultated for crackles and asymmetrical breath sounds. Asymmetry of breath sounds may be found in patients with spontaneous pneumothorax. Absent lung sounds also may occur in pneumothorax and pleural effusions.

The extremities should be examined for pulses, edema, and signs of atherosclerotic vessel disease. Absence of pedal pulses may occur in aortic dissection. Calf swelling or edema raises the odds of pulmonary embolism as the cause of chest pain.

Testing

All patients with chest pain should have a 12-lead ECG (**most important test**) to evaluate the cause. It should be done immediately after initial stabilization and taking of vital signs. In patients with acute coronary syndromes, the ECG is the sole test required to select patients for emergency reperfusion.

Most patients with MI will have an abnormal initial ECG:

- 50% with acute MI will have diagnostic findings (ST elevation, new LBBB, or Q waves)
- 35% will have findings consistent with ischemia (ST depression and/or T wave inversion)
- In patients presenting with acute chest pain who have **normal ECG**, the chance of acute MI is much less than 10% (in some studies 1–2.6%).
- An abnormal ECG can be seen in many non-cardiac conditions (pulmonary embolism, electrolyte abnormalities, aortic dissection).

Chest x-ray should be obtained on patients with chest pain.

- May show pneumothorax, pneumomediastinum (i.e., from esophageal rupture), pleural effusion, or infiltrates
- Aortic dissection can cause widening of the mediastinum
- Subtle findings such as loss of lung volume or unilateral decrease in vascular markings may suggest PE

Serum cardiac biomarkers also play a vital role in the evaluation of acute chest pain and the diagnosis of acute MI.

- **CK-MB isoenzyme** (typically measured upon ED admission and repeated 6–12 hours later)
 - Cardiac-specific; useful for early diagnosis of acute myocardial infarction
 - Typically detectable in serum 4–6 hours post-onset of ischemia, peaks in 12–24 hours and normalizes in 2–3 days
 - Peak CK-MB level can be useful for detecting early reinfarction since it normalizes 2–3 days post-initial MI (does not predict infarct size)
 - CK-MB subforms/isoforms (**not routine**): CK-MB1 is found in plasma, while CK-MB2 is found in myocardial tissue
- Cardiac troponins (**preferred markers**) (typically measured upon ED admission and repeated 6–12 hours later)
 - Troponins (T-I-C) are found in striated and cardiac muscle; because the cardiac and skeletal muscle isoforms of troponin T and I differ, they are known as the “cardiac troponins”

Note

Make every effort to obtain a previous ECG for comparison. Any ECG finding is assumed to be new unless proven otherwise by an old ECG (if one is available).

Note

Some markers are **no longer used in cardiac disease testing**, due to low specificity.

- Serum markers such as aspartate transaminase, lactate dehydrogenase, and lactate dehydrogenase subforms
- Total creatine kinase (CK), found in striated muscle and tissues of the brain, kidney, lung, and GI tract



- Troponins T and I (**preferred in most settings**) have similar sensitivity for the detection of myocardial injury, but T (unlike I) may be elevated with renal disease, polymyositis, and dermatomyositis
- Elevated T or I is helpful for identifying those at increased risk of death or of developing acute myocardial infarction. "Increased risk" relates to the high serum troponin level.
- Troponins also can help identify those at low risk who may be sent home with close follow-up; those with a normal (or nearly normal) ECG and a normal troponin I test 6 hours post-admission have a very low risk of major cardiac events during the next 30 days
 - **Normal CK-MB and elevated troponin** = minor myocardial damage, or microinfarction
 - **Elevated CK-MB and elevated troponin** = acute myocardial infarction
- May remain elevated up to 2 weeks after symptom onset, which makes them useful as late markers of recent acute MI
- **Myoglobin** begins to rise as early as 1–4 hours after the onset of pain. Normal myoglobin at 4 hours has a very high negative predictive value.

Especially if a noncardiac diagnosis is suspected, arterial blood gases, BNP, and CT angiogram may be helpful for evaluating acute chest pain.

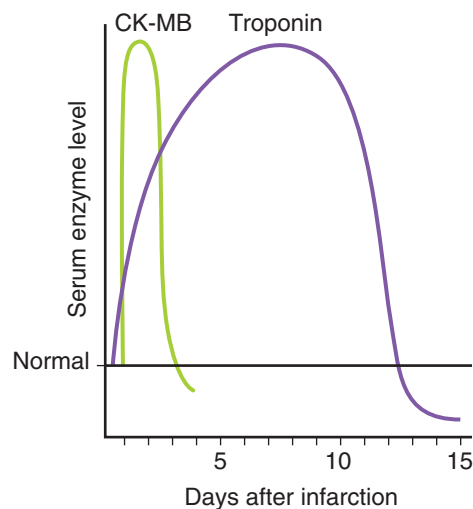


Figure 5-1. Progression of Cardiac Enzyme Serum Levels

Causes of Chest Pain

Aortic dissection. The pain is sharp/tearing/very severe; typically radiates to the back, and a loss of pulses or aortic insufficiency often develops.

- On chest x-ray, mediastinum is widened
- MI may occur if dissection extends into coronary artery
- Diagnosis confirmed by MRI, CT scan, or transesophageal echocardiogram

Pulmonary embolism. Dyspnea, tachycardia, and hypoxemia are prominent; pain is usually pleuritic, especially when pulmonary infarction develops.

- ECG is usually nonspecific but may show S wave in lead I, Q wave in lead III, or inverted T wave in lead III
- Diagnosis confirmed by CT angiogram

Pericarditis. May be preceded by viral illness; pain is sharp, positional, pleuritic, and relieved by leaning forward.

- Pericardial rub often present
- Diffuse ST elevation occurs without evolution of Q waves
- CK level usually normal
- Responds to anti-inflammatory agents

Table 5-1. Differential Diagnosis of Conditions Causing Chest Pain

Noncardiovascular Disorders	Differentiating Features
Costochondritis	Pain exacerbated with inspiration; reproduced with chest wall palpitation
Hiatal hernia	Reflux of food; relief with antacids
GERD	Acid reflux; relief with antacids
Peptic ulcer	Epigastric pain worse 3 h after eating
Gallbladder disease	Right upper quadrant abdominal pain and tenderness
Cardiovascular Disorders	Differentiating Features
Myocardial infarction	Pain more severe, usually >20 min in duration
Aortic stenosis	Typical systolic ejection murmur
Myocarditis	Pain is usually vague and mild if present
Pericarditis	Pain is sharper, pain worse with lying down and relieved by sitting up
Dissecting aortic aneurysm	Pain is sharp, tearing, often occurs in back
Mitral valve prolapse	Transient pain, midsystolic click murmur, and young female with no risk factors
Pulmonary Disorders	Differentiating Features
Pulmonary embolus-infarction	Tachypnea, dyspnea, cough, pleuritic pain, hemoptysis, calf pain
Pulmonary hypertension	Signs of right ventricle (RV) failure
Pneumothorax	Sudden onset of pain and dyspnea



Myocarditis. May be preceded by viral illness; pain is generally vague and mild if present; total CK and MB fraction of CK (CK-MB) are often elevated; conduction abnormalities and Q waves may occur.

Musculoskeletal disorders. Most common cause of chest pain. Includes costochondritis, cervical osteoarthritis, radiculitis; pain is atypical, stabbing, localized, may be pleuritic; reproduced by motion or palpation; ECG changes absent.

GI disorders. Esophageal reflux is often made worse with recumbency or after meals; may be associated with regurgitation and relieved by antacids; episodes of spasm may be brought on by cold liquids, relieved by nitroglycerin, and may closely resemble angina or infarction; diagnosis may be confirmed by upper endoscopy or esophageal manometry. Peptic ulcer disease, pancreatitis, and cholecystitis may occasionally mimic infarction; abdominal tenderness is present, with radiation to back and elevated amylase in pancreatitis; sonography can confirm cholecystitis.

Pneumothorax. Onset abrupt with sharp pleuritic chest pain and dyspnea; breath sounds absent; chest x-ray confirms.

Pleuritis. Pain is sharp and increases on inspiration; friction rub or dullness may be present; other respiratory symptoms and underlying pulmonary infection usually present.

Clinical Recall

Which of the following is the single most important test in the management of chest pain?

- A. CKMB
- B. Troponin
- C. Echocardiography
- D. Electrocardiogram
- E. Chest CT

Answer: D

ISCHEMIC HEART DISEASE

Ischemic heart disease (IHD) (or coronary heart disease) is an imbalance in coronary oxygen demand and supply resulting from insufficient blood flow. In nearly all cases, the reduction in blood flow is caused by coronary atherosclerotic disease.

When the atherosclerotic plaque ruptures, there is superimposed thrombus formation that acutely occludes the artery; this is the most common cause of life-threatening acute coronary syndromes.

Rarely, other abnormalities may occur (coronary artery embolism, coronary artery spasm, coronary arteritis, and coronary artery dissection) which may cause IHD in the absence of atheroma formation.

IHD is one of the most prevalent diseases in society, and those affected are likely to die from their disease. As part of a systemic process that involves all arteries in the body, it is an insidious process that begins in early adulthood with fatty streaks; these lesions progress into plaques and thrombus formation in middle age.

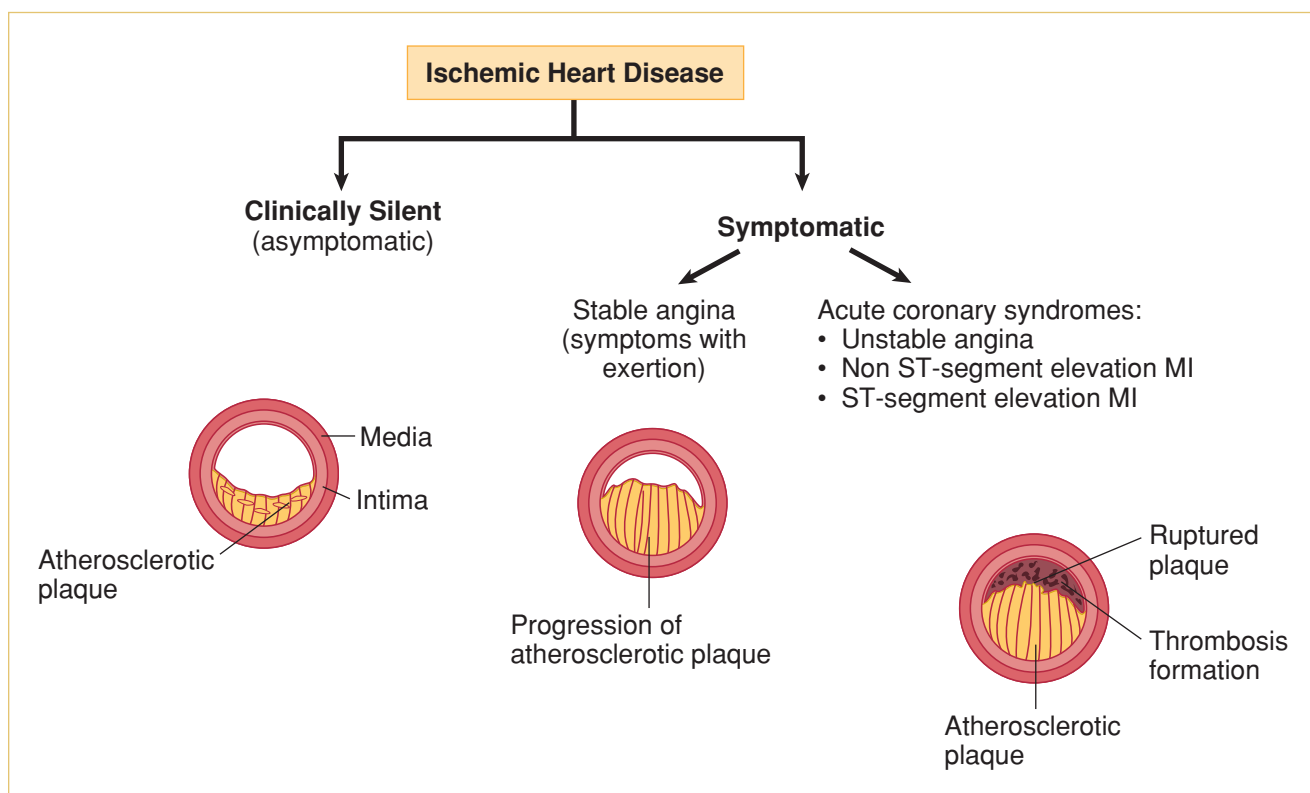


Figure 5-2. Ischemic Heart Disease

The more risk factors a person has, the greater the chance that he will develop heart disease. Also, the greater the level of each risk factor, the greater the risk. For example, a person with total cholesterol 260 mg/dL has a greater risk than someone with total cholesterol 220 mg/dL, even though all people with total cholesterol ≥ 220 mg/dL are considered high risk.

Major Modifiable Risk Factors

Some major risk factors for IHD can be controlled with lifestyle change and medication.

- **Elevated cholesterol** (especially lipid fractions e.g., HDL and LDL)
 - LDL is most important subgroup but low HDL, hypertriglyceridemia, increased ratio of total-to-HDL, and increased lipoprotein A also increase risk
 - When other risk factors (such as high BP and tobacco smoke) are present, the risk increases even more
 - **High intensity statin** (high dose atorvastatin or rosuvastatin) should be given in the following situations:
 - Patient with clinical ASCVD (CAD, CVA, TIA, PAD, AAA)
 - LDL > 190 mg/dL
 - Risk score $> 20\%$
 - For high-risk patients, **add ezetimibe** or a **PCSK9 inhibitor** (evolocumab or alirocumab) for additional LDL reduction.

Note

2013 AHA and 2016 USPSTF guidelines do not focus on LDL treatment targets, but rather on the overall risks of developing atherosclerotic cardiovascular disease.

The ASCVD 10-year risk score is based on risk factors and should be calculated. (On the exam, you will be provided with the value.)



Note

Proprotein convertase subtilisin/kexin type 9 (PCSK9) is an enzyme that binds to and degrades LDL receptors in the liver. PCSK9 inhibitors are monoclonal antibodies which reduce the degradation of LDL receptors and increase clearance of LDL cholesterol.

Note

In terms of **risk for IHD**, systolic BP is as important as diastolic BP, especially in older patients.

Note

- Almost 75% of patients with DM die of some form of cardiovascular disease.
- There is compelling evidence that aggressive treatment of HTN and cholesterol, as well as tight glycemic control, reduces the risk of cardiovascular events in these patients significantly.

- **Moderate intensity statin** should be given in the following situations:
 - All patients age 40–75 with DM
 - All patients with ASCVD risk score $\geq 7.5\%$
- Check baseline ALT; check CPK only if there are symptoms of myopathy
- There is no need to monitor after starting therapy.
- **Tobacco:** A smoker's risk of heart attack is $>2\times$ that of a nonsmoker; cigarette smoking also acts with other risk factors (hypertension, dyslipidemia) to greatly increase the risk for IHD
 - Cigar or pipe smokers have a higher risk of death from IHD, though less than cigarette smokers.
 - Secondhand smoke or passive smoking increases the risk of heart disease, even for nonsmokers.
 - The risk for myocardial infarction in those who quit smoking is reduced to that of nonsmokers in 2 years, regardless of how much/how long the patient had smoked.
- **Hypertension (HTN):** HTN is a well-established risk factor for increased risk of myocardial ischemia, stroke, kidney failure, and heart failure. Studies in the general population have shown that the risk for cardiovascular events increases at BP $>110/75$ mm Hg.
 - Treatment of HTN to optimal levels reduces the risk of IHD and all cardiovascular events.
 - In fact, data from recent randomized trials suggest that reducing BP $<130/80$ mm Hg is beneficial in patients with cardiovascular disease and those with calculated 10-year cardiovascular risk $>10\%$.
- **Physical inactivity and exercise:** Inactivity and sedentary lifestyle are risk factors for IHD. Even moderate exercise has a protective effect, and more vigorous exercise has added benefits. Specifically, exercise can increase HDL cholesterol, control diabetes/obesity, and lower blood pressure.
- **Obesity:** Increased body fat (elevated body mass index)—especially if concentrated in the waist area—increases one's risk for heart IHD and stroke. Excess weight raises BP, blood cholesterol, and triglyceride levels, and it lowers HDL cholesterol. It can also increase risk for type 2 diabetes by causing insulin resistance.
- **DM:** Elevated blood glucose and insulin resistance are associated with IHD and overall cardiovascular events. Even when glucose is under control, diabetes greatly increases the risk of IHD.

Major Non-modifiable Risk Factors

- **Age:** About 80% of people who die of IHD are age ≥ 65 . Also, women who develop myocardial ischemia at an older age have a higher mortality than men within the first few weeks of the cardiac event.
- **Sex:** Men have a greater risk of IHD than women, and overall they develop cardiovascular disease earlier in life.
- **Heredity:** Family history is a significant independent risk factor if there is a family history of premature disease (age <55 in male relative and <65 in female relative).

Minor Contributing Risk Factors

- **Sex hormones**
 - Women before menopause have fewer heart attacks than men
 - Women after menopause have a higher risk of heart disease than men (studies show that the decrease of natural estrogen as women age may contribute to the higher risk)
- **Stress:** There is a proven relationship between IHD risk and stress, whether it is a true association or just a secondary correlation. For example, people under stress may overeat, start smoking, or be less active than people who are not under stress.

Myocardial Ischemia as a Manifestation of IHD

During ischemia, an imbalance occurs between myocardial oxygen supply and demand. Ischemia may manifest in any of the following ways:

- Anginal chest discomfort
- ST-segment deviation on ECG
- Reduced uptake of tracer during myocardial perfusion scanning
- Regional or global impairment of ventricular function

Myocardial ischemia can be caused by increased myocardial oxygen demand, reduced myocardial oxygen supply, or both. In the presence of coronary obstruction, an increase of myocardial oxygen requirements caused by exercise, tachycardia, or emotion leads to a transitory imbalance. (This condition is called “**demand ischemia**” and is responsible for most episodes of chronic stable angina.)

In other situations, the imbalance is caused by acute reduction of oxygen supply secondary to marked reduction or cessation of coronary flow as a result of platelet aggregates or thrombi. This condition (“**supply ischemia**”) is responsible for myocardial infarction (MI) and most episodes of unstable angina (UA). In many circumstances, ischemia results from both an increase in oxygen demand and a reduction in supply.

Angina (Stable Angina)

A 62-year-old man presents with substernal chest pain that occurs with exertion and is relieved by rest, occurring on-and-off for 8 months. The last episode occurred 3 days ago while he was running to the bus. He has a history of well-controlled diabetes and dyslipidemia. Vital signs, physical examination, and ECG are normal. Exercise stress test shows a 2-mm ST depression.

Stable angina occurs when the myocardium becomes ischemic. This occurs during periods of increased demand for oxygen, such as exercise, or decreased supply, such as hypotension or anemia (see demand ischemia). Stable angina is typically a substernal pressure lasting 5–15 minutes. It may be accompanied by radiation to the jaw, neck, shoulders, or arms. It is less likely to have the symptoms often associated with MI: sweats, nausea, and shortness of breath. Anginal pain is not typically affected by respiration or by position. Typically, patients with stable angina will have pain after a predictable amount of exertion and will have identical symptoms with each attack.

Note

Studies have shown that weight loss of as little as 10–20 lb can significantly reduce the risk of cardiovascular disease.

Note

All-cause mortality in diabetic patients is comparable to that of all-cause mortality in patients with prior myocardial ischemia. Therefore, **diabetes is now considered an “IHD equivalent.”**



Note

The EST provides a controlled environment for observing the effects of increases in the myocardial demand for oxygen.

In certain patients, symptoms other than pain may occur. For example, a profound sense of weakness and breathlessness may be an “angina equivalent.” These symptoms are more likely to occur in women, the elderly, and diabetics.

The physical exam is usually normal. A new S4 may be heard, suggesting a stiff ventricle due to ischemia.

Most patients with angina will have ECG changes **during an attack**. Most commonly, ST segment depression is seen. ST segment elevation occurs in variant angina (Prinzmetal angina) where coronary artery spasm is responsible, and rarely during ischemia caused by stable angina (where atherosclerotic disease is responsible).

Diagnosis. The **exercise stress test (EST)** (treadmill test) is the most useful test for evaluating the cause of chronic chest pain when there is concern about IHD (stable angina).

To do an appropriate and accurate analysis, a target heart rate must be reached. Target heart rate is 85% of predicted maximum heart rate: $85\% \times (220 - \text{patient's age})$.

Significant fixed stenoses (>50%) of the coronary arteries will result in ECG evidence of ischemia. Low-grade stenoses (<50%) may not produce sufficient impairment of blood flow to affect the ECG; in these cases the stress test will be normal.

An EST is considered positive for myocardial ischemia when large (>2 mm) ST-segment depressions or hypotension (a drop >10 mm Hg in systolic pressure) occur either alone or in combination. In general, the earlier the angina or ECG abnormalities occur, the more significant they will be. The exercise stress testing can help to do the following:

- Determine the severity of IHD and the need for further intervention, i.e., severe symptoms (hypotension) early in the test usually occur in those with triple-vessel disease
- Assess the effectiveness of treatment, i.e., CAD patients who have undergone surgical intervention or are receiving medical therapy have an exercise stress test when they are medically stable and symptom-free
- Determine functional capacity and identify any ECG changes or symptoms during (low level) exercise for patients who are post-MI

EST is contraindicated when it may place the patient at increased risk of cardiac instability, e.g., aortic dissection, acute myocardial infarction, unstable angina, or symptomatic supraventricular arrhythmia.

Patients who are unable to exercise or walk should be considered for **chemical stresstesting**, such as dipyridamole (Persantine) or dobutamine stress test. Presence of baseline ECG abnormalities such as bundle branch block, left ventricular hypertrophy, or with a pacemaker may make it more difficult to interpret test results. In those cases patients should be evaluated by nuclear stress imaging instead of the exercise stress test. These tests may also be used in patients who are taking digoxin.

For baseline LBBB or ventricular pacing, use a vasodilator stress radionuclide myocardial perfusion imaging, which has higher specificity. Exercise or dobutamine may result in a false-positive perfusion defect in the basilar septum.

In most cases, medications should not be withheld in preparation for an exercise stress test. Certain medications require special consideration:

- Beta blockers may blunt the heart rate during exercise and thus should be held 24 hours prior to the test. While patients receiving beta blockers may perform the exercise required for the test, the usual age-adjusted target heart rate may not be a realistic end point for them.
- Also, the antihypertensive effect of beta blockers, alpha blockers, and nitroglycerin may cause significant hypotension during exercise.

Digoxin may depress the ST segments, so if ST-segment depression of ≥ 1 mm is present on baseline ECG, the stress test results will be difficult to interpret.

A number of other situations or conditions may reduce the validity of the exercise stress test. Exercise testing in **asymptomatic young women** yields an increased number of false-positive results, while exercise testing in patients with known CAD may result in an unacceptably high false-negative rate (e.g., a negative stress test in a 64-year-old man with diabetes, hyperlipidemia, and typical stable angina is likely to be a false-negative result).

A 29-year-old woman has a routine stress test done that shows a 1-mm ST depression. She has no history of chest pain, and she exercises routinely (runs 2–3 miles per day, 3 times per week). Her physical examination is unremarkable.

The most likely cause of this patient's abnormal stress test is a false-positive test.

Other types of stress tests include:

- **Nuclear stress test:** After injection of a radioactive substance, perfusion of heart tissue is visualized (perfusion pictures done both at rest and after exercise). An abnormal amount of thallium will be seen in those areas of the heart that have a decreased blood supply.
 - Higher sensitivity and specificity than regular stress test (92 and 95% versus 67 and 70%)
 - Not affected by baseline changes in ECG (LBBB, ST-segment depression at baseline, etc.)
- **Dobutamine or adenosine stress test:** used in those who are unable to exercise; a drug is given to induce tachycardia, as if the person were exercising
- **Stress echocardiogram:** combines a treadmill stress test and an echocardiogram; the latter can recognize abnormal movement of the walls of the left ventricle (wall motion abnormalities) that are induced by exercise

Invasive testing (angiography) is used when noninvasive tests are contraindicated or inadequate, or after a positive conventional stress test to identify whether patient will benefit from stent placement or bypass surgery.

Treatment.

- **Individual episodes of angina:** nitroglycerin (NTG) sublingual tablets (will alleviate pain within a few minutes)
- **Stable angina:** long-acting nitrates and/or beta blockers (nitrates must have a nitrate-free period of 8–12 hours (overnight) to prevent tachyphylaxis)

Note

Do not give adenosine if the patient is wheezing.

**Note****High-yield points:**

- Beta-blocker dose must be adjusted to achieve a resting HR of 60/min. Do not give if there is decompensated HF or active wheezing.
- Use verapamil or diltiazem if there is severe reactive airway disease.

Note

Almost all patients with chronic stable CAD will need statin therapy, unless contraindicated.

Note

CABG involves the construction of ≥ 1 grafts between the arterial and coronary circulations. (Many patients receive both arterial and venous grafts.) Long-term graft patency is significantly better with the arterial graft (e.g., internal mammary artery). Potential consequences of graft failure (loss of patency) include the development of angina, myocardial infarction, or cardiac death.

- Lifestyle change, e.g., tobacco cessation, exercise, hypertension control
- Unless contraindicated, add aspirin (reduces risk of stroke, MI, death) and high-intensity statins (for lipid lowering)
- Evaluate severity of IHD (cardiac angiography or stress testing) and whether revascularization (stent or bypass surgery) would be helpful
- Add ranolazine if no response with BBs, CCBs, and nitrites (monitor for QT prolongation)

Lipid lowering treatment for secondary prevention is important in IHD patients who should be treated aggressively. Most patients will require both pharmacologic and nonpharmacologic interventions. Target goals for hyperlipidemic patients with CAD include:

- LDL <100 mg/dL (<70 mg/dL if very high risk)
- HDL ≥ 40 mg/dL
- Triglycerides <150 mg/dL

Every effort should be made to ensure that patients with CAD receive optimal lipid therapy. **Statins** are strongly supported as first-line medications due to compelling evidence of mortality reduction. If patients are intolerant to a statin, consider other statins in reduced doses.

Better medical therapy with aspirin, beta blockers, ACE inhibitors, and statins are decreasing the need for all revascularization procedures.

Revascularization procedures include coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI).

- **Acute coronary syndrome:** PCI or CABG
- **Stable angina:** medical management first; if symptoms persist, consider PCI; for triple vessel and left-main disease, CABG has mortality benefit
- **Obstructive coronary artery disease:** CABG for the following patients:
 - Patients whose survival will be improved over medical therapy or PCI, e.g., patients with left main disease or triple-vessel disease and low ejection fraction
 - Patients with angina refractory to medical therapy
 - Diabetics

Clinical Recall

Which of the following is most likely to decrease a patient's risk for developing ischemic heart disease?

- A. Tight glycemic control of patients with DM
- B. Aggressive treatment of HTN
- C. Aggressive treatment of hyperlipidemia
- D. Smoking cessation
- E. All of the above

Answer: E

ACUTE CORONARY SYNDROME

Acute coronary syndrome (ACS) describes a range of thrombotic coronary diseases including unstable angina (UA), non-ST elevation myocardial infarction (NSTEMI), and ST-elevation myocardial infarction (STEMI). Collectively they represent one of the most common causes of acute admission to U.S. hospitals.

ACS is caused by coronary vessel atherosclerotic obstruction with superimposed thrombotic occlusion. The natural course of coronary atherosclerotic plaque development and subsequent occlusion does not proceed in a step-wise, uniform manner, gradually progressing to luminal obstruction (and symptoms) over many years.

- The process is characterized by plaque disruption and mural thrombosis.
- Angiographic data support the concept that noncritical lesions account for the majority of the ACS.
- Thus, the pathogenic rate-limiting mechanism of the ACS appears to be acute thrombosis and the resultant obstruction of the coronary lumen.

An operational classification allows one to distinguish the types of ACS. In this classification, the ECG is the most important clinical tool. The initial ECG findings, in particular, the presence or absence of ST-segment elevation, will further define the patient's condition and dictate treatment options.

Note

- The term **ACS** is clinically useful because the initial presentation and early management of UA, STEMI, and NSTEMI are frequently similar.
- **Distinguish ACS from stable angina**, which develops during exertion and resolves at rest.

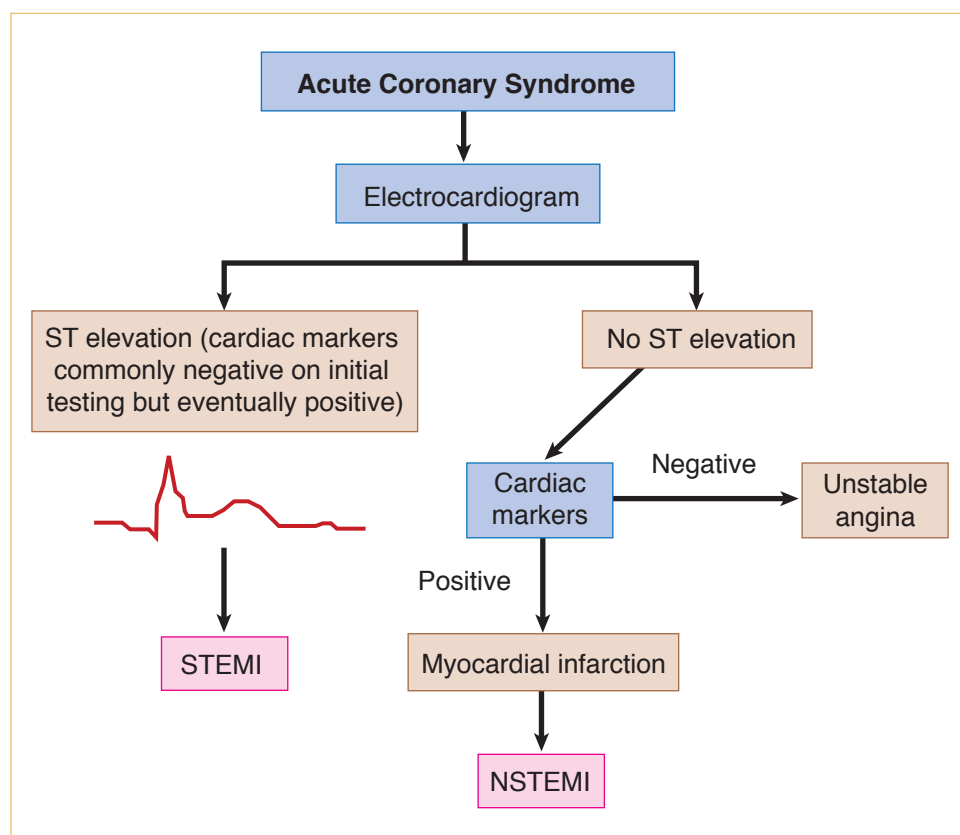


Figure 5-3. Acute Coronary Syndromes



UA and NSTEMI

UA and NSTEMI are closely related in terms of clinical presentation and pathogenesis, but patients with these conditions have widely varying risks. Both are usually caused by atherosclerotic CAD and present an increased risk for death and MI.

- At the time of presentation, UA and NSTEMI may be indistinguishable and can be identically managed. Use cardiac troponins to distinguish NSTEMI from UA (elevated enzymes show evidence of infarction).
- NSTEMI is more severe than UA and is considered to have occurred if ischemia produces damage detectable by biochemical markers of myocardial injury (troponin I or CK-MB).
- If there are no detectable serum markers of myocardial injury 12–18 hours after symptom onset, the diagnosis should be UA.

Outcomes in UA/NSTEMI are generally better than in STEMI, but certain UA/NSTEMI patients are at high risk for MI or death, and it is important to identify these patients at initial screening because they may require intensive monitoring and management.

Thrombolytic therapy is not effective in UA or NSTEMI and may be harmful, unlike the clear benefit in STEMI.

Sometimes referred to as “crescendo” or “preinfarction” angina, UA is defined as angina of increasing severity/frequency/duration, angina showing increased resistance to nitrates, or angina occurring at rest. Experts also regard **any new-onset angina** as unstable. Sudden change in the pattern of angina usually means a physical change within the coronary arteries, such as hemorrhage into an atherosclerotic plaque or rupture of a plaque with intermittent thrombus formation.

- About 35% of patients with the clinical syndrome of UA will already have coronary thrombosis on catheterization. In fact, untreated UA progresses to MI in 50% of cases. Thus, the patient with new-onset UA should be hospitalized for intensive medical treatment.
- Most patients with NSTEMI have a normal physical examination. An abnormal ECG, particularly dynamic ST-segment deviation (≥ 0.5 mm) or new T-wave inversion (≥ 2 mm), will confirm the diagnosis, but the ECG may be normal or show minor changes in up to 50% of cases.

High-risk features for patients with presumed UA/NSTEMI include:

- Repetitive or prolonged chest pain (>10 min)
- Elevated cardiac biomarkers
- Persistent ECG changes of ST depression >0.5 mm or new T-wave inversion
- Hemodynamic instability (SBP <90)
- Sustained ventricular tachycardia
- Syncope
- LV ejection fraction $<40\%$
- Prior angioplasty or prior CABG
- Diabetes
- Chronic kidney disease

Treatment.

- **Initial nonspecific management** in all cases of possible MI (anyone with a compatible chest pain history)
 - Cardiac monitor
 - Aspirin (unless contraindicated) as early as possible
 - Nitroglycerin and pain control (morphine) as needed
 - **High-risk patients:** aggressive medical management with coronary angiography and possible revascularization (unless contraindicated); age alone should not be a barrier to aggressive therapy
 - Antiplatelet therapy: clopidogrel, prasugrel, or ticagrelor (avoid clopidogrel if emergency coronary bypass surgery is likely to be required or at least discontinue 5 days beforehand)
 - Antithrombin therapy: unfractionated heparin, subcutaneous enoxaparin, or the bivalirudin (direct thrombin inhibitor) until angiography or for 48–72 hours
 - Reduce the enoxaparin dose for those with impaired renal function.
 - Give BB (unless contraindicated, i.e., severe asthma or cardiogenic shock).
 - Glycoprotein (GP) IIb/IIIa inhibitors to inhibit platelet function (block a key receptor involved in platelet aggregation)
 - Tirofiban or eptifibatide is recommended for high-risk patients in whom a PCI/stenting is planned (drug is given after PCI)
 - Concomitant tirofiban is recommended for patients with diabetes.
 - Side effects of all GP IIb/IIa agents include bleeding and thrombocytopenia (monitor patients closely for 24 hours)
 - IV nitroglycerin for refractory pain; initiate a high intensity statin immediately and an ACE inhibitor within 24 hours
- **Invasive management**
 - For patients with NSTEMI and high-risk features (unless contraindicated): early coronary angiography (within 24 hours) and revascularization
 - Pain or ischemia refractory to medical therapy and high-risk features on early exercise testing can also identify patients suitable for early invasive therapy.

For patients with diabetes, good glycemic control should be targeted in the hospital and after discharge. This may require considering an insulin-based regimen in hospital.

Note

Caution: Giving oxygen during an MI without hypoxemia has been shown to increase mortality.



Clinical Correlate

Glycoprotein (GP) IIb/IIIa inhibitors provide a more comprehensive platelet blockade than aspirin + heparin alone. These drugs take advantage of the fact that platelets play an important role in the development of ischemic complications, which may occur in those with UA/NSTEMI.

Note

Patients with UA/NSTEMI do not benefit from thrombolytics.

Note

The strongest indication for PCI is an ACS.

Clinical Recall

Which of the following medications must be withheld before an exercise stress test?

- A. Clopidogrel
- B. Metoprolol
- C. Nimodipine
- D. Aspirin
- E. Lisinopril

Answer: B

STEMI

STEMI is defined as clinical symptoms consistent with ACS and ECG features, including any of the following:

- Persistent ST-segment elevation of ≥ 1 mm in 2 contiguous limb leads
- ST-segment elevation of ≥ 2 mm in 2 contiguous chest leads
- New LBBB pattern

Initially, increased cardiac biomarkers (troponin, CPK-MB, etc.) are not needed to make the diagnosis of typical MI (STEMI), although those are usually positive at some point during the course of the disease.

The pain that occurs with STEMI is substernal and diffuse, with a pressure quality. It may radiate to the neck or jaw, shoulders, or arms. Often, there are additional symptoms such as dizziness, nausea/vomiting, diaphoresis, or shortness of breath (dyspnea).

- Symptoms last >20 minutes and do not respond completely to nitroglycerin
- Duration of the pain is variable, i.e., may resolve in a few hours or may persist for more than 1 day
- Women, elderly, and diabetics are prone to atypical symptoms (e.g., nausea or dyspnea) as sole symptoms of infarction

As many as 20% of MI are “**silent**,” i.e., whatever symptoms were present did not impress the patient enough to seek medical care or even to remember the incident.

- Exam usually shows patient to have anxiety and pain
- Diaphoresis often present
- Pulse may be normal, but there may be possible bradycardia (inferior infarctions) or tachycardia (large infarctions)
- Blood pressure often elevated
- Cardiac exam usually normal
- Signs of ventricular failure or valve dysfunction (large infarctions)
- Mitral regurgitation if papillary muscles malfunction

- Fourth heart sound (S₄) (common) due to a stiffened ventricle
- Second heart sound may be paradoxically split as the left ventricular contraction time increases due to LBBB and weakened left ventricle

In advanced disease, mild fever, pericardial friction rub, ventral septal defect murmur due to septal rupture, or severe mitral regurgitation due to papillary muscle rupture may be seen.

Treatment.

Immediate treatment for STEMI is cardiac angiography. However, patients with STEMI usually have a completely occluded coronary artery with thrombus at the site of a ruptured plaque. This eventually leads to myonecrosis.

- Restoring coronary patency (emergency reperfusion) as promptly as possible is a key determinant of short-term and long-term outcomes.
- PCI (**preferred**) in <90 minutes of time of presentation (<120 minutes if transfer to another facility is required).
- If PCI not possible in required time interval, give thrombolytics.

Treatment for those with STEMI who present within 12 hours of the onset of ischemic symptoms is prompt reperfusion via fibrinolytic therapy or PCI.

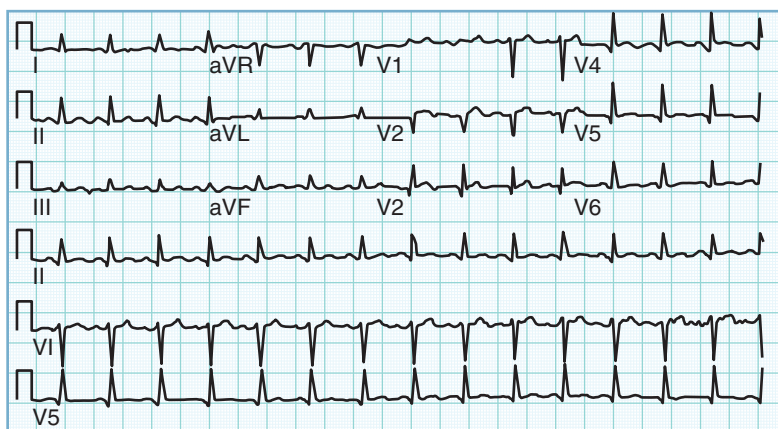


Figure 5-4. Anteroseptal STEMI with Changes in V₁–V₃

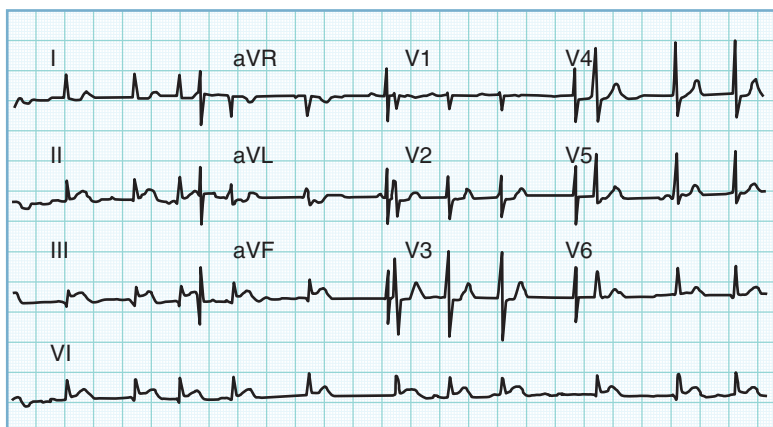


Figure 5-5. Inferior STEMI with Changes in II, III, and aVF

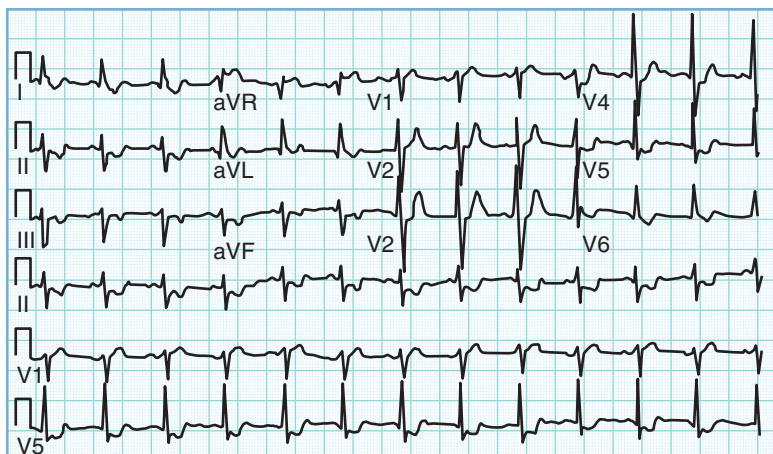


Figure 5-6. NSTEMI Affecting Leads II, III, and aVF

Table 5-2. Localization of STEMI

Area of Infarction	EKG Changes (Q Waves, ST Elevation, T Wave Inversions)	Artery Involved
Inferior	II, III, aVF	Right coronary
Anteroseptal	V ₁ –V ₃	Left anterior descending
Anterior	V ₂ –V ₄	Left anterior descending
Lateral	I, aVL, V ₄ , V ₅ , and V ₆	Left anterior descending or circumflex
Posterior	V ₁ –V ₂ : tall broad initial R wave, ST depression, tall upright T wave; usually occurs in association with inferior or lateral MI	Posterior descending

Table 5-3. Typical Electrocardiographic Evolution of a STEMI

ECG Abnormality	Onset	Disappearance
Hyperacute T waves (tall, peaked T waves in leads facing infarction)	Immediately	6–24 hours
ST-segment elevation	Immediately	1–6 weeks
Q waves longer than 0.04 seconds	One to several days	Years to never
T wave inversion	6–24 hours	Months to years

Reperfusion therapy is with either PCI or thrombolysis therapy.

- **PCI (best option if provided promptly)**
 - Improves short- and long-term outcomes (reduction of deaths and MI) in patients with STEMI presenting within 12 hours, when compared with thrombolytic therapy
 - Benefit over thrombolysis is seen only if additional time delay associated with PCI is <1 hour; in general, a delay of 120 minutes from first medical encounter to PCI is the maximum desirable
 - Where PCI is delayed or not available, reperfusion with thrombolytic therapy should be used (unless contraindicated)
- **Thrombolytics (fibrinolytics)** such as streptokinase or tissue-type plasminogen activator (tPA) restore perfusion to the ischemic area by lysing the clot, thereby reducing infarct size and improving survival.
 - Can improve all types of ST elevation infarction, but has greatest benefit with anterior infarction
 - The earlier the treatment is given, the greater the absolute benefit (greatest benefit in patients who have had symptoms <12 hours)
 - tPA (**most common**)
 - Streptokinase and alteplase (IV infusion) (do not use streptokinase more than 1× in 12 months, as prolonged persistence of antibodies may reduce effectiveness of subsequent treatment)
 - Reteplase and tenecteplase (rapid bolus injection)

Thrombolytic therapy does have several contraindications.

- **Absolute contraindications**
 - Active bleeding or known bleeding diathesis
 - Significant closed head or facial trauma <1 month
 - Aortic dissection
 - Prior intracranial hemorrhage, tumor, or AVM
 - Ischemic stroke <3 months
 - GI bleed <1 month

Note

Consider thrombolytic therapy in candidates with ST-elevation MI (>1 mm ST elevation in 2 contiguous leads) or new LBBB.



- **Relative contraindications**
 - Recent major surgery (<3 weeks)
 - Pregnancy or <1 week post-partum
 - Traumatic or prolonged cardiopulmonary resuscitation
 - Active peptic ulcer
 - Severe, poorly controlled HTN (>180/110 mm Hg)
 - Advanced liver disease
 - Ischemic stroke (<3 months)
- **Late presentation (>12 hours after symptom onset):**
 - Reperfusion therapy with PCI or fibrinolysis is not routinely recommended in patients who are asymptomatic and hemodynamically stable, or in patients who present >12 hours after symptom onset.
 - Other interventions may include CABG, which may be appropriate for those who have suitable anatomy and are not candidates for fibrinolysis or PCI. CABG surgery may also be considered for those with cardiogenic shock or in association with mechanical repair.

Adjuvant therapy used together with reperfusion includes the following:

- **Antiplatelet therapy**
 - Aspirin should be given to all patients with presumed STEMI unless contraindicated, and, in the absence of significant side effects, low-dose therapy should be continued in the long term.
 - For patients undergoing PCI with a stent, add clopidogrel, prasugrel, or ticagrelor.
 - For patients selected for fibrinolytic therapy, add clopidogrel (however, if patient is likely to require CABG acutely, withhold clopidogrel).
 - Continue clopidogrel for at least 1 month after fibrinolytic therapy, or for 9–12 months after stent implantation (depending on type of stent used).
- **Antithrombin therapy**
 - **With PCI:** the dose of unfractionated heparin therapy will depend on concomitant use of GP IIb/IIIa inhibitors; it may be advisable to give a bolus of heparin while the patient is in transit to the catheterization laboratory; the role of enoxaparin in acute STEMI in conjunction with PCI is still unclear, but it appears to be safe and effective.
 - **With fibrinolysis:** use IV unfractionated heparin (shorter half-life) when rapid reversal is needed; give as an initial bolus, adjusted to attain APTT at 1.5–2× control
- **Glycoprotein IIb/IIIa inhibitors**
 - It is reasonable to use abciximab with primary PCI.
 - Eptifibatide and tirofiban are the other GPIIb/IIIa inhibitors.
 - Avoid full-dose GP IIb/IIIa inhibitors with fibrinolytic therapy, as that combination can cause excessive bleeding (including intracranial hemorrhage)

Emergency bypass surgery should be considered in patients with STEMI and one of the following conditions:

- Failed PCI with persistent pain or hemodynamic instability and coronary anatomy suitable for surgery
- Persistent or recurrent ischemia refractory to medical therapy and suitable anatomy

Discharge medications after ACS include the following:

- Aspirin, daily for all patients
- Clopidogrel (or prasugrel) for up to 12 months after acute myocardial infarction, particularly after stent placement; clopidogrel may also be used when aspirin is contraindicated, in patients with recurrent cardiac events
- BBs for all patients after an ACS, continued indefinitely (asthma is not a contraindication for BBs)
- Metoprolol or carvedilol for patients after ACS who have heart failure
- ACE inhibitors for patients who have CHF with left ventricular dysfunction (ejection fraction <40%); monitor and discontinue if the heart failure resolves
- Statins (for all patients with ACS, initiated when inpatient) (only exception is the rare ACS that is not related to atherosclerosis)
- Nitrates: long-acting nitrates (isosorbide) for patients with persistent chest pain
- Warfarin after ACS for those at high risk of systemic thromboembolism due to Afib or mural thrombus

Discharge planning should also include discussion of lifestyle modification, e.g., hyperglycemia in patients with DM, HTN control, tobacco cessation, and physical activity.

Other testing in ACS

- **Exercise ECG testing:** submaximal testing is often performed 4–7 days after infarction; maximal testing can be performed at 3–6 weeks postinfarction. It is used to assess prognosis and to identify those patients with reversible ischemia who should then have an angiogram (if one has not been done) to assess the need for coronary artery bypass graft.
- **Myocardial perfusion imaging** can be performed before hospital discharge to assess the extent of residual ischemia if the patient has not already undergone cardiac catheterization and angiography.

Complications of ACS fall into cardiac and non-cardiac categories.

Cardiac Complications of ACS

- Electrical disturbances dysrhythmias
 - Bradycardia: sinus, atrioventricular junctional, idioventricular; treatment is atropine if acute and temporary pacing if severe
 - Premature beats: atrial, ventricular; no treatment is needed for ectopy such as these
 - Tachyarrhythmias (supraventricular): atrial tachycardia, Afib, atrial flutter, AV junctional; seldom caused by ischemia
 - Tachyarrhythmias (ventricular): ventricular tachycardia, accelerated idioventricular rhythm, ventricular fibrillation

Note

To remember issues that need to be considered at the time of discharge, remember “ABCDE” (aspirin and anti-anginals, beta blockers and blood pressure, cholesterol and cigarettes, diet and diabetes, education and exercise).



- Conduction abnormalities
 - Atrioventricular nodal: first-, second-, and third-degree block
 - Intraventricular: hemiblocks (left anterior, left posterior), bundle branch block, third-degree atrioventricular block
- Pump dysfunction
 - Contractile dysfunction: left ventricular, right ventricular, and biventricular failure; true ventricular aneurysm; infarct expansion
 - Mechanical disruption: acute mitral regurgitation (papillary muscle dysfunction or rupture), ventricular septal rupture, free wall rupture, pseudoaneurysm; treatment is emergency surgical repair
 - Electromechanical dissociation
- Ischemia
 - Postinfarction ischemia: ischemia in the infarct and ischemia distant to the infarct
 - Early recurrent infarction or infarct extension
 - Postinfarction angina after thrombolytics or PCI; treatment is bypass surgery
- Pericarditis (Dressler syndrome)
 - Rare after PCI or CABG
 - Positional CP 2–4 weeks after MI
 - Treatment is aspirin and/or NSAIDs; if no response, try steroids
- Thromboembolic
 - Mural thrombus with systemic embolism
 - Deep vein thrombosis with prolonged immobilization
- Sudden cardiac death
 - Most often due to arrhythmia
 - Ventricular fibrillation (most common)
 - Ventricular tachycardia
- Right ventricular infarction (30% of inferior MIs): hypotension, JVD, clear lungs, ST elevated on V4R on right-sided ECG; treatment is fluids

Non-Cardiac Complications of ACS

- Depression (3× more common in heart attack patients than in general population): beyond the accompanying emotional distress, depression also increases one's risk of having another heart attack; treatment is antidepressant medication; psychotherapy; SSRIs such as sertraline and citalopram (safe with CAD); and cognitive behavioral therapy
- Erectile dysfunction (ED) (very common with CAD and post-MI)
 - ED is a complication of the conditions that are primary risk factors for developing CAD, e.g., diabetes, hypertension, dyslipidemias, and arteriosclerosis
 - Smoking and stress are implicated in the development of ED.

- Treatment is management of depression, reassurance, and modification of medications which may cause ED.
- Sildenafil is contraindicated in men post-MI who are taking nitrates up to 55 mm Hg, because it can cause a drop in BP.
- Although sexual activity can trigger MI, the relative risk is low with a slight increase in risk within 2 hours of sexual activity (applies equally to men and women)
- After MI, patients can be risk-stratified and counseled about safely returning to sexual activity:
 - **Low risk:** asymptomatic patients with <3 risk factors for CAD, stable angina, recent uncomplicated MI, mild valvular heart disease, mild CHF, controlled hypertension, or post successful revascularization; manage medically
 - **Intermediate risk:** those with recent MI (but >2 wks), moderate CHF (New York Heart Association class II), and those with >3 risk factors for CAD; patients may benefit from functional testing, i.e., EST, echocardiography, or nuclear imaging study with re-stratification. EST can assist in gauging cardiac risk of sexual activity, both for induction of ischemia or arrhythmia. In general, if a patient can achieve 5 METs on ETT without demonstrable ischemia or significant arrhythmia, he is not at high risk to resume normal sexual activities. Similarly, if echocardiography does not yield evidence of more than moderate left ventricular dysfunction, resumption of sexual activity is probably safe
 - **High-risk:** those with UA, MI within 2 weeks, poorly controlled hypertension, severe CHF (New York Heart Association class III/IV), significant arrhythmias, severe cardiomyopathies; patients have cardiovascular evaluation and stabilization before resumption of sexual activity

Nonatherosclerotic Acute Coronary Syndromes

Although thrombotic complications of the atherosclerotic process account for most cases of ACS, a few rare etiologic factors are likely causes of (or contributors to) acute coronary occlusion.

- Coronary artery spasm
- Spontaneous coronary dissection
- Coronary artery embolization
- Coronary arteritis
- Hypercoagulability states such as factor V gene mutation
- Deficiencies of proteins C and S
- Antithrombin III deficiency
- Antiphospholipid antibody syndrome
- Prothrombin gene mutation
- Cocaine use has been documented to induce coronary vasoconstriction in nondiseased coronary segments but is more pronounced in atherosclerotic segments.

**Causes of MI without Coronary Atherosclerosis**

- Vasculitis
 - SLE
 - Polyarteritis nodosa
 - Takayasu arteritis
 - Mucocutaneous lymph node syndrome (Kawasaki)
- Anomalous origin of coronary artery
- Coronary spasm
 - Variant angina
 - Cocaine abuse
- Coronary artery embolus
 - Atrial myxoma
 - Atrial or ventricular thrombus
- Hypercoagulable states
 - Polycythemia vera
 - Thrombocytosis
 - Factor V Leiden
 - Protein C deficiency
 - Antiphospholipid antibodies

Prinzmetal angina, or variant angina, is a rare condition in which episodes of severe angina are triggered when one of the major coronary arteries suddenly goes into spasm. The episodes are accompanied by ST-segment elevation on ECG. Although the spasm almost always stops spontaneously, Prinzmetal angina may be associated with acute MI, serious ventricular arrhythmias, and sudden death.

- Usually occurs during periods of rest, often at night and in the early morning (unlike typical angina)
- Episodes appear in clusters
- In men, associated with atherosclerosis
- In women, not associated with atherosclerosis but rather with a history of migraines (another condition associated with arterial spasm); also, women with Prinzmetal tend to have few risk factors for CAD

Exercise testing and routine coronary angiography usually give normal results. Ergonovine has been used to trigger coronary artery spasm in susceptible patients, confirming the diagnosis. Treatment with CCBs or nitrates eliminates spasm in most of these patients. Once adequately treated, their prognosis is good.

During an acute episode of pain and ST segment elevation, you cannot tell who has Prinzmetal variant angina and who has an acute ST elevation MI. Therefore, you must initially treat everyone with chest pain and ST elevation as if they were having an acute MI.

Prinzmetal angina can be confirmed only after coronary angiography.

Clinical Recall

Which of the following is not an absolute contraindication to thrombolytic therapy?

- A. Active bleeding from factor VIII deficiency
- B. Epidural hematoma within the last 3 months
- C. Cholecystectomy 3 weeks ago
- D. Prior basal ganglia hemorrhage
- E. Large MCA stroke within the last 3 months

Answer: C

CONGESTIVE HEART FAILURE

Heart failure (HF) arises from the inability of the ventricle to efficiently pump blood throughout the circulation. Clinically, HF presents with symptoms of breathlessness, exercise intolerance, and fatigue.

Case 1:

A 62-year-old man with hypertension and dyslipidemia presents with dyspnea and lower-extremity edema for 2 months. On exam there is jugular venous distention (about 9 cm), an S3 gallop, and the apical impulse is displaced to the left of the mid-clavicular line at the 6th intercostal space. Chest x-ray shows enlarged cardiac silhouette. Echocardiogram shows a dilated left ventricle with ejection fraction 35%.

Case 2:

A 57-year-old man with history of multiple myeloma presents with dyspnea and lower-extremity edema for 2 months. On exam there is jugular venous distention (about 8 cm), an audible S4, and the apical impulse is non-displaced at the 5th intercostal space. Chest x-ray shows normal cardiac silhouette. Echocardiogram shows a thickened left ventricle with ejection fraction 65%.

As HF evolves, changes in vascular function, blood volume, and neurohumoral status occur throughout the body. These changes serve as compensatory mechanisms to help maintain cardiac output (primarily by the Frank-Starling mechanism) and arterial blood pressure (by systemic vasoconstriction). However, these compensatory changes over time can worsen cardiac function. Cardiac changes during HF include increased end-diastolic volume; ventricular dilatation or hypertrophy; decreased stroke volume and cardiac output; reduced



ejection fraction (systolic dysfunction) or impaired filling (diastolic dysfunction). Compensatory mechanisms during HF include:

- **Cardiac:** Frank-Starling mechanism, tachycardia, ventricular dilatation
- **Neuronal:** increased sympathetic adrenergic activity, reduced cardiac vagal activity
- **Hormonal:** activation of angiotensin-aldosterone system with renal sodium retention and ECV expansion), vasopressin, catecholamines, and natriuretic peptides

In clinical practice, HF is commonly categorized by whether the abnormality is due to contraction or relaxation of the heart.

- **Systolic HF** (systolic dysfunction) (also known as heart failure with reduced EF [HFrEF])
 - Caused by a loss of contractile strength of the myocardium accompanied by ventricular dilatation
 - Accompanied by a decrease in normal ventricular emptying (ejection fraction <45%)
 - Examples include ischemic and dilated cardiomyopathy (Case 1 in this section)
- **Heart failure with preserved ejection fraction** (diastolic dysfunction) (also known as heart failure with preserved EF [HFpEF])
 - Results when the filling of one or both ventricles is impaired while the emptying capacity is normal (ejection fraction >50%)
 - Examples include hypertensive heart disease and the infiltrative cardiomyopathies (amyloidosis) (Case 2 in this section)

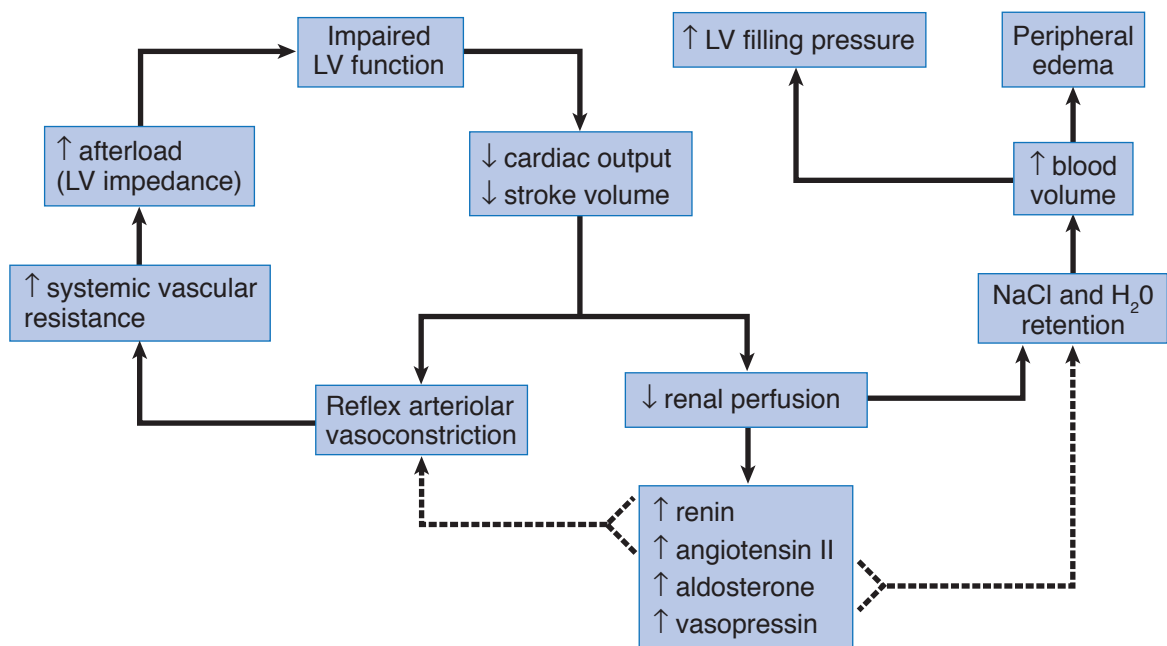


Figure 5-7. Inter-related Cycles in Congestive Heart Failure

Congestive HF indicates a clinical syndrome of dyspnea and fatigue as well as evidence of features of circulatory congestion (peripheral edema, elevated JVP). In heart failure, intravascular congestion occurs with elevation of left ventricular diastolic and pulmonary venous pressures that eventually causes transudation of fluid from the pulmonary capillaries into the interstitial space. The kidneys retain salt and water, worsening the EVC expansion. **Pulmonary edema** develops when the rate of fluid accumulation goes above the rate of lymphatic absorption. Pulmonary edema is detected by audible crackles, increased JVP and edema on exam, and chest x-ray findings.



Wikipedia, James Heilman, MD

Figure 5-8. Elevated JVP

Decompensated HF or exacerbation of HF denotes worsening of symptoms and clinical findings in pre-existing HF. This can be due to precipitating factors such as non-adherence to medication, increase in dietary salt, acute ischemia, tachycardia, or pulmonary infection.

In evaluating patients with HF or worsening of pre-existing HF, it is also important to exclude precipitating factors. Commonly, HF manifests for the first time when a precipitating factor places additional burden on the heart. Such factors include:

- Cardiac ischemia and myocardial infarction
- Infections (especially pulmonary infections)
- Arrhythmias (especially Afib)
- Excessive dietary salt (commonly after holiday meals)
- Uncontrolled hypertension (especially after abrupt cessation of anti-hypertensive medication)
- Thyrotoxicosis
- Anemia

HF may occur as a consequence of most causes of heart disease, but ischemic heart disease is responsible for over 70% of all cases in the western world. Other common causes include hypertensive heart disease, the cardiomyopathies (idiopathic, alcohol related, etc.), and valvular and congenital heart diseases.

Note

Both *hyper- and hypothyroidism* can cause heart failure. Always check TSH with heart failure.

Clinical Pearl

In the work-up of patients with new-onset HF, always try to identify potentially reversible causes.



Clinical Pearl

In the work-up of patients with exacerbation of HF, always:

- Check cardiac enzymes to exclude myocardial ischemia or infarction
- Do a chest x-ray to exclude infection

Clinical Presentation of CHF

Symptoms of HF include dyspnea (differentiate from pulmonary dyspnea), orthopnea, paroxysmal nocturnal dyspnea, and fatigue/weakness.

Table 5-4. Most Common Causes of Acute Pulmonary Edema

Ischemia
Arrhythmia
Non-adherence with medication
Dietary indiscretion
Infection

Physical findings in HF:

- Pulmonary rales
- Peripheral edema, ascites
- Hepatomegaly
- Jugular venous distention
- Displaced apical impulse (systolic HF)



Wikipedia, James Heilman, MD

Figure 5-9. Pitting Edema

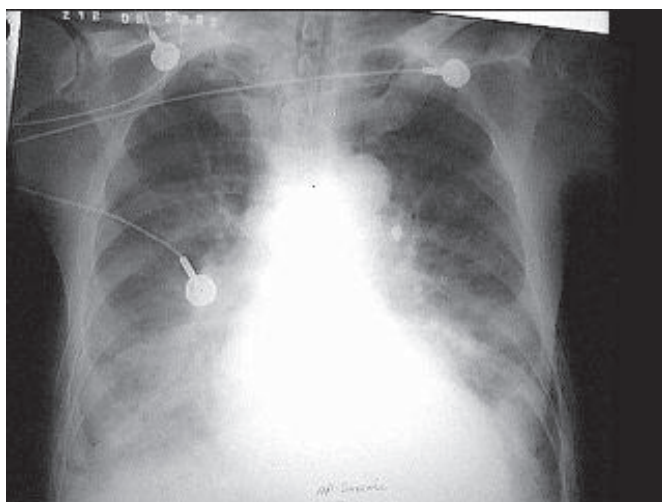
The severity of heart failure is commonly classified by using an HF staging system. The New York Heart Association Functional Classification (NYHA staging system) relates symptoms to everyday activities and the patient's quality of life:

- **Class I:** patients have no limitation of activity; they suffer no symptoms from ordinary activities
- **Class II:** patients with slight, mild limitation of activity; they are comfortable with rest or with mild exertion

- **Class III:** patients with marked limitation of activity; they are comfortable only at rest
- **Class IV:** patients are confined to bed or chair; any physical activity brings on discomfort and symptoms occur at rest

Diagnosis. An echocardiogram is the best test to confirm the diagnosis of HF and classify the type. With the echocardiogram, the clinician is able to determine ejection fraction and to identify valvular heart disease and other cardiac anomalies (dilated ventricle, thickened ventricle, etc.). Chest x-ray is also used the diagnosis of heart failure; it may show cardiomegaly, vascular redistribution, Kerley B-lines, or interstitial edema.

Electrocardiogram is used to identify ventricular hypertrophy and/or the presence of ischemic heart disease, arrhythmias, or conduction delays which may cause or precipitate HF.



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Figure 5-10. Chest X-ray Showing Acute Exacerbation of Congestive Heart Failure

Brain natriuretic peptide (BNP) (or type B natriuretic peptide) is a polypeptide secreted by the heart in response to excessive stretching of the myocytes. It is a valuable screening tool in the evaluation of presumed HF or decompensated HF in the acute setting.

- High sensitivity (97% sensitivity): almost always elevated in patients with decompensated HF (except obesity, where BNP can be falsely low)
- Low specificity (renal failure and old age can cause elevated BNP)
- Best used for ruling out HF
- Normal BNP generally excludes CHF as the cause of dyspnea
- Positive BNP warrants a follow-up echocardiogram.

Treatment. Treatment goals in HF are to improve hemodynamics, relieve symptoms (improve quality of life), and prolong survival. Always evaluate for reversible causes at the same time.

Note

Echocardiography is the best test to confirm CHF. **BNP** is best used to rule out CHF and save further workup.



Note

In terms of HF treatment, all ACE inhibitors are considered equal. If they are contraindicated, ARBs are an alternative.

Note

Hydralazine + nitrates is the best treatment for the following scenarios:

- African American patient with EF <40% and NYHA class III-IV while on standard therapy (do not pick this unless patient is on a BB and ACE inhibitor or ARB or NI/ARB and spironolactone)
- Patient cannot tolerate ACE inhibitors or ARBs

- **Non-pharmacologic treatment:** reduction of salt intake
- **Pharmacologic treatment**
 - ACE inhibitors for all patients with HF, especially systolic HF, irrespective of BP status
 - Improve survival
 - Reduce ventricular hypertrophy (and eventually, symptoms)
 - Reduce preload and afterload (through vasodilation), thereby reducing right atrial, pulmonary arterial, and pulmonary capillary wedge pressures
 - Side effects include cough and angioedema
 - Newer drugs
 - Valsartan-sacubitril, an angiotensin receptor-neprilysin inhibitor (ARNI) (valsartan is an ARB, while sacubitril inhibits the degradation of natriuretic peptide); neprilysin is a neutral endopeptidase that degrades several vasoactive peptides, including natriuretic peptides (ANP, BNP) and bradykinin. Inhibition of neprilysin increases levels of these substances, which then counteract the effects of neurohormonal activation such as vasoconstriction and sodium retention. They block the RAAS system and lead to natriuresis and decrease cardiac hypertrophy and fibrosis.
 - Ivabradine, used for heart failure and tachycardia unresponsive to BBs, is an inhibitor of the If or “I-funny” channel, which contributes to normal sinus node function. Its sole effect is to slow the heart rate by decreasing sinus node automaticity.
 - Diuretics, especially loop diuretics, e.g., furosemide, to relieve symptoms of acute pulmonary edema (**treatment of choice**); thiazide diuretics (hydrochlorothiazide) are useful only in mild HF. Spironolactone and eplerenone (aldosterone antagonists) are used as add-on therapy to ACE inhibitors in severe HF to prolong survival by presumed aldosterone inhibition.
 - BBs play a role in helping to decrease mortality, reduce hospitalizations, improve functional class, and improve ejection fraction. Give a BB after patient is stabilized with diuretics and ACE inhibitor if BP is high. Metoprolol succinate, carvedilol, and bisoprolol are best shown to benefit mortality.
 - BBs are contraindicated in cardiogenic shock and severe active asthma.
 - BBs should never be given to someone with decompensated HF.
 - When ACE inhibitors/ARBs are contraindicated, another vasodilator such as combination hydralazine/isosorbide is helpful to reduce deaths and hospitalizations.
 - For severe HF or if no response to standard therapy, spironolactone may be helpful to reduce deaths and hospitalizations. Spironolactone is used in patients with NYHA class III-IV. Monitor serum potassium closely for possible hyperkalemia. Eplerenone is an alternative to spironolactone that does not cause gynecomastia.

Monitoring of patients with HF includes calculation of fluid intake and excretion (inpatient) and monitoring of body weight (outpatient).

Table 5-5. Vasodilators Used in Congestive Heart Failure

Drug	Site of Action	Route of Administration	Complications
Captopril Enalapril Lisinopril Sacubitril	Arteriolar and venous ACE inhibitor	Oral	Rash, nonproductive cough, proteinuria, renal failure, taste disturbance, agranulocytosis, hypotension
Nitroprusside	Arteriolar and venous	IV	Thiocyanate toxicity, methemoglobinemia
Nitroglycerin	Venous (arteriolar at high doses IV)	SL, IV, cutaneous ointment, or patch	Headache, postural hypotension, methemoglobinemia
Isosorbide dinitrate	Venous	Oral or SL	Headache, postural hypotension
Hydralazine	Arteriolar	Oral	Positive ANA, SLE-like syndrome (10–20% if >400 mg/d) drug fever, rash

Table 5-6. Commonly Used Diuretics in Heart Failure

Drug	Site of Action	Complications
Thiazides (inhibits NaCl cotransport); used mostly for treatment of hypertension • Hydrochlorothiazide • Chlorothiazide	Distal tubule	Hyponatremia, hypokalemia, hypercalcemia, metabolic alkalosis, hyperuricemia, allergy, agranulocytosis, leukopenia, pancreatitis, glucose intolerance
Indapamide	Distal tube (direct vasodilator)	As above, but hypokalemia and lipid abnormalities less common
Loop diuretics (inhibitors Na/K, 2Cl cotransport); most commonly used diuretics in heart failure • Furosemide • Ethacrynic acid • Bumetanide	Loop of Henle	Hyponatremia, hypokalemia, hypocalcemia, metabolic alkalosis, hyperuricemia, interstitial nephritis, ototoxicity, thrombocytopenia, agranulocytosis, leukopenia
Potassium-sparing diuretics • Spironolactone (aldosterone antagonist)	Distal tubule	Hyperkalemia, gynecomastia (spironolactone only)

Note

Recent **guideline updates**, as per the American College of Cardiology/AHA, include the following:

- **ARNI** (not an ACEi or ARB) for patients with CHF and reduced ejection fraction (HFrEF) who are mildly/moderately symptomatic. Valsartan-sacubitril has been shown to lower risk for the composite endpoint of cardiovascular death or HF hospitalization compared with enalapril in patients with HFrEF. Do not administer valsartan-sacubitril concurrently, or within 36 hrs, of an ACEi, due to angioedema risk. Also, avoid in those with a history of angioedema.
- **Ivabradine** for reduction of heart failure-associated hospitalizations in patients with chronic symptomatic heart failure with left ventricular ejection fraction $\leq 35\%$ if they are in sinus rhythm, taking guideline-directed medical therapy, and HR >70/min while on maximum dose of BB.

Note

ACEi (any) and a diuretic are considered first line for all patients with HF. Once the patient is stable, add carvedilol or metoprolol. Do not substitute BBs in HF since they are not all equally effective.

**Note**

Digitalis should be added only after all mortality-reducing drugs have been tried. Then it can be used for the treatment of systolic HF, Afib/flutter, and paroxysmal atrial tachycardia/SVT.

Note

ACE inhibitors/ARB, BBs, spironolactone, AICD, and biventricular pacing **all lower mortality** in systolic CHF.

Digitalis and diuretics do not reduce mortality but help in management.

Note

Before either type of medical device is considered, the patient must have first tried 90 days of medical therapy.

For **severe HF**, add an inotropic agent to improve quality of life and reduce hospitalizations (but will not improve survival). Digitalis (**most common**) inhibits Na^+/K^+ -ATPase pump, which results in increased intracellular concentration of Na^+ and decreased exchanges of intracellular Ca^{2+} . The end result is improved cardiac contractility.

- Digitalis will increase both the force and the velocity of the myocardial contraction. It will also promote a more complete emptying of the ventricles.
- Monitor serum potassium in patients taking digitalis. Remember that K^+ and digitalis compete for myocardium binding sites. Hyperkalemia will decrease digitalis action, while hypokalemia increases digitalis toxicity.
- Other conditions that predispose to digitalis toxicity are renal insufficiency; electrolyte disturbances (hypercalcemia, hypomagnesemia); advanced age; sinoatrial and atrioventricular block; and thyroid disease (especially hypothyroidism).
- Effects of digitalis toxicity include nausea and vomiting; gynecomastia; blurred vision; yellow halo around objects; arrhythmias (commonly paroxysmal atrial tachycardia) with block PVCs (premature ventricular contractions), and bradycardia. Treatment is to stop the drug and then add lidocaine and phenytoin (for arrhythmia). Digibind is used only for acute overdose.

Cardiac glycosides work by inhibition of Na^+/K^+ -ATPase pump, which results in:

- Increased intracellular concentration of Na^+
- Decreased exchange of intracellular Ca^{2+} for extracellular Na^+
- The end result is an increase in the intracellular concentration of Ca^{2+} , which gives the (+) inotropic effect characteristic of glycosides

Table 5-7. Drug Interactions Associated with Digoxin

Drug	Effect*	Mechanism
Quinidine	Increase	Decreases renal clearance of digoxin
Verapamil, diltiazem	Increase	Decreases renal clearance of digoxin
Cholestyramine, colestipol	Decrease	Binds digoxin in GI tract; interferes with enterohepatic circulation
Spironolactone	Increase	Inhibits tubular secretion of digoxin
Thiazides, furosemide	Increase	Diuretic-induced hypokalemia and/or bumetanide hypomagnesemia potentiates digitalis action

*Increase enhances digitalis effect; decrease diminishes digitalis effect.

Medical Devices for Systolic Dysfunction

After medical management has been initiated, several mechanical devices may be added to further improve prognosis in HF.

- Automatic implantable cardioverter/defibrillator (AICD) is a standard therapy for severe ischemic dilated cardiomyopathy ($\text{EF} < 35\%$). Since the most common cause of death in CHF is an arrhythmia, it logical that a device which interrupts arrhythmia will lower mortality in patients with systolic CHF. Indications include ischemic or nonischemic dilated cardiomyopathy with persistent ejection fraction $< 35\%$ and NYHA class II–III **or** ejection fraction $< 30\%$ and NYHA class I on medical therapy.

- Biventricular pacemaker will “resynchronize” the heart when there is dilated cardiomyopathy. When there is a wide QRS, the 2 ventricles do not beat or depolarize in synchrony. The biventricular pacemaker will “resynchronize” the 2 ventricles, causing an immediate decrease in symptoms. This device also includes an automatic defibrillator, since patients are at risk for ventricular arrhythmia. Indications include dilated cardiomyopathy NYHA class II–IV, ejection fraction <35%, and LBBB with QRS >150 ms.

Treatment for dilated cardiomyopathy

The following classes of medications lower mortality in systolic HF:

- ACE inhibitor or ARBs (one or the other but not both); ARNI is better and should be used for class II or greater
- BBs (not all are equal; best mortality benefit is metoprolol succinate, carvedilol, or bisoprolol)
- Spironolactone (or eplerenone)
- AICD (if EF <35%)
- Biventricular pacemaker (LBBB with QRS >150 ms)

Treatment for Severe Systolic CHF

Additional support may be needed in hospitalized patients with cardiogenic shock. Patients are admitted to critical care units for support and treatment of hypotension and pulmonary edema. Fluid management is difficult, since increasing preload with fluids in an attempt to raise blood pressure may worsen pulmonary edema. In such hypotensive patients, BBs are now contraindicated, unlike outpatient CHF where they are first line.

Sympathomimetic inotropic amines (especially **dobutamine**) and phosphodiesterase inhibitors (amrinone, milrinone) are sometimes used to raise cardiac output in the management of severe acute systolic HF in hospitalized patients.

- Must be given by IV infusion
- Require continuous monitoring of BP and cardiac rhythm
- Do not use in renal failure
- Patients with ongoing infarction or ischemia are challenging, in that increasing the cardiac output also increases cardiac work and energy consumption, thus potentially extending the myocardial infarction.

In extreme HF with hypotension, the medications may fail, and the patient’s heart may not be able to support circulatory function. In that case, an intra-aortic balloon pump can be used to improve perfusion and improve mortality. Extracorporeal membrane oxygenation (ECMO) may be used to remove the patient’s RBCs, remove the CO₂ and supply O₂, then re-infuse into the patient. Biventricular assist devices (previously called “artificial hearts”) may be used if the patient is awaiting heart transplantation. Heart transplantation is typically the only long-term effective treatment for very severe HF.

Pulmonary edema may occur in any patient with CHF, but is particularly likely in hospitalized patients with cardiogenic shock. It is considered a medical emergency and requires hospitalization. It leads to impaired gas exchange and may cause respiratory failure. There are non-cardiogenic causes of pulmonary edema, but in this section we will discuss only cardiogenic pulmonary edema. Cardiogenic pulmonary edema is caused by an acute increase in left



ventricular pressure due to ventricular dysfunction, which leads to fluid accumulation in the pulmonary interstitium.

Signs and Symptoms

- Tachypnea
- Cough with pink frothy sputum
- Cyanosis
- Pulmonary crackles or wheezes

Lab workup includes monitoring of blood oxygen and CO₂ content; chest x-ray (prominent pulmonary vessels, effusions, Kerley B lines); and ECG to exclude arrhythmias and ongoing MI.

Treatment in hospitalized patients includes all CHF treatments but also includes oxygen; IV loop diuretics (furosemide); morphine sulfate; nitroglycerin (reduces preload); IV ACE inhibitors; non-invasive positive-pressure ventilation in patients with severe hypoxia or hypercapnia after medications; and intubation/ventilation in patients who fail all of the above.

Management of Diastolic HF

Patients with diastolic HF (thick ventricles, preserved EF) do not benefit from inotropic agents, since their cardiac contractility is normal. ACE inhibitors are less useful than in systolic HF. Diuretics must be used cautiously, since limited preload (filling) is a hallmark of their disease.

Preferred management for HF with preserved systolic function includes the following:

- Diuresis as needed for volume overload
- BP control (CCBs, BBs, or ACE inhibitors/ARB)
- Exercise program and cardiac rehabilitation

BBs are now used less often but may be added for rate control of Afib or if patient has concurrent CAD.

Clinical Recall

What is the best therapy for hypertrophic cardiomyopathy?

- A. Digoxin
- B. Hydralazine/nitroglycerin
- C. Lisinopril
- D. Metoprolol
- E. Nifedipine

Answer: D

VALVULAR HEART DISEASE

Mitral Stenosis

Mitral stenosis is the most common lesion caused by rheumatic fever, with possible progression to right ventricular failure. It becomes clinically symptomatic during pregnancy. Mitral stenosis consists of thickened mitral valve leaflets, fused commissures, and chordae tendineae.

Most cases are secondary to rheumatic fever. Rarely, it is caused by a congenital defect, calcification of the valve, or post-radiation treatment to the chest.

Pathogenesis. Mitral valve stenosis impedes left ventricular filling. Increased left atrial pressure is referred to the lungs, causing pulmonary congestion. Forward cardiac output becomes reduced, secondary pulmonary vasoconstriction occurs, and eventually right ventricular failure results.

Clinical Symptoms. Usually manifest slowly over years.

- Dyspnea
- Orthopnea
- Paroxysmal nocturnal dyspnea
- Fatigue
- Wasting
- Hemoptysis (due to rupture of pulmonary vessels)
- Systemic embolism (due to stagnation of blood in an enlarged left atrium)
- Hoarseness (due to impingement of an enlarged left atrium on the recurrent laryngeal nerve)
- Right-sided heart failure: hepatomegaly, ascites, peripheral edema

Physical Signs

- Afib (irregular cardiac rhythm)
- Pulmonary rales
- Decreased pulse pressure
- Loud S1
- Opening snap following S2
- Diastolic rumble (low-pitched apical murmur)
- Sternal lift (due to right ventricular enlargement)

Diagnosis is made with the following:

- **ECG:** possible signs of right ventricular hypertrophy; possible left and right atrial abnormalities; Afib (common)
- **Chest x-ray:** large left atrium (indicated by a double-density right heart border, posterior displacement of esophagus, and elevated left mainstem bronchus), straightening of left heart border; possible signs of pulmonary hypertension, including Kerley B lines and increased vascular markings; large pulmonary artery
- **Echocardiogram (best test):** thickening of mitral valve leaflets and a reduction in the excursion and area of the valve leaflets; possible left atrial enlargement; trans-esophageal echocardiogram often needed to visualize valve

**Treatment.**

- Medical therapy
 - Diuretics and salt-restricted diet
 - BBs or nondihydropyridine CCBs to control the ventricular rate in patients with Afib
 - Anticoagulants in patients with Afib
 - Balloon valvotomy (**standard of care**) (concurrent MR or left atrial thrombus is a contraindication to valvotomy); favorable characteristics include pliable leaflets, minimal commissural fusion, and minimal calcification
- Surgical management (repair) when patient remains functional class III-IV after medical therapy
 - Mitral commissurotomy or valve replacement when balloon valvotomy is contraindicated
 - Pulmonary hypertension is not a contraindication for surgery.

Note

All patients with Afib and MS should be on warfarin, regardless of CHA₂DS₂-vasc score.

DOACs cannot be used in MS.

Mitral Regurgitation

Mitral regurgitation is backflow of blood from the left ventricle into the left atrium due to inadequate functioning (insufficiency) of the mitral valve, most commonly from ischemia. Men > women.

The etiology of mitral regurgitation is due to abnormalities of the mitral leaflets, annulus, and chordae tendineae. Common causes include hypertension, CHF, ischemic heart disease, rheumatic fever, and any cause of dilation of the left ventricle.

Table 5-8. Acute versus Chronic Etiologies of Mitral Valve Regurgitation

Acute	Chronic
• Rupture chordae tendineae (permits prolapse of a portion of a mitral valve leaflet into the left atrium) • Papillary muscle rupture • Endocarditis (may lead to valvular destruction) • Trauma	• Rheumatic heart disease (causing scarring and retraction of valve and leaflets) • Papillary muscle dysfunction • Mitral valve prolapse (click-murmur syndrome, Barlow syndrome, floppy mitral valve) • Endocarditis • Calcification of the mitral valve annulus • Accompanying hypertrophic obstructive cardiomyopathy • Congenital endocardial cushion defect, corrected transposition • Endocardial fibroelastosis • Severe left ventricular dilatation

Pathogenesis

- A portion of the left ventricular stroke volume is pumped backward into the left atrium instead of forward into the aorta, resulting in increased left atrial pressure and decreased forward cardiac output. Traditional measurement of the cardiac output by EF may be normal, since the LV empties well. It is just not all in the correct direction. A regurgitant fraction needs to be estimated by Doppler during echocardiography.

- Volume overload occurs, increasing preload.
- Afterload is decreased as the left ventricle empties part of its contents into the relatively low-pressure left atrium.
- This helps to compensate for the regurgitation by augmenting ejection fraction.
- Left ventricular dysfunction occurs after prolonged compensation.

Clinical Manifestations

Left ventricular failure is manifested by dyspnea, orthopnea, and paroxysmal nocturnal dyspnea.

Severe and chronic mitral regurgitation lead to right-sided failure, presenting with edema, ascites, anorexia, and fatigue.

Pulmonary hypertension may be a late finding.

Physical Signs

- Hyperdynamic and displaced (downward and to the left) left ventricular impulse
- Carotid upstroke diminished in volume but brisk
- Holosystolic apical murmur radiating to the axilla and often accompanied by a thrill
- S3 heard with a soft S1 and widely split S2
- Distended neck veins when severe or acute

Diagnosis

- ECG shows signs of left ventricular hypertrophy and left atrial enlargement.
- Chest x-ray shows cardiac enlargement, with vascular congestion when the regurgitation has led to heart failure.
- Echocardiography (**best first test**): The mitral valve can prolapse into the left atrium during systole in cases of a ruptured chordae or mitral valve prolapse. Regardless of the cause, left atrial and left ventricular enlargement occurs if the condition is chronic.
- Left-heart catheterization is the single most accurate test.

Treatment

Medical therapy. The goal is to relieve symptoms by increasing forward cardiac output and reducing pulmonary venous hypertension. ARBs/hydralazine, arteriolar vasodilators (ACE inhibitors), digitalis, and diuretics are used.

Surgical therapy. Mitral valve replacement is indicated when symptoms persist.

- Indicated with significantly limiting symptoms and severe mitral regurgitation; the risk of surgery rises in chronic heart failure.
- Indicated when symptoms persist despite optimal medical management.
- Repair is preferable to replacement.

Patients with regurgitation but few symptoms should defer surgery, as their condition may remain stable for years.

Mitral Valve Prolapse

Mitral valve prolapse is the most common congenital valvular abnormality (2–3% population) typically seen in young women. It may occur with greater frequency in those with Ehlers-Danlos syndrome, polycystic kidney disease, and Marfan syndrome.



Most patients are asymptomatic. Lightheadedness, palpitations, syncope, and chest pain may occur (often due to arrhythmias, which may occur.)

Auscultation

- Mid-to-late systolic click and a late systolic murmur at the cardiac apex
- Worsens with Valsalva or standing
- Improves with squatting or leg raise

Complications (all very rare)

- Serious arrhythmias
- Sudden death
- CHF
- Bacterial endocarditis (but does not mean routine dental prophylaxis is indicated)
- Calcifications of valve
- Transient cerebral ischemic attacks

Lab tests include 2-dimensional/Doppler echocardiography showing marked systolic displacement of mitral leaflets with coaptation point at or on the left atrial side of the annulus; moderate systolic displacement of the leaflets with at least moderate mitral regurgitation.

Treatment. No specific treatment is needed in most cases. Use beta blockers for chest pain and palpitations. Mitral valve replacement is rarely needed.

Aortic Stenosis

Aortic stenosis is most commonly caused by calcification and degeneration of a congenitally normal valve. It is common in the elderly. Other etiologies include:

- Calcification and fibrosis of a congenitally bicuspid aortic valve
- Rheumatic valvular disease, i.e., if the aortic valve is affected by the rheumatic fever, the mitral valve is also invariably affected

Aortic stenosis results in elevation of left ventricular systolic pressure, and the resultant left ventricular hypertrophy maintains cardiac output without dilation of the ventricular cavity. Therefore, the stroke volume is normal until the late stages of the disease.

Forceful atrial contraction augments filling at the thick, noncompliant ventricle and generates a prominent S4 gallop that elevates the left ventricular end-diastolic pressure.

Left ventricular hypertrophy and high intramyocardial wall tension account for the increased oxygen demands and, along with decreased diastolic coronary blood flow, account for the occurrence of angina pectoris.

As the myocardium fails, mean left ventricular diastolic pressure increases, and symptoms of pulmonary congestion ensue.

Clinical Presentation.

- Angina, syncope, and dyspnea from CHF (classic symptoms)
- Pulsus tardus et parvus
- Carotid thrill

Clinical Pearl

Look for AS in older patients presenting with syncope related to exertion.

- Systolic ejection murmur in aortic area, usually with thrill, harsh quality, radiates to carotids
- S4 gallop
- A2 decreased, S2 single or paradoxically split
- Aortic ejection click

Diagnosis. ECG often shows left ventricular hypertrophy. Chest x-ray may present with calcification, cardiomegaly, and pulmonary congestion. Echocardiography shows thick aortic valve leaflets with decreased excursion and LVH.

Treatment. Endocarditis prophylaxis is no longer recommended.

- Surgery (valve replacement) is advised when symptoms develop, usually when the valve area is reduced $<0.8 \text{ cm}^2$ (normal aortic orifice, $2.5\text{--}3 \text{ cm}^2$). Generally, if patient has symptoms, surgery is the treatment of choice.
- Balloon valvuloplasty may be useful in those too ill to tolerate surgery.

Table 5-9. Differential Diagnosis of Aortic Valve Stenosis

Disease Entity	Differentiating Features
Aortic valve sclerosis of the elderly, without stenosis	Systolic murmur does not peak late Carotids do not have delayed upstrokes No left ventricular hypertrophy by ECG Echocardiographic visualization of excursion of valve leaflets usually normal or mildly reduced, but valves may not be visualized No hemodynamically significant aortic valve gradient by cardiac catheterization
Hypertrophic obstructive cardiomyopathy	Brisk bifid carotid upstrokes Murmur usually does not radiate into neck Characteristic change in murmur with various maneuvers Pseudoinfarct pattern (large septal Q waves) on ECG Characteristic echocardiographic features
Mitral regurgitation	Murmur is holosystolic and radiates to axilla and not carotids Carotid upstroke may be normal Dilated left ventricle Aortic valve normal on echocardiogram unless there is associated aortic valve disease
Pulmonic stenosis	Murmur does not radiate into neck; loudest along the left sternal border; increases with inspiration Physical examination, chest x-ray, and ECG may reveal enlarged right ventricle Echocardiogram reveals right ventricular enlargement and hypertrophy

Note: All of the above have a systolic murmur that can be confused with aortic stenosis.

**Table 5-10. Effect of Various Maneuvers on Systolic Murmurs**

	Valsalva	Phenylephrine Handgrip	Squatting	Amyl Nitrite	Leg Raising
Aortic stenosis	Decrease	Decrease	Increase or decrease	Increase	Increase
Hypertrophic obstructive cardiomyopathy	Increase	Decrease	Decrease	Increase	Decrease
Ventricular septal defect	Decrease	Increase	No change	Decrease	Increase
Mitral regurgitation	Decrease	Increase	Increase	Decrease	Increase

Aortic Regurgitation

The most common causes of aortic regurgitation are systemic hypertension and ischemic heart disease.

- May occur after infectious endocarditis
- May result from a condition which affects the ascending aorta: syphilis, ankylosing spondylitis, Marfan syndrome, rheumatic fever, aortic dissection, aortic trauma

Pathophysiology

Aortic regurgitation results in a volume overload of the left ventricle.

- The ventricle compensates by increasing its end-diastolic volume according to the Frank-Starling mechanism.
- The left ventricular dilation is thought to overstretch the myofibrils, leading to less actin-myosin interaction and decreased contractility.
- In acute severe aortic regurgitation, the left ventricle has not had the opportunity to dilate, its compliance is relatively high, and the aortic regurgitation therefore leads to very high left ventricular end-diastolic pressure.
- If mitral regurgitation ensues, the elevated left ventricular diastolic pressure is reflected back to the pulmonary vasculature, and acute pulmonary edema may occur.

Acute aortic regurgitation results in a lower cardiac output, narrower aortic pulse pressure, and a smaller left ventricle than does chronic aortic regurgitation.

Aortic diastolic pressure decreases in chronic aortic regurgitation because of both the regurgitation of blood into the left ventricle and a compensatory decrease in systemic vascular resistance to maintain forward cardiac flow to the periphery. The increased pulse pressure in chronic aortic regurgitation is due to the large stroke volume, causing increased systolic and decreased diastolic pressure.

Clinical Manifestations

- Dyspnea (most common complaint)
- Diastolic decrescendo murmur is the most typical.
- Systolic flow murmur

Note

Remember, aortic regurgitation can cause 3 different murmurs.

- Duroziez sign: systolic and/or diastolic thrill or murmur heard over the femoral arteries
- S3 in early left ventricular decompensation
- Austin-Flint murmur

Diagnosis

- **Echocardiography (best initial test):** dilated LV and aorta; left ventricular volume overload; fluttering of anterior mitral valve leaflet
- ECG: LV hypertrophy often with volume overload pattern (narrow deep Q waves in left precordial leads)
- Chest x-ray: LV and aortic dilation

Treatment. Endocarditis prophylaxis is no longer recommended.

- Salt restriction, diuretics, afterload reduction (e.g., ACE inhibitors)
- Aortic valve replacement when symptoms worsen or ejection fraction decreases.
- Vasodilators such as an ACE, ARB, or nifedipine are the standard of care.
- Perform aortic valve replacement when the ejection fraction is <50% with HF symptoms (NYHA level II-IV) or left ventricular systolic diameter is >55 mm.

Clinical Recall

Which of the following is most appropriate in the management of a patient with aortic stenosis?

- Warfarin to patients who develop atrial fibrillation
- Surgical replacement when the EF <60% or LV end systolic diameter >40 mm
- Surgical replacement when the valve area <0.8 cm²
- Surgical replacement when the EF <55% or LV systolic diameter >55 mm
- None of the above

Answer: C



CARDIOMYOPATHIES

Cardiomyopathy is a disease involving the heart muscle itself. Cardiomyopathies can be classified according to morphologic and hemodynamic characteristics.

Table 5-11. Morphologic and Hemodynamic Characteristics of Cardiomyopathies

	Dilated	Hypertrophic	Restrictive
	Biventricular dilatation	Marked hypertrophy of left ventricle and occasionally of right ventricle; can have disproportionate hypertrophy of septum	Reduced ventricular compliance; usually caused by infiltration of myocardium (e.g., by amyloid, hemosiderin, or glycogen deposits)
Cardiac output	↓	Normal or ↓	Normal to ↓
Stroke volume	↓	Normal or ↑	Normal or ↓
Ventricular filling pressure	↑	Normal or ↑	↑
Chamber size	↑	Normal or ↓	Normal or ↑
Ejection fraction	↓	↑	Normal to ↓
Diastolic compliance	Normal	↓	↓
Other findings	May have associated functional mitral or tricuspid regurgitation.	Obstruction may develop between interventricular septum and septal leaflet of mitral valve.	Characteristic ventricular pressure tracing that resembles those recorded in constrictive pericarditis, with early diastolic dip-and-plateau configuration

Dilated (Congestive) Cardiomyopathy

Characterized by diminished myocardial contractility, usually involving both ventricles; most common cause for heart transplants.

Etiologies include:

- Ischemic (**most common**)
- Idiopathic (**next most common**)
- Alcoholic
- Peripartum
- Postmyocarditis due to infectious agents (viral, parasitic, mycobacterial, *Rickettsiae*)
- Toxins (cobalt, lead, arsenic)

- Doxorubicin hydrochloride, cyclophosphamide, vincristine
- Metabolic: chronic hypophosphatemia, hypokalemia, hypocalcemia, uremia

Clinical Manifestations. Symptoms and signs of left and right ventricular failure. Typical symptoms of systolic dysfunction.

Diagnosis

- X-ray: cardiomegaly with pulmonary congestion
- ECG: sinus tachycardia, arrhythmias, conduction disturbances
- Echo (key diagnostic study): dilated left ventricle, generalized decreased wall motion, mitral valve regurgitation; transesophageal echo is more sensitive and specific than transthoracic
- Catheterization: dilated hypocontractile ventricle, mitral regurgitation

Treatment is the same as those with systolic heart failure. ACE, BBs, and spironolactone lower mortality. Diuretics and digoxin decrease symptoms. Implantable defibrillator may decrease risk of sudden death when ejection fraction <35%.

Hypertrophic Cardiomyopathy

These disorders with thickened ventricles present with diastolic dysfunction.

- Hypertensive cardiomyopathy (from years of untreated hypertension, similar to hypertensive nephrosclerosis in the kidney)
- Hypertrophic obstructive cardiomyopathy (HOCM)

Hypertrophic Obstructive Cardiomyopathy

Although hypertrophic obstructive cardiomyopathy (HOCM) can apparently develop sporadically, it is hereditary in >60% of cases and is transmitted as an autosomal dominant trait.

- An abnormality on chromosome 14 has been identified in the familial form of the disease.
- The distinctive hallmark of the disease is unexplained myocardial hypertrophy, usually with asymmetric thickening of the **interventricular septum**.

Pathophysiology. As a result of the hypertrophy, left ventricular compliance is reduced, but systolic performance is not depressed. Diastolic dysfunction is characteristic, resulting in decreased compliance and/or inability for the heart to relax.

- The heart is hypercontractile, and systole occurs with striking rapidity.
- Ejection fractions are often 80–90% (normal is 60%, $\pm 5\%$), and the left ventricle may be virtually obliterated in systole.
- An aberrantly protruding mitral valve with long leaflets may obstruct LV outflow (the obstructive component of HOCM).
- Obstruction is influenced by several factors.

**Table 5-12. Factors That Modify Obstruction in Hypertrophic Obstructive Cardiomyopathy**

Increase Obstruction		Decrease Obstruction	
Mechanism	Physiologic or Pharmacologic Factors	Mechanism	Physiologic or Pharmacologic Factors
Increase in contractility	Tachycardia Digitalis glycosides β -adrenergic stimulation (e.g., epinephrine, exercise) Premature beats	Decrease in contractility	β -adrenergic blockade Heavy sedation and general anesthesia Calcium channel blockers, disopyramide, and other drugs that depress myocardial function
Reduction in preload	Valsalva maneuver Decrease in intravascular volume Standing Nitroglycerin Vasodilator drugs Tachycardia	Increase in preload	Intravascular volume expansion Squatting Bradycardia β -adrenergic blockade
Reduction in afterload	Hypovolemia (diuretics) Nitroglycerin and related drugs Vasodilator drugs	Increase in afterload	Intravascular volume expansion Squatting α -adrenergic stimulation (e.g., phenylephrine) Handgrip

Clinical Manifestations

- Dyspnea, angina, presyncope, syncope with exertion, and palpitations
- Large jugular A wave, bifid carotid pulse, palpable S4 gallop, systolic murmur and thrill, mitral regurgitation murmur
- Sudden death can sometimes be the first manifestation.

Diagnosis

- ECG: left ventricular hypertrophy, pseudo Q waves (often seen V_1 – V_3), ventricular arrhythmias
- **Echocardiogram** is the mainstay of diagnosis. It typically shows hypertrophy, systolic anterior motion of mitral valve, and midsystolic closure of aortic valve.

Treatment

- Beta-blockers
- Calcium channel blockers that reduce heart rate: diltiazem, verapamil
- Disopyramide, occasionally
- Use implantable defibrillator if there is syncope
- Surgery in severe cases—septoplasty

Restrictive Cardiomyopathy

Restrictive cardiomyopathy (least common cause of cardiomyopathy) is a myocardial disorder characterized by rigid noncompliant ventricular walls.

Etiologies are infiltrative (sarcoidosis/amyloidosis; hemochromatosis; neoplasia); scleroderma; and radiation.

Pathophysiology. The myocardium is rigid and noncompliant, impeding ventricular filling and raising cardiac filling pressures from abnormal diastolic function. Systolic performance is often reduced, but the overriding problem is impaired diastolic filling, which produces a clinical and hemodynamic picture that **mimics constrictive pericarditis**.

Clinical manifestations

- Dyspnea, exercise, intolerance, weakness
- Elevated jugular venous pressure, edema, hepatomegaly, ascites, S4 and S3 gallop, Kussmaul sign

Diagnosis

- X-ray: mild cardiomegaly, pulmonary congestion
- ECG: low voltage, conduction disturbances, Q waves
- Echo: characteristic myocardial texture in amyloidosis with thickening of all cardiac structures
- Catheterization: square root sign; elevated left- and right-sided filling pressures

Treatment. There is no good therapy; death ultimately results from CHF or arrhythmias. Consider heart transplantation.

Clinical Pearl

With HOCM, avoid the following:

- Digitalis
- Diuretics
- Vasodilators
- Exercise



PERICARDIAL DISEASE

Acute Pericarditis

Acute pericarditis is inflammation of the pericardial lining around the heart.

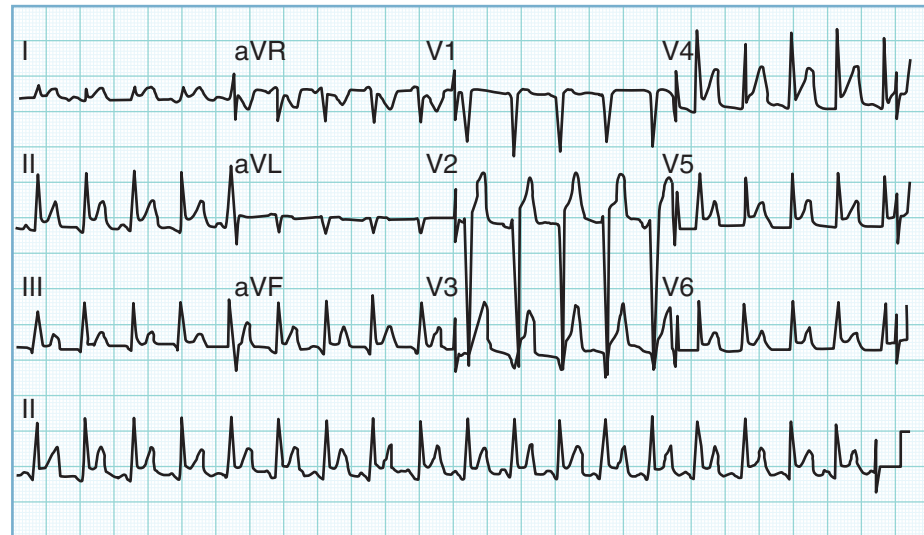


Figure 5-11. Acute Pericarditis with Diffuse ST Segment Elevation

Causes include:

- Idiopathic
- Infections (viral)
- Uremia
- Vasculitis (connective tissue diseases)
- Lupus (and other rheumatoid disorders)
- Disorders of metabolism
- Neoplasms
- Trauma

Clinical Manifestations. Chest pain, often localized substernally or to the left of the sternum, is usually worsened by lying down, coughing, and deep inspiration (which helps in the differential diagnosis with MI) and is relieved by sitting up and leaning forward.

Pericardial friction rub (diagnostic of pericarditis) is a scratchy, high-pitched sound that has 1 to 3 components corresponding to atrial systole, ventricular systole, and early diastolic ventricular filling. The ventricular systole component is present more consistently. The rub is often transient and is best heard with the diaphragm of the stethoscope as the patient sits forward at forced-end expiration.

Diagnosis.

- ECG reveals a diffuse ST-segment elevation with upright T waves at the onset of chest pain.
- PR segment depression is very specific.
- The diffuseness of the ST-segment elevation, absence of reciprocal leads, and absence of the development of Q waves **distinguish acute pericarditis** from **acute MI**.

Treatment is to treat the underlying cause. In idiopathic pericarditis, use NSAIDs, aspirin, and corticosteroids. Adding colchicine to an NSAID will decrease recurrence.

Pericardial Effusion

Fluid may accumulate in the pericardial cavity in virtually all forms of pericardial disease. The fluid may be a transudate, as in the serous cavity effusions that develop in patients with CHF, overhydration, or hypoproteinemia. More often, however, the pericardial effusion is an exudate, reflecting the presence of pericardial injury.

- Serosanguineous pericardial fluid is a classic sign in TB and neoplastic diseases.
- Frank blood in the pericardial space may occur in cases of aortic aneurysm or aortic dissection.
- Hemopericardium may also be produced by closed or penetrating trauma, rupture of the heart in acute MI, and bleeding caused by coagulation defects.
- When fluid accumulates slowly, the pericardium expands to accommodate it. When fluid accumulates rapidly, however, it compresses the heart and inhibits cardiac filling (cardiac tamponade).

Diagnosis. Echocardiography is the most effective laboratory technique available. The presence of pericardial fluid is recorded as a relatively echo-free space between the posterior pericardium and the posterior left ventricular epicardium in patients with small effusions. In patients with large effusions, the heart may swing freely within the pericardial sac, and this motion may be associated with electrical alternans.

Chest x-ray may show a “water-bottle” configuration of the cardiac silhouette.

Treatment. Treatment includes fluid aspiration and management of the etiology.

Cardiac tamponade

Cardiac tamponade is a life-threatening condition in which a pericardial effusion has developed so rapidly or has become so large that it compresses the heart. Symptoms include:

- Neoplasia
- Idiopathic (usually viral) pericarditis
- Nonviral infection: tuberculous; suppurative
- Intrapericardial hemorrhage with or without pericarditis
- Wounds, including surgery of chest; heart; pericardium
- Postpericardiotomy syndrome



- Uremia
- Mediastinal and juxtamediastinal radiation therapy
- Vasculitis–connective tissue disease group

Clinical Manifestations. Most patients with cardiac tamponade complain of dyspnea, fatigue, and orthopnea.

- Pulsus paradoxus, characterized by a decrease in systolic blood pressure >10 mm Hg with normal inspiration (very common)
 - The paradoxical pulse often can be noted by marked weakening or disappearance of a peripheral pulse during inspiration.
 - Paradoxical pulse is not diagnostic of cardiac tamponade; it can occur in chronic lung disease, acute asthma, severe CHF, and even hypovolemic shock.
- Neck vein distension with clear lung
- Shock (hypotension)
- Decreased heart sounds
- Beck's triad is associated with acute tamponade: low blood pressure, distended neck veins, and decreased heart sounds

Diagnosis. Clinical manifestations followed by echocardiogram. A surgical pericardial window may be needed for chronic effusions. Cardiac catheterization will confirm that left and right atrial pressures are equal.

Treatment is pericardiocentesis and subxiphoid surgical drainage.

Constrictive Pericarditis

Constrictive pericarditis is the diffuse thickening of the pericardium in response to prior inflammation, resulting in reduced distensibility of the cardiac chambers.

- Cardiac output is limited, and filling pressures are increased to match the external constrictive force placed on the heart by the pericardium.
- The fundamental hemodynamic abnormality is abnormal diastolic filling.

The disease is idiopathic, with an unknown etiology. Risk factors include open-heart surgery, thoracic radiation, and postviral infection.

Symptoms include:

- Dyspnea on exertion due to limited cardiac output (**common**)
- Orthopnea (50% of patients)
- Symptoms and signs related to systemic venous hypertension: ascites, edema, jaundice, hepatic tenderness, and hepatomegaly (manifestations of right-side failure)
- Jugular venous distension increased with inspiration (Kussmaul sign)
- Distant heart sounds
- Early diastolic apical sound ("pericardial knock") (**common**) can be confused with an S3 gallop

Diagnosis

- Chest CT or MRI (**best test**): thickened pericardium; pericardial calcifications may be seen in tuberculous constriction
- ECG: low-voltage and nonspecific T-wave changes
- Chest x-ray: heart is usually normal in size
- Cardiac catheterization
 - Marked “y” descent is present in right atrial pressure tracing
 - Characteristic “dip and plateau” or “square root” sign is present in left and right ventricular pressure tracing
 - Equalization of end-diastolic pressures in all 4 chambers and pulmonary artery

Treatment is conservative at first with mild sodium restriction and diuretics. Pericardiectomy may be needed.

Clinical Recall

Which of the following finding is most specific for the diagnosis of acute pericarditis?

- Echocardiography showing ventricular wall thickening with a Kussmaul sign
- Echocardiography showing echo-free space between the posterior pericardium and the posterior LV epicardium with distant muffled heart sounds
- Cardiac catheterization showing a marked “y” descent in the right atrial pressure tracing with a Kussmaul sign
- ECG showing a decrease in SBP >10 mm Hg with normal inspiration
- ECG showing diffuse ST-segment elevation with PR segment depression

Answer: E

Peripheral Artery Disease

Risk factors include age, smoking, diabetes, and hyperlipidemia. Symptoms typically include intermittent claudication (cramping, tightness, aching of buttock, hip and lower extremities with exercise and improved with rest).

Diagnosis. Perform resting ankle-brachial index (ABI) (normal 0.9–1.40).

- $ABI \leq 0.9$ is compatible with PAD.
- $ABI \leq 0.4$ is associated with ischemic rest pain.
- When $ABI > 1.4$, perform toe-brachial index; this is due to calcified, noncompressible arteries

Clinical Correlate

It can be difficult to distinguish **constrictive pericarditis** from **restrictive cardiomyopathy**. In the latter, left ventricular ejection fraction is more likely to be decreased.

Note

Toe-brachial index will provide a better assessment of the lower extremity perfusion.

**Note**

- Do not use cilostazol in low EF or history for CHF.
- Beta blockers are not contraindicated in PAD.

CTA or MRA is performed in patients requiring surgical or endovascular intervention.

Treatment.

- Exercise training for all patients (**most effective treatment for improving functional status**)
- Goal BP <130/80 mm Hg
- Aspirin
- High intensity statin
- Cilostazol to improve pain and walking distance
- Angioplasty or surgery if no response to medical therapy, pain at rest, or poorly healing ulcers

RATE AND RHYTHM DISTURBANCES**Sinus Bradycardia**

Ventricular complexes are normal width, evenly spaced, rate <60/min.

- Excessive vagal tone causes: acute MI (particularly diaphragmatic); carotid sinus pressure; vomiting; Valsalva maneuver; phenothiazines; digitalis glycosides
- Depression of sinus node automaticity: beta-adrenergic blocking agents; calcium-blocking drugs
- Marathon running and swimming
- Hypothyroidism
- Normal variant

Treatment is atropine, but only if there are symptoms. For persistent symptoms and bradycardia, consider a pacemaker.

Atrioventricular Block

Atrioventricular (AV) block can be classified as **anatomical** (based on site of block as determined by His bundle electrocardiography), or as **clinical** (based on the routine ECG); classic types are first-, second-, and third-degree (or complete) AV block.

- **First-degree AV block** is pulse rate (PR) interval >0.20 s at heart rate 70 beats/min. It is caused by a cardiomyopathy or by a degenerative change in the AV conduction system due to aging, digitalis, exaggerated vagal tone, ischemia (diaphragmatic infarction), or inflammation (myocarditis, acute rheumatic fever). No treatment is needed.
- **Second-degree AV Block:** see table below
- **Third-degree (complete) AV block** is when all atrial beats are blocked, and the ventricles are driven by an escape focus distal to the site of block. The most common cause in adults is simple fibrous degenerative changes in the conduction system as a result of aging (Lenègre disease).

- Inferior or posterior infarction
- Infectious and inflammatory processes such as abscesses, tubercles, tumors, infiltrative disease of the myocardium, sarcoid nodules, gummas, myocarditis, and rheumatic fever
- Drugs like digitalis
- Ankylosing spondylitis

Table 5-13. Type I versus Type II Second-Degree AV Block

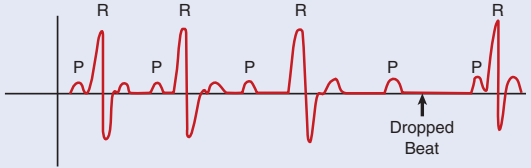
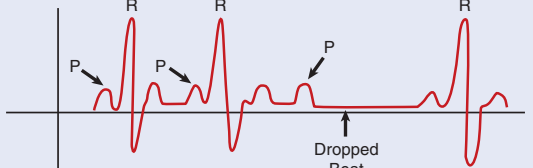
	Type I (Mobitz I, Wenckebach)	Type II (Mobitz II)
	Mobitz Type I  Progressive prolongation of the PR interval until a P wave is completely blocked and a ventricular beat is dropped. PR interval of the next conducted beat is shorter than preceding PR interval.	Mobitz Type II  Blocked beat occurs suddenly and is not preceded by a change in duration of the PR interval. Patient is equipped with a pacemaker, which cuts in to sustain a regular ventricular rhythm.
Site of block	Usually AV nodal (supra-Hisian)	Infranodal (intra- or infra-Hisian)
QRS complex	Usually normal in width	Usually wide (bundle branch block) with infra-Hisian block; narrow with intra-Hisian block
Causes	Degenerative changes in AV node; diaphragmatic myocardial infarct; digitalis toxicity; myocarditis; rheumatic fever; increased vagal tone	Extensive anterior myocardial infarct; degenerative changes in His-Purkinje system; massive calcification of mitral or aortic valve anulus
ECG	PR interval lengthens progressively until ventricular beat is dropped PR interval shortens after dropped beat RR interval lengthens progressively up to the dropped beat	PR interval is usually normal in duration and constant in length if PR interval is prolonged, the duration of prolongation is fixed Blocked beats occur suddenly without progressive lengthening of the PR interval RR interval of conducted beats is constant or a multiple of a basic RR interval cycle length
Effect of carotid sinus pressure	May increase degree of block	No effect
Effect of atropine	Frequently shortens PR interval and increases AV conduction	No effect
Consequences of progression to complete heart block	Escape focus usually junctional; narrow QRS complex; rate >45 beats/min; Adams-Stoke attacks uncommon	Escape focus infrajunctional (usually ventricular) wide QRS complex; rate <45 beats/min; Adams-Stoke attacks common. Junctional escape may be present with intra-Hisian block.
Treatment	None unless symptoms	Pacemaker



Figure 5-12. Third-Degree AV Block

Clinical Correlate

Adams-Stoke attacks are caused by sudden asystole or a ventricular tachyarrhythmia (transient ventricular tachycardia or ventricular fibrillation) and can lead to circulatory arrest.

Symptoms are associated with Adams-Stoke attacks and occasionally CHF. The bradycardia associated with complete heart block may lead to congestive heart block in patients with myocardial disease.

Treatment is pacing.

Supraventricular Arrhythmias

Sinus tachycardia is normal rhythm with rate $>100/\text{min}$. The ventricular complexes are of normal width, evenly spaced, and a P-wave precedes a QRS complex. It usually represents a physiologic response to fever, hypotension, volume depletion, anxiety, and pain. Other causes include thyrotoxicosis, anemia, and some drugs.

Transient sinus tachycardia is occasionally the result of a rebound phenomenon following the discontinuation of beta-adrenergic blocking drugs.

Treatment is of the underlying cause. Beta blockers are useful for symptoms.

Paroxysmal supraventricular tachycardia is a group of ectopic tachyarrhythmias characterized by sudden onset and abrupt termination. They are usually initiated by a supraventricular premature beat (includes paroxysmal atrial tachycardia). Eighty percent are caused by re-entry, mainly in the AV node. It manifests as an absolutely regular rhythm at a rate 130–220 beats/min (average 160).

Treatment.

- Carotid (particularly right carotid) sinus massage, which increases vagal tone
- IV adenosine (effective in $>90\%$ of cases) (do not give if patient is wheezing)
- Others: IV propranolol or esmolol, verapamil; IV digitalis
- Synchronized external cardioversion if patient is unstable

Multifocal atrial tachycardia is characterized by an irregular supraventricular rhythm, at 100–200/min.

- The morphology of the P waves (at least 3 different P wave forms) varies from beat to beat, as does the PR interval. Each QRS complex, however, is preceded by a P wave.
- Generally seen in elderly patients or those with chronic lung disease who are experiencing respiratory failure
- Use diltiazem, verapamil, or digoxin; avoid beta blockers because of lung disease

Atrial flutter generally presents as an absolutely regular rhythm with a ventricular rate 125–150/min and an atrial rate 250–300/min (i.e., 2:1 block). It has been associated with:

- Chronic obstructive lung disease
- Pulmonary embolism
- Thyrotoxicosis
- Mitral valve disease
- Alcohol
- Paroxysmal arrhythmia in persons with normal heart

Treatment is cardioversion if hemodynamically unstable (e.g., hypotension), digitalis, verapamil, diltiazem, and beta-blockers.

Unlike Afib, radiofrequency ablation is very successful and is preferred over medical therapy. Guidelines for anticoagulation are similar to Afib.

Atrial fibrillation (Afib) is the most common sustained cardiac rhythm disturbance. It is associated with heart disease but also occurs with no detectable disease. Thromboembolic events occur with Afib and can cause significant morbidity and mortality.

Afib is a supraventricular tachyarrhythmia characterized by uncoordinated atrial activation with subsequent decline of atrial function.

- On ECG, there is replacement of consistent P waves by fibrillatory waves that vary in size, shape, and timing, associated with an irregular, frequently rapid ventricular response (irregularly, irregular).
- The ventricular response to Afib depends on electrophysiologic properties of the AV node, the level of vagal and sympathetic tone, and the action of drugs.
- Extremely rapid rates (>200 bpm) suggest the presence of an accessory pathway (W-P-W syndrome), which may manifest as Afib.

When compared with atrial flutter, atrial flutter is found to be more organized than Afib, with a sawtooth pattern of regular atrial activation called flutter (f) waves on the ECG, particularly visible in leads II, III, and aVF.

The diagnosis of Afib should be considered in elderly patients who present with complaints of shortness of breath, dizziness, or palpitations. The arrhythmia should also be suspected in patients with acute fatigue or exacerbation of CHF. In some patients, Afib may be identified on the basis of an irregularly irregular pulse or ECG obtained for another condition.

Afib has both cardiac and noncardiac associations:

- **Cardiac conditions:** rheumatic mitral valve disease, CAD, CHF, and hypertension (cause atrial structures to dilate)
- **Noncardiac conditions:** hyperthyroidism, hypoxemia, and alcohol intoxication

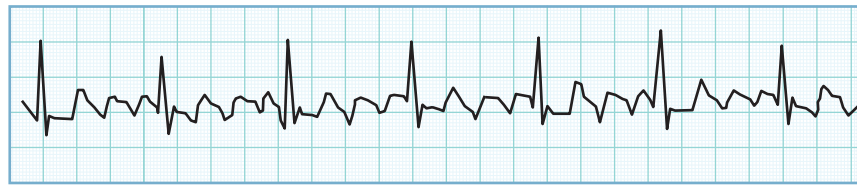


Figure 5-13. Atrial Flutter

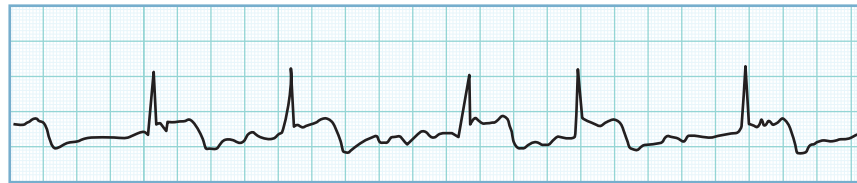


Figure 5-14. Atrial Fibrillation

Diagnosis of Afib begins with a minimum workup:

- **H and P:** identifies severity of symptoms associated with Afib, as well as the clinical type (paroxysmal, persistent, first episode); also allows assessment of frequency and duration of Afib, as well as identification of precipitating factors and presence of underlying heart or lung disease
- **ECG:** verifies the rhythm as well as identifies LVH, pre-excitation, prior MI
- **Chest x-ray:** allows evaluation of lung parenchyma and identifies coexisting lung disease
- **Echocardiogram:** identifies LVH, valvular disease, atrial size, and possible left atrial thrombus.
- **Thyroid function tests:** excludes hyperthyroidism as a cause of Afib

Treatment. The goals of initial management are hemodynamic stabilization, ventricular rate control, and prevention of embolic complications. When Afib does not terminate spontaneously, the ventricular rate should be treated to slow ventricular response and anticoagulation started.

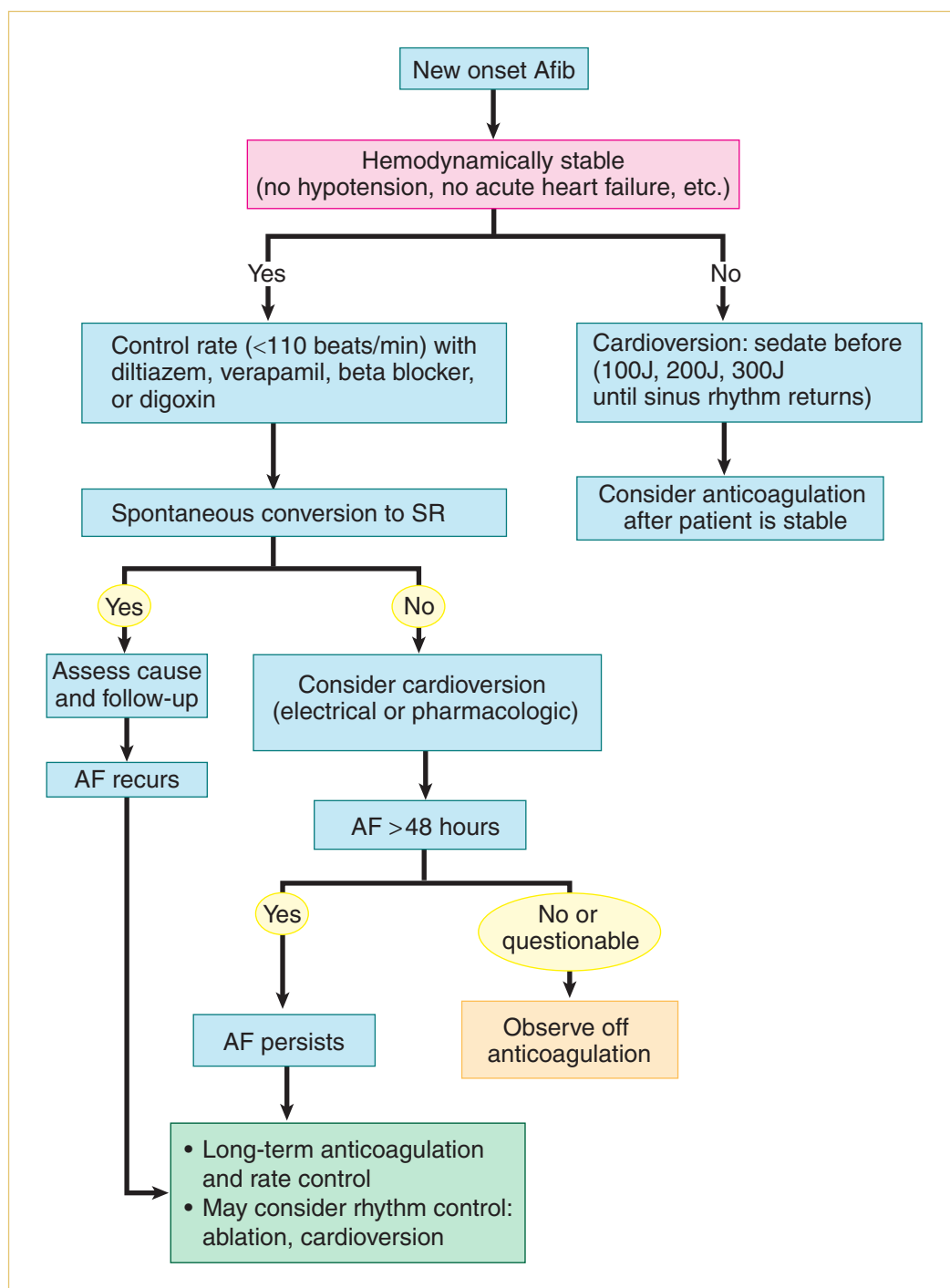


Figure 5-15. Management of Atrial Fibrillation



Note

There is little difference in outcome between rate control and pharmacologic rhythm control. Fewer than 25% of patients on an antiarrhythmic regimen remained in sinus rhythm at the end of 1 year.

Note

Routine rhythm control for Afib is appropriate in younger patients with persistent symptoms.

Note

In patients with Afib and low EF, only amiodarone and dofetilide are safe options.

Two approaches are used in management:

- **Ventricular rate control** (usually preferred) often considered for the patient who notices very few symptoms of the arrhythmia; initial goal <100–110/min but slower rates may be recommended for severely ill patients.
 - BBs, CCBs, and digoxin are most commonly used (note that they do not convert Afib to sinus rhythm and should not be used for that purpose); consider patient's condition and presence of concomitant heart failure when selecting a medication.
 - BBs and CCBs are effective at reducing the heart rate at rest and during exercise in patients with Afib.
 - Digoxin (because of the inotropic effects) is the drug of choice for patients with coexisting systolic heart failure.
 - Atenolol, metoprolol, verapamil, and diltiazem are effective in rate control at rest and during exercise.
- **Rhythm control** (attempts to convert to and maintain sinus rhythm) (for patients who are symptomatic on rate control, who immediately notice the arrhythmia and experience SOB, etc., or who develop heart failure)
 - **Mechanical cardioversion (more effective)** involves an electrical shock synchronized with the intrinsic activity of the heart. The synchronization ensures that electrical stimulation does not occur during the vulnerable phase of the cardiac cycle.
 - Performed electively to restore sinus rhythm in patients with persistent Afib
 - Performed for immediate need, i.e., when arrhythmia is main factor responsible for hemodynamic instability (acute heart failure, hypotension, or angina)
 - Carries a risk of thromboembolism, so when elective cardioversion, initiate anticoagulation beforehand
 - **Pharmacologic cardioversion** (with medications) is less effective than electrical cardioversion but does not require sedation or anesthesia, as does mechanical cardioversion.
- Carries a risk of thromboembolism, so initiate anticoagulation
- Drugs proven effective for Afib include amiodarone, dofetilide, flecainide, ibutilide, propafenone, and quinidine
- Drugs used to maintain sinus rhythm in patients with Afib include amiodarone, disopyramide, dofetilide, flecainide, propafenone, and sotalol

Catheter ablation of Afib foci is a nonpharmacologic therapy for eradicating Afib, used when rhythm control is unsuccessful and patients are symptomatic. The procedure evolved from the understanding that most Afib is initiated by ectopic beats from focal areas that may be targeted for ablation. These foci arise more commonly from the 4 pulmonary veins. Techniques now focus identifying and eliminating these foci. After the procedure, patients must remain on anticoagulation.

Anticoagulation. The rate of ischemic stroke among patients with nonrheumatic Afib averages 5% per year, which is 2–7× the rate for people without Afib. Therefore, anticoagulation is beneficial for many patients despite its risk of bleeding.

The CHA₂DS₂-VASc score is a clinical prediction rule for estimating the risk of stroke in a patient with Afib. It is used to determine whether anticoagulation or antiplatelet therapy is more appropriate. A high CHADS score corresponds to a greater risk of stroke.

- **C** for CHF
- **H** for hypertension
- **A** for age ≥ 75
- **D** for diabetes
- **S** for prior stroke or TIA

Assign 1 point each for CHF, HTN, age 65–74, DM, female sex, and vascular disease (previous, MI, PAD, aortic plaque). Assign 2 points each for CVA or TIA and age ≥ 75 .

For score ≥ 1 (men) and ≥ 2 (women), give anticoagulation.

- Dabigatran, rivaroxaban, or edoxaban is used for nonvalvular Afib.
- Warfarin is used for valvular Afib, i.e., the presence of a mechanical heart valve or mitral stenosis due to rheumatic heart disease.
- Heparin is not necessary before starting oral anticoagulants.

Anticoagulation is continued indefinitely.

Pre-excitation syndrome

Pre-excitation is a condition in which all or some portion of the ventricle is activated by atrial impulses earlier than if the impulses were to reach the ventricles by way of the normal cardiac conduction pathways. This is achieved by the use of accessory pathways (Kent bundle). **Wolff-Parkinson-White (WPW)** syndrome is the most common of these syndromes.

- ECG shows a short PR interval, followed by a wide QRS complex with a slurred initial deflection, or delta wave, representing early ventricular activation.
- WPW is associated with paroxysmal supraventricular arrhythmias alternating with ventricular arrhythmias, Afib, and atrial flutter.

Treatment is immediate synchronized cardioversion if the patient is hemodynamically **unstable**, and procainamide if the patient is hemodynamically **stable**. **Avoid digoxin, BBs, and CCBs**, as they can inhibit conduction in the normal conduction pathway, increasing aberrant conduction. That could increase the likelihood of developing ventricular or supraventricular tachycardia.

Ablation is used as definitive treatment.

Note

Control the heart rate, then anticoagulate.

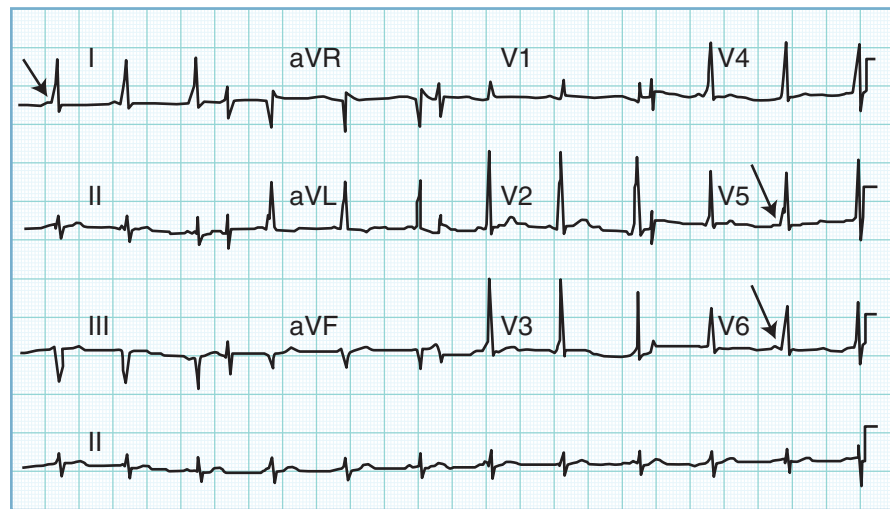


Figure 5-16. Wolff-Parkinson-White Syndrome

Ventricular arrhythmia

Ventricular tachycardia (VT) is ≥ 3 consecutive beats of ventricular origin at a rate >120 beats/min. QRS complexes are wide and often bizarre. Causes include:

- After an acute MI
- Cardiomyopathies
- Hypokalemia, hypercalcemia, hypomagnesemia, and hypoxia
- Digitalis toxicity
- Thioridazine drugs

Symptoms include concomitant hypotension, CHF, syncope, or cardiac arrest.

- Independent and asynchronous atrial and ventricular contractions produce the following signs. These signs are absent when Afib is present.
 - Variation in systolic BP, as measured peripherally
 - Variation in intensity of the heart sounds
 - Intermittent cannon A waves in jugular venous pulses caused by the simultaneous contraction of the atrium and ventricles
 - Extra heart sounds
- Because of asynchronous activation of the right and left ventricles, the first and second sounds are widely split.

Table 5-14. QRS Complex

Wide (>0.12 s)		Narrow (<0.12 s)	
Regular	Irregular	Regular	Irregular
Ventricular tachycardia	Afib (rarely)	Sinus tachycardia	Afib
Supraventricular tachycardia (aberration)		Paroxysmal supraventricular tachycardia	Multifocal atrial tachycardia
Wolff-Parkinson-White syndrome		Atrial flutter	

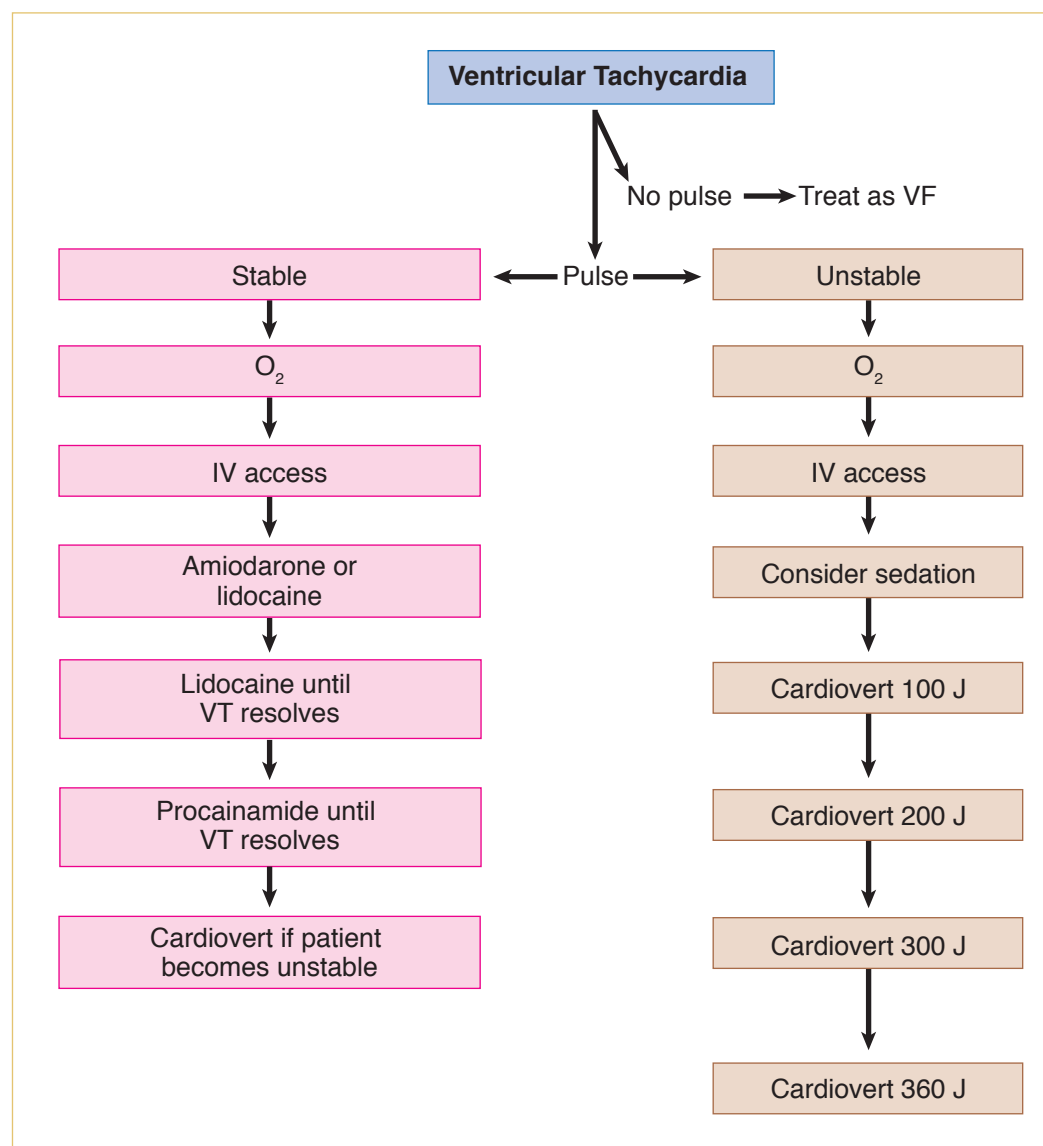


Figure 5-17. Management of VT



Clinical Recall

Which of the following is the most appropriate management for Wolf-Parkinson-White syndrome?

- A. Procainamide
- B. Propranolol
- C. Verapamil
- D. Nimodipine
- E. Sotalol

Answer: A

Torsade de Pointes

Torsade de Pointes, a type of VT, is characterized by undulating rotations of the QRS complexes around the electrocardiographic baseline. Arrhythmias are initiated by a ventricular premature beat in the setting of abnormal ventricular repolarization characterized by prolongation of the QT interval.

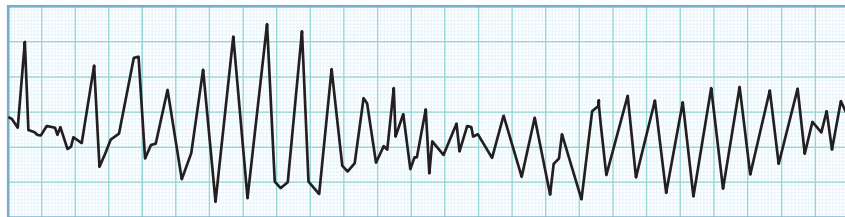


Figure 5-18. Torsade de Pointes

Causes of torsade include antiarrhythmic drugs which prolong ventricular repolarization:

- Antiarrhythmics: quinidine, procainamide, disopyramide
- Psychotropic drugs: phenothiazines, thioridazine, tricyclics, lithium
- Electrolyte imbalance: hypokalemia, hypomagnesemia
- CNS lesion: subarachnoid or intracerebral hemorrhage

Patients with long QT interval syndrome are prone to recurrent dizziness or syncope from the ventricular tachycardia. Sudden auditory stimuli, such as the ringing of the telephone at night, may initiate torsade in these patients.

Treatment addresses the underlying disorder. For the antiarrhythmics, use a drug such as lidocaine. For the electrolyte imbalances, replace potassium and magnesium. Cardiac pacing or isoproterenol infusion may suppress episodes of tachycardia, useful for emergency treatments.

If patient is hemodynamically unstable (e.g., hypotension), consider cardioversion (but this dysrhythmia often reoccurs).

Ventricular Fibrillation

See the Emergency Medicine section.

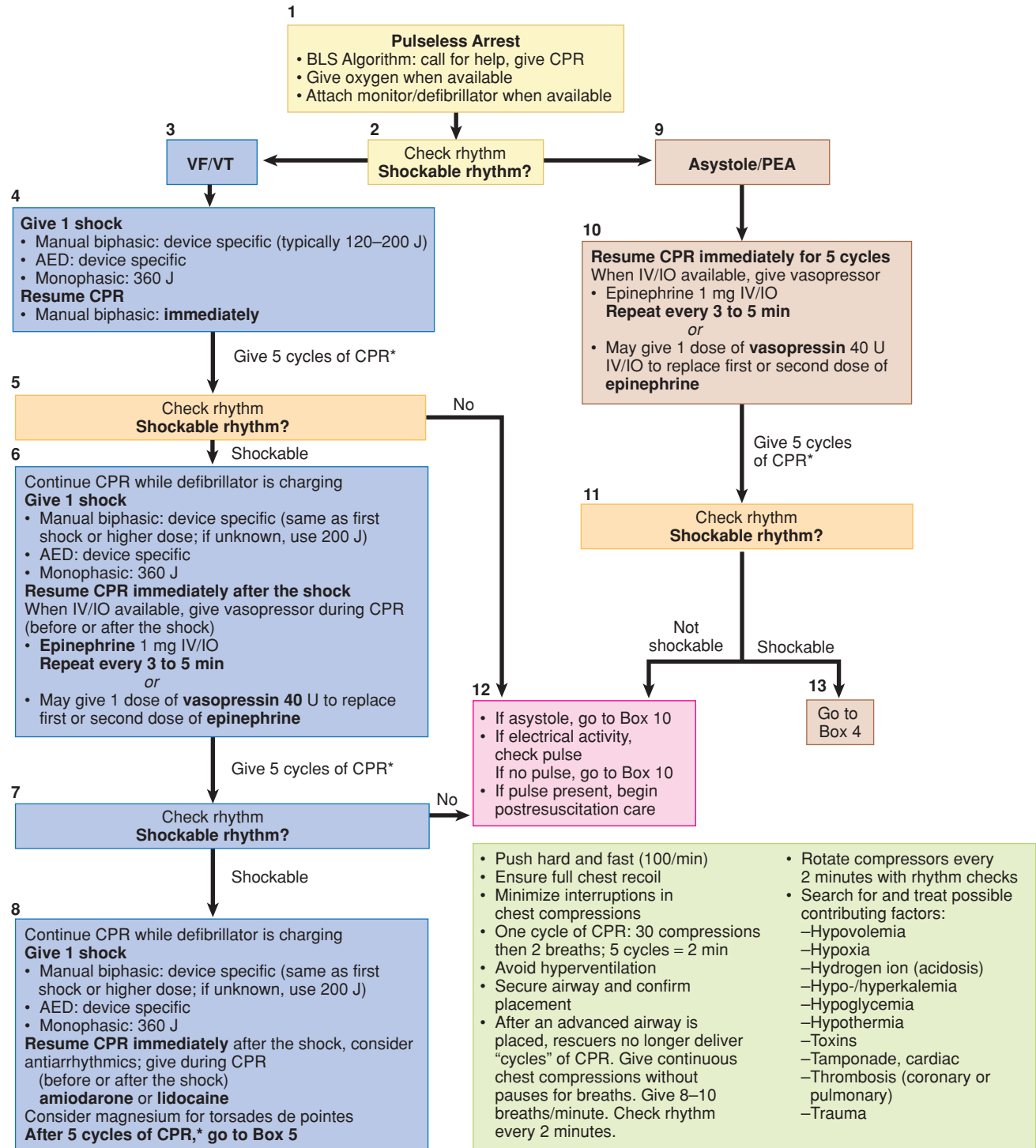


Figure 5-19. ACLS Pulseless Arrest Algorithm



DRUGS FOR CARDIOVASCULAR DISEASE

Amiodarone

Amiodarone is a very effective antiarrhythmic drug and can be used in ventricular tachycardia, Afib, and atrial flutter. Because it has a long half-life (>50 days), drug interactions are possible for weeks after discontinuation.

Side effects may be severe, even fatal:

- **Lungs:** severe interstitial disease with hypoxia, cough, fever, and chest pain
- **Nervous** (20%): abnormal gait, coordination, and balance, tremor, muscle weakness, numbness
- **Thyroid:** hypo- or hyperthyroidism (the drug is structurally similar to thyroxine)
- **Dermatology:** photosensitivity, blue-grey skin discoloration
- **Eye:** visual loss, blurriness, halos, corneal deposits

Nitrates

In **low doses**, nitrates increase venous dilation and subsequently reduce preload. In **medium doses**, they increase arteriolar dilatation and subsequently decrease afterload and preload. In **high doses**, they increase coronary artery dilatation and subsequently increase oxygen supply.

Side effects of nitrates include orthostatic hypotension, reflex tachycardia, throbbing headache, and blushing—all caused by vasodilation. Nitrates are contraindicated if systolic BP <90 mm Hg. There must be a window-free period of >8 hours with nitrate therapy to reduce the incidence of tachyphylaxis.

Antiarrhythmics

Table 5-15. Antiarrhythmic Drugs

Drug	Adverse Effects
Disopyramide	Anticholinergic effects; hypotension; heart failure; heart block; tachyarrhythmia
Lidocaine	CNS (drowsiness, agitation, seizures); heart block
Phenytoin	CNS (ataxia, nystagmus, drowsiness); hypotension and heart block with rapid IV injection
Procainamide	Lupus-like syndrome; GI; rash; hypotension; aggravation of arrhythmia; blood dyscrasias
Quinidine	Aggravation of arrhythmias (“quinidine syncope”); thrombocytopenia; fever, rash; cinchonism; GI symptoms; digoxin-quinidine interaction (elevation of digoxin levels)
β -adrenergic blocking agents	Heart block; hypotension; asthma; hypoglycemia; lethargy; impotence
Verapamil	CHF, asystole, constipation
Adenosine	Transient dyspnea, noncardiac chest pain, rarely hypotension
Mexiletine	Lidocaine-like drug; local anesthetic
Tocainide	Lidocaine-like drug
Amiodarone	Very long half-life (20–40 d); may increase digoxin level; may worsen existing cardiac conduction disturbances; may prolong Coumadin effect
Encainide	Negative inotropism; QRS and PR prolongation
Flecainide	Negative inotropism; QRS and PR prolongation
Propafenone	Negative inotropism; QRS and PR prolongation

Beta Blockers

Beta blockers (BBs) have been shown to improve survival after an acute MI and in CHF. They decrease heart rate, BP, and contractility, which decrease myocardial oxygen requirement.

BBs are safe in most patients with asthma and should be used in asthma if indicated (EF <40% or CAD).

Nonselective BBs may mask hypoglycemic symptoms in insulin-dependent diabetics.

- BBs can cause fatigue/insomnia, mental depression, lipid abnormalities, hallucinations, Raynaud phenomenon, bronchoconstriction, and sexual dysfunction.
- BBs can mask signs/symptoms of insulin-induced hypoglycemia.
- Nebivolol is a unique BB; it is a beta-1 specific blocker that increases nitric oxide and thus does not cause erectile dysfunction.

**Table 5-16. Pharmacologic Properties of Select β -Blocking Agents**

Name	Cardio-Selective
Metoprolol	Yes
Atenolol	Yes
Propranolol	No
Nadolol	No
Timolol	No
Pindolol	No
Acebutolol	Yes
Labetalol	No
Esmolol (IV)	Yes

Note

In HFrEF:

- Verapamil and diltiazem should not be used.
- Amlodipine and felodipine are safe and can be used.

Calcium Channel Blockers

Calcium channel blockers (CCBs) work by decreasing preload and afterload. They may be harmful in the postinfarction period, especially if the patient has left ventricular failure. Their efficacy in angina is very limited—there is no mortality benefit.

Side effects of CCBs can be cardiac or noncardiac.

- **Cardiac:** CHF, reflex tachycardia, hypotension, lightheadedness, AV block
- **Noncardiac:** flushing, headache, weakness, constipation, nasal congestion, wheezing, peripheral edema, gingival hyperplasia

SHOCK SYNDROMES

Shock is a broad term that describes a state where oxygen delivery to the tissues is inadequate to meet the demands. It could be described as the imbalance between tissue oxygen supply and demand.

Four general types of shock syndromes are recognized: distributive, cardiogenic, hypovolemic, and obstructive. There are many etiologies within each class.

- **Distributive shock:** caused by pathologic peripheral blood vessel vasodilation; examples are sepsis (especially gram-negative), anaphylaxis, neurogenic
- **Cardiogenic shock:** related to impaired heart pump function; examples are acute coronary syndrome, valve failure (especially acute) and dysrhythmia
- **Hypovolemic shock:** caused by decreased circulatory volume; examples are hemorrhage (GI bleed) and fluid loss
- **Obstructive shock:** non-cardiac obstruction to blood flow; examples are pulmonary embolus, tension pneumothorax, and cardiac tamponade

Note

Septic shock is most common form of shock among those admitted to the ICU, followed by cardiogenic and hypovolemic shock.

The diagnosis of shock is a clinical diagnosis.

Table 5-17. Physiologic Characteristics of Various Forms of Shock

Type of Shock	Heart Rate	Central Venous Pressure	Contractility	Systemic Vascular Resistance
Cardiogenic	↑	↑	↓↓	↑
Hypovolemic	↑	↓↓	±↑	↑
Distributive (sepsis)	↑	↓↓	±	↓
Obstructive	↑	±↑	±	↑ (tamponade, PE) ↑ (tension PTX)

In shock, cardiac output varies, **increasing** in the hyperdynamic state of distributive shock (and sometimes in hypovolemic shock depending on how much volume has been lost), but is always **decreasing** in cardiogenic shock. Treatment should begin quickly, since delayed therapy worsens outcomes.

- Start with ABCs and consider intubation for airway protection and to enhance ventilation and oxygenation, given the high incidence of cardiogenic and non-cardiogenic pulmonary edema.
- Maximize arterial oxygen saturation.
- Circulatory support with normal saline or blood is used early. (The exception might be in cardiogenic shock with pulmonary edema where ECV is already expanded.)
- Blood transfusion is the norm in traumatic hypovolemic shock.
- Hypotensive patients who do not respond to saline or blood will need pressor support: dopamine, vasopressin, or epinephrine in distributive shock, and dobutamine in cardiogenic shock.
- Hypotensive patients with septic shock who do not respond promptly to saline should be given norepinephrine and vasopressin.
- A single dose of hydrocortisone should be given if patient is still hypotensive on pressors, since adrenal insufficiency is common in severely ill patients. An ACTH stimulation test can also be done quickly to diagnose unsuspected adrenal failure.

Clinical Recall

Which of the following is a side effect of amiodarone?

- Constipation
- Orthostatic hypotension
- Pulmonary fibrosis
- Thrombocytopenia
- Major depression

Answer: C

Learning Objectives

- ❑ List the types of anemia and describe their pathophysiology, diagnosis, and treatment
- ❑ Describe the presentation and diagnosis of hematologic neoplasias including acute leukemia, chronic leukemias, plasma cell disorders, and lymphomas
- ❑ Describe common platelet disorders
- ❑ List defects that can occur in the coagulation cascade and their associated disorders



ANEMIA

Anemia is caused by a lack of (or impaired) RBCs in the body, resulting in a decreased flow of oxygen to the organs. It is marked by one of the following:

- Hematocrit <41% in men or <36% in women
- Hemoglobin <13.5 g/dL in men or <12 g/dL in women

Anemia is most easily classified according to cell size.

- **Microcytic anemia** is characterized by a low mean corpuscular volume (MCV) <80, most commonly caused by iron deficiency, thalassemia, sideroblastosis, lead poisoning, or anemia of chronic disease (either microcytic or normocytic).
- **Macrocytic anemia** is characterized by an elevated MCV >100, most commonly caused by vitamin B12 or folic acid deficiency but also caused by the toxic effects of alcohol, liver disease, or chemotherapeutic agents (e.g., methotrexate, AZT, phenytoin).
- **Normocytic anemia** is characterized by a normal MCV, most commonly caused by the early form of the conditions described, plus hemolysis and aplastic anemia.

The symptoms of anemia tend to be based on the severity of the anemia, rather than the etiology.

- Early symptoms include fatigue and poor exercise tolerance.
- As the anemia worsens, there is dyspnea on exertion and lightheadedness.
- Eventually, confusion and altered mental status may develop as oxygen delivery to the brain decreases.
- Death from anemia is most often caused by decreased oxygen delivery to the heart and resulting myocardial ischemia.



The severity of symptoms is related to the patient's underlying condition. A healthy young patient may have no symptoms at all with hematocrit 27–29%, while an older patient with heart disease may develop dyspnea or anginal symptoms with the same hematocrit.

Diagnosis. Once a diagnosis of anemia is determined based on a low hematocrit or hemoglobin, the first step is to determine the MCV. Iron studies, reticulocyte count, peripheral smear, red cell distribution width (RDW), Coombs test, vitamin B12, folate level, and even a possible bone marrow biopsy may be necessary to determine a specific etiology.

Treatment. Besides blood transfusion, treatment cannot be generalized. Packed RBCs are used to maintain a hematocrit >25–30%. This is based on the underlying condition of the patient. A healthy young patient can have transfusion withheld until hematocrit is in the low 20%. An older patient with coronary artery disease will need to be maintained when hematocrit >30%. Hematocrit should rise approximately 3 points for every unit of packed RBCs given. Whole blood is rarely, if ever, used.

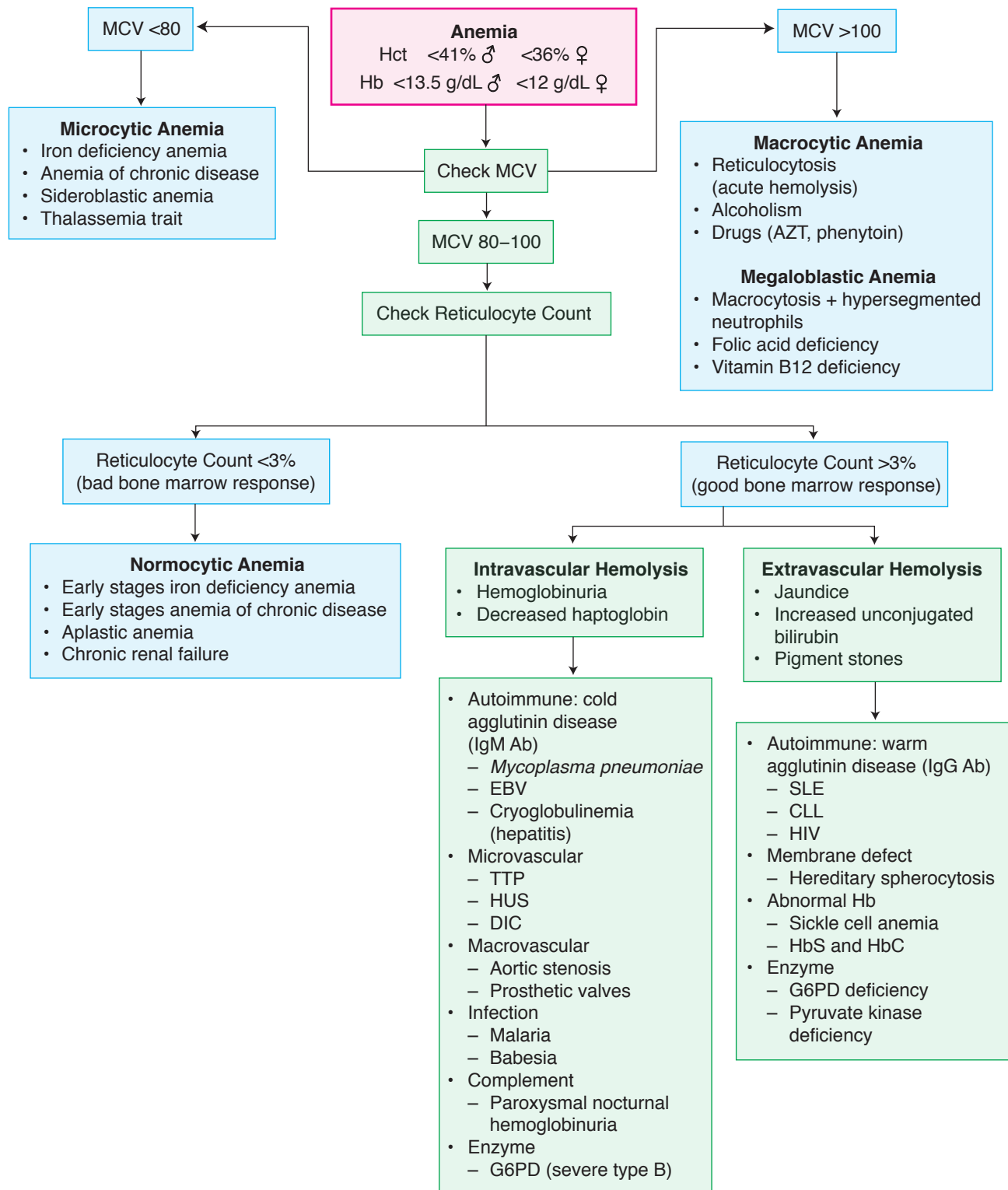


Figure 6-1. Evaluation of Patients with Anemia



Microcytic Anemia

Iron Deficiency Anemia

Iron deficiency anemia is anemia with diminished RBC production and MCV <80 , characterized by hypochromic cells and low levels of stored iron. It is almost always caused by blood loss, most commonly GI or menstrual.

Iron absorption is tightly regulated. A man requires 1 mg per day and a woman 2–3 mg per day on average. It is difficult for the body to increase the level of iron absorption. If there is even a modest increase in blood loss—occult blood in the stool, heavier menstrual flow, or increased demand such as in pregnancy—the body is poorly equipped to increase its level of absorption to exceed 3–4 mg per day. Other etiologies are increased urinary loss of blood, malabsorption, hemolysis, and poor oral intake.

Clinical Presentation. Mild anemia may have no or very limited symptoms. As hematocrit approaches 30%, fatigue and poor exercise tolerance may develop. As hematocrit lowers to 25%, tachycardia, palpitations, dyspnea on exertion, and pallor develop. Older patients and those with coronary artery disease may become dyspneic at higher levels of hematocrit. More severe anemia results in lightheadedness, confusion, syncope, and chest pain. A systolic ejection murmur (“flow” murmur) may develop in any patient with moderately severe anemia. These symptoms are not specific for iron deficiency anemia and may develop with any form of anemia provided it is sufficiently severe.

Symptoms specific to iron deficiency are rare and cannot be relied upon to determine the diagnosis: brittle nails, spoon-shaped nails, glossitis, and pica. Iron deficiency anemia as a specific diagnosis is determined by laboratory findings, not symptoms.

Diagnosis. A low serum ferritin <10 ng/mL is the most characteristic finding of iron deficiency anemia. Low ferritin has good specificity ($>99\%$) but poor sensitivity (60%); the ferritin level may be falsely elevated because it is an acute phase reactant and may be elevated in other inflammatory states or with malignancy. MCV is low except in very early cases. The serum iron is low and the total iron binding capacity (TIBC) is high. The RDW is elevated. The most specific test, although rarely necessary, is a bone marrow biopsy looking for stainable iron stores. The reticulocyte count is low. Platelet levels rise.

Treatment.

- Oral therapy with ferrous sulfate tablets, continued until Hb and Hct have normalized + an additional 2–3 months to “restore” iron stores (a brisk increase in reticulocytes will be seen 2 weeks into treatment)
- Parenteral iron for those with malabsorption, kidney disease, or an intolerance to oral therapy
- Blood transfusion (most effective way to deliver iron) only for those with severe symptoms

Aside from iron replacement, it is imperative to look for the source of the iron loss (i.e., GI, gynecological, or rarely urinary).

Anemia of Chronic Disease

Anemia of chronic disease is a defect in the body’s ability to make use of iron sequestered in stores within the reticuloendothelial system. It can be microcytic or normocytic. Anemia can accompany virtually any chronic inflammatory, infectious, or neoplastic condition.

Clinical Pearl

In early iron deficiency, serum iron may be normal. (Ferritin is low and TIBC is elevated.)

Hepcidin, a regulator of iron metabolism, plays an important role in this condition.

- In states where hepcidin is **abnormally high** (e.g., inflammation), serum iron falls due to iron trapping within macrophages and liver cells and decreased gut iron absorption. This typically leads to anemia caused by an inadequate amount of serum iron being available for developing red cells.
 - Hepcidin inhibits iron transport by binding to the iron export channel ferroportin located on the surface of gut enterocytes and the plasma membrane of macrophages.
 - The ferroportin inhibition has the following results:
 - Prevents iron from being exported and it is instead sequestered in the cells
 - Prevents enterocytes from allowing iron into the hepatic portal system, thereby reducing dietary iron absorption
 - Reduces the iron release from macrophages
- In genetic diseases where hepcidin is **abnormally low**, iron overload may occur (hemochromatosis) due to unwarranted ferroportin facilitated iron influx.

Clinical Presentation. Symptoms are based on the severity of the anemia. The only other symptoms are based on the specifics of the underlying disease.

Diagnosis.

- Normal or elevated serum ferritin
- Low serum iron
- Low TIBC
- Low reticulocyte count

Treatment. Correct the underlying disease.

- Iron supplementation and erythropoietin will not help, except in renal disease and anemia caused by chemotherapy or radiation therapy.
- Transfusion of packed RBCs is not generally used unless hemoglobin <7 g/dL.

Sideroblastic Anemia

Sideroblastic anemia is a microcytic anemia caused by a disorder in the synthesis of hemoglobin, characterized by trapped iron in the mitochondria of nucleated RBCs.

- The **hereditary form** is due to a defect in aminolevulinic acid synthase or an abnormality in vitamin B6 metabolism.
- The **acquired form** is due to drugs such as chloramphenicol, isoniazid, or alcohol. Lead poisoning can cause sideroblastic anemia as well.

There is an association with myelodysplastic syndromes and refractory anemia. Sideroblastic anemia may progress to acute myelogenous leukemia in a small percentage of patients.

Clinical Presentation. Symptoms are related to the severity of the anemia. There is no specific finding that will be sufficiently suggestive of sideroblastic anemia to allow a diagnosis without significant lab evaluation.

Note

Anemia of chronic disease often starts as a normocytic anemia and becomes slightly microcytic over time.

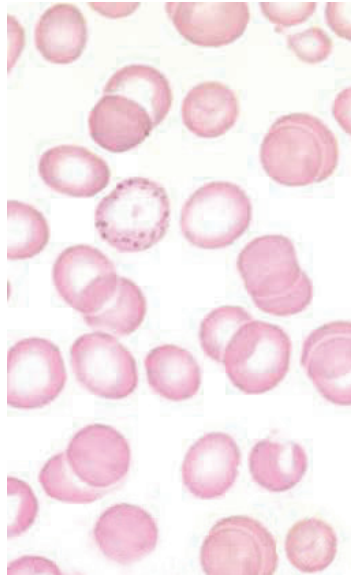
**Note**

- Iron deficiency and anemia of chronic disease can cause **decreased serum iron**.
- Sideroblastic anemia is the only microcytic anemia that causes **elevated serum iron**.

Diagnosis.

- Elevated serum ferritin
- Very high transferrin saturation, and very low TIBC
- High serum iron (**the only microcytic anemia with elevated iron**)
- Prussian Blue stain (**most specific test**) of RBCs in the marrow will reveal the ringed sideroblasts
- Strikingly high marrow reticuloendothelial

Treatment. Remove the offending drug. Some patients, especially those with INH-associated sideroblastic anemia, will respond to pyridoxine therapy 2-4 mg per day. Consider transfusion for serious cases and BMT for refractory cases. If the patient has lead intoxication, use chelators (patient should refrain from the use of alcohol).



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Figure 6-2. Basophilic Stippling, a Feature of Lead Poisoning and Other Diseases

Thalassemia

Thalassemia is a hereditary underproduction of either the alpha or beta globin chains of the hemoglobin molecule, resulting in a hypochromic, microcytic anemia. Gene deletion results in variable levels of disease.

There are 4 genes coding for the alpha chain of hemoglobin. There can be deletions of 1, 2, 3, or all 4 genes.

- Beta thalassemia can be mutated in either 1 or 2 genes.
- Alpha thalassemia is more common in Asian populations, while beta thalassemia is more common in Mediterranean populations.

Clinical Presentation. Presentation depends on the number of abnormal genes.

- **Alpha thalassemia**

- 1 gene deletion yields a normal patient; CBC, hemoglobin, and MCV are normal.
- 2 gene deletion yields a mild anemia with hematocrit 30–40% and strikingly low MCV.
- 3 gene deletion yields a more profound anemia with hematocrit 22–32% and very low MCV.
- 4 gene deletion alpha thalassemia causes patients to die in utero, secondary to gamma chain tetrads called hemoglobin Barts.

- In **beta thalassemia** trait there is a mild anemia with marked microcytosis (low MCV).

- Patients with beta thalassemia major (or Cooley's anemia) are homozygous for mutations of both genes coding for the beta hemoglobin gene. Patients become severely symptomatic starting age 6 months, when the body would normally switch from fetal hemoglobin to adult hemoglobin. They are severely symptomatic with growth failure, hepatosplenomegaly, jaundice, and bony deformities secondary to extramedullary hematopoiesis. They are later symptomatic from hemochromatosis, cirrhosis, and CHF from chronic anemia and transfusion dependence.

Diagnosis. Clues to the diagnosis of thalassemia trait is a mild anemia with a profound microcytosis. Beta thalassemia major has the severe symptoms, large spleen, and bone abnormalities described. Both forms of thalassemia are diagnosed by having a microcytic anemia with normal iron studies. Hemoglobin electrophoresis differentiates which type of thalassemia is present. In beta thalassemia, there is an increased level of hemoglobin F and hemoglobin A2. In beta thalassemia major, the hemoglobin is as low as 3–4 g/dL. Those with alpha thalassemia will have normal amounts of hemoglobins F and A2. Tetrads of beta chains are called hemoglobin H. Hemoglobin H is present in alpha thalassemia with 3 of 4 genes deleted. Target cells are present in all forms of thalassemia trait and thalassemia major. The RDW is normal in all forms because all of the cells are of the same size. Thalassemia is the only anemia where the RBC count is normal or even high. Thus, while patients have a low hemoglobin, the total number of RBCs is normal to elevated.

Treatment. Thalassemia traits of both the alpha and beta types do not require specific treatment. Beta thalassemia major patients require blood transfusions once or twice a month. The chronic transfusions lead to iron overload, which requires treatment with deferasirox. Oral deferasirox is the standard of care. This is easier to give than deferoxamine, which requires a subcutaneous pump. Splenectomy eliminates a major area of hemolysis and therefore helps reduce transfusion requirements. A small number of patients can be treated with a bone marrow transplantation.

Clinical Pearl

Thalassemia trait syndromes are asymptomatic.

**Table 6-1. Iron Indices in Microcytic Anemia Syndromes**

Fe Panel	Iron Deficiency Anemia	Anemia of Chronic Disease	Sideroblastic Anemia	Thalassemia Minor
Serum Iron	Decreased	Decreased	Increased	Normal
Serum Ferritin	Decreased or Normal (early)	Increased	Increased	Normal
Transferrin/TIBC	Increased	Decreased	Decreased	Normal
% Saturation	Decreased	N/Decreased	Increased	Normal

Clinical Recall

Which of the following laboratory investigations has the highest specificity and sensitivity in the diagnosis of iron deficiency anemia?

- A. Serum ferritin level
- B. Serum iron level
- C. Serum TIBC
- D. Serum MCV
- E. Bone marrow biopsy

Answer: E

Macrocytic Anemia

A 72-year-old alcoholic man presents with several weeks of memory loss and tingling in his feet. His hematocrit is 32% and MCV 110.

Vitamin B12 (Cyanocobalamin) Deficiency

Vitamin B12 deficiency is decreased absorption or intake of B12, resulting in hematologic and/or neurologic abnormalities.

Causes include:

- Pernicious anemia (**most common**), a disorder causing decreased intrinsic factor production due to autoimmune destruction of parietal cells
 - Gastrectomy and atrophic gastritis can also decrease intrinsic factor production.
 - The incidence of pernicious anemia increases with age.

- Forms of malabsorption, e.g., sprue, regional enteritis, and blind loop syndrome
- Pancreatic insufficiency
- Tapeworm infection with *Diphyllobothrium latum* (rarely the cause)
- Certain medications

Symptoms vary with the severity of the anemia. As such, diagnosis of B12 deficiency cannot be made only from the symptoms of anemia.

Symptoms include hematologic and neurologic deficits—seen individually or combined.

- Neurologic manifestations (at almost any level of neurologic system): peripheral neuropathy, position sense abnormality, vibratory, psychiatric, autonomic, motor, cranial nerve dysfunction
- Bowel/bladder dysfunction
- Sexual dysfunction
- Possible glossitis, diarrhea, and abdominal pain

Diagnosis.

- Anemia with macrocytosis (increased MCV)
- Neurologic deficits (a small number of patients have these alone)
- WBCs with hypersegmented neutrophils and mean lobe count >4
- RBCs characterized by macro-ovalocytes
- Reduced reticulocyte count, with hypercellular bone marrow
- Possible pancytopenia
- Possible elevated LDH, bilirubin, and iron as a result of mild hemolysis of immature erythrocytes within the bone marrow (in some cases LDH may be very elevated)
- Elevated methylmalonic acid (useful if B12 level is equivocal)

While the low B12 level (most specific test) confirms diagnosis, the antibodies to intrinsic factor and parietal cells confirm the etiology as pernicious anemia.

The Schilling test is rarely used to determine the etiology of vitamin B12 deficiency. It is not necessary if the patient has a low B12 plus antibodies to intrinsic factor.

Treatment.

- Replacement of vitamin B12 (lifelong); response is rapid, with reticulocytosis seen in 2–5 days and hematocrit normalizing within weeks
 - Oral (daily) intake
 - Parenteral (monthly intramuscular or subcutaneous) preparations (**recommended for those with neurologic symptoms**)
- Cobalamin to halt progression of the B12 deficiency process (but will not fully reverse more advanced neurologic effects)
- Treat the underlying etiology of the B12 deficiency if possible (e.g., fish tapeworm infection, bacterial overgrowth).
- Folic acid replacement to correct the hematologic abnormalities of B12 deficiency (but will not fully reverse more advanced neurologic effects)

Note

The hematologic pattern of B12 deficiency is indistinguishable from that of folate deficiency.

Note

- Although macrocytosis can occur with hemolysis, liver disease, and myelodysplasia, these produce **round macrocytes**.
- B12 and folate deficiency produce **oval macrocytes**.

Note

Once parenteral loading of B12 has been initiated, long-term B12 replacement is usually the oral form. This is quite effective, cheaper, and easier for the patient. IV replacement is not recommended because too much of the vitamin would be lost in the urine.



If megaloblastic anemia accompanies the B12 deficiency, early treatment might lead to severe hypokalemia and fluid overload due to increased erythropoiesis, cellular uptake of potassium, and increased blood volume. Once patients are treated for their B12 deficiency, lifelong cobalamin therapy will be required.

Folic Acid Deficiency

Folic acid deficiency is almost always caused by some form of decreased dietary intake. It can lead to anemia. Occasionally, increased requirements from pregnancy, skin loss in diseases like eczema, or increased loss from dialysis and certain anticonvulsants such as phenytoin may occur. Consumption of high amounts of alcohol may have a direct effect on the folate absorption, due to inhibition of the enzyme intestinal conjugase. Folate is presented in foods as polyglutamate, which is then converted into monoglutamates by intestinal conjugase.

Clinical Presentation. Presentation depends entirely on the severity of the anemia.

Diagnosis. The hematologic presentation of folic acid deficiency is identical to B12 deficiency. The diagnosis is based on a low red-blood-cell, folic acid level.

Treatment is folic acid replacement, almost always orally.

Normocytic Anemia

Hemolysis

Hemolytic anemias are caused by decreased RBC survival from increased destruction of the cells. The destruction may be inside the blood vessels (intravascular) or outside (extravascular), which generally means inside the spleen. Hemolytic anemia may be **chronic** (sickle cell disease, paroxysmal nocturnal hemoglobinuria, and hereditary spherocytosis) or **acute** (drug-induced hemolysis, autoimmune hemolysis, or glucose 6-phosphate dehydrogenase deficiency).

Table 6-2. Classification of Hemolytic Anemias

Hereditary Anemias	Acquired Anemias
Membrane: hereditary spherocytosis, hereditary elliptocytosis	Immune • Autoimmune: warm antibody type, cold antibody type • Alloimmune: hemolytic transfusion reactions, hemolytic disease of the newborn, allografts (especially stem cell transplantation) • Drug-associated
Metabolism: G6PD deficiency, pyruvate kinase deficiency	Red Cell Fragmentation Syndromes
Hemoglobin: genetic abnormalities (Hb S, Hb C, unstable)	Infections: malaria, clostridia
	Chemical and Physical Agents: drugs, industrial/domestic substances, burns
	Secondary: liver and renal disease
	Paroxysmal Nocturnal Hemoglobinuria

Clinical Presentation. The usual symptoms of anemia are present based on the severity of the disease, not necessarily the etiology. Fatigue and weakness occur with mild disease. Dyspnea and later confusion occur with more severe disease. The major difference between hemolytic anemia and the micro- and macrocytic anemias is that hemolysis is more often the etiology when the onset is sudden. This is, of course, provided that simple blood loss has been excluded. Hemolysis is often associated with jaundice and dark urine as well. Specific findings associated with each disease are described. Fever, chills, chest pain, tachycardia, and backache may occur if the intravascular hemolysis is particularly rapid.

Diagnosis. Patients with hemolytic anemias generally have a normal MCV, but the MCV may be slightly elevated because reticulocytes are somewhat larger than older cells. The reticulocyte count is elevated. The LDH and indirect bilirubin are elevated. Bilirubin levels above 4 are unusual with hemolysis alone. The peripheral smear may aid in the specific diagnosis, and the haptoglobin may be low with intravascular hemolysis. Hemoglobin may be present in the urine when intravascular hemolysis is sudden and severe because free hemoglobin spills into the urine. There should not be bilirubin in the urine because indirect bilirubin is bound to albumin and should not filter through the glomerulus. Hemosiderin is a metabolic product of hemoglobin. Hemosiderin may be present in the urine if the hemolysis is severe and lasts for several days.

Treatment. Transfusion is needed as in all forms of anemia when the hematocrit becomes low. Hydration is, in general, useful to help prevent toxicity to the kidney tubule from the free hemoglobin. Specific therapy is discussed with each disease. Patients with chronic hemolytic anemia need to be maintained on chronic folic acid therapy, as there is an increase in cell turnover.

Sickle Cell Disease

Sickle cell disease is a hereditary form of chronic hemolysis, ranging from asymptomatic to severe, overwhelming crisis. It is characterized by irreversibly sickled cells and recurrent painful crises.

- Autosomal recessive hereditary disease
- Hemoglobin S is due to a substitution of a valine for glutamic acid as the sixth amino acid of the beta globin chain.
- **Heterozygous form (trait)** (8% of African-Americans); all those with the trait are asymptomatic
- **Homozygous form (disease)** (1 in 400 African-Americans)
- A sickle cell acute painful crisis may be precipitated by hypoxia, dehydration, acidosis, infection, and fever. However, the crisis may occur without the presence of these factors.
- Sickle cell crisis is usually not associated with an increase in hemolysis or drop in hematocrit.
 - If increased hemolysis occurs, consider another etiology such as concomitant glucose 6 phosphate dehydrogenase deficiency (G6PD) or acute splenic sequestration in a child.
 - If a sudden drop in hematocrit occurs, consider another etiology such as Parvovirus B19 infection or folate deficiency. The drop in hematocrit is from acute aplasia (decrease in cell production), not from hemolysis.

**Note**

The **acute chest syndrome** seen in sickle cell disease is indistinguishable from pneumonia. It is a life-threatening manifestation of sickle cell disease.

Clinical Presentation.

- **Acute crisis**
 - Back, rib, chest, and leg pain
 - Possible manifestations of sickling (production of sickle-shaped RBCs) may be severe and life-threatening:
 - Acute chest syndrome (severe chest pain, fever, leukocytosis, hypoxia, and lung infiltrates on chest x-ray) causing infarction and infection
 - Atelectasis (common) as a result of the pain with infection
- **Chronic disease**
 - Renal concentrating defects (isosthenuria)
 - Hematuria
 - Ulcerations of the skin on the legs
 - Bilirubin gallstones
 - Aseptic necrosis of the femoral head
 - Osteomyelitis,
 - Retinopathy
 - Recurrent infections from *Pneumococcus* or *Haemophilus*
 - Growth retardation
 - Splenomegaly (followed in adulthood by autosplenectomy)

Treatment is incentive spirometry, pain control, antibiotics and oxygen. If no response, consider exchange transfusions.

Stroke and TIA may also occur. Priapism can occur from infarction of the prostatic plexus of veins. Blindness and even myocardial infarction and cardiomyopathy may also occur. Pregnant patients experience increased rates of spontaneous abortion and low birth weight.

Sickle trait gives normal hematologic picture with no anemia and a normal MCV. The only significant manifestation of trait is the renal concentrating defect presenting with isosthenuria and **microscopic hematuria**. Sickle trait also increases the frequency of UTI. Those with trait will rarely develop the acute pain crisis under conditions of profound hypoxia and acidosis.



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Figure 6-3. Sickie Cells Noted on a Peripheral Blood Smear

Diagnosis. Patients with sickle cell disease typically have a mild to moderate anemia with a normal MCV. The reticulocyte count should always be elevated in the 10–20% range unless they have folate deficiency or Parvovirus B19 aplastic crisis. LDH and bilirubin are elevated as in all types of hemolytic anemias. The hemoglobin electrophoresis is the most specific test. The peripheral smear shows sickled cells. The sickle prep (or Sickledex) is a quick screening test used to diagnose evidence of sickle cell trait and cannot distinguish between trait and homozygous disease. The urinalysis usually has blood present, although it is often microscopic. The white blood cell count is often elevated in the 10,000–20,000 range, although this can also indicate the presence of infection.

Treatment.

- **Acute crisis:** fluids, analgesics, and oxygen
 - For any infection, or even for fever + leukocytosis but no identified site of infection: antibiotics (ceftriaxone is preferred because it covers *Pneumococcus* and *H. influenza*)
 - For severe/life-threatening manifestations: RBC transfusion if hematocrit is low, and exchange transfusion if hematocrit is high
- **Chronic disease**
 - Folic acid replacement
 - Vaccinations against *Pneumococcus* and influenza
 - Hydroxyurea to decrease the frequency of the vaso-occlusive pain crisis
 - Bone marrow transplantation (curative) for severe cases
 - Exchange transfusion for stroke, priapism, acute chest syndrome and sickle cell patients going into labor or a surgical procedure



Autoimmune, Cold Agglutinin, and Drug-Induced Hemolytic Anemia

Various forms of acquired hemolytic anemia can result from the production of IgG, IgM, or activation of complement C3 against the red cell membrane. They are often sudden and idiopathic. The lysis can be intravascular or extravascular (far more common). That is because the destruction of the cells most often occurs through macrophages in the spleen or by Kupffer cells in the liver.

Autoimmune destruction is often idiopathic. Known causes of autoimmune destruction are from antibodies produced in relationship to various forms of leukemia, especially chronic lymphocytic leukemia, viral infections, lymphoma, collagen vascular diseases like lupus, or in relationship to drugs. The most common drugs are the penicillins, cephalosporins, sulfa drugs, quinidine, alpha-methyldopa, procainamide, rifampin, and thiazides.

Ulcerative colitis can also lead to autoimmune hemolytic anemia.

- **Cold agglutinin** disease is an IgM antibody produced against the red cell in association with malignancies such as lymphoma or Waldenstrom macroglobulinemia and infections such as *Mycoplasma* or mononucleosis. Cold agglutinin destruction occurs predominantly in the liver. Liver-mediated destruction is not affected by steroids. Up to 50% of patients do not have an associated underlying disorder.
- Autoimmune hemolytic anemia due to a **warm agglutinin** (an IgG) is more aggressive often due to SLE, lymphoma, CLL and medications. This can lead to severe hemolysis and requires high doses of corticosteroids followed by other immunomodulating agents. In intractable cases, splenectomy is needed.

Clinical Presentation. Symptoms are generally related to the severity of the anemia, not the etiology. The onset may be very sudden, resulting in fever, syncope, congestive failure, and hemoglobinuria. Mild splenomegaly is present when the disease has been occurring long enough for the time it takes for the spleen to enlarge. The drug history is often the clue with drug-induced varieties. Cold agglutinin disease results in cyanosis of the ears, nose, fingers, and toes. Weakness, pallor, jaundice, and dark urine may occur as it can in all forms of hemolysis of sufficient severity.

Diagnosis. Autoimmune hemolysis gives a normocytic anemia, reticulocytosis, increased LDH, absent or decreased haptoglobin, and increased indirect bilirubin, as can all forms of hemolysis. The Coombs test is the specific test that diagnoses autoimmune, cold agglutinin, and often even drug-induced hemolysis. Spherocytes are often present on the smear.



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Figure 6-4. Acanthocytes, a Feature of Several Hematologic and Systemic Diseases

Treatment. Mild disease often occurs, which needs no treatment. In cases of drug-induced hemolysis, stop the offending drug. More severe autoimmune hemolysis is treated with steroids first. Splenectomy is done for those unresponsive to steroids. Cold agglutinin disease is primarily managed by avoiding the cold. Most cases of cold agglutinin disease are mild, but in those who have severe disease despite conservative measures, azathioprine, cyclosporine, or cyclophosphamide can be used. Rituximab is also useful. This is an anti-CD20 antibody. Steroids and splenectomy don't work well with cold agglutinin disease because the destruction occurs in the liver. You need to control the lymphocytes which control the production of IgM.

Hereditary Spherocytosis

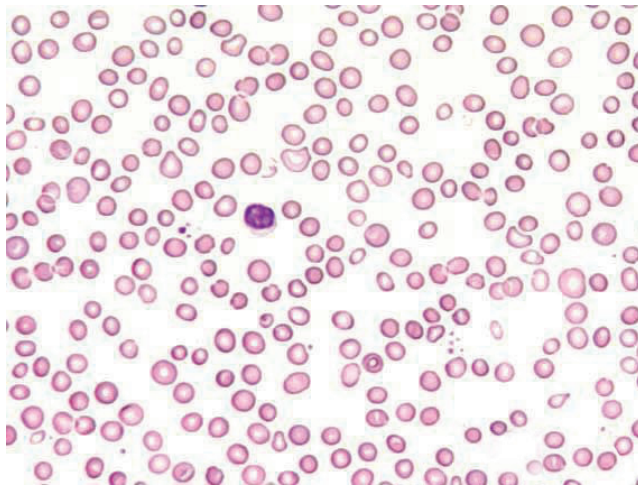
Hereditary spherocytosis is a chronic mild hemolysis with spherocytes, jaundice, and splenomegaly from a defect in the red cell membrane. It is an autosomal dominant disorder where the loss of spectrin in the red cell membrane causes the red cell to form as a sphere, rather than as a more flexible and durable biconcave disc. Hemolysis occurs because the spheres are not able to pass the narrow passages in the spleen.

Clinical Presentation. A chronic disorder with mild to moderate symptoms of anemia. Because the hemolysis occurs in the spleen, there is often splenomegaly and jaundice. Severe anemia occasionally occurs from folate deficiency or Parvovirus B19 infection such as in sickle cell disease. Bilirubin stones often occur, leading to cholelithiasis, often at a young age.



Diagnosis. A normal to slightly decreased MCV anemia with the elevated LDH; indirect bilirubin and reticulocyte count similar to any kind of hemolysis. Although spherocytes may be present with autoimmune hemolysis, hereditary spherocytosis has a negative Coombs test. The cells have increased sensitivity to lysis in hypotonic solutions known as an osmotic fragility test. The mean corpuscular hemoglobin concentration (MCHC) is elevated.

Treatment. Most patients require no treatment beyond folate replacement chronically. In those with more severe anemia, removal of the spleen will eliminate the site of the hemolysis. The symptoms and jaundice will resolve but the spherocytes will remain.



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Figure 6-5. Features of Hereditary Spherocytosis
Seen on Peripheral Blood Smear

Note

Decay accelerating factor (DAF) is also known as CD55 and CD59. DAFs are the main proteins that protect RBCs from complement destruction.

Paroxysmal Nocturnal Hemoglobinuria

Paroxysmal nocturnal hemoglobinuria (PNH) is a red cell membrane defect leading to intermittent dark urine and venous thrombosis and a chronic form of hemolysis. A red cell membrane defect in phosphatidyl-inositol glycan A (PIG-A) allows increased binding of complement to the red cell, leading to increased intravascular hemolysis. It is a clonal stem-cell disorder, and so can develop into aplastic anemia and leukemia. The cells are more susceptible to lysis by complement in an acid environment. Everyone becomes a little acidotic at night because of a relative hypoventilation.

PNH is often associated with bone marrow failure.

Clinical Presentation. In addition to symptoms of anemia, patients typically present with dark urine due to intravascular hemolysis. Thrombosis of major venous structures, particularly the hepatic vein (Budd-Chiari syndrome), is a common cause of death. The hemoglobinuria is most commonly in the first morning urine, since patients typically develop a mild acidosis at night.

Diagnosis. Besides the usual lab findings of hemolysis, such as an increased LDH, bilirubin, and reticulocyte count, these patients have brisk intravascular hemolysis and therefore have a low haptoglobin and hemoglobin in the urine. Hemosiderinuria occurs when the capacity of renal tubular cells to absorb and metabolize the hemoglobin is overwhelmed, and the sloughed off iron-laden cells are found in the urine. The gold standard test is flow cytometry for CD55 and CD59 on white and red cells. In PNH, levels are low or absent.

Treatment. Treatment for PNH depends on the severity of symptoms. Some patients with few or no symptoms require only folic acid and possible iron supplementation. Over time, the disease may progress and thus require more aggressive care.

- **For the anemic patient with signs of hemolysis:** prednisone to slow the rate of RBC destruction
- **For the patient with acute thrombosis:** thrombolytic therapy (streptokinase, urokinase, or tissue plasminogen activator), followed by long-term anticoagulation drugs to help prevent further blood clots
- Antiplatelet agents such as aspirin and ibuprofen to help prevent blood clots
- Antithymocyte globulin, but more often, red cell and/or platelet transfusions
- Allogeneic bone marrow transplantation (**mainstay of curative therapy**)
- New drug eculizumab (brand name Soliris) to treat symptoms of PNH (but still very expensive)

Avoid medications that increase the risk for thrombosis, such as oral birth control pills.

Glucose-6-Phosphate Dehydrogenase Deficiency

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is a hereditary deficiency of an enzyme for producing the reducing capacity necessary for neutralizing oxidant stress to the red cell resulting in acute hemolysis.

Various forms of oxidant stress result in sudden hemolysis. The most common type of oxidant stress is actually from infections, not drugs. The most commonly implicated drugs are sulfa drugs, primaquine, dapsone, quinidine, and nitrofurantoin.

Clinical Presentation. Patients are normal until exposed to the stress. A sudden, severe, intravascular hemolysis can occur including jaundice, dark urine, weakness, and tachycardia. The history of recent drug ingestion is the main clue to the diagnosis.

Diagnosis. The usual findings of an intravascular hemolysis include high LDH, bilirubin, and reticulocyte count with a normal MCV, low haptoglobin, and hemoglobinuria. Heinz bodies are precipitated hemoglobin inclusions seen in red cells. Bite cells are seen on smear indicating the removal of the Heinz bodies. The definitive test is the G6PD level, which can be falsely normal immediately after an episode of hemolysis. Hence, the level is best tested about 1 week after the event.

Treatment. There is no specific therapy beyond hydration and transfusion if the hemolysis is severe. The main therapy is to avoid oxidant stress in the future.

Note

Unfortunately, some patients will continue to develop blood clots despite aggressive anti-coagulation agents.

Note

Although a new drug (eculizumab) has been approved by the FDA to treat symptoms of PNH, its high cost has limited its use.



Clinical Recall

Which of the following clinical scenarios is an indication for an exchange transfusion in a patient with sickle cell anemia?

- A. Acute chest syndrome with a low hematocrit
- B. Priapism with a normal hematocrit
- C. Pneumococcal sepsis with an elevated hematocrit
- D. Focal neurological deficits with an elevated hematocrit STEMI with a normal hematocrit

Answer: D

Aplastic Anemia

Aplastic anemia is failure of all 3 cell lines produced in the bone marrow, resulting in anemia, leukopenia, and thrombocytopenia (pancytopenia). The marrow is essentially empty with the absence of precursor cells.

Many things can cause bone marrow failure, but the most common cause of true aplastic anemia is not often determined. Causes include:

- Radiation, toxins such as benzene, drugs such as NSAIDs, chloramphenicol, alcohol, and chemotherapeutic alkylating agents
- Infections such as hepatitis, HIV, CMV, Epstein-Barr virus, or Parvovirus B19 in immunocompromised patients

Infiltration of the marrow with infections such as TB or cancer such as lymphoma can cause pancytopenia, but that is not truly aplastic anemia.

Clinical Presentation. Patients typically present with bleeding from the thrombocytopenia, and possibly with a combination of the findings associated with deficiencies in all 3 cell lines. Fatigue from anemia and infections from neutropenia may also occur. The clinical presentation may give a clue to the presence of pancytopenia but is not sufficient to determine a true aplastic anemia by clinical manifestations alone. The absence of a classical association such as benzene, radiation, or chloramphenicol would most certainly not exclude a diagnosis of aplastic anemia. The most common single etiology is idiopathic.

Diagnosis. Pancytopenia on a CBC is the first test. A bone marrow biopsy confirms the diagnosis when alternative etiologies for a pancytopenia are not present. In other words, the marrow is empty of almost all precursor cells as well as evidence of primary or metastatic cancer, infection, or fibrosis. The marrow is hypoplastic and fat filled with no abnormal cells seen.

Treatment.

- Bone marrow transplant when patient is young/healthy and donor is available (cure rate nearly 90% for patients <50)
- Immunosuppressive agents when bone marrow transplant not possible: combination antithymocyte globulin, cyclosporine, and prednisone (can lead to remission in 60–70% of patients)

Note

It is believed that T lymphocytes are primarily causal in the bone marrow failure, so drugs are used to decrease the T-cell response.

LEUKEMIA

Leukemia is cancer of the blood and bone marrow. Acute leukemia involves the immature cells (stem cells), and chronic leukemia involves the mature cells.

Acute Leukemia

Acute leukemia is the rapid onset of bone marrow failure from the derangement of the pluripotent stem cell, causing the relentless destruction of the normal production of the entire bone marrow. Blood cells lose their ability to mature and function normally. Most cases arise with no apparent cause. However, there are several well known associations:

- Radiation exposure
- Benzene
- Chemotherapeutic agents such as melphalan and etoposide
- Some retroviruses
- Genetic disorders such as Down syndrome and Klinefelter
- Myelodysplasia and sideroblastic anemia

Clinical Presentation. Patients typically present with the effects of the leukemic blast cells crowding out the normal marrow cells, leading to symptoms of bone marrow failure (even if total WBC count is elevated or normal).

- Fatigue from anemia (**most common**)
- Bleeding from thrombocytopenia
- Infection from the underproduction or abnormal function of WBCs
- Enlargement of liver and lymph nodes
- Bone pain

Acute lymphocytic leukemia (ALL) is more common in children, and acute myelogenous leukemia (AML) is more common in adults, but they are indistinguishable clinically. ALL is more often associated with infiltration of other organs, but AML can do it as well. Disseminated intravascular coagulation (DIC) is associated with M3 promyelocytic leukemia. CNS involvement resembling meningitis is present at the time of initial diagnosis in a small number of patients (CNS involvement is most characteristic of M4 and M5 monocytic leukemia).

Rarely, a syndrome of “leukostasis” can occur when WBCs are extremely elevated. This results from sludging of the leukemic cell in the vasculature, and will cause headache, dyspnea, confusion, and possible brain hemorrhage. The leukostasis is due to a very high blast count; the blasts are very “sticky.”

Diagnosis.

- CBC shows elevated WBC, thrombocytopenia and anemia
- Bone marrow biopsy showing >20% blasts (**confirms diagnosis**); the presence of blasts confirms acute leukemia but blast analysis cannot be relied upon to identify the type
 - AML is characterized by the presence of Auer rods, myeloperoxidase, and esterase. Auer rods are most specific for M3.
 - ALL is characterized by the presence of the common ALL antigen (CALLA) and terminal deoxynucleotidyl transferase (TdT).
- Hyperuricemia and increased LDH but those are nonspecific

Note

The acute leukemias do not result in splenomegaly.

Clinical Correlate

In about 10% of acute leukemias, depression of all 3 cell lines is evident (aleukemic leukemia). Many other disorders can present as pancytopenia similar to leukemia, i.e., aplastic anemia, infections involving the marrow, metastatic cancer involving the marrow, B12 deficiency, SLE, hypersplenism, and myelofibrosis.

None of these will have leukemic blasts circulating in the peripheral blood, however.



Note

The FAB classification of the acute leukemias is often used but many centers are now using the WHO criteria, which focus on chromosomal changes that are identified. For example, ALL with 9,22 translocation (Philadelphia chromosome has a very bad prognosis).

For the exam, it is not needed to memorize these classifications.

Note

“Remission” means removal of over 99.9% of the leukemic cells in the body and the elimination of peripheral blasts in circulation.

Note

CML can be confused with a leukemoid reaction. They are distinguishable based upon the leukocyte alkaline phosphatase score.

Ultimately, diagnosis rests upon the use of monoclonal antibodies, which recognize specific types of leukemia as well as the expression of specific CD antigens on the surfaces of the cells.

Treatment.

- Chemotherapy (all patients) to induce a remission
 - For AML: cytosine arabinoside (AraC) plus daunorubicin or idarubicin
 - For ALL: daunorubicin, vincristine, and prednisone
- Then, further rounds of chemotherapy to “consolidate” the leukemia
- For promyelocytic leukemia, add the vitamin A derivative all-trans-retinoic acid (ATRA)
- For leukostasis events, add leukapheresis to chemotherapy
- Later, adults with AML or ALL should be referred for allogeneic bone marrow transplantation

ALL patients must also undergo prophylaxis of the CNS to prevent relapse there; the best agent is intrathecal methotrexate.

Chronic Leukemia

Chronic Myelogenous Leukemia

Chronic myelogenous leukemia (CML) is a chronic myeloproliferative disorder characterized by the massive overproduction of myeloid cells. The cells retain most of their function until later in the course of the disease. Although the Philadelphia chromosome is characteristic of the disease, the cause of the production of this chromosome is unknown. It is a clonal disorder of myelocytes. The Philadelphia chromosome is a translocation between chromosomes 9 and 22, resulting in a gene producing an enzyme with tyrosine kinase activity.

Clinical Presentation. A markedly elevated WBC is found on routine blood count.

- Fatigue, night sweats, low-grade fever (**most common symptoms**)
- Abdominal pain from massive enlargement of the spleen (common)
- Bone pain from infiltration with WBCs
- Enlarged lymph nodes (rare)
- Infection and bleeding (rare, because the WBCs retain the majority of their function)

Diagnosis. The main feature of the disease is elevated WBCs, consisting predominantly of neutrophils with a left shift. Blasts are absent or present in very small amounts. The leukocyte alkaline phosphatase score (LAP) is diminished. Basophilia is characteristic of CML and *all* myeloproliferative disorders such as polycythemia vera. Although the B12 is often elevated, this would not be enough to establish the diagnosis. The Philadelphia chromosome is a far more specific test for CML and should be done in a patient with a markedly elevated white cell count. A low LAP score is not as important as the PCR for Bcr/Abl. The platelet count can also be markedly elevated.

Treatment.

- Imatinib (known by the brand name, Gleevec®), a direct inhibitor of the tyrosine kinase produced by the Philadelphia chromosome
 - Success rate nearly 90% (the milder the disease, the greater the degree of hematologic response)
 - Nearly 70% of patients may lose the Philadelphia chromosome
- Bone marrow transplantation if no response to imatinib

Chronic Lymphocytic Leukemia (CLL)

Chronic lymphocytic leukemia (CLL) is a massive overproduction of mature—but still leukemic—lymphocytes, usually from the monoclonal production of B lymphocytes. Etiology is unknown.

Clinical Presentation. CLL can often present as an asymptomatic elevation of WBCs found on routine blood count.

- Commonly older age (90% age >50)
- When symptoms are present, they are nonspecific: fatigue, lethargy, and uncomfortable enlargement of lymph nodes
- Infiltration of other parts of the reticuloendothelial system, i.e., spleen, liver, and bone marrow
- Infection and bleeding (rare)

CLL can be associated with various autoimmune phenomena such as thrombocytopenia and autoimmune hemolytic anemia.

Staging for CLL is as follows:

- Stage 0:** lymphocytosis alone
- Stage 1:** lymphadenopathy
- Stage 2:** splenomegaly
- Stage 3:** anemia
- Stage 4:** thrombocytopenia

Diagnosis. CLL is strongly suspected when an older patient has a marked elevation in WBCs with a marked lymphocytic predominance in the range of 80–98% lymphocytes. The marrow is often infiltrated with the leukemic lymphocytes. CD19 is an antigen strongly associated with CLL. Cell count is usually elevated (30,000–50,000, but may go as high as 150,000). “Smudge cells” seen on a smear are characteristic of CLL.

Treatment.

- **Early stage CLL with only elevated WBCs or enlarged lymph nodes:** no treatment
- **Advanced CLL with symptoms:** fludarabine (**drug of choice**), which is more effective than chlorambucil
- Autoimmune hemolysis and thrombocytopenia: prednisone
- Rituximab for patients who express CD20, especially with autoimmune ITP or hemolytic anemias
- Newer agents are now available for more select cases, e.g., bendamustine and ibrutinib.

Note

Bone marrow transplantation is no longer the clear first choice as treatment for CML. That is because of the extraordinary response to imatinib, as well as the high mortality associated with bone marrow transplant.

Note

Staging for CLL is important:

- **Survival of untreated stage 0 and 1 disease:** 10–12 years (even without treatment)
- **Survival of stage 3 and 4 disease:** 1–2 years

Note

A good **first-line therapy** for CLL is cyclophosphamide + fludarabine + rituximab.



Hairy cell leukemia (HCL), a subtype of CLL, is characterized by an accumulation of abnormal B lymphocytes. The malignant B lymphocytes (“hairy cells”) accumulate in the bone marrow, interfering with the production of normal cells commonly causing pancytopenia.

HCL may be associated with repeated infections, often with unusual organisms as well as vasculitis.

Patients develop infections, anemia and fatigue, or easy bleeding. Early satiety may occur from massive splenomegaly.

- HCL is commonly considered in the differential diagnosis after routine blood count shows unexpectedly low numbers of cell lines or after unexplained bruising or recurrent infections in an otherwise apparently healthy patient.
- Bone marrow biopsy is necessary for final diagnosis: the biopsy is used to confirm both the presence of HCL and the absence of any additional diseases.
- Diagnosis can be confirmed by viewing the cells with a special stain known as TRAP (tartrate resistant acid phosphatase).
- Pancytopenia in HCL is caused primarily by marrow failure and splenomegaly. Bone marrow failure is caused by the accumulation of hairy cells and reticulin fibrosis in the bone marrow, as well as by the unfavorable effects of dysregulated cytokine production.
- For treatment, use the purine analogs cladribine (2CDA) or pentostatin (first-line). Almost all new patients will respond, with most experiencing a disease-free remission of 10+ years after taking one of these drugs just once. For cladribine-resistant disease, consider a monoclonal antibody (rituximab most common), which destroys the malignant B cells. Alpha interferon can stabilize the disease or produce a slow, minor improvement in 60% of patients.

Myelodysplastic Syndrome

Myelodysplastic syndrome (MDS) is an idiopathic disorder that is considered “pre-leukemic,” in that a number of people go on to develop AML. The etiology is probably a genetic defect. The most common defect is 5q deletion or “5q-.”

- Patients are commonly elderly
- Pancytopenia
- Elevated MCV
- Fatigue
- Infections
- Bleeding due to low cell counts
- Small number of blasts from 1–20%

Most patients die of infection or bleeding before they develop AML. This is because the disorder is slowly progressive and older patients “wear out” so to speak from cytopenias, more often than not going into the “blast phase” that characterizes AML. By definition, you must exclude B12 and folate deficiency because the disorder is so similar.

CBC and bone marrow are indispensable. You may find a bi-lobed neutrophil called a Pelger-Huet cell, which is characteristic. Genetic testing for the 5q- is essential.

Treatment is periodic transfusions and control of the infections as they arise. Disease-specific therapy consists of the TNF inhibitor lenalidomide or thalidomide. Azacitidine or decitabine is useful when the 5q- is present. Some patients who are young enough with a match can undergo bone marrow transplantation.

Polycythemia Vera

Polycythemia vera is a disorder of RBC production. RBCs are produced in excessive amounts in the absence of hypoxia or increased erythropoietin.

Clinical Presentation.

- Markedly elevated hematocrit
- Splenomegaly
- Sometimes elevation of the platelet and white cell counts
- Thrombosis often in unusual locations such as the GI vessels
- “Plethora” or redness and fullness of the face
- Pruritis (40% of patients), particularly after exposure to warm water as in a shower, and possibly caused by abnormal histamine or prostaglandin production

Diagnosis. Diagnose with a high hematocrit in the absence of hypoxia, carbon monoxide poisoning, or elevated erythropoietin level. The most specific test is the Janus Kinase or JAK-2 mutation.

Treatment is phlebotomy. Hydroxyurea may be added or used as an alternative. Aspirin is used to reduce the risk of thrombotic events.

Recently, ruxolitinib, an inhibitor of kinases, has been used to treat severe cases of polycythemia not manageable with more conventional therapies. This same drug may be used in myelofibrosis with myeloid metaplasia.

Essential Thrombocythemia

Essential thrombocythemia is a type of platelet cancer. Platelet count may be over a million. There is either thrombosis or bleeding. The most specific test is JAK-2 mutation.

Treatment is hydroxyurea and sometimes anagrelide. The use of anagrelide is limited due to severe side effects.

Note

It is the percentage of blasts present that tells how “close” a person with MDS is to developing AML.



Clinical Recall

Which of the following treatment options could be used in the management of stage 1 CLL?

- A. Observation
- B. Fludarabine
- C. Prednisone
- D. Rituximab
- E. Fludarabine plus chlorambucil

Answer: A

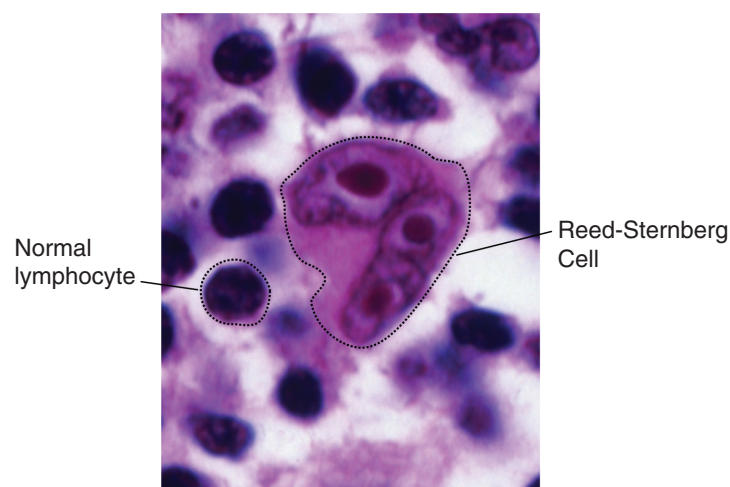
LYMPHOMA

Hodgkin Disease

A 32-year-old woman presents with a neck mass for the last several weeks. She also has fever, weight loss, and sweats.

Hodgkin disease is a neoplastic transformation of lymphocytes particularly in the lymph node. It is characterized by the presence of Reed-Sternberg cells on histology, which spreads in an orderly, centripetal fashion to contiguous areas of lymph nodes.

The disease most commonly presents age 20s or age 60s.



National Cancer Institute

Figure 6-6. Reed-Sternberg Cell

Although there is a clear increase in Hodgkin disease among relatives of those with the disease, there are no clear environmental or infectious etiologies for the disorder.

Clinical Presentation. Enlarged, painless, rubbery, nonerythematous, nontender lymph nodes are the hallmark of the disease. Patients may also develop what are labeled “B” symptoms, which are drenching night sweats, 10% weight loss, and fevers. Although pruritus is common in the disease, it is not one of the “B” symptoms. Cervical, supraclavicular, and axillary lymphadenopathy are the most common initial signs of disease. Lymphadenopathy may develop anywhere in the body, however. Extralymphatic sites such as splenic involvement, skin, gastric, lung, CNS, or any other organ may possibly be involved. Extralymphatic involvement is more common with non-Hodgkin lymphoma.

Staging is as follows:

- Stage 1:** one lymphatic group or single extra lymphatic site
- Stage 2:** two lymphatic groups or extra lymphatic sites on same side of the diaphragm
- Stage 3:** involvement of lymphatic groups on both sides of the diaphragm or involvement of any extralymphatic organ contiguous to the primary
- Stage 4:** widespread disease with involvement of diffuse extralymphatic sites such as bone marrow or liver

Staging is the same for both Hodgkin and non-Hodgkin lymphoma. In Hodgkin lymphoma, staging is the single most important predictor of outcomes.

Diagnosis.

- Excisional lymph node biopsy (essential first step)
- After diagnosis is made, determine the extent (stage) of disease
- Chest x-ray/CT, abdominal CT, or MRI will determine if the disease is localized to the supraclavicular area (bone marrow biopsy will definitively determine if disease is localized)
- CT scan is sensitive enough to detect any involved lymph nodes
- Size alone is insufficient to determine the content of some enlarged nodes. PET scan can also be used, in that it will stage the disease with accuracy. Further, it can be used to monitor for response and cure, and to determine the number of chemotherapy cycles that are required.
- Other labs tests that are often abnormal, but do not directly alter the stage of the disease, include the following:
 - CBC looking for anemia or increased WBC or platelets
 - Eosinophilia (common)
 - Elevated LDH indicates an adverse prognosis
 - ESR is useful prognostically
 - Elevated LFTs help determine the need for liver biopsy

Note

Adverse prognostic factors for Hodgkin include:

- Large mediastinal lymphadenopathy
- Age >40
- “B” symptoms
- Elevated ESR

Note

Lymphangiography and laparotomy are no longer routinely used for staging of Hodgkin.



Clinical Correlate

HIV and Epstein-Barr are more often associated with Burkitt lymphoma, and HIV is also associated with immunoblastic lymphoma—both high-grade lymphomas with an aggressive progression of disease.

Note

Because the presence of marrow involvement in NHL means the patient has stage IV disease and will thus need combination chemotherapy, invasive testing such as the laparotomy is not needed.

Treatment.

- **Localized disease, i.e., stage IA and IIA:** radiation + adjunct chemotherapy
- **Evidence of “B” symptoms, and stage III-IV disease:** chemotherapy
 - Most effective combination chemotherapeutic regimen for Hodgkin disease is **ABVD** (adriamycin [doxorubicin], bleomycin, vinblastine, dacarbazine)
 - ABVD is superior to MOPP (mechlorethamine, [vincristine], prednisone, and procarbazine) in that it has fewer side effects, e.g., permanent sterility, secondary cancer formation, leukemia, aplastic anemia, and peripheral neuropathy

Hodgkin disease has several histologic subtypes. Lymphocyte-predominant has the best prognosis, and lymphocyte-depleted has the worst prognosis. The histologic subtype does not alter anything described. The lab tests, staging, and treatments are the same.

Non-Hodgkin Lymphoma

Non-Hodgkin lymphoma (NHL) is the neoplastic transformation of both the B and T cell lineages of lymphatic cells. It causes the accumulation of neoplastic cells in both the lymph nodes and (more often) diffusely in extralymphatic organs and the bloodstream. The Reed-Sternberg cell is absent.

There are a number of infectious and autoimmune disorders associated with NHL: hepatitis C, HIV, Epstein-Barr, HTLV-I, and *H. pylori*.

Clinical Presentation. Enlarged, painless, rubbery, nonerythematous, nontender lymph nodes are the hallmark of the disease. Patients may also develop what are labeled “B” symptoms, which are drenching night sweats, 10% weight loss, and fevers. Although pruritus is common in the disease, it is not one of the “B” symptoms. In this sense, NHL is the same as Hodgkin disease. The difference is that Hodgkin disease is localized to cervical and supraclavicular nodes 80–90% of the time, whereas NHL is localized only 10–20% of the time. NHL is far more likely to involve extralymphatic sites, as well as to have blood involvement similar to CLL. CNS involvement is also more common with NHL. HIV-positive patients often have CNS involvement.

Staging for NHL is the same as that for Hodgkin disease.

Diagnosis.

- First, excisional lymph node biopsy
- Then, determine the stage of disease to identify appropriate therapy
- Although this is quite similar to that described for Hodgkin disease, there are important differences because **NHL is far more likely to be widespread at initial presentation.**
 - Lymphangiography is never necessary
 - Bone marrow biopsy is more central as an initial staging tool
 - Staging laparotomy is rarely needed
 - As with Hodgkin disease anemia, leukopenia, eosinophilia, high LDH, and high ESR often accompany the disease.
 - PET scan is highly sensitive and specific for nodal and extranodal sites but not for bone marrow disease.

Treatment.

- **Localized disease, i.e., stage IA and IIA:** radiation
- **Evidence of “B” symptoms and stages III and IV:** combination chemotherapy; the **preferred regimen** is CHOP (cyclophosphamide, hydroxy-adriamycin, vincristine, prednisone)
- **CNS lymphoma:** radiation + CHOP
- Relapses of NHL can be controlled with autologous bone marrow transplantation
- Some patients with NHL express CD20 antigen in greater amounts; for these patients, use monoclonal antibody rituximab, an anti-CD20 antibody
 - Adds survival benefit to the use of CHOP (thus, R-CHOP would then become first-line therapy)
 - Has limited toxicity
 - Can cause fulminant liver injury in those with active hepatitis B or C disease, so before using R-CHOP, test completely for hepatitis B and C

Tumor lysis syndrome

Tumor lysis syndrome (TLS) is an oncologic emergency caused by massive tumor cell lysis, with the release of large amounts of potassium, phosphate, and uric acid into the systemic circulation.

- Uric acid excretion can cause uric acid to build up in the renal tubules; it can also induce renal vasoconstriction, reduced renal blood flow, and inflammation, resulting in acute kidney injury.
- Hyperphosphatemia with calcium phosphate deposition in the renal tubules can also cause acute kidney injury.

TLS most often occurs after the initiation of cytotoxic therapy in patients with high-grade lymphoma (particularly Burkitt’s and acute lymphoblastic leukemia), though it can occur spontaneously and with other tumor types having a high proliferative rate or large tumor burden.

- For patients about to receive chemotherapy for a cancer with a high cell turnover rate, e.g., lymphoma and leukemia, give prophylactic oral or IV allopurinol + IV hydration to maintain high urine output (>2.5 L/day)
- Rasburicase may be used as an alternative to allopurinol and is reserved for those at high-risk for developing TLS.

Alkalization of the urine as a treatment of TLS is controversial.

Note

Testing for hepatitis B is especially critical before starting rituximab therapy. If a patient is HBsAg-positive, then rituximab may be used cautiously as long as drugs to treat hepatitis B are also given (e.g., tenofovir).

Note

On the exam, you are not required to know the histologic subtypes of NHL or the specific chemotherapeutic regimens.



Clinical Recall

A 25-year-old man presents with enlarged, rubbery, non-erythematous, painless, non-tender cervical lymphadenopathy. He also admits to having weight loss, fever, and night sweats. What is the best initial diagnostic step?

- A. Complete blood count with erythrocyte sedimentation rate
- B. PPD or IFN-gamma release assay with CXR
- C. Upper endoscopy with gastrointestinal biopsy
- D. Excisional lymph node biopsy
- E. Abdominal CT

Answer: D

PLASMA CELL DISORDERS

Multiple Myeloma

Multiple myeloma is a clonal abnormality of plasma cells resulting in their overproduction replacing the bone marrow, as well as the production of large quantities of functionless immunoglobulins. The disease is characterized by various systemic manifestations such as bone, kidney, and infectious complications. Etiology is unknown.

Clinical Presentation. Bone pain is the most common clinical manifestation, usually in the back and the ribs, secondary to pathologic fractures. Radiculopathy from the compression of spinal nerve roots is also common. Infection particularly with encapsulated organisms such as *Pneumococcus* and *Haemophilus* is common. Renal failure and anemia are common. The symptoms of hypercalcemia such as polyuria, polydipsia, and altered mental status may occur. Weakness, fatigue, and pallor are common. Rarely, symptoms of a hyperviscosity syndrome such as blurry vision, confusion, and mucosal bleeding may occur.

Diagnosis. Although a normochromic, normocytic anemia is the most common laboratory finding, this is not specific for myeloma. A protein electrophoresis with a markedly elevated monoclonal immunoglobulin spike is present in almost all cases. This is most commonly IgG but may be IgA, IgD, or rarely a combination of two of these. In about 80% of individuals, routine x-ray will reveal the punched-out lytic lesion caused by the overproduction of osteoclast activating factor from the plasma cells and/or pathologic fractures at the time of diagnosis. Most commonly involved are the vertebrae, ribs, pelvic bones, and bones of the thigh and upper arm. If multiple myeloma is suspected with normal x-ray, consider MRI, CT, or PET. Serum B2 microglobulin is elevated in 75% of patients, as is the production of IL-6. Hypercalcemia from the destruction of bone is common, as is an elevation in the BUN and creatinine from the damage to the kidney from the immunoglobulins, Bence-Jones protein, calcium, and hyperuricemia. A bone marrow biopsy with >10% plasma cells confirms a diagnosis of multiple myeloma. Bence-Jones protein is often not detected by a standard protein test on a urinalysis, which mainly is meant to detect albumin. A specific test for Bence-Jones protein involving acidification of the urine is required. Increased gamma globulin levels will increase the total protein and decrease the albumin level.

Clinical Pearl

Multiple myeloma causes a low anion gap.

Treatment.

- **Patients age <70:** autologous bone marrow transplantation in an attempt to cure the disease
- **Patients age >70:** melphalan and prednisone
- **Candidates for transplant:** thalidomide (or lenalidomide) and dexamethasone
- Non-candidates for transplant: melphalan, prednisone, and thalidomide
- Hydration and loop diuretics first, and then IV bisphosphonates, e.g., zoledronic acid to reduce bone pain and pathologic fractures
- Bortezomib, a proteasome inhibitor, is useful for relapsed myeloma or as an addition to the other medications; it can be combined with steroids, melphalan, or lenalidomide (thalidomide)

Note

The level of B2 microglobulin may be predictive of outcome. A higher level is associated with a poorer outcome.

Monoclonal Gammopathy of Uncertain Significance (MGUS)

MGUS is the overproduction of a particular immunoglobulin by plasma cells, without the systemic manifestations of myeloma such as bone lesions, renal failure, anemia, and hypercalcemia. It is a very common abnormality, seen in 1% of all patients age >50 and 3% of patients age >70.

The cause of MGUS is unknown. Some patients with this condition may progress to multiple myeloma.

Clinical Presentation. Patients are asymptomatic. The condition is found on routine blood testing.

Diagnosis.

- Elevated monoclonal immunoglobulin spike of serum protein electrophoresis (SPEP) in amounts lower than those seen in myeloma
- Normal creatinine, calcium, and hemoglobin
- Elevated total serum protein (**clue to diagnosis**)
- No lytic bone lesions; bone marrow has <10% plasma cells
- Normal beta-2 microglobulin level in most patients

Treatment is neither effective nor necessary, but monitor carefully.

PLATELET DISORDERS**Immune Thrombocytopenic Purpura**

Immune thrombocytopenic purpura (ITP) is the idiopathic production of an antibody to the platelet, leading to removal of platelets from the peripheral circulation by phagocytosis by macrophages. The platelets are bound by the macrophage and brought to the spleen, leading to low platelet count.

ITP is often associated with lymphoma, CLL, HIV, connective tissue diseases, and *H. pylori*, but it may be idiopathic.



Clinical Pearl

Platelet disorders can broadly be classified into 2 groups:

- Quantitative (low platelet count, eg, ITP)
- Qualitative (normal platelet count but abnormal platelet function, eg, von Willebrand, Bernard Soulier)

Note

Today, bone marrow examination is rarely done to diagnose ITP. Because the megakaryocytes are normal or high, the platelets that are present will be younger (thus, larger and more functional), i.e., the large platelets work better. Hence bleeding is less common in ITP than it used to be.

Clinical Presentation. Like all platelet disorders, initial symptoms include signs of bleeding from superficial areas of the body, e.g., the skin, nasal/oral mucosa, GI tract, urine, and vagina. Women > men, and patients are otherwise healthy.

- Commonly young age
- Epistaxis
- Bruising
- Hematuria
- Dysfunctional uterine bleeding and possible GI bleeding
- Petechiae, purpura, and ecchymoses (common)
- Splenomegaly is absent

Diagnosis.

- Thrombocytopenia (**major finding**)
- Normal spleen on exam and on imaging (**characteristic**)
- Antiplatelet antibodies have a high sensitivity but poor specificity
- Bone marrow should be filled with megakaryocytes, indicating that there is a problem with platelet destruction and not platelet production. The bone marrow will also exclude other causes of thrombocytopenia such as primary or metastatic cancer, infiltration by infections such as TB or fungi, or decreased production problems such as drug, radiation, or chemotherapy effect on the bone marrow.
- Large platelets will be round on peripheral smear
- High MPV (mean platelet volume), indicating a high overall platelet volume (and correlating with younger platelets, which are bigger)
- Normal peripheral smear and creatinine, excluding other platelet destruction problems such as HUS, TTP, and DIC

Treatment.

- Prednisone (**first-line**) for almost all patients
- If no response to repeated steroids and platelets continue to be very low ($<10,000\text{--}20,000/\text{mm}^3$), consider splenectomy
- If no response to splenectomy, use thrombopoietin agents romiplostim or eltrombopag (rituximab is an alternative)
- For profoundly low platelet counts ($<10,000/\text{mm}^3$) or patients at risk for life-threatening bleeding, use IVIG or RhoGAMTM (equally effective but RhoGAM can only be used in Rh-positive patients)

Von Willebrand Disease (vWD)

A 22-year-old woman comes to the ED with epistaxis and heavy periods. Her PT is 11 seconds (normal), PTT 40 seconds (prolonged), and platelets 217,000/mm³.

vWD (**most common congenital disorder of hemostasis**) is an autosomal dominant disorder leading to decreased amounts of von Willebrand factor. As a result of the decreased von Willebrand factor, there is an increased predisposition to platelet-type bleeding.

vWD also results in a decreased ability of platelets to adhere to the endothelial lining of blood vessels. This is different from platelets aggregating with each other, which is mediated by fibrinogen. In vWD, aggregation is normal, whereas adherence is abnormal.

Clinical Presentation. Patients with vWD manifest platelet-type bleeding such as that described for ITP. This is mucosal and skin bleeding such as epistaxis, petechiae, bruising, and menstrual abnormalities. Both platelet problems as well as clotting factor abnormalities can result in GI and urinary tract bleeding. There is often a marked increase in bleeding after the use of aspirin.

Diagnosis.

- Normal platelet count and appearance
- Increased bleeding time, especially after the use of aspirin
- Low level of von Willebrand factor (or factor VIII antigen)
- Abnormal ristocetin platelet aggregation test (which examines the ability of platelets to bind to an artificial endothelial surface [ristocetin])
- Elevated PTT (some patients) because of a concomitant decrease in levels of factor VIII coagulant portion

Treatment.

- Mild bleeding or for minor surgical procedures: desmopressin acetate (DDAVP) to release subendothelial stores of von Willebrand factor
- If no response with desmopressin: factor VIII replacement, which contains von Willebrand factor (replaces the use of cryoprecipitate, which is now seldom necessary)
- Fresh frozen plasma (FFP) is not useful.
- Patients should avoid aspirin.

Clinical Correlate

In an autosomal dominant disorder, the mutated gene is a dominant gene located on a nonsex chromosome (autosome). Only one mutated copy of the autosomal gene is needed to cause disease.

Note

For the exam, you will not need to know the various subtypes of vWD.

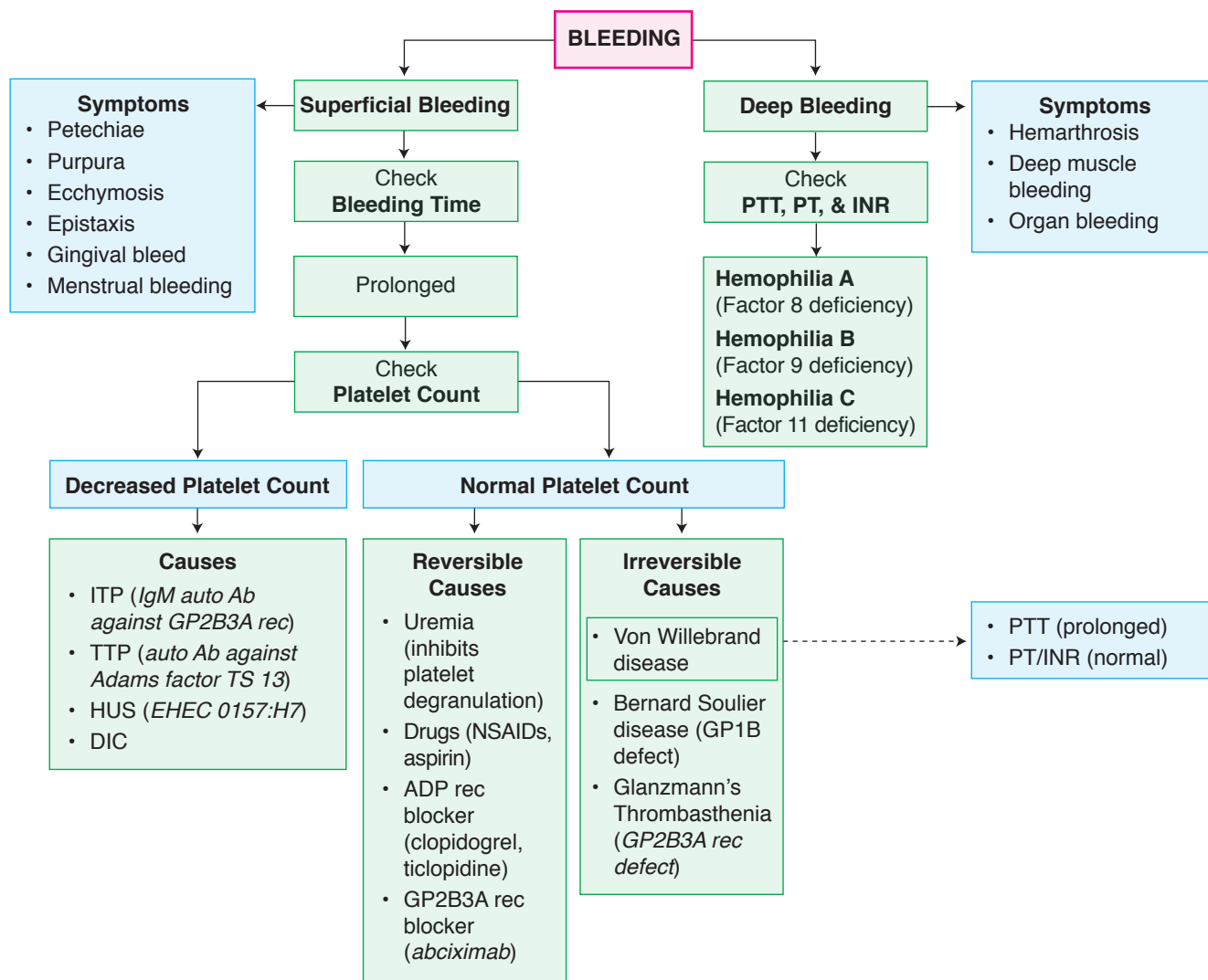


Figure 6-7. Evaluation of Patients with Bleeding

Clinical Correlate

Hemophilia A and B are both X-linked recessive disorders. Males have disease, while females are carriers.

COAGULOPATHY

Hemophilia A and B

Hemophilia A is a deficiency of clotting protein factor VIII, while **hemophilia B** is a deficiency in clotting protein factor IX. Both conditions result in an increased risk of bleeding.

Hemophilia A is far more common than B.

Clinical Presentation.

- **Mild deficiencies** (25% or greater activity): asymptomatic or symptomatic only with surgical procedures or trauma
- **More severe deficiencies** (<5–10% activity): spontaneous bleeding
 - Factor-type bleeding is generally deeper than bleeding from platelet disorders
 - Factor-type bleeds include hemarthrosis, hematoma, GI bleeding, and urinary bleeding
 - Bruising and CNS bleeding can also occur
- Severe hemophilia is obvious in most patients by age 2. The disorder becomes apparent often at the time of circumcision.

Diagnosis. A prolonged PTT with a normal PT is expected. A factor deficiency is strongly suspected when a 50:50 mixture of the patient's blood is created with a normal control and the PTT drops to normal (known as a “mixing study”).

If PTT does not correct with mixing, then an antibody inhibitor of the factor is suspected. The next step is to identify the specific factor that is deficient. Proceed with testing of factor VIII and IX levels to get a precise diagnosis.

Treatment.

- **Mild hemophilia:** desmopressin (works by releasing subendothelial stores of factor VIII)
 - Desmopressin can also be used prior to surgical procedures in mild hemophiliacs.
 - Desmopressin does not work for hemophilia B.
- **Severe hemophilia:** replacement of the specific factor (cryoprecipitate and FFP rarely used)

Clinical Correlate

Females do not express hemophilia because they would have to be homozygous, which is a condition resulting in intrauterine death of the fetus.

Note

With diagnosis of hemophilia, the mixing study will only confirm a deficiency; it will not identify the specific factor. Factor VIII or IX levels are needed for a precise diagnosis.

Table 6-3. Causes of Prolonged PT or PTT

	Prolonged PT	Prolonged PTT	Prolonged PT and PTT
Inherited causes	Factor VII deficiency	vWF and factors VIII, IX, XI, or XII deficiencies	Prothrombin, fibrinogen, factor V, factor X, or combined factor deficiencies
Acquired causes	• Vitamin K deficiency • Liver disease • Warfarin use • Factor VII inhibitor	• Heparin • Antiphospholipid antibody	• Vitamin K deficiency • Liver disease • Disseminated intravascular coagulation • Supratherapeutic heparin or warfarin • Combined heparin and warfarin use • Direct thrombin inhibitors • Inhibitor of prothrombin, fibrinogen, or factor V or X

PT, prothrombin time; PTT, partial thromboplastin time; vWF, von Willebrand factor.

Vitamin K Deficiency

Vitamin K deficiency can lead to decreased production of factors II, VII, IX, and X.

It can result from dietary deficiency, malabsorption, or antibiotics, which kill the bacteria in the colon that produce vitamin K (most commonly broad-spectrum drugs such as fluoroquinolones, cephalosporins, and other penicillin derivatives).



Clinical Correlate

With liver disease, **factor VII levels** are the first to be depleted.

Clinical Presentation. Bleeding may mimic that of hemophilia and may occur at any site. Look for oozing at venipuncture sites.

Diagnosis. Both the PT and PTT are elevated. The PT usually elevates first and more severely.

Correcting the PT and PTT in response to giving vitamin K is the most common way to confirm diagnosis.

Treatment.

- **Severe deficiency and bleeding:** infusions of FFP + parenteral vitamin K replacement to correct the underlying production defect
- **Mild deficiency:** oral vitamin K replacement (very effective and easy to use)

Liver Disease

Liver disease can be caused by coagulopathy due to decreased production of clotting factors by the liver. Any severe liver disease or cirrhosis will lead to decreased production of the majority of clotting factors that are generally all made in the liver—except for factor VIII and von Willebrand factor. The first factor to be depleted is factor VII.

Clinical Presentation. Bleeding may occur at any site, but the GI tract is the most common site.

The disorder is clinically indistinguishable from vitamin K deficiency except that there is no improvement when vitamin K is given.

Diagnosis.

- Elevated PT and PTT, but PT elevates first and is often more severely affected
- Clear history of liver disease (common), suggesting the diagnosis; low platelets are also common as a result of the hypersplenism that accompanies the liver disease

Treatment. For acute situations such as severe bleeding, e.g., melena, FFP is used. For long-term management, evaluate the nature of the liver disease.

Disseminated Intravascular Coagulation

DIC is consumptive coagulopathy from major underlying illness, resulting in the consumption of both platelet and clotting factor type and occasionally thrombosis. The bleeding is associated with a marked production of fibrin degradation products such as d-dimers.

Although DIC is essentially an idiopathic disorder, there is almost always a major underlying disease in the case history.

- Evidence of sepsis (**most common**); gram-negative sepsis causes DIC by the releasing endotoxin
- Rhabdomyolysis
- Adenocarcinoma
- Heatstroke
- Hemolysis from transfusion reactions
- Burns

- Head trauma
- Obstetrical disasters such as abruptio placenta and amniotic fluid embolism
- Pancreatitis
- Snakebite

Promyelocytic leukemia (M3) is a classic association with DIC. In the acute form, the destruction of leukemic granulocyte precursors causes large amounts of proteolytic enzymes to release from their storage granules, resulting in microvascular damage.

Other malignancies may also cause DIC by augmenting the expression of various oncogenes that result in the release of tissue factor.

DIC can be acute or chronic.

- **Acute DIC** develops when sudden exposure of blood to procoagulants (tissue factor, tissue thromboplastin) generates intravascular coagulation. The compensatory hemostatic mechanisms are quickly overwhelmed, and, as a consequence, a severe consumptive coagulopathy leading to hemorrhage develops.
- **Chronic DIC** reflects a compensated state that develops when blood is continuously or intermittently exposed to small amounts of tissue factor. Compensatory mechanisms are not overwhelmed. Chronic DIC is more frequently observed in patients with solid tumors and in those with large aortic aneurysms.

Clinical Presentation. Bleeding from any site in the body is possible because of a decrease in both the platelet as well as clotting factor levels. Thrombosis is less common. Hemolysis is often present and may lead to acute renal failure, jaundice, and confusion.

Diagnosis. DIC is suspected when a patient has a serious underlying disorder as described with bleeding and there is elevation in both the PT and PTT with a decrease in the platelet count. The fibrinogen level is often low because it has been consumed. D-dimers and fibrin-split products are present in increased amounts, suggesting the consumption of all available elements of the coagulation system. The peripheral blood smear often shows the schistocytes as fragmented cells consistent with intravascular hemolysis.

Treatment. Because most patients present with severe bleeding, FFP and sometimes platelet transfusions are necessary to correct the bleeding. Heparin is controversial and is rarely used, except in those patients presenting predominantly with thrombosis. Don't forget to correct the underlying disorder.

Thrombotic Thrombocytopenic Purpura/Hemolytic Uremic Syndrome

Thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS) are varieties of the same disease, with considerable overlap. There is no specific diagnostic test, so the diagnosis is based on the clinical triad (HUS) or pentad (TTP).

- Most cases of TTP are idiopathic and arise from inhibition of the enzyme ADAMTS13, which is responsible for cleaving large multimers of von Willebrand factor into smaller units. The increase in circulating multimers of vWF increase platelet adhesion to areas of endothelial injury, particularly the arteriole-capillary junctions.
- Some cases of TTP are associated with specific diseases (cancer, HIV) and drugs (ticlopidine, clopidogrel, cyclosporine, and interferon) and are referred to as secondary TTP. ADAMTS13 activity is generally not as depressed in secondary TTP.



HUS predominantly affects children. Most cases are caused by a shiga-like toxin produced by *E. coli* O157:H7, although *Campylobacter*, *Shigella*, and some viruses have also been implicated. It is one of the most common causes of acute renal failure in childhood and carries up to 10% mortality.

HUS consists of a triad of hemolytic anemia, uremia, and thrombocytopenia. TTP has the same 3 findings, and is also associated with fever and neurologic problems. You do not have to have all 5 findings simultaneously to be considered to have TTP. The anemia in both will be intravascular in nature and will have an abnormal blood smear showing schistocytes, helmet cells, and fragmented red cells. LDH and reticulocyte count will be elevated and haptoglobin decreased.

Treatment.

- **TTP:** plasmapheresis (for very severe cases, add rituximab)
- **HUS:** plasmapheresis for severe cases only; mild disease resolves spontaneously
- Do not give antibiotics to those with possible HUS (organism may release more toxins as it dies and may worsen the disease).
- Do not transfuse platelets, even if platelet count is low (can worsen the CNS and renal abnormalities by giving more platelets as a substrate to precipitate; small platelet plugs are actually the cause of the problem).

Heparin-Induced Thrombocytopenia

Heparin-induced thrombocytopenia (HIT), a complication of heparin therapy, can occur with any form of heparin. It is more common with IV unfractionated heparin than with low molecular weight (LMW) heparin.

Type 1 HIT presents within first 2 days after exposure to heparin.

- Non-immune-mediated disorder that results from the direct effect of heparin on platelet activation
- This form of thrombocytopenia is benign, self-limited, and not associated with bleeding or increased risk of thrombosis

Type 2 HIT (generally referenced as HIT) occurs 4-10 days after exposure to heparin.

- Immune-mediated disorder
- Has life- and limb-threatening thrombotic complications (low platelet count causes thrombosis)

Suspect HIT when a patient who is receiving heparin has a decreased platelets, particularly if the drop is >50% of the baseline count, even if the platelet count nadir remains >150,000.

Clinically, HIT is not often marked by bleeding; the most common complication is venous thromboembolism (deep venous thrombosis, pulmonary embolism), and less often, arterial thrombosis (stroke, myocardial infarction). Thrombosis develops in approximately 20% of patients with HIT, with mortality as high as 30%.

Diagnosis of HIT is based on the combined clinical findings, thrombocytopenia characteristics, and lab studies of HIT antibodies (positive in ~85% of patients with type 2 HIT).

Note

Because the most common complications of HIT are venous thromboembolism and arterial thrombosis, it is sometimes called **heparin-induced thrombocytopenia and thrombosis**.

Treatment.

- Discontinue all heparin products (including heparin flushes of IV catheters)
- Replace with an alternative anticoagulant such as argatroban or fondaparinux (parenteral factor X inhibitor)

Patients diagnosed with HIT should avoid all forms of heparin for life.

Warfarin

Warfarin is the most widely prescribed anticoagulant for the prevention and treatment of thromboembolic disease. It was initially introduced as a pesticide against rodents, and long-acting forms of warfarin are still used for this purpose.

Warfarin anticoagulates by inhibiting an enzyme that recycles oxidized vitamin K to its reduced form. Warfarin does not antagonize the action of vitamin K, but rather antagonizes vitamin K recycling. Once vitamin K is reduced, the vitamin K dependent factors (factors 2,7,9,10) are eventually reduced (3-5 days).

Despite its efficacy, treatment with warfarin has several limitations.

- Many commonly used medications interact with warfarin, as do some foods—particularly green vegetables—since they typically contain large amounts of vitamin K.
- Warfarin activity has to be monitored by the PT and international normalized ratio (INR) to ensure an adequate yet safe dose (typically **INR 2–3** is considered adequate and safe anticoagulation). The pharmacologic action of warfarin may always be reversed by fresh vitamin K.

Table 6-4. Recommended Management of a Supratherapeutic INR

INR	Bleeding Present	Recommended Action
<Ther to 5.0	No	• Lower warfarin dose, or • Omit a dose and resume warfarin at a lower dose when INR is in therapeutic range, or • No dose reduction needed if INR is minimally prolonged
>5.0 to 9.0	No	• Omit the next 1–2 doses of warfarin, monitor INR more frequently, and resume treatment at a lower dose when INR is in therapeutic range, or • Omit a dose and administer 1–2.5 mg oral vitamin K*
>9.0	No	• Hold warfarin and administer 5–10 oral vitamin K. Monitor INR more frequently and administer more vitamin K as needed. Resume warfarin at a lower dose when INR is in therapeutic range.
>20	—	• Hold warfarin and administer 10 mg vitamin K by slow IV infusion; supplement with FFP, or recombinant human factor VIIa, depending on clinical urgency. Monitor and repeat as needed.
Any	Life-threatening	As per “INR >20” above

Ther: therapeutic INR range for the patient in question INR

*Preferred in patients at increased risk for bleeding (e.g., history of bleeding, stroke, anemia).



Clinical Recall

What is the most appropriate step in the management of a patient with heparin-induced thrombocytopenia and thrombosis?

- A. Continue heparin and administer warfarin
- B. Discontinue heparin and administer argatroban
- C. Discontinue the heparin substitute with warfarin
- D. Continue heparin and add lepirudin
- E. Continue heparin and monitor closely

Answer: B

Infectious Diseases

7

Learning Objectives

- ❑ Provide an overview of common antibiotics and their uses
- ❑ Describe the unique conditions and considerations for infections which occur in the CNS, head, neck, lung, pericardium, endocardium, GI tract, urinary tract, bones, and joints
- ❑ Present the treatment of acute herpes viral hepatic infections
- ❑ Describe the diagnosis and management of Lyme disease and Rocky Mountain spotted fever
- ❑ Describe the epidemiology, presentation, and treatment of genital/sexually transmitted diseases and AIDS

Note

In March 2020, the WHO declared a global pandemic of a new coronavirus, **COVID-19**. This topic is **unlikely to be on the USMLE this year**, but preliminary research shows the following:

- ssRNA enveloped coronavirus transmitted via droplets to the lungs
- Highly contagious and likely a zoonotic infection (bats)
- Incubation time 4–14 days
- Can be spread by asymptomatic carriers

Note

Do not use vancomycin if the organism is oxacillin-sensitive.

ANTIBIOTICS

Antibiotics can be grouped by their chemical class or by the type of organism they are effective against.

The organisms that cause specific diseases do not change much over time. For example, MRSA, *Staphylococcus aureus* is still the most common cause of osteomyelitis, and *Escherichia coli* is still the most common cause of pyelonephritis.

What does change over time is the antibiotic that is effective against each organism and the sensitivity pattern of each organism.

Gram-Positive Cocci

Semisynthetic penicillinase-resistant penicillins

Staphylococcal and streptococcal organisms are effectively treated by medications such as the semisynthetic penicillins, including oxacillin, cloxacillin, dicloxacillin, and nafcillin. These agents are exclusively effective against gram-positive cocci, in particular staphylococci.



Note

- **Methicillin** was one of the original drugs in this class. However, it may cause interstitial nephritis and so is not used clinically. Thus, the term “methicillin-sensitive” or “methicillin-resistant *Staphylococcus aureus* (MRSA)” is a misnomer because methicillin is not actually used.
- When the term MRSA is used, think of oxacillin, cloxacillin, dicloxacillin, and nafcillin.

Note

On the exam, your answers should correspond most specifically to the organism you are treating. If you are treating a sensitive *Staph aureus* or *Strep*, answer with a specific gram-positive drug. Do not give an answer which provides more coverage than needed, unless there is evidence to support the presence of other organisms. If you are treating a gram-positive infection, answer with a first-generation agent.

When *Staphylococcus* is sensitive to the semisynthetic penicillins, and concurrent gram-negative infection is not suspected, these are the ideal agents. They are more effective than vancomycin when the organism is sensitive. These drugs are also sometimes referred to as “beta-lactamase-resistant penicillins” or “antistaphylococcal penicillins.” Nevertheless, the latter term is somewhat misleading because they are also effective against a number of streptococci, such as *S. pneumoniae*, the Viridans group, and groups A, B, C, and G Strep.

Penicillin G, penicillin VK, ampicillin, and amoxicillin

These agents are effective against streptococci, such as *S. pyogenes*, viridans group streptococci, and *S. pneumoniae*, but not against staphylococci.

- Ampicillin and amoxicillin are effective against staph only when **ampicillin is combined with the beta-lactamase inhibitor sulbactam** or when **amoxicillin is combined with clavulanate**.
- Ampicillin has some activity against *E. coli*.
- Both ampicillin and amoxicillin are effective against enterococci and *Listeria*.
- Penicillin is effective against *Actinomyces* (think of this with dental abscess in someone with periodontal disease).

Cephalosporins

The first- and second-generation cephalosporins all cover the same range of organisms that the semisynthetic penicillins cover, i.e., staphylococci and streptococci, plus some gram-negative organisms.

- First-generation agents (**cefazolin, cefadroxil, cephalexin**) only reliably cover *E. coli*, *Proteus mirabilis*, and *K. pneumoniae*; cefazolin has been proven more effective for MSSA than nafcillin or oxacillin.
- Second-generation agents (**cefotetan, cefuroxime, cefprozil, loracarbef**) will cover everything a first-generation cephalosporin covers, as well as a few more gram-negative bacilli such as *Providencia*, *Haemophilus*, *Klebsiella*, *Citrobacter*, *Morganella*, and *Proteus*.
- Third-generation agents, particularly ceftazidime, are not reliable in their staphylococcal coverage.
- Fourth-generation cephalosporins such as cefepime will cover staph and strep, although this should never be the answer when the infection is exclusively gram-positive.

For those with allergy to penicillin, there is only a <1% risk of cross-reaction with cephalosporins. When this reaction occurs it is seldom an anaphylactic reaction.

- When the allergic reaction is described as a rash, a cephalosporin can safely be used.
- When the allergic reaction is severe, e.g. anaphylaxis, a cephalosporin should not be used.
- For minor infections, use a macrolide (clarithromycin or azithromycin) or one of the new fluoroquinolones (levofloxacin, gemifloxacin, or moxifloxacin).
- For serious infections in those with a life-threatening penicillin allergy, use vancomycin, linezolid, or daptomycin.

Macrolides, fluoroquinolones, and clindamycin

For gram-positive infections, macrolides (erythromycin, clarithromycin, azithromycin), fluoroquinolones (levofloxacin, gemifloxacin, moxifloxacin), and clindamycin are alternatives to penicillins and cephalosporins. Macrolides should not be used for serious staph infection.

The respiratory quinolones are very good for streptococcal infections, particularly *Strep pneumoniae*, especially in penicillin-resistance. They are also sufficient against staph. Ciprofloxacin is a quinolone as well, but it does not cover *Strep pneumoniae*. Ciprofloxacin has no gram-positive coverage.

Vancomycin, linezolid, tigecycline, ceftaroline, telavancin

For gram-positive infections, vancomycin (side effects include thrombocytopenia; do not use if MIC >2), linezolid (side effects include thrombocytopenia and lactic acidosis; do not use with SSRIs), and tigecycline are effective. Alternatives include ceftaroline, telavancin, daptomycin (monitor CPK; do not use for pneumonia; neutralized by surfactant). Other options are dalbavancin (2 doses one week apart, via IV) and oritavancin (one dose via IV).

When there is a life-threatening penicillin-allergy or MRSA, use the listed agents (vancomycin is preferred for MRSA).

Ceftaroline is used like a third-generation cephalosporin, such as ceftriaxone, combined with a MRSA agent, such as vancomycin. Ceftaroline is the only cephalosporin to cover MRSA. These medications should not be used if the organism is sensitive to methicillin.

Gram-Negative Bacilli

Penicillins

Penicillins (piperacillin, ticarcillin, mezlocillin) are fully active against the full range of gram-negative bacilli, such as *Pseudomonas*, as well as the Enterobacteriaceae. Enterobacteriaceae include *E. coli*, *Proteus*, *Enterobacter*, *Citrobacter*, *Morganella*, *Serratia*, and *Klebsiella*. They are **only active against staph when combined with a beta-lactamase inhibitor** such as piperacillin/tazobactam or ticarcillin/clavulanate. Ampicillin/sulbactam and amoxicillin/clavulanate will also cover staph and gram-negative bacilli, but not *Pseudomonas*.

All penicillins will cover sensitive streptococci, but if the patient has only a sensitive strep, give a narrower agent, such as penicillin G or penicillin VK.

Cephalosporins

Third- and fourth-generation agents (ceftazidime; cefotaxime; ceftriaxone, and cefepime) are fully active against the full range of gram-negative bacilli, such as the Enterobacteriaceae.

- Only ceftazidime and cefepime cover *Pseudomonas*.
- Cefepime also covers staph.
- Side effects of ceftriaxone include biliary/gallbladder sludge and autoimmune hemolytic anemia.

Second-generation agents cover some of the Enterobacteriaceae, but not *Pseudomonas*. Although predominantly for use against gram-negative organisms, ceftriaxone and cefotaxime are the best answers for penicillin-insensitive pneumococci-causing meningitis or pneumonia.

Note

Daptomycin, ceftaroline, and tigecycline are also effective against MRSA.

Note

Quinupristin/dalfopristin is no longer used.

Note

Cephalosporins are safe in penicillin allergy if it is only a rash.



Clinical Pearl

Ceftriaxone does not have adequate pseudomonal coverage.

Note

The FDA has recently issued a warning to avoid using fluoroquinolones because of severe side effects—tendonitis, tendon rupture, peripheral neuropathy. These medications can also cause QT prolongation.

Quinolones

Quinolones (ciprofloxacin, levofloxacin, delafloxacin, moxifloxacin, ofloxacin) cover most of the Enterobacteriaceae, such as *E. coli*, *Proteus*, *Enterobacter*, *Haemophilus*, *Moraxella*, *Citrobacter*, *Morganella*, *Serratia*, and *Klebsiella*. Only ciprofloxacin reliably covers *Pseudomonas*.

The respiratory fluoroquinolones (moxifloxacin, levofloxacin, and gemifloxacin) are also active against gram-positive cocci, in particular *Strep pneumoniae*. They are among the first-line therapies for empiric treatment of pneumonia because they will also cover *Mycoplasma*, *Chlamydia*, and *Legionella*.

Ciprofloxacin does not cover gram-positives and cannot be used for pneumonia or cellulitis.

Aminoglycosides and monobactams

Aminoglycosides (gentamicin, tobramycin, amikacin) and monobactams (aztreonam) have essentially the same gram-negative coverage as listed for the other agents. Although aminoglycosides can be synergistic with a penicillin in the treatment of staph, they are essentially exclusively gram-negative agents. Aztreonam is exclusively a gram-negative agent, with no strep or staph coverage at all.

Carbapenems

Carbapenems (imipenem, meropenem, ertapenem, doripenem) are fully active against Enterobacteriaceae and *Pseudomonas*; they are similar in gram-negative coverage to the aminoglycosides and third-generation cephalosporins. In addition, they have excellent staph and anaerobic coverage. Although effective in polymicrobial infections, they are best used in gram-negative infections.

All carbapenems are equally effective against anaerobes, as compared to metronidazole. Ertapenem will not cover *Pseudomonas*.

Anaerobes

The agent most active against anaerobes is metronidazole.

- Metronidazole has some advantages against anaerobic gram-negative bacteria in the bowel, such as *Bacteroides fragilis*.
- Clindamycin is less active against intra-abdominal anaerobes, but has some advantages against anaerobic streptococci in the mouth.
- The other agents with excellent anaerobic coverage virtually equal to metronidazole are the carbapenems and the beta-lactam/beta-lactamase combination medications (piperacillin/tazobactam, ticarcillin/clavulanate, ampicillin/sulbactam, or amoxicillin/clavulanate)
- The second-generation cephalosporins cefoxitin and cefotetan have fair activity against anaerobes but are less effective.

Skin MRSA

- TMP/SMZ, clindamycin, doxycycline, and linezolid are oral agents useful for MRSA; use them for minor MRSA infections.
- TMP/SMZ, clindamycin, and doxycycline cannot be used for MRSA bacteremia.
- Clindamycin also covers Group A strep and MSSA.

Think of MRSA cellulitis when there is purulent cellulitis or an abscess. When there is nonpurulent cellulitis, cover beta-hemolytic streptococci and MSSA, using dicloxacillin, cefazolin, cephalexin, or clindamycin.

CENTRAL NERVOUS SYSTEM INFECTIONS

Meningitis

A 45-year-old man is brought to the ED with 1–2 days of fever, headache, nausea, and vomiting. On physical examination he is found to have neck stiffness and photophobia.

Meningitis is an infection or inflammation of the meninges, the connective tissue covering the CNS. Most cases arise sporadically, and the precise method of spread of the microorganism into the CNS stem is not known. Overall, most meningitis cases are caused by viruses.

- *Streptococcus pneumoniae* is the most common cause of bacterial meningitis for all patients beyond the neonatal period.
- *Neisseria meningitidis*, spread by respiratory droplets, is the most common cause of meningitis in adolescents.
- *Listeria monocytogenes* is more common in those with immune system defects, particularly of the cellular (T-cell) immune system and sometimes neutrophil defects. These defects include HIV, steroid use, leukemia, lymphoma, and various chemotherapeutic agents. Since neonates and the elderly have decreased T-cell immune function, *Listeria* is more common in them.

Even with immune deficits, *Streptococcus pneumoniae* is still the *most* common etiology—it is just that *Listeria* is *more* common in these patients, as compared to fully immunocompetent patients. *Staphylococcus aureus* is more common in those who have had any form of neurosurgery because instrumentation and damage to the skin introduce the organism into the CNS. *Cryptococcus* is more common in those who are HIV positive and who have profound decreases in T-cell counts to levels <100 cells.

Rocky Mountain spotted fever (RMSF) is common in those who have been exposed to ticks in the appropriate geographic area. The areas with the highest RMSF infection are in the mid-Atlantic areas, such as the Carolinas, Kentucky, and Tennessee. Lyme disease can also cause meningitis and is more common in the Northeast, such as Massachusetts, Connecticut, New York, and New Jersey. TB and syphilis are also associated with meningitis. Viruses are the most common cause of aseptic meningitis, a syndrome in which patients present in a manner similar to bacterial meningitis, but CSF analysis mostly reveals a lymphocytic pleocytosis and bacterial cultures are negative. Viruses causing aseptic meningitis include enteroviruses,

Note

Do not treat sensitive *Staph* with TMP/SMZ or doxycycline.

Note

In the past, *Haemophilus influenzae* was the most common cause of meningitis in children, but that is no longer the case with the *Haemophilus* type B vaccine.



arboviruses (St. Louis encephalitis virus, West Nile virus), HIV, herpes simplex, and lymphocytic choriomeningitis virus. In the past, most of these were not diagnosed, but with the availability of PCR-based testing, more cases of aseptic meningitis are being accurately classified. Group B *Streptococcus* (*Streptococcus agalactiae*) is the most common cause of meningitis in the neonatal period.

The spread of the organism into the CNS can be by sporadic (unknown) mechanisms or by means of contiguous local infection or by hematogenous spread. Local infections that can lead to meningitis include otitis media, sinusitis, mastoiditis, and dental infections. Hematogenous spread could possibly occur from any infection but is more common with endocarditis and pneumonia.

Clinical Presentation. Regardless of microbiologic etiology, all forms of meningitis present with fever, photophobia, headache, nuchal rigidity (neck stiffness, positive Kernig and Brudzinski signs), as well as nausea and vomiting. Altered mental status is possible, and can make a patient appear to have encephalitis. Any form of CNS infection can present with seizures. Focal neurologic deficits can also occur, the most common being visual field and cranial nerve deficits. The most common long-term neurologic deficit from bacterial meningitis is damage to the 8th cranial nerve.

Rash is associated with several types of meningitis.

- Petechial rash is suggestive of *Neisseria*
- Rash on the wrists and ankles with centripetal spread toward the body is suggestive of RMSF
- Facial nerve palsy is suggestive of Lyme disease; the target-like erythema migrans rash of Lyme disease is seldom present by the time the meningitis develops
- Pulmonary symptoms or abnormal chest x-ray suggest TB

Diagnosis.

- LP (**essential for establishing diagnosis**)
 - Culture of the CSF (**most accurate test for bacterial meningitis**); the results are always delayed for several days, however, and are rarely available at the time the initial therapy must be instituted.
 - Protein levels are elevated most commonly with bacterial meningitis (but can be elevated in any type of meningitis).
 - Elevated protein and/or decreased glucose by themselves are relatively nonspecific findings.
 - The opening pressure can be elevated with any cause of meningitis.
- CT scan of the head
 - Best initial diagnostic test if patient has papilledema, focal motor deficits, new onset seizures, severely abnormal mental status, or immunocompromised status
 - If none of the above is present, CT scan is not needed first
 - CT scan can delay the diagnosis; if LP is delayed >20–30 min while waiting for the CT scan, give an empiric dose of antibiotics

- Gram stain has a limited sensitivity and is positive in 50–70% of patients at most; when positive, however, it has a high specificity.
- Cell count (**initially, most useful test**); although elevated cell count by itself is nonspecific, the differential of the cells is useful. Only bacterial meningitis gives thousands of cells that are all neutrophils. A mild-to-moderate elevation in lymphocytes, with several dozen to several hundred cells, can occur with viral infection, *Rickettsia*, Lyme, TB, syphilis, or fungal (cryptococcal) etiology. Normal CSF cell count is <5 cells/mm³, which should be predominantly lymphocytes.
- **Nonbacterial meningitis** can be diagnosed according to the nature of the organism.
 - Lyme and RMSF are best detected with a specific immunologic response and serology.
 - *Cryptococcus neoformans* is detected with elevated serum and CSF cryptococcal antigen titer.
 - Syphilis is confirmed by the presence of a positive VDRL or FTA on CSF.
 - TB is rarely detected by an AFB smear; a culture for TB has a much higher yield, particularly on several repeated LPs, and PCR can also help with TB diagnosis.

Treatment.

- Vancomycin (empiric therapy of bacterial meningitis in adults because of the increasing prevalence worldwide of pneumococci with decreasing sensitivity to penicillins) plus a third-generation cephalosporin such as ceftriaxone
- For the immunocompromised or those age >50 or ≤ 1 month, add ampicillin to cover *Listeria* (*Listeria* is resistant to all forms of cephalosporins)
- If hospital-acquired or post-neurosurgical procedure, must cover *Pseudomonas* and MRSA: use vancomycin and cefepime, ceftazidime, or meropenem (for penicillin-allergy, replace moxifloxacin for cephalosporin) and TMP/SMX for ampicillin)
- Lyme disease: ceftriaxone
- *Cryptococcus*: amphotericin B and flucytosine initially, followed by fluconazole for HIV-positive patients (life-long or until patient is on HAART and is asymptomatic with CD4 count $>100/\mu\text{L}$ for at least 3–6 months)
- Neurosyphilis: high-dose IV penicillin
- TB meningitis: same treatment as pulmonary TB but for longer duration, 9–12 months
 - For TB and bacterial (adult) meningitis, steroids are appropriate.
 - Dexamethasone decreases morbidity, mortality, and rates of deafness
 - Benefit is greatest for pneumococcal meningitis
 - Administer 15–20 min before or concurrently with antibiotics
 - Give for 4 days if bacterial meningitis is confirmed (i.e., positive Gram stain of CSF fluid or >1000 WBCs within the CSF)
 - Discontinue if etiology is nonbacterial (viral, fungal, etc.)

Clinical Pearl

In patients presenting with symptoms and signs of meningitis, treat empirically for bacterial meningitis while awaiting the LP test results.

Note

Vancomycin is used if there is a known/suspected pneumococcal resistance to penicillin or if there is a chance of staphylococcal infection after neurosurgery.



Note

The rationale for steroid use with bacterial meningitis is the inflammatory response elicited in the subarachnoid space due to bacterial cell wall lysis after antibiotics are administered; this inflammatory reaction can worsen morbidity and mortality due to bacterial meningitis.

Note

Think of West Nile encephalitis when the patient has acute asymmetric flaccid paralysis.

Note

Encephalitis usually presents with altered mental status, erratic behavior, etc (brain parenchyma involved).

Clinical Recall

A 65-year-old man presents to the ED with fever, stiff neck, and photophobia. Which of the following is the best empiric treatment?

- A. Vancomycin, ceftriaxone, ampicillin, and dexamethasone
- B. Nafcillin, ceftriaxone, and ampicillin
- C. Vancomycin and ceftriaxone
- D. Vancomycin, cefepime, and dexamethasone
- E. Vancomycin, ceftriaxone, and ampicillin

Answer: A

Encephalitis

A young man is brought to the ED by his friends because of 1–2 days of confusion and strange behavior. He had originally complained of a headache and fever. On the day of admission he became markedly worse and is now delirious. He is generally healthy. On physical examination you find a lethargic, confused man with an elevated temperature. You are unable to determine if he has focal neurologic findings or to obtain an accurate neurologic exam because his confusion makes him unable to follow commands.

Encephalitis is an infection of the brain, whether in the meninges or the brain parenchyma. Although any bacterial, protozoal, or rickettsial infection can cause encephalitis, most cases are caused by viruses.

- Herpes simplex (usually type I [HSV-1]) (**most common**)
- Varicella-zoster virus, CMV, enteroviruses, Eastern and Western equine encephalitis, St. Louis encephalitis, and West Nile encephalitis (less common)

Symptoms include:

- Altered mental status with fever and headache (**clue to diagnosis**)
- Any level of neurologic deficit, from slight confusion to lethargy or coma
- Focal deficits
- Stiffness similar to that found in meningitis (making it difficult to distinguish from meningitis)
- Seizures

Diagnosis. Although CT or MRI of the head should be performed, it cannot give a specific diagnosis. HSV has a predilection for involvement of the temporal lobes, which can sometimes be seen on CT. LP is the key to the diagnosis. Formerly, a brain biopsy was necessary, but PCR (polymerase chain reaction) amplification techniques have virtually eliminated that need. PCR for HSV has a 98% sensitivity and >95% specificity, making it at least equal to the biopsy. HSV PCR may be negative early on. If imaging and clinical presentation is consistent with HSV, continue acyclovir and repeat HSV PCR in 3–5 days.

Treatment. HSV encephalitis is best treated with IV acyclovir. Although famciclovir and valacyclovir have activity against HSV, they are not available intravenously. Ganciclovir and foscarnet are active against CMV. Acyclovir-resistant herpes is treated with foscarnet.

Autoimmune Encephalitis

Autoimmune encephalitis is caused by anti-NMDA receptor antibodies. About >50% of cases are associated with ovarian teratomas.

Clinical Presentation.

- Choreoathetosis
- Psychiatric symptoms
- Seizures
- Autonomic instability
- Coma

Diagnosis. CSF anti- NMDA receptor antibodies.

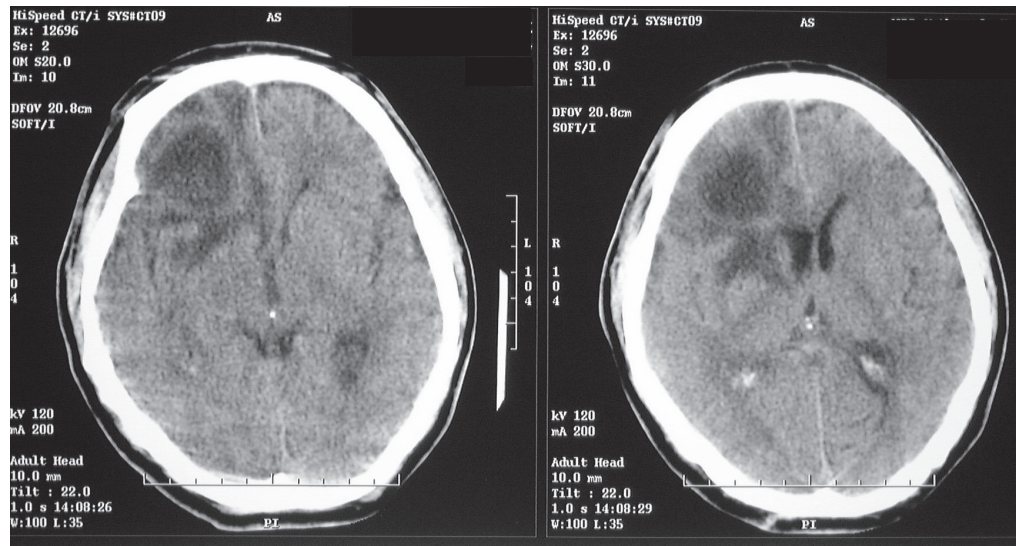
Treatment is removal of the teratoma when present; corticosteroids; rituximab; cyclophosphamide; and IVIG.

Brain Abscess

An HIV-negative man is brought to the hospital because of a seizure. When he becomes more alert, you find that he has aphasia and weakness of the right hand and leg. CT scan of the head with contrast shows enhancement of the lesion with a “ring” around the lesion.

Brain abscess is a collection of infected material within the brain parenchyma. Bacteria can spread into the brain from contiguous infections such as otitis media, sinusitis, mastoiditis, or dental infection. Organisms may also spread through the bloodstream from endocarditis or pneumonia and seed the brain. Toxoplasmosis can reactivate in those with severe HIV disease when CD4 counts are very low (<50–100/ μ L). Brain abscesses most commonly have *Streptococcus* in 60–70%, *Bacteroides* in 20–40%, Enterobacteriaceae in 25–35% and *Staphylococcus* in 10%, and are often polymicrobial. Because of the diversity of the organisms potentially involved, it is difficult to have a single standard therapy.

Headache is the most common symptom. Fever can be present. Focal neurologic deficits are the initial complaint in about 60% of patients. Seizures may occur, as with any form of anatomic abnormality of the CNS. All CNS infections can cause seizures.



aic.cuhk.edu.hk/web8

Figure 7-1. CT Scan Demonstrating Large Cerebral Abscess

Diagnosis. The initial test is the CT scan. Contrast is used to help identify the lesion, although CNS malignancy enhances with contrast as well. MRI is more accurate than the CT scan, although no radiologic test alone can give the precise etiology. In the case of bacterial brain abscess, examination of the abscess fluid (obtained by stereotactic aspiration or surgical excision of the abscess) for Gram stain and culture is essential. In HIV-positive patients, 90% of brain lesions will be either toxoplasmosis or lymphoma. This is the only circumstance where empiric therapy is sufficient to establish a specific diagnosis. If the lesion responds to 10–14 days of therapy with pyrimethamine and sulfadiazine, continue to administer this therapy, as it accurately predicts cerebral toxoplasmosis.

Treatment is almost always a combination of surgical and medical management. Focus on the underlying cause.

- Surgical: stereotactic aspiration (**preferred**) or surgical excision of the abscess (rarely done because of significant complications)
- Medical: one example is penicillin, metronidazole, and a third-generation cephalosporin such as ceftazidime
 - Penicillin to cover the streptococci, metronidazole to cover the anaerobes, and ceftazidime to cover the gram-negative bacilli
 - For HIV-positive patients: pyrimethamine and sulfadiazine

HEAD AND NECK INFECTIONS

Otitis Media

Otitis media is an infection of the middle ear between the eustachian tube and the tympanic membrane. Viral upper respiratory infection can cause edema of the eustachian tube, which often leads to middle ear infection. The most common organisms are *Strep pneumoniae* (35–40%), *H. influenzae* (nontypeable; 25–30%), and *Moraxella catarrhalis* (15–20%). Viruses probably account for the rest of the cases (roughly the same breakdown of organism type and frequency that occurs in bronchitis and sinusitis).

Symptoms include ear pain, decreased hearing, and ear pain. On physical examination a red, bulging tympanic membrane is found, with loss of the light reflex. The most sensitive clinical finding is immobility of the membrane on insufflation of the ear with air. Perforation of the tympanic membrane with otorrhea occurs rarely.

Diagnosis is made through physical examination of the ear. Radiologic tests are not useful. A specific bacteriologic diagnosis can be obtained with tympanocentesis for culture, but that is rarely performed.

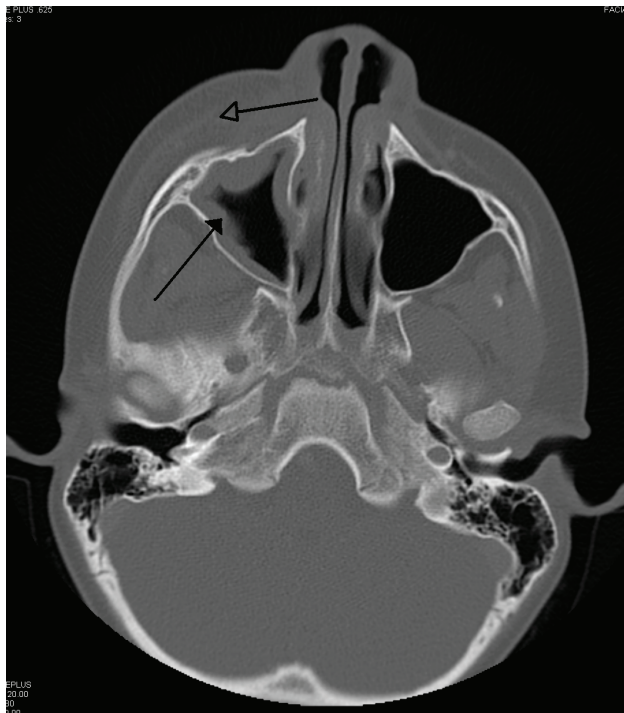
Treatment is oral amoxicillin.

- If there is no response or if the patient has been recent amoxicillin use, use amoxicillin-clavulanate; a second-generation cephalosporin (cefuroxime, loracarbef, cefprozil); or a third-generation agent (cefdinir, cefixime).
- For severe penicillin allergy, give a macrolide such as azithromycin or clarithromycin.
- New fluoroquinolones such as levofloxacin, moxifloxacin, or gatifloxacin are microbiologically acceptable but are broader coverage than needed, so do not use in children (concern for arthropathy).
- TMP/SMZ is sometimes used but is poorly active against *Streptococcus pneumoniae*.

Sinusitis

A young woman presents with several days of facial pain, a headache, cough, fever, and discolored nasal drainage. On physical examination, tenderness over the maxillary sinuses and decreased transillumination of the maxillary sinuses are found.

Sinusitis is an infection of the sinuses. The most common site is the maxillary sinus, followed by ethmoid, frontal, and sphenoid sinuses.



Wikipedia, James Heilman, MD

Figure 7-2. Sinusitis

Viruses are responsible for most cases of sinusitis. Bacterial organisms that cause sinusitis are the same ones causing otitis media. Bacterial infection is more likely in one of the following situations:

- Persistent symptoms >10 days
- Severe symptoms of fever lasting 3–4 days
- Double-sickness (worsening symptoms following a period of improvement over 3–4 days)

Symptoms include:

- Facial pain
- Postnasal drainage, purulent nasal drainage
- Headache (**common**) is worse when leaning forward
- Fever (50% of cases)
- Tooth pain (due to proximity of sinuses to the teeth)

Diagnosis. Obvious cases of sinusitis do not always need radiologic confirmation prior to treatment. Sinus x-rays are of little value, and routine imaging as a rule is not recommended. If imaging is required because of concern for complications, uncertain diagnosis, or lack of response to treatment, CT scan of the sinuses is the test of choice since it provides greater detail. For those who are immunocompromised, CT should be done to evaluate for fungal infection.

Treatment.

- For uncomplicated sinusitis (mild or acute), use NSAIDs and decongestants, e.g., oral pseudoephedrine or oxymetazoline spray; most cases resolve in 7–10 days
- If antibiotics are needed, amoxicillin-clavulanate is first-line; use doxycycline for penicillin allergy

Pharyngitis

Pharyngitis is irritation or inflammation of the back of the throat (or the pharynx). Although most cases are caused by viruses, the most important cause is group A beta-hemolytic streptococci (*S. pyogenes*) (only 5–15% of cases) because that could progress to rheumatic fever or glomerulonephritis.

Sore throat with cervical adenopathy and inflammation of the pharynx with an exudative covering is highly suggestive of *S. pyogenes*. Most viruses do not give an exudate, although the Epstein-Barr virus can. Mild *S. pyogenes* infections may not give an exudate, which is one of the reasons diagnostic testing is useful. Hoarseness and cough are not suggestive of pharyngitis.



Wikipedia, James Heilman, MD

Figure 7-3. Strep Throat

Diagnosis. The Centor criteria include 4 findings:

- Fever by history
- Tonsillar exudates
- Anterior cervical lymphadenopathy
- Absence of cough

Centor criteria <3 should not be treated or tested, while criteria 3 or 4 should get a rapid antigen detection test. If that is negative and the patient is high risk for complications, a throat culture should be done.



The rapid streptococcal antigen test is 80% sensitive but >95% specific. A positive test can be considered the equivalent of a positive culture, whereas a negative test should be confirmed with a culture.

Treatment is penicillin or amoxicillin. Use macrolides, clindamycin, or oral, first-generation cephalosporins for penicillin-allergy.

A rare complication of pharyngitis is **Lemierre syndrome**. Think of this in young adults with prolonged/severe pharyngitis, recent sore throat, persistent fever while on appropriate antibiotics, and neck pain/swelling.

- Etiology is septic thrombophlebitis of the internal jugular vein resulting in metastatic pulmonary infections due to septic emboli
- Causative organism is *Fusobacterium necrophorum*
- Diagnosis is made with CT contrast of the neck.
- Treatment is anything that covers anaerobes, i.e., ampicillin/sulbactam, clindamycin, carbapenem.

Influenza

Influenza is a systemic viral illness from influenza A or B, usually occurring in an epidemic pattern and transmitted by droplet nuclei. Influenza can lead to damage to the respiratory epithelium, leading to sinusitis, otitis media, bronchitis, and pneumonia.

Patients present with a systemic illness characterized by fever, myalgias, headache, and fatigue. Upper respiratory symptoms tend to predominate. These include runny nose (coryza), nonproductive cough, sore throat, and conjunctival injection.

Diagnosis is initially confirmed with rapid antigen detection methods of swabs or washings of nasopharyngeal secretions. Viral culture is the most accurate test but is usually not available rapidly enough to make it useful in acute patient management.

Treatment.

- For symptomatic disease
 - Acetaminophen and antitussives
 - Oseltamivir and zanamivir, neuraminidase-inhibitors specific for influenza A and B (use within 48 hours of onset of symptoms)
- Amantadine and rimantadine should not be used in the empiric therapy of influenza.
- **Influenza vaccination** is recommended annually for the general public.
 - Most important candidates include those who have chronic lung/cardiac disease or are immunosuppressed, pregnant women (any trimester), residents of chronic care facilities, health-care workers, and those with diabetes/renal dysfunction
 - Influenza vaccine contains egg protein, but because studies show that severe reaction in those with true egg protein allergy is rare, no precaution is needed.
 - As with any vaccine administration, monitor patients for any allergic manifestations.

Note

For influenza, chemoprophylaxis with oseltamivir should be initiated as soon as possible (and no later than 48 hours after exposure) and then continued for 7 days.

Note

- Flu vaccine is indicated annually for everyone age >6 months.
- Flu vaccine contains egg protein, but because severe reaction in those with egg protein allergy is rare, no precaution is needed. Monitor patients afterward.

Clinical Recall

An elderly, HIV-positive man comes to the ED with fever, headache, and muscle weakness. Imaging shows a brain abscess. Which of the following is the most appropriate next step in management?

- A. Brain biopsy to confirm pathogen
- B. Ceftriaxone, vancomycin, ampicillin, and steroids
- C. 10–14 days of therapy with pyrimethamine and sulfadiazine
- D. HSV PCR followed by IV acyclovir
- E. LP with culture of CSF fluid

Answer: C

LUNG INFECTIONS

Bronchitis

A 63-year-old man presents with a cough productive of yellowish sputum for several days. He has smoked 1 pack of cigarettes a day for 30 years. On physical examination the lungs are clear. His temperature is 38.3 C (101 F). Chest x-ray is normal.

Bronchitis is an infection of the lung, limited to the bronchial tree with limited involvement of the lung parenchyma. Acute exacerbations of chronic bronchitis (COPD) are often difficult to distinguish from a pneumonia until chest x-ray is performed.

- **Acute bronchitis** is an acute inflammation of the tracheobronchial tube. The vast majority of cases are caused by viruses. *S. pneumoniae* and *H. influenzae* have not been implicated. A small percentage of nonviral cases are due to *M. pneumoniae*, *C. pneumoniae*, and *B. pertussis*.
- **Chronic bronchitis** is caused by agents similar to those causing sinusitis and otitis media: *Streptococcus pneumoniae*, nontypeable *H. influenzae*, and *Moraxella*. Viruses account for a significant percentage but are often not confirmed. Cigarette smoking is the most common cause.

Clinical Presentation.

- Cough often with sputum production (discolored sputum suggests a bacterial etiology, but it is impossible to determine the specifics by that characteristic alone)
- Clear lungs (common) (however, lung exam may reveal rales)
- Signs of consolidation, e.g., increased fremitus, are absent
- Possible low-grade fever, but patients are more often afebrile

Diagnosis. Signs of respiratory infection, such as cough and sputum, with a normal chest x-ray confirm the diagnosis.

Note

Cigarette smoking is the most common cause of chronic bronchitis. Even 1 cigarette per day is enough to paralyze the cilia, which clear the bronchial tree of mucus and inhaled impurities for 24 hours.

**Treatment.**

- Mild acute cases: no treatment needed
- Acute exacerbations of chronic bronchitis: amoxicillin, doxycycline, or TMP/SMZ (if there has not been recent antibiotic use)
- Repeat infections or if no response to amoxicillin, one of the following:
 - Amoxicillin/clavulanate
 - Clarithromycin
 - Azithromycin
 - Oral second- or third-generation cephalosporin
 - New fluoroquinolone: gemifloxacin, levofloxacin, or moxifloxacin

Lung Abscess

A 58-year-old alcoholic man was admitted last night for several weeks of cough, sputum, and fever. He has lost 15 pounds and is feeling weak. On initial examination he is febrile and appears thin. He has very poor dentition. The lung examination is normal. The patient also exhibits a foul odor on the oral examination.

Lung abscess is necrosis of the pulmonary parenchyma caused by microbial infection.

- 90% have at least some anaerobes involved
- The most commonly implicated anaerobes are *Peptostreptococcus*, *Prevotella*, and *Fusobacterium* species, which are oral anaerobes found in the gingival crevices
- 45% only anaerobic, 45% mixed with aerobes, 10% aerobes only
- Aerobic bacteria, most frequently involved are *S. aureus*, *E. coli*, *Klebsiella*, and *Pseudomonas*

85–90% of cases have a clear association with periodontal disease or some predisposition to aspiration (e.g., altered sensorium, seizures, dysphagia). Pulmonary infarction, cancer, and vasculitis (like Wegener granulomatosis) are examples of noninfectious causes of lung cavities.

Patients present with the usual symptoms of pulmonary infection, such as fever, cough, sputum production, and chest pain, plus the following:

- Putrid, foul-smelling sputum (60–70% of cases)
- A more chronic course, i.e., several weeks of weight loss, anemia, and fatigue prior to diagnosis (likely due to the 1–2 week delay between the aspiration of oral contents and the development of necrosis and cavitation)

Diagnosis. Sputum for Gram stain and culture will not be able to show the causative anaerobic organism in a lung abscess. Chest x-ray in an abscess will often show a thick-walled cavitory lesion. Chest CT can help define the exact extent of the cavity. In the upright position the lower lobes are the most common sites of aspiration. In the supine position the posterior segment of the right upper lobe is the most common site. Aspiration of the abscess fluid is necessary for a specific bacteriologic diagnosis.

Treatment. In the absence of specific microbiologic diagnosis, clindamycin is good empiric coverage for the “above the diaphragm” anaerobes most often found. Penicillin is also acceptable.

In contrast to most abscesses where drainage is the rule, lung abscesses rarely require drainage in the antibiotic era. Most respond to antimicrobial therapy and drain spontaneously by communicating with larger bronchi. Therefore, the answer to the question, *what is the best initial therapy for a lung abscess*, is antibiotics such as clindamycin, not drainage.

Pneumonia

Pneumonia, a leading cause of death in the United States, is an infection of the lung parenchyma. Causes include:

- Community-acquired pneumonia (CAP)
 - *S. pneumoniae* (**most common cause** when an actual cause is identified)
 - In children age <5, viruses (**most common cause**)
 - Subsequent causes may vary, but *S. pneumoniae* is always number 1
- Hospital-acquired pneumonia (HAP) or ventilator-associated pneumonia (VAP)
 - Gram-negative bacilli such as *E. coli*, the other *Enterobacteriaceae*, or *Pseudomonas*
 - MRSA

Table 7-1. Frequency of Infectious Agents Causing Pneumonia

“Typical”	40–60%
<i>Strep pneumoniae</i>	15–35%
<i>Haemophilus</i>	2–10%
<i>Moraxella</i>	<5%
“Atypical”	10–30%
<i>Legionella</i>	0–15%
<i>Mycoplasma</i>	10%
<i>Chlamydia</i>	5–10%
Viral	2–20%
Unknown	30–60%

Specific predispositions are as follows:

- *Haemophilus influenzae*: smokers, COPD
- *Mycoplasma*: young, otherwise healthy patients
- *Legionella*: epidemic infection in older smokers, particularly when located near infected water sources, such as air-conditioning systems

Note

Pneumonia is the only cause of death from an infectious disease in the top 10 causes of death in the United States.

Note

With pneumonia diagnosis, a particular predisposing condition is not essential (although some conditions do predispose to having pneumonia, i.e., cigarette smoking, diabetes, alcoholism, malnutrition, obstruction of the bronchi from tumors, and immunosuppression in general).

Neutropenia and steroid use predispose to *Aspergillus* infection.



- *Pneumocystis jirovecii* (formerly *carinii*) pneumonia: HIV-positive persons with <200 CD4 cells not on prophylaxis
- *Coxiella burnetii* (Q-fever): exposure to animals, particularly when they are giving birth
- *Klebsiella*: alcoholics
- *Staphylococcus aureus* (MRSA): following viral syndromes or viral bronchitis, especially influenza; cavity infiltrates
- *Pseudomonas aeruginosa*, *Burkholderia cepacia*, *Stenotrophomonas*: structural lung disease (bronchiectasis including CF; recent steroid use; broad-spectrum antibiotics in past month)
- *Coccidioidomycosis*: exposure to the deserts of the American Southwest, particularly Arizona; associated with erythema nodosum and monoarthritis
- *Chlamydia psittaci*: birds
- *Blastomycosis*: skin lesions; bone and prostate involvement
- *Histoplasma capsulatum*: exposure to bat or bird droppings, spelunking (recreational cave exploration); oral ulcers; hepatosplenomegaly; pancytopenia; hilar lymphadenopathy; cavitary lung lesions
- *Bordetella pertussis*: cough with whoop and post-tussive vomiting
- *Francisella tularensis*: hunters, or exposure to rabbits; abrupt fever; hilar lymphadenopathy; pleural effusions
- SARS, Avian influenza: travel to Southeast Asia
- *Bacillus anthracis*, *Yersinia pestis*, and *Francisella tularensis*: bioterrorism
- *Invasive aspergillosis*: neutropenic fever; “halo sign” on CT scan; possible positive serum galactomannan (treatment is voriconazole)

Patients with pneumonia present with cough, fever, and often sputum production. Severe pneumonia of any cause may present with dyspnea. The quality and degree of sputum produced might provide useful clues to the microbiologic etiology of pneumonia at the initial presentation. Bacterial infections such as *S. pneumoniae*, *Haemophilus*, and *Klebsiella* have significant purulent sputum production because they are infections of the alveolar air space.

- The sputum with *S. pneumoniae* is described as rusty. The “rust” is simply hemoptysis. As the blood oxidizes, it becomes brownish-red color. Any form of persistent cough may be associated with hemoptysis, however, and hemoptysis by itself is nonspecific.
- The sputum with *Klebsiella pneumoniae* is described as currant jelly. This is simply hemoptysis with mucoid characteristics from a combination of the necrotizing nature of *Klebsiella* with the organism’s thick mucopolysaccharide coating.
- Interstitial infections such as those caused by *Pneumocystis* pneumonia (PCP), viruses, *Mycoplasma*, and sometimes *Legionella* often give a nonproductive or “dry” cough.

Any cause of pneumonia may be associated with pleuritic chest pain. This is pain worsened by inspiration. Commonly, pleuritic pain is associated with lobar pneumonia, such as that caused by *Pneumococcus*. This is because of localized inflammation of the pleura by the infection. Lobar pneumonia is the type most commonly associated with signs of consolidation on examination.

On physical examination pneumonia presents with rales, rhonchi, or signs of lung consolidation, including dullness to percussion, bronchial breath sounds, increased vocal fremitus, and egophony (E to A changes).

The respiratory rate is essential in determining the severity of a pneumonia. The respiratory rate is often a close correlate of the level of oxygenation. Severe pneumonia leads to hypoxia, which leads to hyperventilation.

Organism-specific presentations are as follows:

- *Mycoplasma*: dry cough and chest soreness. Dyspnea is rare. Bullous myringitis and anemia from hemolysis from cold agglutinin disease are occasionally present. Patients with *Mycoplasma pneumoniae* rarely need to be admitted to the hospital; therefore, any patient presented to you as an inpatient is less likely to have *Mycoplasma*.
- *Legionella*: CNS manifestations such as confusion, headache, and lethargy. GI manifestations include diarrhea and abdominal pain.
- PCP: marked dyspnea, particularly on exertion, with chest soreness with cough in an HIV-positive person. Patients invariably have AIDS with CD4 count $<200/\mu\text{L}$.

Diagnosis. The most important initial test for pneumonia is the chest x-ray, which both shows the presence of disease and gives the initial clues to determining the diagnosis.

- Infiltrates are either localized to a single lobe of the lung or bilateral and interstitial (**most important clue**).
- *S. pneumoniae* (and other causes of “typical” pneumonia) usually appear as a lobar pneumonia with parapneumonic pleural effusion.
- Interstitial infiltrates are associated with PCP, viral, *Mycoplasma*, *Chlamydia*, *Coxiella*, and sometimes *Legionella pneumoniae*.
- Sputum culture should be obtained for both Gram stain as well as culture. Sputum culture is the **most specific diagnostic test** for lobar pneumonia, such as with *S. pneumoniae*, *Staphylococcus*, *Klebsiella*, and *Haemophilus*.
- The other “atypical” organisms (viral, *Mycoplasma*, *Chlamydia*, *Coxiella*, etc.) will not show up on Gram stain or regular bacterial culture for various reasons.
- Bronchoscopy, thoracentesis, pleural biopsy, or culture of pleural fluid (infrequently needed)
- Open lung biopsy (**most specific diagnostic test**)

Organism-specific diagnostic methods are as follows:

- *Mycoplasma*: specific serologic antibody titers; cold agglutinins have both limited specificity and sensitivity
- *Legionella*: specialized culture media with charcoal yeast extract, urine antigen tests, direct fluorescent antibodies, and antibody titers
- PCP: bronchoalveolar lavage, increased LDH
- *Chlamydia pneumoniae*, *Coxiella*, *Coccidioidomycoses*, and *Chlamydia psittaci*: specific antibody titers

Note

The urine *Legionella* test is not sensitive.

**Note**

CURB-65 indicates need for hospitalization in pneumonia:

Confusion

Uremia

Respiratory distress

Blood pressure low

Age >65

Note

Co-morbidities include chronic heart failure, COPD, asthma, DM, kidney disease, nephrotic syndrome, malignancy, alcoholism, smoking, asplenia, and immunosuppression.

Treatment. Mild disease can be treated outpatient, and more severe disease requires inpatient IV antibiotics. Severity is determined by the following:

- Degree of hypoxia, such as a $pO_2 < 60$ mm Hg, oxygen saturation $< 94\%$ on room air, or respiratory rate $> 30/\text{min}$
- Confusion/disorientation
- Uremia
- Hypotension (systolic BP < 90 mm Hg and diastolic BP < 60 mm Hg)
- High fever
- Hypothermia
- Hyponatremia
- Leukopenia ($WBC < 4,000/\text{mm}^3$)
- Rapid pulse ($> 125/\text{min}$)
- Dehydration as determined by elevated BUN

Patients with serious underlying disease often do better inpatient with IV medication.

The specific organism causing pneumonia is rarely known when the initial treatment decision must be made.

CAP.

- Inpatient treatment
 - Levofloxacin, moxifloxacin, or gatifloxacin
 - Second- or third-generation cephalosporin such as cefotaxime or ceftriaxone plus a macrolide antibiotic, e.g., azithromycin, clarithromycin, doxycycline
- Outpatient treatment
 - Macrolides, e.g., azithromycin or clarithromycin only for those who are young and healthy, with low risk of resistance; use a respiratory fluoroquinolone for those with co-morbidities or recent antibiotics
 - Oral second- and third-generation cephalosporins or amoxicillin/clavulanate + a macrolide or doxycycline to cover the atypical pathogens

Table 7-2. Empiric Therapy of Community-Acquired Pneumonia

Outpatient	Inpatient
Young, healthy patients with no comorbidities or antibiotic use in preceding 3 months Azithromycin, clarithromycin, or doxycycline Respiratory fluoroquinolones, comorbidities, or antibiotic use in preceding 3 months Levofloxacin, moxifloxacin, gemifloxacin, or oral beta-lactam + a macrolide or doxycycline	Respiratory fluoroquinolones (levofloxacin, moxifloxacin, or gemifloxacin) or Second- or third-generation cephalosporins (cefuroxime or ceftriaxone) combined with a macrolide or doxycycline or Beta-lactam/beta-lactamase combination drug (ampicillin/sulbactam; ticarcillin/clavulanate; piperacillin/tazobactam) combined with doxycycline or a macrolide • If risk factors for CA-MRSA, use above therapy + vancomycin or linezolid or ceftaroline + a macrolide or doxycycline • If risk factors for <i>Pseudomonas</i>, use antipseudomonal beta-lactam (like cefepime or meropenem) + ciprofloxacin; for penicillin-allergy, use a respiratory quinolone + aztreonam

HAP.

Those patients who develop pneumonia after 5–7 days in the hospital are at increased risk of infection from drug-resistant, gram-negative bacilli (*Pseudomonas*, *Klebsiella*, *E. coli*, etc.) or gram-positive bacilli such as MRSA.

- Third-generation cephalosporin with antipseudomonal activity (e.g., ceftazidime) or carbapenem (e.g., imipenem)
- Beta-lactam/beta-lactamase inhibitor combinations (such as piperacillin/tazobactam) and vancomycin or linezolid to cover MRSA.
- Possible addition of an aminoglycoside (gentamicin, tobramycin, amikacin) to empiric gram-negative coverage

Treatment of specific organisms is as follows:

- *Haemophilus influenzae*: second- or third-generation cephalosporins
- *Mycoplasma*: macrolides, doxycycline, or a quinolone
- *Legionella*: macrolides, doxycycline, or a quinolone
- *Pneumocystis pneumonia*: TMP/SMZ
 - Use steroids if the infection is severe (severe is defined as arterial pO₂ <70 mm Hg or A-a gradient >35 mm Hg).
 - If patient is allergic to TMP/SMZ, use IV pentamidine or atovaquone. (Dapsone or atovaquone can be used prophylactically).
- *Coxiella burnetii* (Q-fever): doxycycline or erythromycin

Note

With HAP, adding an aminoglycoside to empiric gram-negative coverage is done for synergy and to ensure that patient gets at least one drug if the bacteria are multi-drug resistant. Antibiotic therapy can then be adjusted when culture results (sputum, blood, bronchoalveolar lavage, and/or pleural) become available.



- *Klebsiella*: third-generation cephalosporin and the other drugs for gram-negative bacilli
- *Staphylococcus aureus*: semisynthetic penicillin (oxacillin, nafcillin, etc.) if methicillin-sensitive; in the nosocomial setting, isolates are invariably methicillin-resistant, and vancomycin or linezolid is administered
- *Coccidioidomycosis*: no treatment for primary pulmonary disease; treatment used only for disseminated disease or in those with pulmonary disease who are immunosuppressed.
 - Mild disease: fluconazole or itraconazole
 - Life-threatening disease: amphotericin

Pneumococcal vaccine

For those who are immunocompromised, the PPSV23 should be given 8 weeks after the PCV13 vaccine.

Table 7-3. Pneumococcal Immunization

Risk Group	PCV13	PPSV23
Those who are immunocompromised and age ≥ 65	Recommended	Recommended 1 year after PCV13; revaccinate after 5 yrs if age < 65 at first dose
Those who are immunocompromised and have chronic heart/lung/liver disease, DM, alcoholism, or smoke	Not recommended	Recommended; revaccinate after 5 yrs if age < 65 at first dose
Those with functional or anatomic asplenia	Recommended	Recommended
Those who are immunocompromised and have HIV, lymphoma, Hodgkin, nephrotic syndrome	Recommended	Recommended

Note

In generally healthy persons vaccinated age > 65 , a single dose of pneumococcal vaccine is enough to confer lifelong immunity.

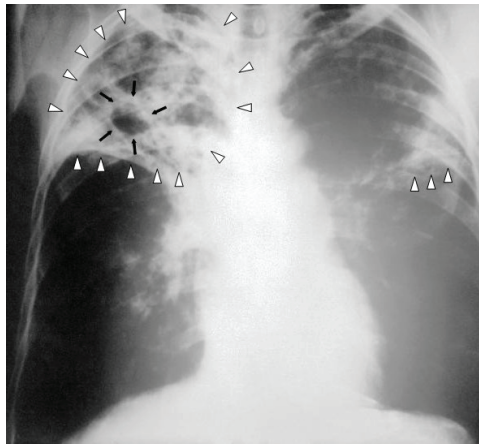
Tuberculosis

A 37-year-old resident of a maximum-security correctional facility has been having a cough, voluminous sputum production and fever for the last few weeks. He has had a 10-pound weight loss and feels very weak.

TB is an infection with *Mycobacterium tuberculosis*. Worldwide, TB is one of the top 3 causes of all deaths.

TB is spread exclusively by person-to-person transmission by means of respiratory droplet infection. There is no animal reservoir of the disease. Bacillus Calmette-Guérin (BCG) vaccination is used in many parts of the world outside the United States to try to prevent infection. It is, at best, 50% effective and is never indicated for routine use in the United States.

Besides immigrants, TB occurs predominantly in persons with specific risk for exposure, such as alcoholics, healthcare workers, prisoners, homeless shelter residents, nursing home residents, and chronically debilitated patients whose weakened immune systems allow for more frequent re-activation of latent infection. Impairment of T-cell-mediated cellular immunity is the most significant defect associated with re-activation. This is why steroid use, organ transplantation, leukemia, lymphoma, and HIV are such important risk factors.



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Figure 7-4. Tuberculosis X-ray

Patients present with cough, sputum, fever, and an abnormal lung exam. They may be impossible to distinguish clinically from those with pneumonia.

Even when untreated, TB usually takes up to 5 years to become fatal.

- Weight loss (common) because of the chronicity of the infection
- Night sweats
- Cough >3 weeks
- Hemoptysis
- Presentation depends on site involved
 - Any part of the body can be involved
 - In extrapulmonary TB, the **lymph node** (adenitis), meningeal, GI, and GU are most commonly seen
 - Can occur outside lungs (15–20% of cases)

Diagnosis. Latent TB is diagnosed with a positive PPD or IGRA in the absence of symptoms, plus a normal chest x-ray.

- Chest x-ray is the **best initial test**, as it is with all forms of pulmonary infection.
 - Apical involvement with infiltrates and sometimes cavitation is the most common finding.
 - Adenopathy, effusion, and calcified nodules (Ghon complex) are associated findings.

Note

Nearly 25% of the world's population has been exposed to TB and would be reactive to PPD testing. Until the middle of this century, TB was the most common cause of death in the United States, but it is now at an all-time low, with <15,000 cases per year (over half of those are recent immigrants).

Note

Lymph node involvement (adenitis) is the most frequently involved extrapulmonary site in TB.

Note

If sputum AFB stain is positive, that is usually the trigger to start treatment for TB.



Clinical Pearl

Newer tests may provide TB sensitivity testing in a few weeks, thus the period of using 4 drugs is significantly shortened.

- Sputum examination with specific staining for AFB allows specific diagnosis (false-negative in 25% of cases).
 - Sputum or tissue culture is the **gold standard**, but takes up to 6 weeks to grow and is not often available to guide initial therapy. The culture is also necessary in order to do sensitivity testing.
 - If sputum AFB stain is positive, that is usually the trigger to start treatment for TB.
 - If sputum AFB stain is unrevealing, consider other diagnostic tests: thoracentesis (to examine pleural fluid), gastric aspirate in children, biopsy or FNA of specific extrapulmonary organ involved, and lumbar puncture with meningitis.
- Pleural biopsy is the single most sensitive diagnostic test. A single pleural biopsy can have up to 75% sensitivity. TB will give caseating necrosis on biopsy of any tissue. Pleural fluid of adenosine deaminase is helpful in diagnosing pleural TB.

Do not use PPD testing to diagnose acute cases of TB. PPD is relatively insensitive and nonspecific particularly with acute illness. Use IGRA for screening in patients with a history of BCG, high risk of progression, or those who will not likely return to be tested.

Treatment. Initial therapy of TB before the results of sensitivity testing are known consists of 4-drug therapy with isoniazid (INH), rifampin (Rif), pyrazinamide (PZA), and ethambutol (ETB).

- All 4 drugs are continued for the first 2 months or until sensitivity testing is known.
- PZA and ETB are then discontinued, and treatment continues with INH and rifampin for another 4 months. That means routine therapy last for 6 months.
- The fourth drug, ETB, is given if the sensitivity is not known.
- The only forms of TB that must be treated for more 6 months are TB meningitis (12 months), TB in pregnancy (9 months), and osteomyelitis.
- Those who are HIV-positive may be treated for 6–9 months, but there is no clear evidence that 9 months is necessary, i.e., even in HIV-positive persons, 6 months of therapy is effective.
- INH use should generally be combined with vitamin B6 (pyridoxine) to prevent peripheral neuropathy that can be a side effect of INH.

Pregnant patients should not receive PZA or streptomycin. Steroid use with TB medications is only your answer for TB meningitis and TB pericarditis.

All the TB medications can cause liver toxicity, except streptomycin. Other side effects include:

- INH causes peripheral neuropathy due to pyridoxine deficiency.
- Rifampin is associated with causing a benign change in the color of all bodily fluids to orange/red.
- Ethambutol is associated with optic neuritis, which can cause color blindness and other visual disturbances.
- PZA can cause a benign hyperuricemia (do not treat the hyperuricemia unless there are symptoms/history of gout)

Diagnosis and Treatment of Latent TB Infection. The PPD test and IGRA are used to screen asymptomatic populations at risk of TB to see if they have been exposed and are at increased risk of re-activating the disease. The AFB stain and culture of the affected tissues should be performed. PPD is considered positive based on the amount of induration of the skin 48–72 h after the intradermal (not subcutaneous) injection of the PPD. Erythema is irrelevant. A positive PPD or IGRA roughly indicates a 10% lifetime risk of developing TB in HIV-negative persons. Most of the active cases will develop within the first 2 years after converting to a positive test. HIV-positive persons have a roughly 7–10% risk per year of developing active disease. Previous BCG vaccination does not alter these recommendations. The cutoffs are as follows:

≥5 mm:

- Close contacts of active TB cases
- HIV-positive persons
- Abnormal chest x-ray consistent with old, healed TB
- Steroid use or organ transplantation recipients

≥10 mm: High-risk groups, such as healthcare workers, prisoners, and nursing home residents; recent immigrants (within 5 years) from areas with a high prevalence; homeless patients; persons with immunocompromise other than those described, such as those with leukemia, lymphoma, diabetics, dialysis patients, and injection drug users who are HIV-negative or whose HIV status is unknown; and children <4 years of age, or infants, children, and adolescents exposed to adults at high risk of TB.

≥15 mm: Low-risk populations, i.e., *not* the people described, i.e., people who should never have been tested in the first place

Two-Stage Testing: All patients who have not had a recent PPD test but now show some reactivity that is <10 mm should have a second test within 2 weeks, to make sure the first test was not a false-negative. A reaction of >10 mm on the second test is simply a positive test, not a recent converter. You cannot make a PPD-negative person become positive with repeated testings.

- Anyone who tests positive on the PPD test or IGRA should have a chest x-ray to see if they have early asymptomatic evidence of TB on their film.
 - Those with abnormal chest x-ray should have 3 sputum AFB stains done to see if they have active disease.
 - Positive AFB stains indicate the need to start the 4 TB drugs described.
- Anyone with a positive PPD or IGRA but no evidence of active disease should receive 9 months of INH or 4 months of rifampin.
- Although 6 months of INH/B6 is an acceptable alternative, the recommendation is that all patients, including those who are HIV positive, should receive the same 9-month course of therapy. (Previously, this was referred to as “prophylaxis”; today, this is called “treatment of latent TB.”)

The IGRA is not altered at all with previous BCG vaccine. The IGRA has the same meaning and treatment as a positive PPD skin test. Patients who received the BCG or are unlikely to return to have the PPD read should have IGRA instead of PPD. Previous BCG will not make the IGRA positive.

Note

For TB, **active disease can be excluded** with one of the following conditions:

- Normal chest x-ray
- Abnormal chest x-ray + 3 negative AFB sputum stains

**Clinical Recall**

Which of the following is not an indication for hospitalization in patients with pneumonia?

- A. pO_2 50 mm Hg
- B. Creatinine 2.5 mg/dL
- C. Temperature 104 F
- D. Leukocytosis 11,000
- E. Underlying COPD

Answer: D

GASTROINTESTINAL INFECTIONS**Infectious Diarrhea/Food Poisoning**

A 27-year-old medical student leaves class at 12:30 to go to lunch. At 3:00 she starts to have repeated episodes of diarrhea. The diarrhea contains blood and mucus. She is also febrile and has abdominal pain.

Most infectious diarrhea is caused by contaminated food and water, so the overlap between infectious diarrhea and food poisoning is considerable.

There are several types of food poisoning, such as *Bacillus cereus* and *Staphylococcus aureus*, which present predominantly with vomiting, so the two terms are not entirely synonymous.

A wide variety of agents can cause food poisoning.

- *Campylobacter* (most common)
- *Salmonella* (most commonly associated agent with contaminated poultry and eggs)
- *E. coli* (most common cause of travelers' diarrhea; produces a wide spectrum of disease depending on whether it makes toxin or is invasive)
 - *E. coli* 0157:H7 is associated with undercooked hamburger meat.
 - *Bacillus cereus* is associated with fried rice; the rice becomes contaminated with bacillus spores, and as it is prepared for serving it is warmed only at a moderate temperature not hot enough to kill the spore.
 - *Giardia lamblia* and cryptosporidiosis are acquired from contaminated water sources that have not been appropriately filtered, such as fresh water on a camping trip. Cryptosporidiosis is also associated with HIV, particularly when there is profound immunosuppression and CD4 <50 cells.

- There are several types of *Vibrio* causing human disease.
 - *V. cholera* (very rare in the United States)
 - *V. parahaemolyticus* (associated with ingestion of contaminated shellfish)
 - *V. vulnificus* (associated with ingestion of raw shellfish); causes severe disease in those with underlying liver disease; also associated with iron overload and bullous skin lesions
- Viral infections such as rotavirus or Norwalk agents (very common in children)
- Ciguatera fish toxin, most commonly in red snapper and grouper
- Clostridia associations are as follows:
 - *C. difficile* with previous antibiotic use
 - *C. botulinum* with ingestion of infected canned foods
 - *C. perfringens* with ingestion of meat contaminated with spores due to unrefrigeration

Although it is important to be familiar with these associations, virtually any food can be contaminated by almost any organism. The most important thing is not what food you eat but whose dirty hands touched your food and what were they contaminated with.

Clinical Presentation.

- Presence or absence of blood in the stool (**most important feature**); blood is most commonly associated with invasive enteric pathogens such as *Salmonella*, *Shigella*, *Yersinia*, invasive *E. coli*, and *Campylobacter*
- The time between ingestion of food and the diarrhea is less important than the presence of blood.
- The invasive enteric pathogen may be causing infection in the absence of blood, and the absence of blood does not exclude them.
- *Campylobacter* is rarely associated with Guillain-Barré syndrome.
- Scombroid poisoning causes symptoms within a few minutes after eating scombroid fish (tuna, mackerel, mahi mahi), which may contain a lot of histamine: rash, diarrhea/vomiting, and wheezing, along with a burning sensation in the mouth, dizziness, and paresthesias.
- Ciguatera fish toxin causes symptoms within 2–6 hours (there is no specific treatment)
 - Paresthesias, numbness, nausea/vomiting/abdominal cramps
 - Neurologic symptoms (weakness, reversal of hot-cold sensations) in severe disease can be progressive and debilitating
 - Cardiovascular symptoms (hypotension) in severe disease
- *E. coli* 0157:H7 and *Shigella* are associated with hemolytic uremic syndrome (HUS).
- *Bacillus cereus* and *Staphylococcus* predominantly present with vomiting within 1–6 hours of their ingestion because they contain a preformed toxin. They can cause diarrhea later.
- *Giardia*, *Cryptosporidium*, *Cyclospora*, and most other protozoans do not cause bloody diarrhea. The major protozoan associated with blood in the stool is *Entamoeba histolytica*.
- Viruses can give voluminous watery diarrhea but do not cause bloody diarrhea.

Note

Incubation times are helpful only if there is a group outbreak and you can pinpoint a common source of contamination. In other words, the last thing you eat is not necessarily the thing that was contaminated.



Diagnosis. Stool studies should not be sent unless there is diarrhea for more than 1 week. *Giardia* and *Cryptosporidia* are detected by direct examination of the stool for the parasites, as well as for their eggs. A special modified AFB stain is necessary to detect *Cryptosporidia*. Stool ELISA is also used for *Giardia*.

Treatment. Therapy is determined by the severity of disease. Mild infections with the invasive pathogens and viruses usually require only oral fluid and electrolyte replacement. More severe infections, such as those producing high fever, abdominal pain, tachycardia, and hypotension, require IV fluids and oral antibiotics.

The specific etiology is rarely known when the initial treatment decisions must be made. The best initial empiric therapy for an invasive pathogen is a fluoroquinolone, e.g., ciprofloxacin.

Organism-specific therapy is as follows:

- *Campylobacter*: erythromycin
- *Giardia*: metronidazole
- *Cryptosporidium*: control of underlying HIV disease with antiretrovirals, nitazoxanide
- Nitazoxanide is the first truly useful therapy for cryptosporidiosis.
- Scombroid: antihistamines such as diphenhydramine

HEPATIC INFECTIONS

Viral Hepatitis

An 18-year-old woman presents at the ED with several days of nausea, vomiting, and fever. She uses no medications. She reports unprotected sex. Her stool is light in color. On physical examination she is jaundiced.

Viral hepatitis is an infection of the liver caused by hepatitis A, B, C, D, or E.

- **Hepatitis A and E** are transmitted by contaminated food and water. They are orally ingested and have an asymptomatic incubation period of several weeks, with an average of 2–6 weeks. They cause symptomatic disease for several days to weeks, have no chronic form, and do not lead to either cirrhosis or hepatocellular carcinoma.
- **Hepatitis B, C, and D** are transmitted by the parenteral route. They can be acquired perinatally or through sexual contact, blood transfusion, needlestick, and needle sharing.
- **Hepatitis G** has been identified in a small number of patients through screening of the blood supply but has not yet been associated with clinical disease.
- **Hepatitis B and C** can lead to a chronic form, which can cause cirrhosis and hepatocellular carcinoma.

All forms can occasionally present with fulminant hepatic necrosis and acute liver failure.

The most common presentation of acute hepatitis of any cause is jaundice, dark urine, light-colored stool, fatigue, malaise, weight loss, and a tender liver. On physical examination the liver may be enlarged.

Note

Four million people in the United States are infected with hep C. Hep C is the most common disease requiring liver transplantation.

You cannot distinguish the precise viral etiology of the hepatitis by initial presentation alone. In fact, drug-induced hepatitis, i.e., that from isoniazid or massive alcohol use, may present with the same symptoms. Hepatitis B and C can also produce symptoms similar to serum sickness, such as joint pain, rash, vasculitis, and glomerulonephritis. They also lead to cryoglobulinemia. Hepatitis B has been associated with the development of polyarteritis nodosa (PAN). Hepatitis E has been associated with a more severe presentation in pregnant women.

Table 7-4. Comparative Features: Hepatitis A, B, C, E, and Delta

Feature	Hepatitis A	Hepatitis B	Hepatitis C	Delta	Hepatitis E
Incubation period (wk)	2–6 (avg. 4)	4–26 (avg. 13)	2–20	4–8	—
Transmission	Fecal-oral	Sexual > parenteral	Parenteral > sexual	Parenteral, sexual	Fecal-oral
Severity	Mild	Occasionally severe	Usually subclinical	Co-infection with B	Mild, except in pregnant women
Fulminant hepatitis	Rare	Very rare (1% of icteric patients)	Extremely rare	Co-infection occasional	Rare
Symptoms	Fever, malaise, headache, anorexia, vomiting, dark urine, jaundice	As with A, but 10–20% with serum sickness-like (joint pain, rash)	Only 20% acutely symptomatic	As with A	As with A
Carrier state	None	Yes	Yes	Yes	None
Chronicity (%)	0	5–10	80	5	0
Associated with blood transfusion (%)	Very rare	5–10	Almost negligible 2% to routine screening	Occurs, but frequency unknown	Rare
Serology	Anti-HAV IgM fraction IgG fraction	HBsAg, HBsAb HBeAg Anti-HBs Anti-HBc Anti-HBe	Antibody to hepatitis C PCR-RNA	Anti-delta IgM fraction IgG fraction	Anti-Hep E IgM IgG
Postexposure prophylaxis	Immunoglobulin Hep A vaccine	HBIG/Hep B vaccine	None effective	None	Unknown
Association with cirrhosis	No	Yes	Yes	Yes	No
Association with primary hepatocellular carcinoma	No	Yes	Yes	Yes	No



Note

For the treatment of hepatitis B, entecavir, adefovir, tenofovir, and telbivudine can be used in place of lamivudine.

Diagnosis. All forms of viral and drug-induced hepatitis will produce elevated total and direct bilirubin levels.

- Viral hepatitis will produce both elevated ALT and AST, but ALT is usually greater than the AST.
- With drug- and alcohol-induced hepatitis, AST is usually more elevated than the ALT.
- Alkaline phosphatase and GGTP are less often elevated because these enzymes usually indicate damage to the bile canalicular system or obstruction of the biliary system.
- If there is very severe damage to the liver, prothrombin time and albumin levels will be abnormal.

Hepatitis A, C, D, and E are diagnosed as **acute** by the presence of the IgM antibody to each of these specific viruses. IgG antibody to hepatitis A, C, D, and E indicates old, resolved disease.

- Hepatitis C activity can be followed with PCR-RNA viral load level. However, do not use PCR to establish the initial diagnosis.
- Hepatitis B is diagnosed as acute with the presence of the hepatitis B surface antigen, which is the first viral marker to elevate. The hepatitis B e antigen and IgM core antibody also help establish acute infection.
 - The e antigen indicates high levels of viral replication and is a marker for greatly increased infectivity.
 - Resolution of the infection is definitively indicated by the loss of surface antigen activity and the development of hepatitis B surface antibody.
 - Hepatitis B core antibody of the IgG type and hepatitis e antibody also indicate that the acute infection is about to resolve and may be the only marker present in the 2–6 weeks between the loss of surface antigen activity and development of the surface antibody.

Treatment. There is no effective treatment for acute hepatitis B. For chronic hepatitis B, treatment is interferon, entecavir, or tenofovir. (See GI section for indications for treatment.)

With the approval of the newest hepatitis C drugs, the goal of HCV treatment is to cure the virus, which can be done with a combination of drugs. The specific medications used and the duration of treatment depend on a number of factors:

- HCV genotype
- Viral load
- Past treatment experience
- Degree of liver damage
- Ability to tolerate the prescribed treatment
- Whether patient is waiting for a liver transplant or is transplant recipient

There are a number of approved therapies to treat HCV, such as sofosbuvir/ledipasvir, simeprevir, sofosbuvir, and Viekira Pak (ombitasvir, paritaprevir and ritonavir tablets co-packaged with dasabuvir tablets that may be prescribed with or without ribavirin). Simeprevir and sofosbuvir can be prescribed together with or without ribavirin, or each may be separately combined with ribavirin and in some cases peginterferon as well.

Sofosbuvir/ledipasvir, the current preferred HCV treatment, is 2 drugs formulated in to one daily pill. For genotype 1 success rates of sofosbuvir/ledipasvir are around 94–99%, while treatment duration is 8–12 weeks. Both are direct-acting antivirals which means they directly interfere with hepatitis C virus replication. Sofosbuvir is a polymerase inhibitor, while ledipasvir is an NS5A inhibitor. Patients who have never been treated for HCV—whether they have cirrhosis or not—take sofosbuvir/ledipasvir for 12 weeks. Treatment-naïve patients without cirrhosis whose pre-treatment viral load (HCV RNA) is <6 million IU/mL may be considered for **8 weeks of treatment**.

When hepatitis C treatment is working, the virus will become undetectable within 4–12 weeks and will remain that way throughout treatment. Patients are considered cured when they have achieved what is known as a sustained virologic response (SVR), or continuation of this undetectable status, 12–24 weeks after completing therapy.

After a needlestick from a hepatitis B surface-antigen–positive patient, the person stuck should receive hepatitis B immunoglobulin (HBIG) and hepatitis B vaccine. If the person stuck already has protective levels of surface antibody to hepatitis B present in the blood, then no further therapy is indicated. There is no effective postexposure prophylaxis to hepatitis C, and there is no vaccine. All healthcare workers, IV drug users, and others at risk should be vaccinated for hepatitis B. All newborn children are vaccinated against hepatitis B and A. Hepatitis A vaccine should be given to those traveling to countries that may have contaminated food and water, those with chronic liver disease, and those with high risk sexual behavior.

Clinical Recall

Which of the following hepatitis B markers indicates a high level of infectivity?

- A. HBsAg
- B. HBeAg
- C. HBcAg
- D. HBcAg IgM
- E. HBcAg IgG

Answer: B

GENITAL AND SEXUALLY TRANSMITTED INFECTIONS

Urethritis

A 31-year-old man is in your clinic today with several days of urinary frequency, urgency, and burning.

**Note**

Check for terminal complement deficiency in recurrent *Neisseria* infection.

Urethritis is inflammation of the urethra.

- Gonococcal urethritis caused by *Neisseria gonorrhoeae*
- Nongonococcal urethritis caused by *Chlamydia trachomatis* (50%), *Ureaplasma urealyticum* (20%), *Mycoplasma hominis* (5%), *Trichomonas* (1%), or herpes simplex

Symptoms include purulent urethral discharge, dysuria, urgency, and frequent urination. Disseminated gonococcal infection can cause purulent arthritis alone or arthritis-dermatitis with any of the following:

- Peripheral necrotic pustules, including palms and soles
- Monoarthritis or oligoarthritis
- Tendon sheath inflammation

NAAT of the urine or urethral swabs from men (vagina or cervix from women) is the best test.

Treatment. Single-dose ceftriaxone intramuscularly and single-dose azithromycin orally is the treatment of choice. An alternative regimen with doxycycline for 7 days can also be used.

- Treatment for gonorrhea is single-dose cefixime (same treatment as cervicitis); do not use ciprofloxacin as first-line therapy for gonorrhea.
- Treatment for disseminated gonococcal infection is 7–14 days of ceftriaxone.

Pelvic Inflammatory Disease

Pelvic inflammatory disease (PID) is a group of infections involving the fallopian tubes, uterus, ovaries, or ligaments of the uterus. The etiology is *N. gonorrhoeae*, *Chlamydia*, *Mycoplasma*, anaerobic bacteria, or gram-negative bacteria. Intrauterine devices predispose to PID.

Clinical findings include lower abdominal and pelvic pain on palpation of the cervix, uterus, or adnexa; fever, leukocytosis, and discharge are common. **Uterine, adnexal or cervical motion tenderness** is key. Discharge from the cervix may be present.

To diagnose *N. gonorrhoeae* and chlamydia trachomatis, order a NAAT.

- If there is fluid in the retrouterine cul-de-sac, a culdocentesis is performed (rare).
- Do a pregnancy test.
- If no response to antibiotics, U/S of the pelvis may exclude other pathology, such as an ovarian cyst or tubo-ovarian abscess.
- Clinical presentation is the main method (CMT/adnexal tenderness).

Treatment.

- **Inpatient:** doxycycline and cefoxitin (or cefotetan); indications for treating inpatient include no improvement in 48–72 hours; nausea/vomiting; high fever; pregnancy; or abscess
- **Outpatient:** single-dose ceftriaxone intramuscularly and doxycycline (with or without metronidazole) orally for 2 weeks; alternatively, 2 weeks of oral ofloxacin, with metronidazole as a second-line agent

Complications of PID include infertility and ectopic pregnancy.

Syphilis

A 43-year-old man comes to the clinic with several days of an ulcerated genital lesion. He also has some surrounding adenopathy.

Syphilis is a systemic contagious disease caused by a spirochete; characterized by periods of active manifestations and by periods of symptomless latency. It is **caused by *Treponema pallidum***.

Syphilis can be classified as being congenital or acquired.

Congenital

- **Early:** symptomatic; seen in infants up to age 2
- **Late:** symptomatic, Hutchinson teeth, scars of interstitial keratitis, bony abnormalities (saber shins)

Acquired

- Early infectious syphilis
 - **Primary stage:** chancre appears by week 3 and disappears in 10–90 days; also, regional lymphadenopathy is painless, rubbery, discrete, and nontender to palpation (primary chancres are found on penis, anus, rectum [men], and vulva/cervix/perineum [women] but may appear on lips, tongue, etc.)
 - **Secondary stage:** cutaneous rashes appear 6–12 weeks after infection, usually found symmetrically and more marked on flexor and volar body surfaces (pinkish in white persons; pigmented spots/copper-colored macules in blacks); lymphadenopathy, papules which form at mucocutaneous junctions and moist areas, are called condylomata lata (extremely infectious), and alopecia can be seen
- **Latent stage:** asymptomatic; may persist for life; 35% of patients develop late or tertiary syphilis
- **Late or tertiary syphilis:** most commonly neurologic



Centers for Disease Control and Prevention, M. Rein, VD

Figure 7-5. Syphilis, Primary Chancre



Patients are symptomatic but not contagious.

- Benign tertiary syphilis develops 3–20 years after the initial infection; typical lesion is the gumma (a chronic granulomatous reaction) found in any tissue or organ, which will heal spontaneously and leave a scar
- Cardiovascular (aortitis) syphilis and neurosyphilis are the other manifestations of tertiary syphilis.
 - The Argyll Robertson pupil (usually only with neurosyphilis) is a small irregular pupil that reacts normally to accommodation but not to light.
 - Tabes dorsalis (locomotor ataxia) results in pain, ataxia, sensory changes, and loss of tendon reflexes.
 - Neurosyphilis is rare and is essentially the only significant manifestation of tertiary syphilis likely to be seen.



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Figure 7-6. Syphilis, Secondary Palms

Diagnosis.

- Screening tests are the VDRL and RPR.
 - VDRL and RPR should decrease in titers or become negative after treatment and increase if reinfectd.
- Specific tests are the FTA-ABS, treponema pallidum particle agglutination (TPPA) assay, MHA-TP (microhemagglutination assay for *T. pallidum*), and Darkfield exam of chancre.
 - FTA-ABS and MHA-TP antibodies will remain positive indefinitely.
- VDRL with EBV, collagen vascular disease, TB, and subacute bacterial endocarditis can all have false-positives.
- Diagnosis of neurosyphilis is made if **any of the following** are present:
 - CSF lymphocytes >5/uL
 - Elevated CSF protein
 - Positive CSF VDRL
- CSF examination to confirm neurosyphilis and to confirm any neurological signs/symptoms in primary or secondary syphilis

Treatment. Penicillin is the **drug of choice** for all stages of syphilis.

- Primary, secondary, and latent syphilis are treated with 2.4 million units of intramuscular benzathine penicillin given 1×/week.
 - Primary and secondary syphilis (and early latent, e.g., <1 year) receive 1 week of therapy.
 - Late latent syphilis and tertiary nonneurosyphilis receive 3 weeks of therapy (and are diagnosed when VDRL or RPR titers are elevated >1:8 without symptoms).
 - Neurosyphilis receives 10–14 days of IV penicillin, with 10–20 million units per day.
- Those with penicillin-allergy receive doxycycline for primary and secondary syphilis, but must be desensitized for neurosyphilis. Pregnant patients must also undergo desensitization.

Caution that a reaction called Jarisch-Herxheimer can occur in >50% of patients a few hours after starting penicillin treatment. Symptoms include malaise, fever, headache, sweating rigors, and temporary exacerbations of the syphilitic lesions.

Chancroid

Chancroid is an acute, localized, contagious disease characterized by painful genital ulcers and suppuration of the inguinal lymph nodes. It is caused by *Haemophilus ducreyi* (gram-negative bacillus).



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Figure 7-7. Chancroid Lesion

Patients present with small, soft, painful papules that become shallow ulcers with ragged edges. They vary in size and coalesce. Inguinal lymph nodes become very tender and enlarged.



Diagnosis is made on clinical findings; do a Gram stain initially with culture to confirm. PCR testing is useful. Treatment is azithromycin single dose or ceftriaxone intramuscularly (single dose). Alternatives include erythromycin for 7 days or ciprofloxacin for 3 days.

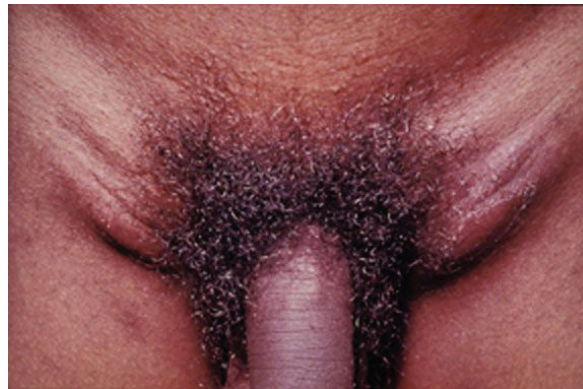
Lymphogranuloma Venereum

Lymphogranuloma venereum is a contagious, sexually transmitted disease having a transitory primary lesion followed by suppurative lymphangitis. It is caused by *Chlamydia trachomatis*.

Clinical findings include the following:

- Small, transient, nonindurated lesion that ulcerates and heals quickly
- Unilateral enlargement of inguinal lymph nodes (tender)
- Multiple draining sinuses (buboes) that develop (purulent or bloodstained)
- Scar formation, persistent sinuses; fever, malaise, joint pains, and headaches (all common)

Diagnosis is made by clinical examination, history, and a high or rising titer of complement fixing antibodies. Isolate chlamydia from pus in buboes. Treat with doxycycline or erythromycin.



Wikimedia, Herbert L. Fred, MD, and Hendrik A. van Dijk

Figure 7-8. Lymphogranuloma Venereum

Granuloma Inguinale

Granuloma inguinale is a chronic granulomatous condition, probably spread by sexual contact. It is caused by *Donovania granulomatis* *Calymmatobacterium granulomatis*.

A painless, red nodule will develop into an elevated granulomatous mass. In men, it is seen on the penis, scrotum, groin, and thighs. (In homosexual men, the anus and buttocks are common areas.) In women it is found on the vulva, vagina, and perineum.

Healing is slow, and there is scar formation. It looks like condyloma lata or carcinoma.

Diagnosis is made clinically and by performing a Giemsa or Wright stain (Donovan bodies) or smear of lesion. Also do punch biopsy. Treat with doxycycline, ceftriaxone, or TMP/SMZ. Erythromycin is an alternative.



phil.cdc.gov

Figure 7-9. Lesions of Granuloma Inguinale Due to *Calymmatobacterium Granulomatis* Infection

Genital Herpes

Genital herpes is generally the **herpes virus type II**, although type I may be seen. Vesicles develop on the skin or mucous membranes; they become eroded and painful and present with circular ulcers with a red areola. Itching and soreness usually precede them. Lesions are commonly seen on the penis (men) and on the labia, clitoris, perineum, vagina, and cervix (women).

The ulcers are scarring and there can be inguinal lymphadenopathy.

- Diagnosis is made with the direct fluorescent antibody test or HSV PCR obtained from the ulcers. Tzanck test and culture are no longer used.
- Serology is not useful for diagnosing herpes infections.
- Treat with oral acyclovir, famciclovir, or valacyclovir. Make sure to educate the patient about the relapsing nature of the disease. Those with frequent recurrence should be given chronic suppressive therapy.
- Foscarnet is used for resistant herpes.

Genital Warts

Genital warts are also known as condylomata acuminata or venereal warts. They are caused by the papilloma virus.

Genital warts are commonly found on warm, moist surfaces in the genital areas. They appear as soft, moist, minute, pink, or red swellings which grow rapidly and become pedunculated. Their cauliflower appearance makes them unique in appearance.

Clinical Correlate

Transmission of genital herpes commonly occurs during an **asymptomatic phase**, when a person who is shedding the virus inoculates virus onto a mucosal surface of the sexual partner.

Note

Erythema multiforme is most commonly caused by HSV recurrences.



Diagnosis is made by clinical appearance. Differentiation must be made between flat warts and condylomata lata of secondary syphilis. Treatment includes the following:

- Destruction (curettage, sclerotherapy, trichloroacetic acid)
- Cryotherapy
- Podophyllin
- Imiquimod (an immune stimulant)
- Laser removal

Clinical Recall

Which of the following is the treatment of choice for tertiary syphilis?

- A. IM penicillin G x 1 dose
- B. PO doxycycline x 14 days
- C. IV penicillin G x 10 days
- D. Doxycycline x 28 days
- E. IV ceftriaxone x 1 day

Answer: C

URINARY TRACT INFECTIONS

Cystitis

A 32-year-old woman presents with dysuria. For the last several days, she has had burning on urination with increased frequency and urgency to urinate.

Cystitis is infection of the urinary bladder. It is very common, mostly in women. In the United States, it causes 6 million office visits each year.

Etiology.

- Roughly the same as for pyelonephritis
- Any cause of urinary stasis or any foreign body predisposes
- Tumors/stones/strictures/prostatic hypertrophy/neurogenic bladder
- Sexual intercourse in women (“honeymoon cystitis”)
- Catheters are a major cause, and the risk is directly related to the length of catheterization (3–5% per day).
- Microbiology: *E. coli* in >80%; second are other coliforms (gram-negative bacilli) such as *Proteus*, *Klebsiella*, *Enterobacter*, etc.; enterococci occasionally, and *Staph. saprophyticus* in young women.

Note

Screen for and treat asymptomatic bacteriuria only in those who are pregnant or about to undergo an invasive urologic procedure.

Common presenting symptoms include dysuria, frequency, urgency, and suprapubic pain. Hematuria is less common. On exam, there is suprapubic tenderness but no flank tenderness.

Diagnosis

- Urinalysis (most important test) looking for WBCs >10 or urine dipstick positive for leukocyte esterase and nitrites
- Nitrites are indicative of gram-negative infection.
- Complicated UTI is UTI with co-morbid conditions, e.g., DM, pregnancy, kidney transplant, stones or anatomic abnormality, catheterization, recent antibiotics, or recent hospitalization. UTI in males is also considered complicated.
- Urine culture with >100,000 colonies of bacteria per mL of urine confirmatory but not always necessary with characteristic symptoms and a positive urinalysis. Obtain cultures if complicated UTI, recurrent UTI, or patient is pregnant.

Treatment

- For **uncomplicated cystitis**, 3 days of TMP/SMZ, 5 days of nitrofurantoin, or 1 dose of fosfomycin. Do not use quinolones.
- For **complicated cystitis**, check cultures and give fluoroquinolones for 7–14 days. For pregnancy, give amoxicillin-clavulanate, nitrofurantoin, cefpodoxime, or cefixime for 7 days and check culture after treatment. Do not use TMP/SMZ if used in the last 3 months.
- For **recurrent UTI**, give antibiotic prophylaxis either postcoital or daily.

Note

- Ceftazidime-avibactam can be used for ESBL and carbapenem-producing gram negatives.
- Ceftolozane-tazobactam and colistin can be used for multi-drug resistant *Pseudomonas*.

Acute Bacterial Pyelonephritis

Acute bacterial pyelonephritis is an acute patchy, most often unilateral, pyogenic infection of the kidney. Infection usually occurs by ascension after entering the urethral meatus.

- Predisposing factors include obstruction due to strictures, tumors, calculi, prostatic hypertrophy, or neurogenic bladder, vesicoureteral reflux
- Women > men
- More common in childhood, during pregnancy, or after urethral catheterization or instrumentation
- *E. coli* is most common pathogen; others include *Klebsiella*, *Proteus*, and *Enterococcus*
- Patients who are immunosuppressed and subjected to indwelling catheters are more prone to *Candida*.

Pathology shows polymorphonuclear neutrophils and leukocytes (in interstitial tissue and lumina of tubules). Clinical findings include chills, fever, flank pain, nausea, vomiting, costovertebral angle tenderness, increased frequency in urination, and dysuria.

Diagnose with fever, dysuria, and flank pain. Confirm with clean-catch urine for urinalysis, culture, and sensitivity. In most cases, **>100,000 bacteria/mL of urine**.

Routine imaging is not required, but if there is no improvement in 48–72 hours or complications are suspected (obstruction, renal, or perinephric abscess), consider U/S or CT.

**Note**

Any of the antibiotics for gram-negative bacilli are effective for acute bacterial pyelonephritis.

Treatment is antibiotics. Fluoroquinolone, piperacillin-tazobactam (a carbapenem), a third-generation cephalosporin (ceftriaxone), or cefepime are all acceptable.

- If **uncomplicated**: 5–7 days
- If **complicated**: 14 days
- Do not use nitrofurantoin, as its effectiveness has been proven only in the lower urinary tract.
- Do not use TMP/SMZ for empiric therapy until culture results and antibiotic sensitivity results are available, because of its increasing resistance throughout the United States.

Most patients can be treated as outpatients, though pregnant women who appear very ill and those unable to tolerate oral medication due to nausea or vomiting should initially be hospitalized.

ESBLs producing *E. coli* and *Klebsiella* are becoming more and more common. Required treatment is a carbapenem.

Perinephric Abscess

Perinephric abscess is a collection of infected material surrounding the kidney and generally contained within the surrounding Gerota fascia. It is very uncommon. Although any factor predisposing to pyelonephritis is contributory, stones are the most important and are present in 20–60%. Other structural abnormalities, recent surgery, trauma, and diabetes are also important.

Pathophysiology

- Arises from contiguous pyelonephritis that has formed a renal abscess
- Rupture occurs through the cortex into the perinephric space
- Microbiology: 1) The same coliforms as in cystitis and pyelonephritis; 2) *E. coli* most common, then *Klebsiella*, *Proteus*; 3) *Staph. aureus* sometimes accounts for hematogenous cases

Signs and Symptoms

- Often insidious; 2–3 weeks of symptoms prior to first physician visit
- Fever is the most common symptom
- Flank pain/palpable abdominal mass/abdominal pain
- Persistence of pyelonephritis-like symptoms despite treatment for pyelonephritis

The best initial tests are urinalysis (normal 30%) and urine culture (normal 40%). Fever and pyuria with negative urine culture or polymicrobial urine culture are suggestive.

Imaging is essential; U/S is the best initial scan but CT or MRI scan offers better imaging. Aspiration of the abscess is needed for definitive bacteriologic diagnosis (should be done if still febrile after 72 hours of antibiotics).

Treatment.

- Antibiotics for gram-negative rods
- Third-generation cephalosporins, antipseudomonal penicillin, or ticarcillin/clavulanate, often in combination with an aminoglycoside, for example
- Antibiotics alone are unlikely to be successful. Drainage (usually percutaneous) is necessary.

BONE AND JOINT INFECTIONS**Osteomyelitis**

A 59-year-old man was admitted last night because of a painful leg for 2 weeks. Over the last 4 days, he developed an ulcer over the proximal portion of his tibia just below the knee. He has a history of peripheral vascular disease and diabetes. He is afebrile. He has a sinus tract in the center of the red, inflamed ulcer that is draining purulent material.

Osteomyelitis is an infection of any portion of the bone including marrow, cortex, and periosteum. There are 3 types:

- **Acute hematogenous** occurs mostly in children in the long bones of the lower extremities and is secondary to a single organism 95% of the time.
 - Most common organism is *Staphylococcus aureus*
 - Most commonly involved bones are tibia and femur
 - Most commonly involved location is metaphyseal due to the anatomy of the blood vessels and endothelial lining at the metaphysis
 - In adults, hematogenous osteomyelitis accounts for about 20% of all cases and the most common site is the vertebral bodies (lumbar vertebrae are most frequently involved)
 - The infection can extend posteriorly to form an epidural abscess; a patient with this diagnosis would present with fever and back tenderness.
- **Secondary to contiguous infection** can occur in anyone with recent trauma to an area or placement of a prosthetic joint. Although this is secondary to a single organism most of the time, a higher percentage is polymicrobial in origin. *S. aureus* is the most common organism.
- **Vascular insufficiency** is mostly seen age >50, with diabetes or peripheral vascular disease, resulting in repeated minor trauma that is not noticed because of neuropathy and decreased sensation. It is most common in small bones of the lower extremities. The majority is polymicrobial, but the single most common organism is still *S. aureus*.

Clinical Presentation. Pain, erythema, swelling, and tenderness over the infected bone. With vascular insufficiency, there is often an obvious overlying or nearby ulceration or wound. Occasionally, a draining sinus tract is present.

Note

Injection drug use is a significant risk factor for vertebral osteomyelitis in adults.

**Note**

In general, nuclear medicine studies are less sensitive and specific.

Diagnosis. The earliest tests to detect osteomyelitis are the CT scan and MRI.

- Plain x-ray (**usually the initial test** because so easily obtained and inexpensive)
 - First visible abnormality will be a periosteal elevation
 - However, 50–75% of bone calcification must be lost before the bone itself appears abnormal, which usually takes at least 2 weeks to develop.
- MRI if x-ray is negative; if not available, do a CT with IV contrast
- ESR: nonspecific, but useful to follow during treatment; a normal value strongly points away from osteomyelitis
- Bone biopsy and culture: essential to confirm the pathogen and choose antibiotic therapy; not needed if blood cultures are positive

Treatment.

- **Acute** hematogenous osteomyelitis in **children**: antibiotics alone
- Osteomyelitis in **adults**: antibiotics + surgery (wound drainage and debridement, removal of infected hardware)
- **Chronic** osteomyelitis: antibiotics for up to 12 weeks or even longer
- Antibiotic therapy depends on the specific isolate obtained, which must be as precise as possible because empiric treatment for 4–6 weeks would be undesirable.
- Antibiotics should be held until cultures return. Start empiric antibiotics (imipenem and vancomycin) only if patient is unstable.
- The other MRSA drugs are daptomycin, linezolid, ceftaroline, and tigecycline.

Septic Arthritis

A 73-year-old woman presents with a swollen right knee for several days. The knee has an obvious effusion and decreased mobility. There is also redness and tenderness of the knee.

Septic arthritis is an infection of a joint due to virtually any agent. The most common etiology is bacterial; specifically, *Neisseria gonorrhoeae*, staphylococci or streptococci, but *Rickettsia*, viruses, spirochetes, etc., may also cause it. Generally, bacterial arthritis is divided into gonococcal and nongonococcal types.

Pathogenesis. Sexual activity is the only significant risk factor for gonococcal septic arthritis. A total of 1–5% of people with gonorrhea will develop disseminated disease, and 25% will have a history of recent symptomatic gonorrhea. Nongonococcal bacterial arthritis is usually spread by the hematogenous route. Additional routes may include bites (animal or human), direct inoculation of bacteria into the joint through surgery or trauma, or spread of infection from surrounding structures such as bone. Even though both normal or damaged joints can get infected, any previous damage to a joint, such as from rheumatoid arthritis or osteoarthritis, previous surgery, prosthesis placement, gout, sickle cell disease, or the presence of certain risk factors such as IV drug abuse, diabetes mellitus, or HIV infection can predispose a joint to infection. Any cause of bacteremia can seed the joint because the synovium does not have a basement membrane.

Microbiology. Nongonococcal:

- Gram-positive (>85); (*S. aureus* [60%], *Streptococcus* [15%], *Pneumococcus* [5%])
- Gram-negative (10–15%)
- Polymicrobial (5%)

Presentation includes the following:

- **Nongonococcal:** monoarticular in >85%, with a swollen, tender, erythematous joint with a decreased range of motion (knee most common); skin manifestations rare
- **Gonococcal:** polyarticular in 50%; a tenosynovitis is much more common (effusions less common; migratory polyarthralgia common; skin manifestations with petechiae or purpura common)

Diagnosis

- **Nongonococcal.** Culture of joint aspirate fluid is positive in 90–95% and Gram stain is positive in 40–70%. Cell count of synovial fluid is high (>50,000) and is predominantly PMNs with a low glucose. Blood culture is positive in 50%.
- **Gonococcal.** Much harder to culture. Only 50% of joint aspirates have positive synovial fluid culture; <10% of blood cultures are positive. Other sites such as cervix, pharynx, rectum, and urethra may also be positive. In the aggregate, culture of the other sites has a greater yield than culturing the joint itself.

Treatment. Bacterial arthritis is usually treated by a combination of joint aspiration and antimicrobial therapy.

- **Nongonococcal.** In the absence of a specific organism seen on a stain or obtained from culture, good empiric coverage is vancomycin to cover MRSA. Add ceftriaxone or another third-generation cephalosporin for gram-negative coverage if the patient is immunocompromised or with joint trauma.
- **Gonococcal.** Ceftriaxone is the drug of choice.

Gas Gangrene (Clostridial Myonecrosis)

Gas gangrene is the necrotizing destruction of muscle by gas-producing organisms, associated with signs of sepsis. It is largely caused by the spread of infection from wounds contaminated by *Clostridium perfringens* (the toxins produced by clostridia play a significant role in tissue damage). It is strongly associated with traumatic injury (50%), shrapnel in war, and motor vehicles in peacetime. The trauma may be as minor as an intramuscular injection; however, the wound must be deep, necrotic, and without exit to the surface. Postoperative (30%), nontraumatic (20%).

Symptoms usually begin <1–4 days of incubation after the wound; they include pain, swelling, and edema at the site of the wound. Later hypotension, tachycardia, and fever can occur. Crepitation over the site and renal failure are late developments, usually prior to death.

Diagnosis. A Gram stain of the wound shows gram-positive rods, but no white cells. A culture may be positive for *C. perfringens* as early as 1 day; however, this is not necessarily diagnostic because up to 30% of wounds can be colonized by *Clostridia*. Gas bubbles on x-ray are suggestive but may be caused by streptococci as well. Direct visualization (usually at surgery) of pale, dead muscle with a brownish, sweet-smelling discharge is ultimately diagnostic.

Note

Gas gangrene is not common; a large referral center may admit 10 cases per year. However, incidence increases during times of war.

Note

In the past, uterine gangrene was a major complication of improper abortion.



Treatment. High-dose penicillin (24 million/day) and clindamycin (if penicillin allergic) is necessary, but surgical debridement or amputation is the absolute center of treatment.

Hyperbaric oxygen may help, but that is still controversial.

Clinical Recall

What is the most appropriate treatment for gas gangrene?

- A. High-dose penicillin
- B. Clindamycin
- C. High-dose penicillin and hyperbaric oxygen
- D. IV doxycycline and surgical debridement
- E. High-dose penicillin and surgical debridement

Answer: E

VECTOR-BORNE DISEASES

Malaria

- For prophylaxis, use mefloquine or atovaquone/proguanil (avoid mefloquine with history of neuropsychiatric illness)
- Treat with mefloquine or atovaquone/proguanil (for *Plasmodium falciparum*)
- Treat with chloroquine or primaquine (vivax and ovale only) (for non-*falciparum*)
- If severe, treat with artemisinin, not quinine

Dengue

Dengue is transmitted by mosquitos. Clinical presentation includes bone pain (back) and retro-orbital headache.

Symptoms also include severe thrombocytopenia, leukopenia, and transaminitis.

Chikungunya

Chikungunya is transmitted by mosquitos. Clinical presentation includes severe joint pain.

Lyme Disease

A couple presents to your office after a recent camping trip. The woman has found a tick bite but has had no symptoms. The man had a red skin lesion which resolved and was followed by the onset of facial palsy. He does not recall having sustained a tick bite.

Lyme disease is spread by the bite of the *Ixodes scapularis* (dammini) tick. On the basis of animal studies we know that the tick needs at least 24 hours of attachment to transmit the *Borrelia burgdorferi* organism. The tick is small, and the bite is often not remembered.

Symptoms begin 3–30 days after the bite of the tick.

- Erythema migrans rash at the site of the bite (80% of patients)
 - An erythematous patch, which may enlarge in the first few days, may have partial central clearing, giving it a “bull’s-eye” appearance, although this is not commonly seen.
 - The rash will resolve in several weeks, even without treatment.
- Flulike illness with fever, chills, and myalgias (50% of patients)
- Neurologic symptoms several weeks later (10–20% of patients)
 - Paralysis of the seventh cranial nerve (facial paralysis) (**most common**), possibly bilateral
 - Meningitis, encephalitis, headache, and memory disturbance
- Cardiac symptoms (<10% of patients)
 - AV heart block (**most common**)
 - Myocarditis, pericarditis, and various forms of arrhythmias
- Joint involvement months to years later (up to 60% of patients)
 - A migratory polyarthrititis
 - Chronic monoarticular arthritis (**most commonly affecting the knee**)

Diagnosis.

- Erythema migrans rash + at least one late manifestation
- Lab confirmation of the presence of the organism
- Serologic testing (**most commonly used test**)
 - ELISA test + a Western blot (**hallmark tests**)
 - The problem with serologic testing is that it often does not distinguish between current and previous infection.
 - Also, in early disease when patients have the rash, testing is often negative because patients have not had sufficient time to mount an immune response; in those situations, treatment should be given based on strong clinical suspicion, and serologic testing should not be done.
 - Serology will almost always be positive later in the course of the disease.

Treatment. Most patients are treated on the basis of the presence of the rash alone.

- Oral doxycycline for the rash, facial palsy, and joint pain
- Doxycycline or amoxicillin for minor symptoms
- IV ceftriaxone for more serious symptoms such as heart block, meningitis, myocarditis, or encephalitis

Note

When leukopenia and thrombocytopenia are seen with Lyme, think of co-infection with *Anaplasma phagocytophilum* and check a blood smear to evaluate for morulea.

Note

All cardiac and serious neurologic manifestations of Lyme should be treated with IV ceftriaxone.



Centers for Disease Control and Prevention, James Gathany

Figure 7-10. Erythema Migrans – Lyme Disease

Clinical Recall

Which of the following is an indication for prophylactic therapy in the management of infective endocarditis?

- A. Congenital cyanotic heart lesions
- B. Surgically corrected systemic pulmonary shunts
- C. Hypertrophic cardiomyopathy
- D. Mitral valve prolapse with valvular regurgitation
- E. GI surgery

Answer: A

Rocky Mountain Spotted Fever

Rocky Mountain spotted fever (RMSF) is a bacterial infection caused by the organism *R. rickettsii*.

R. rickettsii is transmitted by the wood tick. The most common areas are the mid-Atlantic coast, upper South, and Midwest of the United States.

Clinical Findings.

- More common in spring and summer
- Triad: abrupt onset of fever, headache, and rash (erythematous maculopapules). This disease starts at wrist and ankles and spreads centripetally (can involve palms and soles).
- Differential diagnosis with syphilis

Symptoms include confusion, lethargy, dizziness, irritability, stiff neck, and GI symptoms. Rash starts by day 6.

Diagnosis is made with specific serology and a skin lesion biopsy. Treat with doxycycline.



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Figure 7-11. Rash of Rocky Mountain Spotted Fever on an Infant

FUNGAL INFECTIONS

Aspergillosis

Aspergillosis is a fungus that is widespread in the environment; it primarily causes pulmonary disease in the immunocompromised.

- 90% species known, with *A. fumigatus* the most common
- Ubiquitous in natural decaying organic matter, ceiling tile, and ventilation systems
- Spores can be isolated from air anywhere on earth

Symptoms include:

- Various degrees of respiratory tract invasion
- Rarely it can disseminate to any organ but starts in the lung
- Allergic bronchopulmonary-like asthma with cough/fever/wheezing
- Mycetoma (a “fungal ball” that sets up residence in a pre-existing cavity [hemoptysis is chief complaint] but it is not invasive)
- Invasive pulmonary

Nearly 90% of patients have 2 of the following risk factors:

- Neutropenia <500
- History of steroid use
- History of cytotoxic drugs (e.g., azathioprine, cyclophosphamide)

**Note**

Voriconazole and caspofungin are used to treat aspergillosis and some other fungal infections.

Diagnosis.

- Abnormal chest x-ray and *Aspergillus* in sputum (all cases)
- Allergic bronchopulmonary elevation of allergy/asthma markers, such as eosinophil/IgE
- Positive skin testing
- Mycetoma: abnormal sputum culture/serum precipitins/x-ray
- Invasive disease (sputum culture not sufficient):
 - Biopsy needed to show invasion
 - CT scan (or chest x-ray) will show a “halo” sign, a zone of low attenuation around a nodular lesion (often an early finding in invasive pulmonary aspergillosis)
 - Positive galactomannan antigen test

Treatment. Depends on syndrome (really, they are separate diseases).

- Allergic: steroid taper and asthma medications, not antifungals
- Mycetoma: surgical removal
- Invasive: Voriconazole is superior to amphotericin; there are fewer failures seen with it (and caspofungin) as compared with amphotericin. Itraconazole for very mild disease or after initial treatment with amphotericin. Caspofungin is active against *Aspergillus* and may be superior to amphotericin. Caspofungin is an echinocandin. The other echinocandins are micafungin and anidulafungin. Echinocandins have virtually no toxicity.

Clinical Recall

Which of the following statements regarding HIV in pregnant women is correct?

- A CD4 <200 is an indication for single treatment with AZT
- Emtricitabine is contraindicated in pregnant women
- C-sections are done when the viral load is >1000 copies/mL of HIV-RNA at the time of delivery
- Treatment with HAART triple therapy is done only in women who are at high risk of transmitting the disease
- Only give HAART triple therapy to pregnant patients with opportunistic infections

Answer: C

ENDOCARDITIS

A 40-year-old man with a history of IV drug use presents to the hospital with fever. On physical examination a systolic murmur at the lower left sternal border is noted.

Endocarditis is an infection of the endocardium, the inner lining of the heart chambers and valves. The heart valves are colonized with microbial organisms, causing friable infected vegetations and valve injury. Men > women.

Acute infective endocarditis is caused by bacteremia. *S. aureus* is the most common cause.

- Rapid onset with fever and sometimes sepsis
- Seed previously normal valves, producing necrotizing, ulcerative, invasive infection
- Produces large, bulky vegetations (2 mm to 2 cm) on the atrial side
- IV drug use a major risk factor
- Splenomegaly
- Associated with invasion of myocardium (abscess cavities) and rapid valve destruction
- Embolic complications, particularly to the lungs with right-sided lesions

Subacute infective endocarditis is commonly caused by viridans group streptococci. It is associated with low virulence.

- Slow onset with vague symptoms, leading to malaise, low-grade fever, weight loss, and flu-like symptoms
- Seed previously abnormal valves, producing smaller vegetations composed of fibrin, platelets, debris, and bacteria
- Risk factors include ventricular septal defect with shunt; stenosis of any valve; prosthetic valve; indwelling catheter; bicuspid aortic valve; mitral valve prolapse; and Marfan syndrome
- Destruction of valves

Bacterial endocarditis produces large vegetations and may affect any valve in the heart, although left-sided lesions of the aortic and mitral valves are more common. Predisposing factors include dental procedures that cause bleeding; oral/upper respiratory tract/GU surgery; prosthetic heart valves; catheters in the right heart; pressure-monitoring catheters; and IV drug use.

Note

Subacute infective endocarditis is less fatal than acute endocarditis. With treatment, 5-year survival rate is almost 90%.



Table 7-5. Microorganisms Responsible for Infective Endocarditis

Organism	Incidence, %
<u>Native valves</u>	
<i>Streptococcus viridans</i>	50–60
Enterococci	5–15
Other streptococci: <i>Staphylococcus aureus</i> <i>Staphylococcus epidermidis</i>	15–20 20–30 1–3
Gram-negative bacilli	<5
Fungi (<i>Candida</i> , <i>Aspergillus</i> , <i>Histoplasma</i>)	<3
Culture negative	<5
<u>In narcotic addicts</u>	
<i>Staphylococcus aureus</i> <i>Staphylococcus epidermidis</i>	60–95 5–10
Streptococci	10–20
Enterococci	8–10
Gram-negative bacilli	4–8
Fungi	4–5
Diphtheroids	1–2
<u>Prosthetic valves</u>	
<i>Staphylococcus epidermidis</i> <i>Streptococcus viridans</i> <i>Staphylococcus aureus</i>	Acutely: first 2 months after surgery 40–50 acutely; 10–20 later 5–20 acutely; 40–60 later 15–20 acutely; 20–30 later
Enterococci	5–10
Other streptococci	1–5
Culture negative	<5

Table 7-6. Risk of Predisposing Conditions for Infective Endocarditis

High Risk	Intermediate Risk	Low/Negligible Risk
Prosthetic valves*	Mitral valve prolapse with regurgitation	Mitral prolapse without regurgitation
Aortic valve disease	Mitral stenosis	Atrial septal defect
Mitral regurgitation	Tricuspid valve disease	Luetic aortitis
Patent ductus arteriosus	Hypertrophic obstructive cardiomyopathy	Transvenous pacemakers
Arteriovenous fistula	Calcific aortic sclerosis Tetralogy of Fallot	Surgically corrected congenital lesions (no prosthesis) >6 mo after surgery
Coarctation of the aorta Indwelling right heart catheters (hyperlimentation)	Indwelling right heart and pulmonary artery catheters	Aortocoronary bypass surgery Cardiac pacemakers
Previous infective endocarditis	Nonvalvular intracardiac prosthesis	—
Marfan syndrome	—	—

*Indication for endocarditis prophylaxis

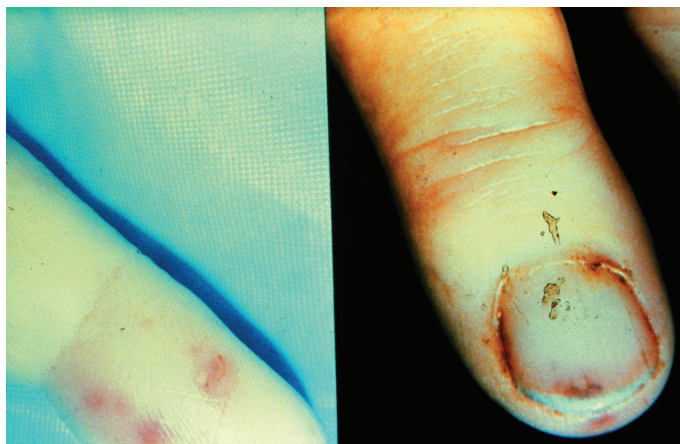
Clinical Manifestations.

Table 7-7. Incidence of Clinical Findings in Infective Endocarditis

Symptoms, %	Signs, %
Chills, 41	Heart murmur or changing murmur, 80–90
Weakness, 38	Fever, 90
Dyspnea, 36	Embolic events, 50
Sweats, 24	Skin manifestations, 50
Anorexia, weight loss, 24	Splenomegaly, 28
Malaise, 24	Septic complications, 19
Cough, 24	Mycotic aneurysms, 18
Skin lesions, 21	Glomerulonephritis, 10
Stroke, 18	Digital clubbing, 12
Nausea, vomiting, 17	Retinal lesions, 5
Chest pain, 16	

**Table 7-8. Peripheral Manifestations of Infective Endocarditis**

Physical Findings (Frequency)	Pathogenesis	Most Common Organisms
Petechiae (20–30%): red, nonblanching lesions in crops on conjunctivae, buccal mucosa, palate, extremities	Vasculitis or emboli	<i>Streptococcus</i> , <i>Staphylococcus</i>
Splinter hemorrhages (15%): linear, red-brown streaks most suggestive of IE when proximal in nailbeds	Vasculitis or emboli	<i>Staphylococcus</i> , <i>Streptococcus</i>
Osler's nodes (5–10%): 2–5 mm painful nodules on pads of fingers or toes	Vasculitis	<i>Streptococcus</i>
Janeway lesions (10–15%): macular, red, or hemorrhagic, painless patches on palms or soles	Emboli	<i>Staphylococcus</i>
Roth's spots (<5%): oval, pale, retinal lesions surrounded by hemorrhage	Vasculitis	<i>Streptococcus</i>



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Figure 7-12. Embolic Features of Acute Endocarditis

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Figure 7-13. Petechial Hemorrhage, an Embolic Phenomenon Due to Septicemia/Endocarditis

The following complications may be seen with infective endocarditis:

- CHF (**most common cause of death**)
- Septic embolization (related to infarctions and metastatic infections): brain (“mycotic” aneurysm); spleen (greater with subacute); kidneys; coronary arteries
- Glomerulonephritis with nephrotic syndrome or renal failure (immune complex)

Diagnosis. To diagnose endocarditis, **2 major criteria** are required: positive blood cultures and abnormal echocardiogram.

- Transthoracic echocardiogram has <60% sensitivity and excellent specificity.
- Transesophageal echocardiogram has >90% sensitivity and >95% specificity.

If 1 major criteria is absent, **1 major + 3 minor criteria** will constitute a diagnosis. The minor criteria are:

- Fever
- Predisposing cardiac lesion
- IV drug use
- Vascular phenomena (arterial embolic, septic pulmonary infarcts, Janeway lesions), immunologic phenomena (such as Osler nodes, Roth spots, glomerulonephritis, or a positive rheumatoid factor)
- Microbiologic evidence (positive blood cultures not meeting major criteria or evidence of active infection with an organism consistent with infective endocarditis)

Treatment is based on the organism found in blood culture and its specific antimicrobial sensitivities. If the patient is very ill or has heart failure and embolic phenomena, treatment can be started before the results come back. Acceptable empiric therapy is as follows:

- For **community-acquired native valve IE**: vancomycin or ampicillin-sulbactam + gentamicin
- For **nosocomial-associated IE**: vancomycin, gentamicin, rifampin and an antipseudomonal beta-lactam
- For **prosthetic valve IE**: vancomycin, gentamicin, and rifampin

As soon as the specific microbiologic agent is known, treatment must be altered.

Note

Always get at TEE in patients with *S. aureus* bacteremia.

**Note**

Look for colon cancer in patients with *Streptococcus bovis* or *Clostridium septicum* endocarditis.

Note

Coxiella burnetii can cause culture negative endocarditis. Think of this in patients exposed to large animals, such as farmers or zoo keepers.

Table 7-9. Treatment of Specific Microorganisms Causing Endocarditis

Organism	Medication	Duration
<i>Strep. viridans</i>	Penicillin	4 weeks
	Penicillin-allergic: ceftriaxone <i>or</i> vancomycin	4 weeks
	Penicillin or ceftriaxone + gentamicin	2 weeks
<i>Staph. aureus</i>, native valve (Methicillin-sensitive)	Nafcillin (+ 5 days of gentamicin)	4–6 weeks
	Penicillin-allergic: cefazolin <i>or</i> vancomycin + gentamicin for first 5 days	4–6 weeks
	(Methicillin-resistant) Vancomycin	4–6 weeks
Enterococcal	Penicillin (or ampicillin) <i>and</i> gentamicin (vancomycin if penicillin-allergic)	4–6 weeks
	Penicillin-allergic or resistant: vancomycin <i>and</i> gentamicin	4–6 weeks

Surgery is required only in specific situations. The criteria for surgery in infective endocarditis are as follows.

Major criteria for surgery

- CHF, progressive or unresponsive to “simple” measures
- Recurrent systemic emboli
- Persistent bacteremia despite adequate antibiotic therapy
- Fungal etiology
- Extravalvular infection (atrioventricular block, purulent pericarditis)
- Prosthetic valve dehiscence or obstruction
- Recurrence of infection despite adequate therapy

Minor criteria for surgery

- CHF, resolved with medical therapy
- Single systemic embolic event
- Large aortic or mitral vegetations on echocardiography
- Premature mitral valve closure in acute aortic insufficiency
- Prosthetic valve infection due to organisms other than highly penicillin-sensitive streptococci
- Tricuspid endocarditis due to gram-negative bacilli
- Persistent fever without other identifiable cause
- New regurgitation in an aortic prosthesis

Prophylaxis

The number of cardiac lesions which are an indication for endocarditis prophylaxis has markedly diminished over the years. AS, MS, AR, and MR **no longer** need prophylaxis, even for dental procedures. Prophylactics are indicated when there is both a serious underlying cardiac defect and a procedure causing bacteremia.

- **Dental procedures:** amoxicillin; for penicillin-allergy, use clindamycin, azithromycin, clarithromycin, or cephalexin
- **Urinary or GI procedures:** prophylaxis no longer needed
- **Cardiac conditions that do require prophylaxis:**
 - Prosthetic cardiac valves, including bioprosthetic and homograft valves
 - Previous bacterial endocarditis, even in the absence of heart disease
 - Most congenital cardiac malformations, especially cyanotic lesions (negligible risk with isolated ASD) if **not** repaired
- **Anatomic conditions that do require prophylaxis:**
 - Prosthetic valves
 - Unrepaired cyanotic heart disease
 - Previous endocarditis
 - Valvulopathy following cardiac transplantation
 - Congenital heart defect repair with prosthesis or shunt done <6 months prior
- **Conditions that do not require prophylaxis:**
 - Surgically corrected systemic pulmonary shunts and conduits
 - Rheumatic and other acquired valvular dysfunction, even after valvular surgery
 - Hypertrophic cardiomyopathy
 - Mitral valve prolapse with valvular regurgitation
 - Surgically repaired intracardiac defects
- **Dental or surgical procedures that predispose to endocarditis:**
 - Dental procedures known to induce gingival or mucosal bleeding, including professional cleaning
 - Procedures that involve incision or biopsy of the respiratory mucosa
 - Tonsillectomy and/or adenoidectomy
 - Surgery to place prosthetic heart valves or prosthetic intravascular or intracardiac materials
 - Procedures on infected skin or tissue

Note

For the exam, prophylaxis for bacterial endocarditis is high yield.

**Note**

The mode of HIV acquisition varies around the world.

- In the United States, the primary mode is men having sex with men (MSM) and heterosexual intercourse (years ago, injection drug use played a larger role). For women, it is heterosexual transmission.
- In most developing nations, the primary mode is heterosexual transmission.

Note

It is possible to have pneumocystis pneumonia (PCP) with a normal chest x-ray.

ACQUIRED IMMUNE DEFICIENCY SYNDROME

Acquired immune deficiency syndrome (AIDS) is caused by the human immunodeficiency virus (HIV).

- Primary mechanism is infection of a subset of T lymphocytes called CD4 cells (or “T cells”)
- Over time, HIV decreases the number of CD4 cells; as that happens, patient becomes at increased risk for opportunistic infections and certain malignancies
- Often a 10-year lag between contracting HIV infection and developing the first symptoms
 - CD4 cells drop at a rate of 50–100/ μ L/year without treatment
 - Would take 5–10 years to drop from normal CD4 count of 700/ mm^3 to a count of 200/ mm^3

Opportunistic Infections in AIDS**Pneumocystis jirovecii (CD4 count <200/ μ L)****Clinical Presentation.**

- Usually subacute onset and progression
- Pneumonia
- Dyspnea on exertion
- Dry cough
- Fever
- Chest pain

Diagnosis.

- Bronchoscopy with bronchoalveolar lavage for direct identification of the organism
- Chest x-ray will reveal bilateral, interstitial infiltrates
- Possible pneumothorax (chest x-ray may be normal)
- Moderately elevated LDH

Treatment.

- TMP-SMZ (**first-line**) for mild to severe disease
 - May cause a rash
 - Can cause hyperkalemia, so do not combine with ACE inhibitors, ARBs, or spironolactone
 - Can inhibit the secretion of creatinine and cause a mild increase in creatinine (.05 mg/dL), but do not stop the medication as this is not a decrease in GFR
- Alternatively, combination treatment with one of the following:
 - Dapsone + trimethoprim
 - Primaquine + clindamycin
 - Leucovorin + atovaquone or trimetrexate

- Pentamidine for sulfa allergy: pancreatitis, hyperglycemia, hypoglycemia
- IV clindamycin + primaquine for sulfa allergy
- Steroids, as adjunct therapy for patients with severe pneumonia (i.e., PaO₂ <70 mm Hg or A-a gradient >35 mm Hg)

Prophylaxis of PCP is as follows (in order of preference):

- TMP/SMZ orally (**most effective**)
- Dapsone
- Atovaquone
- Aerosolized pentamidine (**least effective**)

Prophylaxis may be discontinued if antiretrovirals raise CD4 >200/μL for >6 months.

Cytomegalovirus (CD4 <50/μL)

Clinical Presentation.

- Retinitis: blurry/double vision, or any visual disturbance in a patient with very low CD4
- Colitis: diarrhea (<20% of patients)
- Esophagitis: odynophagia, fever, retrosternal chest pain (endoscopy reveals multiple shallow ulcers in the distal esophagus)
- Encephalitis: altered mental status, cranial nerve deficits

Diagnosis.

- Funduscopy for retinitis
- Colonoscopy with biopsy for diarrhea or upper GI endoscopy with biopsy of ulcers

Treatment.

- Valganciclovir to treat CMV retinitis (along with intravitreal ganciclovir) and GI manifestations of CMV disease
- IV ganciclovir for serious CNS infections and for those who cannot tolerate oral medications
- If no response or if ganciclovir-resistant, use foscarnet and cidofovir; note the following side effects
 - Ganciclovir can cause neutropenia or foscarnet-renal toxicity
 - Cidofovir can cause renal toxicity

Primary prophylaxis is not indicated. Valganciclovir is used for maintenance therapy.

Mycobacterium avium complex (CD4 <50/μL)

Clinical Presentation.

- Ubiquitous atypical mycobacteria found in the environment
- Mode of infection is inhalation or ingestion
- Symptoms include fever, night sweats, bacteremia, wasting, anemia, diarrhea

Note

Severe pneumonia is defined as PaO₂ <70 mm Hg or A-a gradient >35 mm Hg.

Note

Valganciclovir, an oral prodrug of ganciclovir, achieves levels in the serum comparable to IV ganciclovir.

**Note**

CNS lymphoma is usually one lesion (located in the periventricular region, periependymal area, or corpus callosum), whereas toxoplasmosis is multiple lesions.

Diagnosis.

- Blood culture
- Culture of bone marrow, liver, or other body tissue or fluid

Treatment.

- Clarithromycin + ethambutol +/- rifabutin
- Prophylaxis as follows:
 - Oral azithromycin 1x/week or clarithromycin 2x/day if CD4 <50/ μ L
 - May be discontinued if antiretrovirals raise CD4 >50/ μ L over a period of several months

Toxoplasmosis (CD4 <100/ μ L)**Clinical Presentation.**

- Brain mass lesion
- Headache
- Confusion
- Seizures
- Focal neurologic deficits

Diagnosis.

- CT or MRI scan of the head will show several “ring” (contrast) enhancing lesions with edema and mass effect, usually in basal ganglia
- A trial of specific therapy is given for 2 weeks, and the scan is repeated; shrinkage of the lesions is considered diagnostic
- If there is no shrinkage, brain biopsy may be needed (rare)

Treatment.

- Pyrimethamine and sulfadiazine; if patient is sulfa-allergic, substitute clindamycin for sulfadiazine
- Leucovorin to prevent bone marrow suppression
- For prophylaxis: TMP/SMX; dapsone, pyrimethamine, and leucovorin; atovaquone +/- pyrimethamine

Cryptococcosis (CD4 <100/ μ L)

Clinical Presentation. Meningitis; patients mostly present with fever, headache, and malaise.

Diagnosis.

- Lumbar puncture with initial evaluation by India ink and then specific cryptococcal antigen testing. A lower CSF cell count implies worse disease.
- Serum cryptococcal antigen testing. A high antigen titer, high opening pressure, and low CSF cell count all imply a worse prognosis.

Treatment.

- IV amphotericin B for minimum 10–14 days (with flucytosine)
- Follow with oral fluconazole for maintenance and suppressive therapy; once CD4 >100/ μ L for 3 months, stop fluconazole
- Oral fluconazole is not recommended for general use as a prophylaxis. This is because the incidence of cryptococcal meningitis is too low to demonstrate a mortality benefit with its use.

Vaccinations

All HIV-positive persons should receive vaccinations for pneumococcus.

- (Covalent) PCV13 first
- Eight weeks later, the (polysaccharide) PPSV23, influenza, and hepatitis B
- If CD4 >200/ μ L, varicella vaccine can be given

Monitoring the Immune System

CD4 monitoring and viral load testing can be compared to the staging of cancer in terms of assessing prognosis. They are indispensable for determining appropriate treatment.

CD4 cell count

The CD4 count is the most accurate method of identifying the infections or other diseases that the patient is at risk for, i.e., the risk of opportunistic infections.

- Provides an assessment of the extent of immunologic damage at the time of diagnosis
- Critical for deciding the timing of therapy
- Adequacy of response to antiretroviral medications
- Strongest predictor of disease progression and survival

Without treatment, CD4 count drops 50–100 cells per year.

The following is an approximate breakdown of when the risk of certain diseases begins to increase.

CD4 Count	Disease Risk
700–1,500/ μ L	Normal
200–500/ μ L	Oral thrush, Kaposi sarcoma, TB, Zoster
100–200/ μ L	<i>Pneumocystis carinii</i> pneumonia, disseminated histoplasmosis and coccidioidomycosis
<100/ μ L	Toxoplasmosis, <i>Cryptococcus</i> , cryptosporidiosis, disseminated herpes simplex
<50/ μ L	Cytomegalovirus; <i>Mycobacterium avium</i> complex; progressive, multifocal leukoencephalopathy (PML); CNS lymphoma

Note

While CD4 count is helpful for determining the adequacy of response to antiretrovirals, the best test for monitoring response to therapy is the HIV-RNA viral load.

**Note**

Viral load monitoring in HIV can be compared to monitoring for glucose in diabetes.

Note

TB can be seen at any CD4 count.

Note

- Because of greater long-term viral suppression, low resistance, and fewer side effects with current medications, **first-line antiretroviral therapy** is now 2 nucleoside reverse transcriptase inhibitors + an integrase inhibitor.
- Commonly used nucleoside reverse transcriptase inhibitors include **emtricitabine-tenofovir** and **abacavir-lamivudine**.

Viral load monitoring

Tests now exist to give a numerical value to the quantity of HIV in the blood, “viral load.” Monitoring of viral load is the best way to monitor response to antiretroviral treatment.

- High viral load indicates that CD4 level will drop more rapidly.
- High viral load indicates a greater risk of complications and a worse prognosis.
- With current assays, the goal is complete suppression of viremia with **<50–70 copies of HIV-RNA/mL**.

Viral sensitivity/resistance monitoring

Viral sensitivity testing is done in the following situations:

- All patients prior to initiation of antiviral medications
- Patients who are not responding to current medications and require a change in treatment
- Pregnant women who are not fully suppressed on the initial combination of medications

Treatment failure first manifests with a rising PCR-RNA viral load.

Antiretroviral Therapy

First-line antiretroviral therapy is 2 nucleoside reverse transcriptase inhibitors (NRTIs) + an integrase inhibitor.

Preferred regimens include:

- Abacavir/lamivudine/dolutegravir
- Tenofovir alafenamide/emtricitabine/dolutegravir
- Tenofovir alafenamide/emtricitabine/cobicistat/elvitegravir
- Tenofovir alafenamide/emtricitabine/raltegravir

NRTIs and integrase inhibitors inhibit the HIV replication cycle and terminate the DNA chain. NRTIs do so by blocking the action of the viral enzyme *reverse transcriptase*. Integrase inhibitors do so by blocking the action of the viral enzyme *integrase*.

- **NRTIs**
 - Zidovudine (also called azidothymidine): side effects include leukopenia, anemia, GI disturbance
 - Lamivudine (3TC): nothing additional to placebo
 - Emtricitabine: structurally related to lamivudine (rarely well-tolerated; side effects include lactic acidosis and severe hepatotoxicity)
 - Tenofovir, a nucleotide analog as compared to the others that are nucleoside analogs
 - Abacavir: side effects include hypersensitivity reaction in first 6 wks (rash, fever, nausea/vomiting, muscle aches), SOB (stop drug immediately and do not restart); recurrence of hyperactivity symptoms can be rapid and life-threatening

- Tenofovir and emtricitabine (**both commonly used**)
- Abacavir and lamivudine (**both commonly used**)
- **Integrase inhibitors**
 - Dolutegravir
 - Elvitegravir: give with cobicistat as a boost effect because it inhibits the P450 system (can elevate serum creatinine because it inhibits creatinine secretion)
 - Raltegravir

Second-line agents include:

- **Protease inhibitors (PIs):** hyperlipidemia, hyperglycemia, and elevated liver enzymes; abnormal fat loss (lipoatrophy) from the face and extremities, with redistribution of fat in back of the neck and abdominal viscera; are potent inhibitors of CYP3A and have many drug-drug interactions
 - Indinavir: side effects include nephrolithiasis (4%) and hyperbilirubinemia (10%)
 - Ritonavir: side effects include severe GI disturbance
 - Darunavir
 - Lopinavir/ritonavir combination: side effects include diarrhea
 - Atazanavir: side effects include diarrhea and asymptomatic hyperbilirubinemia
- **Non-nucleoside reverse transcriptase inhibitors** (noncompetitive inhibitors of reverse transcriptase)
 - Efavirenz: side effects include neurologic; somnolence and confusion
 - Nevirapine: side effects include rash and hepatotoxicity

Guidelines for starting therapy are to **start therapy once HIV is diagnosed**, regardless of CD4 count. Viral sensitivity testing should be done in all patients prior to starting treatment.

- 2 nucleosides combined with an integrase inhibitor (**most common**)
- 2 nucleosides combined with a protease inhibitor or with efavirenz (**second-line**)

Emtricitabine, efavirenz, and tenofovir are available as a single pill once a day.

- Tenofovir can rarely cause Fanconi syndrome. Patients present with hypokalemia, hypophosphatemia, metabolic acidosis, and glycosuria. It can also cause demineralization.
- Tenofovir has 2 formulations: alafenamide (**preferred**, with fewer side effects) and disoproxil.

Giving “**boosted protease inhibitors**” is the practice of giving most protease inhibitors in combination with a low dose of ritonavir (also a PI). Ritonavir given alone as a PI has modest efficacy and significant drug interactions, but when given in a low dose with other PIs, it decreases their metabolism and enables higher drugs levels of the “boosted” PI over a prolonged period of time. This increases chances of success and also decreases pill burden.

- Any regimen that increases the CD4 count and drops the viral load to undetectable amounts (or close to) is considered adequate therapy.
- A drop of at least 50% of viral load in the first month is expected to indicate adequate therapy.

Note

Before giving abacavir, be sure to check HLA B5701. People carrying this allele are at risk for SJS.

Note

The **only statins safe with PIs** are rosuvastatin, pravastatin, and low-dose atorvastatin. Never give lovastatin or simvastatin in combination with a PI.

**Note**

Most pregnant, HIV-positive women can have normal vaginal delivery.

Pregnant, HIV-Positive Patients

Without treatment, approximately 25–30% of children born to HIV-positive mothers will truly be HIV positive. All children at birth will carry the maternal antibody to the virus and will be positive by ELISA testing, but only 25–30% will remain truly infected.

These patients should receive the following:

- Triple antiretroviral therapy (as nonpregnant people receive)
- Immediate therapy as soon as it is known that the patient is pregnant
- Intrapartum IV zidovudine

The following medications are not recommended:

- Efavirenz
- Elvitegravir-cobicistat
- Tenofovir alafenamide
- Dolutegravir in first 8 weeks of pregnancy

C-section is required only when CD4 count and viral load are not controlled with medications (viral load >1000 copies/mL of HIV-RNA at time of delivery). Otherwise, do normal vaginal delivery. After delivery, the baby should receive zidovudine for 6 weeks.

Breast feeding is associated with transmission of the virus to the infant.

- If a pregnant woman is already on antiretrovirals, she should continue on them.
- If a pregnant woman has high CD4 cells and does not need treatment for herself, combination therapy can end after delivery.

Postexposure Prophylaxis (e.g., Needlestick Injury)

All persons with serious exposure to blood containing body fluids of HIV-positive patients should receive emtricitabine-tenofovir and raltegravir.

Note

Do an HIV test on anyone with ITP, abrupt onset of severe and explosive psoriasis, severe and sudden seborrheic dermatitis, recurrent herpes zoster, or molluscum contagiosum.

Pre-Exposure Prophylaxis (PrEP)

People who are HIV-negative but have high risk behavior should be offered PrEP. On the exam, the question will make it clear that the HIV-negative person is high risk (unprotected sex with multiple partners, shares needles, or has an HIV-positive partner). The preferred agent is emtricitabine/tenofovir-disoproxil-fumarate, which will prevent transmission of HIV.

Patients should continue to take PrEP as long as they exhibit high risk behavior. This is more effective than using condoms (and on the exam, would be the correct answer over using condoms).

Acute HIV

Two weeks after being infected, the patient will present with fever, lymphadenopathy, sore throat, rash, myalgia/arthralgia, and headache (2–4 weeks after exposure).

- Rash: upper thorax, collar region, and face, scalp and extremities, including palms and soles
- Macules or maculopapules: small (5–10 mm), well-circumscribed, oval or round, pink to deeply red-colored
- Diagnosis is made with RT-PCR based viral load test or p24 antigen-testing

Immune reconstitution inflammatory syndrome (IRIS)

IRIS may be seen 3 days to months after starting ART in a patient with low CD4 counts. It can be seen with TB, *Mycobacterium avium* complex, Kaposi sarcoma, CMV, *Pneumocystis jiroveci* pneumonia (PJP), zoster, or *Cryptococcus neoformans*.

- Activation of an opportunistic infection as CD4 count increases
- Patient will have symptoms (e.g., shortness of breath and fever with PJP)
- Treat opportunistic infections; use steroids for severe symptoms
- Do not stop ART

TOXIC SHOCK SYNDROME

Toxic shock syndrome is seen with the use of tampons, sponges, and surgical wounds.

- *Staph aureus* (toxin TSST-1)
- Hypotension, fever, mucosal changes, desquamative rash on hands and feet.
- GI, renal, hepatic symptoms
- Treat with vancomycin and clindamycin

LEPTOSPIROSIS

Leptospirosis is a rare bacterial disease that is contracted by contact with the urine of rodents. It is caused by bacteria of the genus *Leptospira*.

- Renal and liver failure
- Myositis
- **Conjunctival** suffusion is pathognomonic
- Serology with ELISA
- Treat with penicillin, ceftriaxone, or doxycycline

TETANUS

Tetanus is a severe infectious complication of wounds caused by the toxin of *Clostridium tetani* (neurotoxin); takes 1–7 days to develop; spore forming, gram-positive rod.

Clinical Findings. Tonic spasms of voluntary muscles; respiratory arrest; difficulty in swallowing (dysphagia); restlessness; irritability; stiff neck, arms, and legs; headache; lockjaw; flexion of the arms and extension of the lower extremities; and high mortality rate. Diagnosis is clinical.

Treatment is prophylactic:

- Tetanus toxoid (Tdap) booster every 10 years
- Immediate surgical care, debride wound
- Antitoxin, tetanus immunoglobulin
- Penicillin 10–14 days



Wound Management		
Patient	Not Tetanus Prone	Tetanus Prone
	Linear, 1 cm deep cut, without devitalized tissue, without major contaminants, <6 hours old	Blunt/missile, burn, frostbite, 1 cm deep; devitalized tissue present + contaminants (e.g., dirt, saliva); any wound 6 hours old
Not completed primary or vaccination history unknown	Vaccine	Vaccine and TIG*
Completed primary series	Vaccine if >10 years since last booster	Vaccine if >5 years since last booster

*TIG = tetanus immunoglobulin (human)

Learning Objectives

- ❑ Describe the most commonly ordered renal diagnostic tests and their use
- ❑ Outline the approach to investigating kidney problems, fluid and electrolyte disorders, and acid-base disturbances
- ❑ Describe the presentation, diagnosis, and management of acute renal failure, renal tubular acidosis, glomerulonephritis, nephrolithiasis, hereditary cystic disease, and ESRD
- ❑ List the indication and complications of dialysis and criteria to qualify for renal transplantation
- ❑ Describe the causes of primary and secondary hypertension and their management



TESTS IN RENAL DISEASE

Renal diseases may be classified as glomerular, tubulointerstitial, or vascular. The kidney may also be affected by abnormalities in blood supply (CHF, renal artery stenosis) or drainage (ureteral stones, prostatic obstruction). When a patient develops renal disease, it usually presents as one of the following:

- Proteinuria, reflecting a damaged glomerular basement membrane
- Hematuria, reflecting inflammation
- Declining glomerular filtration rate (GFR)

Therefore, renal disease is best detected initially by urinalysis and serum creatinine.

Urinalysis

For the general population, there is no recommendation for routine urinalysis. For those with DM, however, secondary prevention of diabetic nephropathy is recommended; microalbumin/creatinine ratio on a spot urine specimen should be used and not urinalysis.



- **Protein.** The urine protein dipstick detects negatively charged proteins (e.g. albumin) but not other proteins such as immunoglobulin light chains. Proteinuria may be caused by glomerular or tubular disease, although glomerular disease leads to greater amounts. The lower limit of detection for protein on the UA is 300 mg/24 hours, too high to sensitively screen for early diabetic nephropathy. Detected proteinuria may reflect renal disease, but it may also be caused by fever, CHF, or severe exercise. Any positive urine dipstick for protein should be followed up by a quantitative study.
- **Heme and red blood cells (RBC).** The heme dipstick is positive when RBCs are present, but also when there is free hemoglobin (transfusion reactions) or myoglobin (rhabdomyolysis) in the urine. Red cells can be found in the urine from any cause of disease in the urologic system. Etiologies are stones, cancer, bleeding disorders, trauma to urinary system, and treatment such as cyclophosphamide (which causes hemorrhagic cystitis or glomerular disease). Hematuria is also from infections such as cystitis or prostatitis. The red cells change shape (dysmorphic) in some glomerular disease; other clues to glomerular disease are concurrent proteinuria and **RBC casts**, which are pathognomonic for glomerulonephritis.
- **Nitrites.** Gram-negative bacteria reduce nitrate to nitrite, which is a marker of urinary infection.
- **Glucose:** Glucosuria most often reflects hyperglycemia, but may also be caused by defective proximal tubular reabsorption, seen in Fanconi syndrome.
- **Bacteriuria.** By itself, the isolated finding of bacteria in the urine is of very limited significance. The most important exception is in pregnant women, since 30% of those with bacteriuria progress to pyelonephritis. Screen and treat as needed.
- **White blood cells (WBC)** may be due to pyelonephritis, cystitis, or intrarenal inflammation (e.g. eosinophils in eosinophilic granulomatosis). If eosinophils are suspected, they should be stained for with Hansel or Wright staining. If due to bacterial infection, the WBC should be accompanied by visible bacteria, but this may not be the case with all microorganisms (e.g., TB).
- **Renal tubular epithelial cells** appear in the urine during acute tubular necrosis, as dying tubular cells slough into the urine.
- **Casts** are collections of precipitated protein in the renal tubule, often capturing cells which are present there. The most significant casts are RBC casts (seen only in glomerulonephritis) and muddy brown granular casts (seen in acute tubular necrosis).

Table 8-1. Casts

Casts	Significance
Hyaline	Dehydration. These casts develop as an accumulation of the normal amount of tubular protein; they do not necessarily mean disease.
Red cell	Glomerulonephritis
Broad, waxy	Chronic renal failure
Granular	Also called “dirty” or “muddy”; are associated with acute tubular necrosis and represent accumulated epithelial cells
White cell	Pyelonephritis, interstitial nephritis

Urine Protein and Creatinine Concentration

Since the UA is an imperfect screen for small amounts of proteinuria, the best test for this is the spot urine collection for albumin and creatinine (has largely replaced the 24-hour collection done in the past). The ratio of albumin to creatinine is a good estimate of the albumin that would have been collected in a 24-hour collection, and is much easier to do. A 30–300 mcg albumin/mg creatinine suggests incipient diabetic nephropathy in at-risk patients, and would prompt starting an angiotensin-converting enzyme (ACE) inhibitor.

Serum Creatinine, BUN, and Estimated GFR

The glomerular filtration rate (GFR) falls early in many renal diseases, without symptoms. Sensitive testing is thus needed to detect early chronic and acute renal injury. Creatinine, a metabolic product of skeletal muscle, is the main measure of GFR.

An isolated serum creatinine (SCr) test may be deceiving, since it may be low (0.5 mg/dL) just because of decreased muscle mass or high (1.6 mg/dL) due to large muscle bulk. More muscle means more creatinine. Therefore, **serum creatinine values should always be compared to a given patient's baseline**. A doubling of the SCr means a 50% reduction in their GFR.

- Creatinine needs some time to rise. Even if the patient becomes anuric, creatinine will rise only at a rate of 0.5–1.0 point per day. This rise will be faster if the body muscle mass is greater.
- Hence, if the creatinine goes from 1 to 3 over a period of 2 days in a patient with renal injury, this is consistent with nonfunctioning kidneys.

Given the limitations of the isolated serum creatinine, options for better estimation of the GFR include the **creatinine clearance**, which requires a 24 hour urine collection, and the **estimated GFR (eGFR)**, which requires no urine and may be calculated from the patient's SCr, age, race, height, weight, and sex. This builds an estimate of muscle mass to correct the final number.

The eGFR is now the most commonly used way to determine a patient's renal function. It is not useful if the patient's SCr is not at baseline (decreasing or increasing) and should only be used at steady state. The same limitation applies to the creatinine clearance.

Serum BUN is less useful than the creatinine for determining renal function. While it does increase in acute or chronic kidney injury, it may also be falsely elevated even when renal function is normal, in response to increased protein load in the diet or GI bleed. The BUN is derived from protein waste products; blood in the gut acts like a big protein meal and is catabolized to urea. The BUN can be falsely low when there is liver disease, malnutrition, or SIADH.

The BUN is most useful when compared to the serum creatinine, since a ratio >20:1 may suggest prerenal azotemia.

Renal Sonography (Ultrasound)

Renal sonography is the most common test used in renal visualization. It has several uses:

- Detects hydronephrosis in renal obstruction, allowing prompt decompression
- Shows small or scarred kidneys in advanced chronic kidney disease, allowing differentiation from the normal appearing kidneys seen in acute kidney injury
- Shows renal cysts and tumors
- Detects kidney stones in the renal pelvises

**Note**

- **Renal insufficiency** or **azotemia** is AKI but does not require dialysis. (*Azotemia* literally means the buildup of azole groups or nitrogen in the blood.)
- **Uremia** (or ESRD) is very severe AKI or CKD that requires dialysis or transplantation to save life.

Note

Uremia does not necessarily imply CKD. Although most patients develop uremia after years of CKD, it is possible to become uremic in as little as 1–2 weeks with a severe illness causing AKI (e.g., rhabdomyolysis).

ACUTE KIDNEY INJURY

Acute kidney injury (AKI), previously called *acute renal failure*, is a rapid decline in the glomerular filtration rate (elevated BUN and creatinine) over several hours to days. There is no precise duration to define it as *acute*. For example, in rhabdomyolysis or contrast-induced renal failure, it may develop over several hours, while in aminoglycoside toxicity it may take 1–2 weeks.

AKI must be distinguished from **chronic kidney disease** (CKD), which is the slow decline in GFR over years (seen in many glomerular diseases such as diabetic nephropathy).

The distinction between AKI and CKD cannot be made with a single serum creatinine test; it requires serial determinations. The renal sonogram (U/S) can also help in the distinction:

- AKI often shows normal kidneys, despite declining function.
- CKD often shows small or scarred kidneys.

Progressive kidney disease may be life-threatening. Clinical presentation includes:

- Hyperkalemia, severe acidosis, and fluid overload/pulmonary edema
- Anemia, bone disease, and pericarditis
- Bleeding diathesis due to platelet dysfunction
- Altered mental status

AKI is **classified** as prerenal, postrenal, or intrarenal based on the site and mechanism of injury.

- **Prerenal AKI** means decreased perfusion of the kidney (e.g., CHF, renal artery stenosis, volume depletion). The kidney itself is healthy.
- **Postrenal AKI** indicates renal obstruction, causing decreased drainage from the kidney and decreased forward flow of urine (e.g., stones, prostatism, pelvic malignancy). The kidney itself is healthy.
- **Intrarenal AKI** means a reduction in GFR due to a renal tubular, interstitial or glomerular disease (e.g. glomerulonephritis, acute tubular necrosis, acute interstitial nephritis). The kidney is defective.

Clinical presentation. Most AKI is asymptomatic at first, since uremic symptoms do not typically occur until >75% of GFR has been lost. It is commonly a hospital diagnosis, as AKI often accompanies severe illness. Clinical hints of early AKI might include:

- Decreased urine output
- Hypotension or orthostasis (prerenal)
- Hypertension (intrarenal)
- Edema (intrarenal)

Serial measurements of the serum creatinine concentration (SCr) should show rising levels each day. Once a stable value of the SCr is reached, the estimated GFR eGFR can be calculated using standard formulas.

- Urinalysis and fractional excretion of sodium are used to evaluate causes of intrarenal AKI.
- Renal U/S is used to rule out postrenal AKI.
- Serum Na, K, and HCO₃, hematocrit/hemoglobin should be monitored.

Because they are more easily reversed, prerenal and postrenal AKI should always be excluded before launching a workup of renal disease when a declining GFR is detected.

Prerenal Acute Kidney Injury

Prerenal azotemia is a form of AKI caused by diminished perfusion of the kidney. The kidney itself is normal. If the kidney could receive adequate perfusion, the BUN and creatinine would normalize. The causes of prerenal azotemia include:

- Hypovolemia: dehydration, burns, poor oral intake, diuretic, vomiting, diarrhea, sweating, hemorrhage, hypocortisolism, hypoaldosteronism
- Hypotension: septic shock, cardiogenic shock, anaphylactic shock, hepatorenal syndrome
- Third spacing of fluids: peritonitis, osmotic diuresis, low oncotic pressure (hypoalbuminemia of cirrhosis, nephrotic syndrome)
- Decreased renal blood flow: CHF, constrictive pericarditis, renal artery stenosis, aortic coarctation
- Renal arteriolar vasoconstriction/vasodilation: hypercalcemia, cyclosporine, tacrolimus, NSAIDs, ACE inhibitors

Diagnosis is usually made by clinical exam. Volume-depleted patients present with signs of orthostatic or frank hypotension and tachycardia. Skin turgor may be reduced, reflecting low extracellular volume.

In contrast, the prerenal AKI seen in severe CHF, constrictive pericarditis, or coarctation may show edema and fluid overload, yet the kidney is receiving no/low perfusion, thus the rising BUN and creatinine. This demonstrates a reduction of effective arterial volume a physiologic term for perfusion of organs, determined by intravascular volume, blood pressure, and cardiac output.

Regardless of the cause of prerenal AKI, patients may show:

- Elevated serum creatinine concentration
- Normal urinalysis
- Serum BUN:creatinine ratio >20:1 (normally 10:1 in other types of AKI); the BUN elevates because urea undergoes increased proximal tubule reabsorption in states of high sodium absorption (e.g., volume depletion)
- Low urine sodium concentration (<10 mEq/L)
- Low fractional excretion of sodium (FeNa <1%) because the kidney perceives the body as being volume-depleted, leading to a vigorous sodium and water reabsorption by the kidney
- High urine osmolality (>500 mosm/kg) and specific gravity (>1.010)

The urine tests reflect the high renal sodium and water reabsorption driven by the low renal perfusion.

Renal artery stenosis, especially if bilateral, may result in prerenal AKI with a rising creatinine. The kidneys themselves are normal. Similar to the case of renal obstruction, bilateral disease is required for detectable AKI, since loss of a single kidney may be compensated by recruitment of reserve nephrons in the remaining kidney, maintaining the GFR near normal.



In renal artery stenosis, although systemic BP may be markedly elevated (due to high renin/AT/aldosterone levels), the low renal blood flow still leads to AKI. Here, the elevated systemic BP does not matter; all that matters is how much blood is getting to the kidney. This effect is amplified with the use of ACE inhibitors, which will additionally diminish renal perfusion in this setting. Treatment is angioplasty/stenting.

Hepatorenal syndrome is AKI based entirely on the presence of hepatic failure. The kidneys are themselves normal. The rise in BUN and creatinine is believed to be due to an intense vasoconstriction of the afferent arteriole in response to systemic vasodilation caused by the hepatic failure. The local renal vasoconstriction causes decreased renal perfusion and AKI. The syndrome does not respond to volume expansion, unlike AKI in hepatic failure due to simple ECV volume depletion. Lab evaluation is similar to other causes of prerenal AKI. Intrinsic renal disease should be excluded to make a diagnosis (e.g. patients should have a normal urinalysis). A key diagnostic step is lack of improvement of the SCr after a bolus infusion of colloid fluid (e.g. albumin). Treatment is correction of the underlying liver disease (e.g. liver transplantation). Since the underlying physiology is systemic vasodilation, treatment with vasoconstrictors may be useful. Midodrine, an alpha agonist, and octreotide may be beneficial.

- ACE inhibitors may cause prerenal AKI, especially in patients with volume depletion, bilateral renal artery stenosis, or other causes of prerenal AKI. The renal failure is caused by vasodilation of the efferent arteriole.
 - Angiotensin-II constricts the efferent arteriole, a mechanism used to maintain glomerular perfusion pressure in the face of low blood flow. ACE inhibitors block this adaptation, causing a transient decrease in GFR.
 - Despite this ability of ACE inhibitors to worsen GFR, their overall effect on the kidney is to diminish proteinuria and the rate of progression to uremia and renal failure.
 - This beneficial effect is most likely secondary to the decrease in intraglomerular hypertension.
 - ACE inhibitors decrease proteinuria by 35–45% (particularly in patients with diabetic nephropathy).
- NSAIDs may cause prerenal AKI, especially in patients with volume depletion, bilateral renal artery stenosis, or other causes of prerenal AKI. The renal failure is caused by vasoconstriction of the afferent arteriole.
 - NSAIDs inhibit the action of the vasodilatory prostaglandins that maintain dilation of the afferent arteriole (important in maintaining GFR in the face of volume depletion).
 - A similar effect is seen in the calcineurin inhibiting transplant drugs cyclosporine and tacrolimus, which both vasoconstrict the renal arterioles, causing reversible prerenal AKI.
 - NSAIDs may also affect the kidney by causing intrarenal AKI, specifically acute interstitial nephritis, papillary necrosis, or secondary forms of membranous glomerulopathy and minimal change disease.

Postrenal Acute Kidney Injury

Postrenal azotemia is caused by any decrease in the outflow of urine. This may come by obstruction of any part of the renal collection system (renal pelvises to urethra). In order to cause AKI the obstruction must be **bilateral**, since obstruction of a single kidney can be compensated for by the remaining kidney's recruitment of reserve nephrons, maintaining a normal GFR. (This is also why donating a single kidney for transplantation does not change your serum creatinine.) Common causes of postrenal AKI include:

- Renal pelvises: bilateral stones
- Ureters: bilateral stones, bilateral ureteral disease e.g., retroperitoneal fibrosis, strictures
- Bladder: stones, clots, cancer obstructing bilateral ureteral outflow
- Prostate: hyperplasia and cancer
- Neurologic disease: Neurogenic bladder: patients have a history of obstructive symptoms followed by sudden onset of oliguria or anuria. This may be due to multiple sclerosis, spinal cord lesions, or peripheral neuropathy.

Clinical Presentation: Patients may experience a distended bladder in prostatism or neurologic disorders. Urine output may diminish or cease, preceded by incomplete voiding in prostate or bladder diseases. Patients may have pain over the bladder (prostatism) or flanks (stones).

Diagnosis: The serum creatinine elevates unless the disease is unilateral.

- BUN and creatinine will initially elevate in a ratio 20:1 as it does with prerenal azotemia.
- Later the BUN:creatinine ratio will lower to 10:1.

The urinalysis is variable, from normal (neurogenic bladder) to hematuria (stones, bladder cancer, clots).

Diagnosis is confirmed by seeing bilateral hydronephrosis on renal sonogram or non-contrast CT scan. This should be done early in all patients with AKI, since prompt relief of obstruction is essential.

Prostate or bladder outflow disease may be detected by finding large volumes of urine in the bladder after passing a Foley urinary catheter (a large post-void residual volume). After urinating (voiding), there should be no more than 50 mL of urine left in the bladder. If this post-void residual is markedly elevated, it implies an obstruction to the flow of urine out of the bladder.

Treatment is based on quickly relieving the cause of the obstruction: For bladder/prostate disease, do Foley catheter insertion. For ureteral/pelvic obstruction, do nephrostomy tube insertion (percutaneous or transurethral).



Clinical Recall

Which of the following lab values is most likely in patients with prerenal azotemia?

- A. BUN:Cr >20:1, Urine Na <20, FENa <1%, Urine Osmolality >500
- B. BUN:Cr 10:1, Urine Na >40, FENa >1%, Urine Osmolality <350
- C. BUN:Cr >20:1, Urine Na >40, FENa >4%, Urine Osmolality <350
- D. BUN:Cr <10:1, Urine Na >40, FENa >1%, Urine Osmolality <500
- E. BUN:Cr >20:1, Urine Na <20, FENa >4%, Urine Osmolality <350

Answer: A

Intrarenal Acute Kidney Injury

AKI due to intrarenal disease may result from:

- Tubular disorders: acute tubular necrosis, crystal-formations with intrarenal obstruction
- Interstitial disorders: acute and allergic interstitial nephritis
- Acute microvascular disorders: cholesterol embolization and papillary necrosis

Glomerular disease more often causes CKD, except for rapidly progressive glomerulonephritis, where renal failure may be more abrupt (see Glomerular Disease section).

Tubular disorders

Acute tubular necrosis (ATN) is acute renal failure on the basis of tubular damage and necrosis, leading to reduced solute clearance, AKI, and diminished electrolyte and water regulation. Causes include ischemia and hypoperfusion of the kidney (shock, sepsis, heart failure) and tubular toxins (aminoglycosides, contrast dyes, amphotericin, myoglobin [rhabdomyolysis], cisplatin).

Ischemic and toxic effects may be additive, increasing the risk of ATN. The degree, and especially the duration, of ischemia or toxic exposure are important to the prognosis and recovery from ATN. The longer the duration of hypotension/hypoperfusion, the greater the chance of ATN.

With ATN there is often an initial phase that appears similar to prerenal AKI, as the kidney is hypo-perfused. Next comes a reduction/cessation of urine flow (oligo- or anuria) as the tubules necrose and the glomerular ultrafiltrate back-leaks into the blood instead of forming urine. Finally, the tubules regenerate and a polyuric phase may occur. Not all patients go through each stage; for instance, some AKI is non-oliguric (e.g., aminoglycosides).

Diagnosis. With ischemic ATN, the BUN and creatinine will initially rise in a 20:1 ratio similar to prerenal AKI. This reduces to 10:1 as ATN tubular injury becomes established.

With severe or prolonged injury, the tubular cells will necrose and slough off into the urine and become visible as renal tubular epithelial cells or granular/muddy brown/pigmented casts. The rising serum creatinine (over days) is accompanied by reduced urine output or anuria. If available, urine findings can help to distinguish ATN from prerenal AKI.

Table 8-2. Confirming Prerenal versus ATN Based on Lab Values

	Prerenal AKI	ATN
Urine osmolarity	>500	<350
Urine Na ⁺	<20	>40
FeNa ⁺	<1%	>1%
Urine sediment	Scant	Full (brownish pigmented granular casts, epithelial casts may be seen)

Infusion of normal saline is also used to distinguish ATN from prerenal AKI, as only the latter will respond with a decreased SCr.

Treatment is correction of the underlying cause. No treatment can reverse renal failure. Monitor volume status and serum electrolytes.

- Volume repletion with normal saline to ensure there is no prerenal component and to reduce (but not reverse) contrast-induced renal failure
- Diuretics only for critical pulmonary edema; do not “convert” oliguric ATN to the non-oliguric type
- Dialysis if uremic symptoms occur (stop once tubules recover)
- ATN may be caused by filtered pigment injury to the tubules from myoglobin (in rhabdomyolysis) or hemoglobin (in hemolytic anemia).
- Rhabdomyolysis can be caused by sudden/severe crush injury, seizures, severe exertion, or by hypokalemia, hypophosphatemia, or medications (e.g., statins). Large amounts of released myoglobin are filtered into the nephron and cause tubular toxicity and ATN. Similarly, in massive hemoglobinuria from ABO incompatibility filtered hemoglobin causes tubular toxicity. The toxicity is because the pigment is directly toxic to the tubular cells, as well as from precipitation of the pigment in the tubules. The degree of toxicity is related to the duration of contact of the tubular cells with the hemoglobin or myoglobin, so is compounded by dehydration.

Diagnosis: Rhabdomyolysis with myoglobinuria is confirmed with the following:

- Markedly elevated serum CPK level (a biochemical marker of skeletal muscle neurosis); for nephrotoxicity to occur, level must be in 10,000–100,000 range (normal ≤ 500)
- Urinalysis dipstick positive for blood but with no red cells visible. This is because myoglobin can react with the heme reagent on the dipstick. Free hemoglobin will do the same thing.
- Rapidly rising serum creatinine level due to ATN
- Hyperkalemia: check the ECG for peaked T waves
- Metabolic acidosis with decreased serum bicarbonate
- Hyperphosphatemia secondary to muscle breakdown
- Hypocalcemia secondary to the deposition of calcium in damaged muscles and complexing with high phosphate.
- Hyperuricemia due to release of purines from damaged muscles



Treatment is normal saline to increase urine output and decrease toxin contact time. If there is little response, add mannitol, an osmotic diuretic. Alkalinizing the urine with bicarbonate may or may not be useful.

ATN Due to Drugs. The most common toxins that cause ATN are aminoglycosides, IV contrast agents, amphotericin, and cisplatin. For patients on multiple drugs, differentiation of ATN from acute interstitial nephritis is often difficult:

- Allergic interstitial nephritis occurs with the first dose, and is associated with fever, rash, joint pain, and eosinophils in both blood and urine. ATN lacks these.
- Drugs causing ATN often take days to weeks to produce enough cumulative toxicity to cause renal failure. Symptoms are those of acute kidney injury.

The clinical and lab evaluation is as described in the ATN section. There is no test which can confirm a specific toxin as the etiology of the renal failure. Other causes of renal failure must first be excluded, and the toxin must be identified and promptly withdrawn. There is no specific therapy that can reverse the renal insufficiency of any direct-acting toxin.

- **Aminoglycosides.** Aminoglycoside-related nephrotoxicity (10–20% of all drug-induced nephrotoxicity) is usually reversible. Unlike contrast dyes, aminoglycoside toxicity **takes 5–10 days of administration** to result in toxicity. The likelihood of toxicity is associated with high trough levels.
 - Tobramycin is less nephrotoxic than gentamicin or amikacin.
 - Renal failure due to aminoglycosides is often non-oliguric (so K^+ is not usually elevated).
 - Hypokalemia and hypomagnesemia predispose the patient to aminoglycoside toxicity.
 - To prevent, limit duration of use and reduce trough levels by giving the antibiotic once a day. Dosing 1×/day allows high bactericidal levels with the same efficacy and very low trough levels.
- **Amphotericin B.** This antifungal agent is associated with renal insufficiency as well as distal renal tubular acidosis (non-anion gap metabolic acidosis with hypokalemia and high urine pH). Like aminoglycosides, it occurs only **after several days or weeks** of amphotericin use, and is usually reversible with prompt discontinuation of the drug.
- **Contrast Agents.** Unlike the antibiotics, radiocontrast used in radiology can result in renal failure **in as little as 12–24 hours after the use of the agent**. The rise in creatinine peaks at 3–5 days after the injury. Initial vasoconstriction may be reflected in a “prerenal” lab picture, i.e. BUN:Cr of >20:1 and low urine Na. Underlying renal disease, DM, and advanced age increase the risk for ATN. Prevention is with **normal saline** infusion before the agent is administered. N-acetyl cysteine and sodium bicarbonate are often added but are of uncertain value.
- **Other Drugs.** Cisplatin accumulates in tubular cells and causes ATN in 20–30% of patients. Pentamidine, used for pneumonia in AIDS patients, is associated with ATN in 20–30% of patients.

Precipitation of crystals within the tubules can reduce urine flow and GFR, and may occur via endogenous or exogenous (ingested) substances and drugs.

- **Uric acid** toxicity occurs via intratubular crystallization and usually occurs in the setting of **tumor lysis syndrome** after treatment of leukemias and lymphomas. Patients show AKI, oliguria, severe hyperuricemia, hyperkalemia, and metabolic acidosis. Prevention is with vigorous hydration, sodium bicarbonate, and allopurinol prior to receiving chemotherapy. Allopurinol reduces the production of uric acid by inhibiting conversion of xanthine to hypoxanthine to uric acid. Uric acid stones precipitate in an acidic urine, unlike oxalate crystals, which precipitate in alkaline urine. Separately, gout may cause CKD through a slower and milder version of intrarenal urate deposition.
- **Oxalate crystals** cause AKI following **ethylene glycol overdose** after ingestion of antifreeze. Patients display intoxication, an anion gap metabolic acidosis and AKI. Diagnosis is confirmed with oxalate crystals seen on urinalysis (oxalate crystals are shaped like envelopes). Treatment is normal saline, sodium bicarbonate, and **fomepizole** to prevent the conversion of ethylene glycol to toxic oxalic acid. Separately, chronic hyperoxaluria and oxalate kidney stones can be caused by Crohn disease because of fat and calcium malabsorption.
- **Immunoglobulins and light chains** cause AKI in multiple myeloma, where renal filtration of light chains may lead to their precipitation in the tubules and to direct tubular toxicity. Both lead to AKI. The urinalysis may be normal, since the dipstick does not detect the positively charged light chains. Diagnosis is with urine protein electrophoresis. Separately, the light chains may cause proximal tubular dysfunction (Fanconi syndrome with glucosuria, aminoaciduria, phosphaturia, proximal RTA) or AA amyloidosis with glomerular damage.
- **Drugs** may precipitate in the tubule to cause AKI. Indinavir is a protease inhibitor that results in AKI due to the drug precipitating in the tubules. Indinavir stones may be seen on a spiral CT scan.

Interstitial disorders

Acute interstitial nephritis (AIN) accounts for 10–15% of intrinsic AKI. Histopathology shows a robust interstitial inflammation with eosinophils. This allergic reaction can take the form of a rash, Stevens-Johnson syndrome, hemolysis, and/or AIN.

- Cause is usually an adverse immunologic effect to medication that commonly cause allergies, i.e., penicillin, cephalosporins, sulfa drugs, allopurinol, rifampin, and quinolones.
- NSAIDs also cause a form of AIN lacking the eosinophiluria and the severe allergic symptoms (i.e., lacking rash, fever or joint pain, but presenting with a usually asymptomatic rise in serum creatinine).
- AIN is less commonly caused by infections themselves; specifically, leptospirosis, legionella, CMV, rickettsia, and streptococci.
- Rarely, AIN is caused by an autoimmune disorder such as SLE, Sjögren syndrome, sarcoidosis, and cryoglobulinemia. These are more likely to harm the kidney via glomerulonephritis.

Fever is seen in most patients with AIN. It can be very difficult to determine if the fever is from the underlying illness or from the AIN. Rash is present in 25–50% of patients. Joint pain is common because AIN acts somewhat like serum sickness.

**Note**

Other medications causing AIN include NSAIDs, allopurinol, and proton pump inhibitors.

Note

Any sulfa drug can cause an allergic reaction. Besides antibiotics, other examples of sulfa drugs are diuretics such as thiazides, furosemide, and acetazolamide.

Lab studies: The best initial test for AIN is a urinalysis (UA) looking for **white cells**, then **staining for urine eosinophils** (Hansel or Wright stain of the urine). While the kidney biopsy is most accurate, it is rarely done, since patients resolve following discontinuation of the antibiotic. Biopsy is used only in uncertain cases. NSAID-induced AIN typically lacks eosinophiluria and eosinophilia.

Other abnormalities may include eosinophilia, hematuria/mild proteinuria, and increased serum IgE levels.

Treatment. AIN should resolve spontaneously after stopping the offending agent; there is no specific therapy. If renal failure persists or worsens, consider a short course of steroids.

Acute microvascular disorders

Atheroembolic disease (cholesterol emboli syndrome). AKI may develop in some patients with severe atherosclerosis following an invasive arterial procedure (e.g., an arteriogram). Cholesterol emboli scatter throughout the body, including to the kidney. Look for a patient who undergoes a vascular catheter procedure such as angioplasty, who develops bluish discoloration of the fingers and toes, livedo reticularis, and AKI several days later. Labs show **AKI with eosinophilia, low complement levels**. Although the most accurate test is a skin biopsy to see cholesterol crystals in the skin, this is rarely done. There is no therapy for atheroembolic disease.

Acute papillary necrosis is AKI associated with occlusion of small renal capillaries, leading to the ischemia and sloughing of renal papillae, the medullary segments involved in urine concentration, and the least oxygenated area of the kidney. It is the nephron segment most vulnerable to hypoxia or sluggish blood flow. Papillary necrosis is seen in patients with a history of sickle cell disease, diabetes, urinary obstruction, chronic pyelonephritis, or chronic analgesic use, esp. NSAIDs. Volume depletion concentrates the blood and increases the risk. Look for the sudden onset of **flank pain, hematuria, pyuria, and fever** in an at-risk patient, esp. those in sickle crisis. This can be very similar to acute pyelonephritis. Like pyelonephritis, the urinalysis will show white and red cells. Unlike pyelonephritis, there will be no bacteria, and no organisms grow on culture. The patient may sometimes note red “chunks” in the urine that may cause confusion with kidney stones, but the referred ureteral pain of stones is absent.

The most accurate diagnostic test for papillary necrosis is **CT scan**, which will show “bumpy” contours in the renal pelvis where the papillae have sloughed off. There is no specific therapy for papillary necrosis.

GLOMERULAR DISEASES

Glomerular diseases are the most common cause of chronic kidney disease and dialysis-requiring renal failure. The most common of these in the developed world is diabetic nephropathy.

Most glomerular diseases are also called **glomerulonephritis (GN)** or inflammation of the glomerulus, often as the result of an autoimmune event, circulating antibodies, or vasculitis. A few are non-inflammatory and caused by other mechanisms such as hypertensive nephrosclerosis (prolonged high BP), Alport syndrome (defective Type IV collagen in the glomerular basement membrane), and hemolytic-uremic syndrome (microthrombi in renal small vessels).

GN may be classified as follows:

- Primary disease without systemic illness (e.g., membranous GN, IgA nephropathy)
- Secondary disease due to systemic illness (e.g., post-infectious GN, diabetic nephropathy, lupus nephritis)

Based on presentation, it may be further classified as follows:

- Nephritic (sometimes called “acute GN”) with hematuria, RBC casts, edema, hypertension, and renal failure (e.g., post-infectious GN, Goodpasture syndrome)
- Nephrotic with heavy proteinuria, hyperlipidemia, edema, and hypertension (e.g., minimal change disease, diabetic nephropathy)
- Rapidly progressive GN: hematuria, usually nephritic, accompanied by sub-acute renal failure (over 1-2 weeks), often with crescents seen on biopsy

Many glomerular diseases can be diagnosed using clinical evaluation and specific serologies, but the definitive diagnosis is usually made by **renal biopsy**, especially when there is heavy proteinuria or renal insufficiency. In these cases biopsy is usually needed, since treatment varies depending on histology.

Table 8-3. Common Glomerular Diseases

Nephritic Diseases	Nephrotic Diseases
Primary	Primary
IgA nephropathy	Membranous GN
Idiopathic rapidly progressive GN	Focal segmental glomerulosclerosis (FSGS)
	Membranoproliferative GN (also nephritic)
Secondary	Minimal change disease
Postinfectious GN	
Goodpasture syndrome	Secondary
Granulomatosis with polyangiitis	Diabetic nephropathy
Eosinophilic granulomatosis with polyangiitis	Amyloidosis
IgA nephropathy (Berger disease)	Lupus nephritis (also nephritic)
Lupus nephritis (also nephrotic)	
Cryoglobulinemia	
Membranoproliferative GN (due to hepatitis C)	
Polyarteritis nodosa	
Other Glomerular Diseases (usually neither nephritic nor nephrotic)	
Hemolytic-uremic syndrome/TTP	Alport Syndrome
Hypertensive nephrosclerosis	



Nephritic Diseases

Nephritic GN is characterized by hematuria, edema, red cell casts, and hypertension. The red cells often develop an abnormal shape (called “dysmorphic”), which distinguishes them from non-glomerular hematuria due to stones, bladder cancer, or infection. Small or moderate proteinuria is also common.

- The edema of glomerular disease may be anywhere in the body, but is usually first seen in dependent areas (ankles). It is caused by avid renal sodium retention, so labs show a low urine sodium, with fractional excretion of sodium $<1\%$.
- With the salt and water retention, hypertension also develops.
- Nephritic diseases show modest amounts of protein in the urine, with a daily total <2 grams per 24 hrs. In contrast, nephrotic syndrome does not begin until >3.5 grams per 24 hrs.
- The most important distinction between nephritic and nephrotic syndrome is the hematuria (in nephritic) and degree of proteinuria (>3.5 gm/24 hrs in nephrotic).

A good physical exam is crucial, since half are associated with other systemic vasculitides.

In nephritic diseases **the single most important test for diagnosing GN is usually the renal biopsy**. Exceptions are post-infectious GN, where no biopsy is usually done, and systemic vasculitis, where skin or lung biopsy is easier and less risky. Biopsy is always done if the patient is developing subacute renal failure (rapidly progressive GN).

Table 8-4. Causes of Nephritic Syndrome

Vascular (Systemic) Disease	Glomerular Disease
Granulomatosis with polyangiitis	Postinfectious GN
Eosinophilic granulomatosis with polyangiitis	Goodpasture syndrome
Henoch-Schönlein purpura (renal lesion = IgAN)	IgA nephropathy (IgAN)
Polyarteritis nodosa	Lupus nephritis (SLE) (can also be nephrotic)
Cryoglobulinemia	Idiopathic rapidly progressive GN
	Membranoproliferative GN (can also be nephrotic)

Note

All forms of vasculitis are characterized by fever, weight loss, and a generalized malaise.

Nephritic vascular diseases

The following disorders show a nephritic clinical presentation but also involve diffuse vascular injury.

Granulomatosis with polyangiitis (Wegener granulomatosis) is characterized by systemic vasculitis that most often involves the kidney, lung, and upper respiratory tract such as the sinuses or middle ear. It can also involve the skin (50%), eyes (50%), joints, and GI tract.

Neuropathy may be a symptom. If a patient with chronic upper and lower respiratory illness does not respond to antibiotics and then develops renal failure or hematuria, consider this disorder.

- Other lab abnormalities include elevated ESR, rheumatoid factor (50%), anemia, and leukocytosis. These findings are nonspecific.
- Best initial test is C-ANCA or antiproteinase-3 antibody.
- Most accurate test is biopsy of the kidney, nasal septum, or lung, looking for granulomas (sinus biopsy, specifically the nasal septum, is less sensitive and has more false-negatives).
- P-ANCA or anti-myeloperoxidase antibody is found at much lower frequency.
- Complement levels are normal.
- Treatment: cyclophosphamide and glucocorticoids

Eosinophilic granulomatosis with polyangiitis (Churg-Strauss) is a vasculitis similar to granulomatosis with polyangiitis, characterized by chronic lung involvement, neuropathy, skin lesions, GI, cardiac, and renal involvement.

- Diagnostic clues include a history of asthma, eosinophilia, or another atopic disease and elevated eosinophils.
- P-ANCA often positive but is nonspecific.
- Most accurate test is lung biopsy showing the granulomas and eosinophils.
- Treatment: cyclophosphamide and glucocorticoids

PAN is a systemic vasculitis of small- and medium-sized arteries that affects virtually every organ in the body *except the lung*. Renal involvement is common and manifests as hypertension, renal insufficiency, and hemorrhage due to microaneurysms. Like all vasculitis, PAN is associated with fever, weight loss, and malaise. Other organs involved include the skin, eyes, muscles, GI tract, heart, kidneys, and neurologic system. Abdominal pain and joint pain may be prominent. The abdominal pain may mimic mesenteric ischemia, and the pain will occur with eating. Anemia and an elevated sedimentation rate are present but are too nonspecific to be useful.

- Diagnostic clues include multiorgan vasculitis, sparing the lungs.
- Most accurate test is biopsy of an affected area.
 - If there are neurologic symptoms, sural nerve biopsy is high-yield.
 - If there is abdominal pain, angiogram of the involved vessels in the GI tract may eliminate the need for a biopsy.
- Hepatitis B (10–30% of patients, especially injection drug users)
- P-ANCA (uncommon)
- Treatment: cyclophosphamide and glucocorticoids

Renal disease from **cryoglobulinemia** shows the lesion of membranoproliferative GN (type 1) and is associated with chronic hepatitis C, and less commonly hepatitis B.

- Diagnostic clues include hepatitis C and positive serum cryoglobulins.
- Presentation may be nephritic and/or nephrotic.
- Associated with joint pain, neuropathy, and purpuric skin lesions
- No GI involvement
- Elevated ESR and low levels of complement
- Treatment: treat the underlying chronic hepatitis; for severe disease (renal failure, heavy proteinuria), pulse doses of steroids and plasmapheresis

Note

Wegener granulomatosis is now called granulomatosis with polyangiitis (Wegener). Churg-Strauss syndrome is now called eosinophilic granulomatosis with polyangiitis.

Note

Heavy proteinuria and RBC cases are uncommon in PAN, as it is not a true glomerulonephritis (even though there is hematuria).



Nephritic glomerular diseases

The following disorders show a nephritic clinical presentation, but the disease process is limited to the glomerulus.

Postinfectious GN is the classic nephritic disease, with dark urine, hypertension, and edema developing suddenly **1–2 weeks after strep pharyngitis**. If not caused by group A beta hemolytic streptococci (*Streptococcus pyogenes*), it may be caused by throat or skin infection with *Streptococcus pyogenes* (although rheumatic fever occurs only with the strains that cause pharyngitis). Poststreptococcal GN occurs in 10–15% of patients with pharyngitis infected with a nephritogenic strain.

Virtually any infectious agent can cause postinfectious GN, including hepatitis B and C, CMV, and chronic staphylococcal infections such as endocarditis. In the pre-antibiotic era, GN was the most common cause of death from endocarditis. The disease is usually self-limited, so it is unusual among the GNs in not requiring a biopsy if there is a characteristic history and positive serology.

The key to diagnosis is an association with infection. The best initial test is the **antistreptolysin (ASO)** or **antihyaluronic acid (AHT)**.

- Complement levels, particularly C3, are low.
- Renal biopsy is rarely needed, but if done would show epithelial “humps” on electron microscopy. IgG and C3 will be deposited in the mesangium.

Treatment is supportive (management of fluid overload and hypertension with diuretics). Most cases resolve spontaneously. Antibiotics will eradicate the organism from the pharynx. Glucocorticoids are sometimes used for unusual persistence of proteinuria or renal failure in adults.

Goodpasture syndrome (GPS) is an idiopathic **renal and lung disease** characterized by a unique anti-glomerular basement membrane antibody. Presentation includes **hematuria and hemoptysis**. Aside from the lungs and kidneys, GPS does not affect other sites in the body, thus an **absence of skin or eye findings** is a clue to the diagnosis. When there is lung involvement (65%), patients present with hemoptysis, cough, and/or shortness of breath.

The key to diagnosis is nephritic-pulmonary syndrome. The best initial test is the level of **antibasement membrane antibodies** to type IV collagen. The single most accurate test is lung or kidney biopsy, which will show linear deposits on immunofluorescence. Do **lung biopsy**, not renal, if there is pulmonary involvement.

Treatment is **plasmapheresis and glucocorticoids**. Cyclophosphamide may also help.

IgA nephropathy and **Henoch-Schönlein purpura (HSP)** have a common pathophysiology and renal presentation, but differ in that HSP also shows signs of systemic vasculitis.

IgA nephropathy (IgAN) is most commonly seen in Asian or native Americans age <35. It has 2 possible presentations:

- Mild or gross **hematuria appearing 1–2 days after a upper respiratory infection (most common on board exams)**; resolves spontaneously in 30% of patients. (Compare this to poststreptococcal GN, where renal involvement occurs 1–2 weeks later or longer after a sore throat.)
- Hematuria and non-nephrotic proteinuria without infectious precedent which gradually progresses to end-stage renal disease (ESRD) (more insidious form)

Hypertension is common, as in most GN. About 40–50% of IgAN patients progress to ESRD. Renal biopsy shows proliferation with IgA deposits.

HSP has a similar presentation and biopsy, but also shows a skin rash or other vasculitic symptoms. Keys to diagnosis include hematuria, 1–2 day association with URI (for IgAN), and vasculitic rash, hematuria (for HSP).

Management. Renal biopsy is required if renal failure or proteinuria present. In HSP, skin biopsy is best.

Treatment. No proven treatment. In the presence of proteinuria, give ACE inhibitors/ARB. If nephrotic, try glucocorticoids.

Lupus nephritis is a constellation of glomerular diseases associated with SLE. There may be asymptomatic proteinuria or hematuria, nephrotic syndrome (secondary membranous GN), or severe nephritic syndrome with progressive renal failure eventually requiring dialysis. There are almost always other SLE signs or symptoms present, although a few patients present with renal signs only. Biopsy is key to planning therapy and prognosis.

Key to diagnosis: nephritic or nephrotic syndrome with SLE diagnostic criteria; best test is **double-stranded DNA levels** and low complement levels during disease flares. The most accurate test is a **biopsy**.

Treatment. Glucocorticoids with mycophenolate for severe proliferative disease (nephritic). Mycophenolate is superior to cyclophosphamide and has fewer side effects.

Idiopathic rapidly progressive glomerulonephritis (RPGN) presents with nephritic syndrome (occasionally nephrotic as well) and relentless subacute renal failure, with the serum creatinine rising over 1–2 weeks. An early renal biopsy is critical to diagnosis and shows epithelial cell crescents (“crescentic GN”).

The key to diagnosis is rising creatinine; the best test is **renal biopsy**.

Treatment is glucocorticoids (start early to protect GFR) and cyclophosphamide (start after biopsy).

Note

IgA nephropathy is the most common primary GN worldwide.

Clinical Recall

Which of the following is the most accurate diagnostic test for granulomatosis with polyangiitis?

- A. Lung biopsy showing granulomas and eosinophils
- B. Kidney biopsy showing linear deposits on immunofluorescence
- C. Lung and nasal septum biopsy showing granulomas
- D. Kidney biopsy revealing IgA deposits
- E. Renal biopsy showing “humps” on electron microscopy

Answer: C



Nephrotic Diseases

Nephrotic diseases are characterized by heavy proteinuria and may be primary or secondary to other systemic disease. They are often accompanied by a cluster of metabolic abnormalities (termed *the nephrotic syndrome*).

The nephrotic syndrome

The nephrotic syndrome is defined as the presence of GN sufficient to produce a level of **proteinuria >3.5 grams per 24 hrs, hyperlipidemia, edema, and low serum albumin**. Over 50% of nephrotic syndrome is associated with a systemic disease, esp. DM.

Proteinuria arises because the damaged glomerular basement membrane loses its negative charges; negatively charged albumin and key serum proteins then spill into the urine. This may lead to hypoalbuminemia and low serum oncotic pressure. Complications of the nephrotic syndrome include:

- Edema due to increased salt and water retention by the kidney, as well as low oncotic pressure in the serum
- Hyperlipidemia and increased atherosclerosis, most likely from the urinary loss of the lipoprotein markers or signals on the surface of chylomicrons and LDL that lead to the clearance of these lipids from the bloodstream
- Hypercoagulable states or thrombophilia, due to the urinary loss of natural anticoagulant proteins such as antithrombin, protein C, and protein S
- Spontaneous arterial or venous thrombosis due to hypercoagulability
- Iron, copper, and zinc deficiency may be present as a result of the urinary loss of their transport proteins such as transferrin and ceruloplasmin.

Diagnosis of nephrotic syndrome is based on the presence of **>3.5 gm per 24 hrs protein in the urine** (measured on 24-hour urine collection or a spot urine protein/creatinine ratio), low serum albumin, edema, and hyperlipidemia. The urinalysis will commonly only show 4+ protein, although some mild hematuria may be seen in several of the nephrotic glomerular diseases.

The key to specific diagnosis is **renal biopsy**. This may be deferred in diabetic nephropathy with a typical history.

Treatment. Control of the underlying disease, usually with glucocorticoids in the primary disorders. If steroids do not work, add cyclophosphamide or mycophenolate. Azathioprine may be useful. An ACE inhibitor or ARB is used for all patients with proteinuria, but they do not reverse the underlying disease. The following may also be helpful:

- Diuretics for edema
- ACE inhibitors/ARBs (equal efficacy) for control of proteinuria and hypertension
- Statins for hyperlipidemia
- Anticoagulation if DVT or PE ensues
- Good protein-calorie nutrition. Protein restriction is NOT indicated.

Note

Routine urine dipstick detects only albumin and not light chains or Bence-Jones protein (which must be done with urine immune electrophoresis). Lipiduria may lead to an appearance of "Maltese crosses" in the urine.

Primary nephrotic diseases

Focal-Segmental Glomerulosclerosis (FSGS). The most common cause of nephrotic syndrome in adults in the U.S. Secondary forms are seen with HIV (HIV nephropathy) and the use of heroin, as well as morbid obesity (possibly due to hyperfiltration).

Treatment: glucocorticoids (20–40% response); may progress to ESRD over 5–10 years

Membranous Glomerulopathy. Most are idiopathic (primary). Secondary forms associated with SLE, cancers such as lymphoma or breast cancer, infections such as endocarditis or chronic hepatitis B or C, and drugs such as NSAIDs, penicillamine, gold salts, and NSAIDs.

Treatment: glucocorticoids (30–50% response)

Minimal Change Disease. The most common nephrotic disease in children (90–95%); may account for 15% of adult disease. Usually primary, but NSAIDs and Hodgkin lymphoma have been associated with secondary disease. Light microscopy is normal and electron microscopy is needed to see fusion of foot processes.

Treatment: High glucocorticoid response, esp. in children. The disease is often treated in kids without biopsy, with biopsy reserved for non-responders. Adults are biopsied because of wider differential diagnosis.

Membranoproliferative GN (also see cryoglobulinemia in Nephritic Diseases). Now largely type 1, associated with chronic **hepatitis C** and B, with or without cryoglobulinemia and vasculitis. Renal presentation is **nephritic and/or nephrotic**. Shows low serum complement levels.

Secondary nephrotic diseases

Diabetic nephropathy is by far most common glomerular disease in developed countries. The incidence of nephropathy is directly proportional to the duration of the diabetes, and it normally appears as microalbuminuria after at least 10 years of type 1 or type 2 DM.

Microalbuminuria (50–300 mg/24 hours) is detected using the spot urine albumin/creatinine ratio, NOT the routine urinalysis, which is insensitive to low degrees of proteinuria. Screen all diabetic patients annually for microalbuminuria. Following the appearance of microalbumin, the proteinuria worsens and eventually becomes nephrotic (>3.5 grams), followed by worsening renal function with rising serum creatinine. Over 5–10 years the patient progresses to dialysis-requirement or transplantation. The leading cause of death is cardiac disease due to accelerated atherosclerosis. Other complications include hyperkalemia and type IV renal tubular acidosis.

Keys to diagnosis include DM for at least 10 years; microalbuminuria or (later) nephrotic syndrome or decreased GFR. Although a renal biopsy is the most accurate test for renal involvement in diabetes, it is not routinely performed unless there is the possibility of another disease causing the renal failure.

Treatment includes tight control of diabetes and BP (<130/80 mm Hg); ACE inhibitor/ARB and statins for hyperlipidemia.

Renal amyloidosis occurs when amyloid proteins deposit in the glomerulus, causing damage to the GBM, leading to decline in GFR, albuminuria, and the nephrotic syndrome. There are 2 types of amyloidosis:

- **Amyloid light-chain (AL):** plasma cell dyscrasia causing deposition of protein derived from immunoglobulin light chains; may be associated with multiple myeloma
- **Amyloid A (AA):** amyloid is produced in association with a chronic infection, or rheumatoid diseases such as rheumatoid arthritis or IBD



Most patients will also have extrarenal manifestations:

- GI tract: diarrhea, malabsorption
- Heart: restrictive cardiomyopathy, rhythm disorders, and heart block
- ENT: large tongue (macroglossia)
- Neuro: carpal tunnel syndrome, peripheral neuropathy
- Muscles: weakness

The key to diagnosis is **biopsy of an involved organ** such as the fat pad, rectum, nerves, or kidney. Congo red testing shows green birefringence. Patients with AL amyloid will also have elevated urine, serum light chains typical of myeloma, and possible hypercalcemia.

Treatment is for the underlying malignancy or inflammation/infection. This is often very difficult. With AL amyloid, melphalan and prednisone can control protein production.

Other Glomerular Diseases

Several glomerular diseases cannot be categorized under the nephritic and nephrotic syndromes.

Hypertensive nephrosclerosis is the progressive chronic kidney disease associated with long-standing, poorly controlled hypertension. While previously a common cause of ESRD in the United States, it is now less so, due to more extensive treatment of hypertension. Patients' CKD is often attributed to "hypertension," when in fact the hypertension is secondary to a (potentially treatable) glomerular disease.

The renal pathology is characterized by non-immune, non-inflammatory glomerular sclerosis. If the hypertension is untreated, proteinuria and renal insufficiency progress gradually (over decades) to dialysis requirement. ACE inhibitors are the preferred antihypertensive due to their renal protective effect in CKD.

Alport syndrome is a glomerular disease due to genetic defect in type IV collagen, which structurally underlies the glomerular basement membrane. It is most commonly X-linked. Patients present with the combination of mild hematuria and proteinuria, along with ear (sensorineural hearing loss) and eye abnormalities. Men are more susceptible to disease, as they have a single mutated X chromosome. It may progress to dialysis-requirement. There is no treatment.

Hemolytic-uremic syndrome/idiopathic thrombocytopenic purpura (HUS/TTP) are thrombotic microangiopathies that may present with small platelet clots in the renal microvessels, causing secondary glomerular inflammation and renal failure. There is typically acute renal failure, mild hematuria, and low-grade proteinuria (non-nephrotic). Treatment is for the underlying disorder.

Table 8-5. Glomerular Diseases

Disease	Nephritic/ Nephrotic	Clinical	Serology Clue	Causes
Diabetic nephropathy	Nephrotic		Hgb A1c	DM
Membranous GN	Nephrotic			Cancer, Hep B/C, SLE, NSAIDs
Focal segmental glomerulosclerosis (FSGS)	Nephrotic			HIV
Minimal change disease	Nephrotic			NSAIDs
AA amyloidosis	Nephrotic	CHF, fractures		Chronic infections
AL amyloidosis	Nephrotic	CHF, fractures		Myeloma
Idiopathic RPGN	Nephritic	Rapid rise in creatinine		
Post infectious GN	Nephritic	1–2 weeks after infection	ASO, anti-hyaluronidase	Strep A, Staph
Membranoproliferative GN	Nephritic/ Nephrotic		Hep C/B tests	Hep C/B
Cryoglobulinemia	Nephritic/ Nephrotic	Purpura, neuro, joints	Serum cryos	Hep C/B
IgA nephropathy	Nephritic → Nephrotic	1–2 days after URI	IgA	Viral URI
Henoch-Schonlein Purpura	Nephritic	Purpura, GI, joints, abd pain	IgA	
Granulomatosis with polyangiitis (Wegener)	Nephritic	Lung, eye, UR, skin	c-ANCA	
Lupus nephritis	Nephritic	Skin, joints, heme	ANA, anti dsDNA	
Goodpasture	Nephritic	Hemoptysis	anti-GBM	
Eosinophilic granulomatosis with polyangiitis (Churg-Strauss)	Nephritic	Fever, lung, GI, cardiac, neuro, eye, skin	p-ANCA, eosinophilia	
Polyarteritis nodosa	Nephritic	Fever, eye, neuro, muscle, joints, GI	ESR	Hep B, IVDA
HUS (kids)		Hemolytic anemia, plats ↓		<i>E. coli</i>
TTP		Hemolytic anemia, plats ↓, + fever, neuro		
Hypertensive nephrosclerosis		Long hypertension		Long, severe HTN
Alport syndrome		Eye, ear defects		Genetic



END-STAGE RENAL DISEASE

Many chronic kidney diseases, if untreated or resistant to treatment, eventually lead to end-stage renal disease (ESRD). ESRD is characterized by severe reductions in the GFR and uremic symptoms requiring renal replacement therapy (dialysis or transplantation). In the United States the most common cause of ESRD requiring dialysis is diabetic nephropathy. (In some parts of Asia, IgA nephropathy is an equally common cause.)

Complications

Most complications of ESRD do not occur until GFR <20–30% of normal (25 mL/minute). A few complications (altered mental state, acidosis, hyperkalemia) are only seen when GFR <10%.

- **Metabolic acidosis** due to retained acids not filtered from the blood by the failing kidney. The anion gap is elevated. Treatment is dialysis.
- **Hyperkalemia** due to retained potassium not filtered by the failing kidney. This is a common cause of death in dialysis patients. Treatment is a low K diet and dialysis. Loop diuretics and GI binding agents (e.g., kayexalate) may be used prior to dialysis.
- **Hypermagnesemia**. Magnesium accumulates because the falling GFR decreases renal excretion. Treatment is restriction of magnesium intake, e.g., avoidance of milk of magnesia.
- **Hypocalcemia** due to the loss of 1,25-dihydroxy vitamin D production and from hyperphosphatemia (inability of the kidney to excrete phosphate). High phosphate levels contribute to low calcium levels by precipitating out in tissues in combination with the calcium. Treatment is reduction of phosphate and increase of calcium.
 - Hyperphosphatemia is treated with phosphate binders such as calcium carbonate or calcium acetate. Aluminum-containing phosphate binders should not be used, as aluminum is associated with CNS accumulation, dementia, and bone abnormalities. Sevelamer and lanthanum are phosphate binders that do not contain aluminum or calcium. Use when calcium is abnormally high due to vitamin D replacement.
 - Hypocalcemia is treated with 1,25 dihydroxy-vitamin D replacement.
 - Cinacalcet is a substance that simulates the effect of calcium on the parathyroid; it will tell the parathyroid to shut off parathyroid hormone production, thus helping to decrease phosphate. Use in severe, refractory cases.
- **Renal osteodystrophy** (osteitis fibrosa cystica). Bone abnormalities occur because chronic hypocalcemia leads to **secondary hyperparathyroidism**, which removes calcium from the bones. In addition, bones buffer the chronic acidosis ESRD by removing calcium from bone. Patients present with bone pain and fractures. Renal osteodystrophy is controlled with improving calcium and phosphorous levels and with cinacalcet. Parathyroidectomy may be needed for severe hyperparathyroidism that does not respond to medications.
- **Mental state changes**. A variety of cognitive and mood changes occur with uremia, normally only with severe CKD (GFR <10). The only treatment is dialysis.
- **Anemia** from the loss of production of erythropoietin from the kidney. The anemia is normochromic and normocytic. The anemia is treated with erythropoietin replacement, and iron replacement is often necessary when starting erythropoietin due to chronic losses from blood draws, dialysis, and malnutrition.

- **Bleeding.** The coagulopathy in ESRD arises from uremia-induced platelet dysfunction, which prolongs the bleeding time. Treatment is desmopressin, which releases subendothelial stores of von Willebrand factor and factor VIII, which increase platelet aggregation and adherence. A secondary cause in patients still making urine is nephrotic-syndrome associated loss of clotting factors in the urine.
- **Hypertension and accelerated atherosclerosis.** CKD leads to rapidly progressive coronary artery disease, which is the most common cause of death for those on dialysis. The reason for this is not clear. Treatment is good BP control (usually multiple medications and thorough dialysis) and statins for hyperlipidemia.
- **Pericarditis.** Caused by unknown uremic toxins; may or may not be an associated effusion. Requires urgent hemodialysis.
- **Infection.** ESRD patients are at increased risk of infection because neutrophils and other white cells do not work normally in a uremic environment. This is the second most common cause of death in dialysis patients. Vascular access infections (hemodialysis) and peritonitis (peritoneal dialysis) are common. The most common organism is *Staphylococcus* due to the frequent skin punctures required in dialysis.

Treatment

CKD is initially treated conservatively to minimize symptoms. However, when conservative management fails, renal replacement therapy is required. This can either be **dialysis** or **renal transplantation**.

Medical management of CKD includes restriction of fluids, potassium, sodium, protein, magnesium, and phosphate in the diet. Protein restriction is of **no value** and may be harmful. Common medications include erythropoietin, 1,25 dihydroxyvitamin D, phosphate binders, multiple antihypertensives, and furosemide (if patient still makes urine). Taking so many medications is very difficult for patients who often lack energy or who are confused.

Dialysis is used in patients with GFR <20%. (It is covered under Medicaid for all patients in the United States.) Dialysis options are hemodialysis and peritoneal dialysis.

Acute indications for dialysis are life-threatening abnormalities that require hospitalization:

- Pulmonary edema refractory to diuretics
- Hyperkalemia resistant to therapy
- Metabolic acidosis
- Pericarditis
- Altered mental state

Chronic indications for dialysis (usually initiated from the outpatient setting) include:

- Severe neuropathy such as myoclonus, wrist/foot drop
- Persistent nausea and vomiting
- Weight loss/malnutrition
- Bleeding diathesis
- Severe itching
- Fatigue not correctable with anemia correction



Overall, chronic hemodialysis is used in 85% of patients and peritoneal dialysis in 15%. Each can be done at home in properly trained patients.

The most common complications of dialysis are:

- Fluid overload
- Hypertension
- Post-dialysis orthostatic hypotension
- Dialysis access infections (peritonitis or AV access infection)
- Peritonitis (peritoneal dialysis)

Renal transplantation is the preferred treatment for ESRD patients requiring renal replacement therapy. All ESRD patients should be referred for transplant evaluation, ideally so they can be transplanted before dialysis is needed, but not all will qualify. The 5-year survival rate is by far superior with transplantation when compared with dialysis:

- Dialysis alone: 30–40%
- Diabetics on dialysis: 20%
- Live related donor: 72% at 5 years
- Cadaveric donor: 58% at 5 years

The average wait to obtain a kidney for transplantation is 2–4 years, and is becoming longer because of an insufficient donor supply.

Complications of transplantation include acute and chronic rejection, and infections due to immunosuppressive medications. Renal graft rejection is prevented by using cyclosporine, tacrolimus, corticosteroids, and mycophenolate. These are all medications that inhibit T-cell function.

Clinical Recall

Which of the following is not an indication for dialysis in ESRD?

- A. Fluid overload refractory to diuretics
- B. Severe metabolic acidosis
- C. Uremic pericarditis
- D. Severe hyperkalemia
- E. Anemia

Answer: E

NEPHROLITHIASIS

Nephrolithiasis (kidney stones) is a conglomeration of insoluble minerals that form a stone. It can form in the collecting system of the kidney, descend down the ureter, and lead to obstruction.

All stones form more readily in concentrated urine, so volume depletion may precipitate them. There are also genetic predispositions to stone formation, sometimes linked to lack of stone-inhibiting proteins in the urine (e.g., nephropontin).

Types of stones include:

- Calcium oxalate (70%) and calcium phosphate (10%)
- Struvite/infection (Mg/aluminum/phosphate) (5–10%)
- Uric acid (5%)
- Cystine (1%)
- Indinavir

Kidney stones are a common cause of ED visits and are often severely painful.

Calcium Stones

Calcium stones (80% of all stones) have several risk factors:

- **Hypercalciuria**
 - Idiopathic renal hypercalciuria (normal serum calcium)
 - Resorptive from bone: hyperparathyroidism (10–30% of patients present with stones); multiple myeloma, metastatic disease to bone, hypercalcemia of malignancy (serum calcium high)
 - Increased GI calcium absorption: vitamin D intoxication; increased vitamin D with sarcoid and other granulomatous disease; familial (serum calcium high)
- **Hyperoxaluria**
 - Primary familial oxaluria
 - Enteric: with fat malabsorption as in Crohn disease, the fat binds to calcium, leaving unbound oxalate to be reabsorbed in increased amounts and then excreted into the urine.
- **Hypocitraturia**
 - Urine citrate is a stone inhibitor, binding with calcium. Patients with low urinary citrate have a higher risk for calcium stones. Patients with type 1 (distal) renal tubular acidosis often have hypocitraturia.

Struvite/Infection Stones

Chronic urinary infections with urease-producing organisms such as *Proteus*, *Pseudomonas*, and *Klebsiella* give a highly alkaline urine that leads to struvite (Mg/aluminum/phosphate) stones. These often produce large “staghorn” calculi filling the renal pelvis. The urinalysis may show characteristic “coffin lid” crystals.



Uric Acid Stones

Uric acid stones form in an acid environment and are associated with diseases that increase serum uric acid levels such as gout, hematologic malignancies, and Crohn disease. Unlike other stones, they are radiolucent on x-ray but can be seen on renal ultrasound.

Cystine Stones

Cystine stones (least common) are associated with the genetic disorder cystinuria. The urinalysis shows characteristic hexagonal crystals.

For **all stones**, patients present with constant flank or abdominal pain (not colicky) often radiating to the groin, and gross or microscopic hematuria. There is often associated nausea and vomiting, mimicking an acute abdomen or pelvic inflammatory disease. Gross hematuria is common. The patient may recall stone fragments in the urine.

Diagnosis. Best test is a radiologic test; both spiral helical CT scan (no contrast) and renal U/S are equally good. Urine testing may show:

- UA: blood, crystals; WBC, bacteria (infection stones)
- Electrolytes: high calcium, high oxalate, and/or low citrate (calcium stones); high uric acid (urate stones)
- pH: >8 in infection (struvite) stones, otherwise lower

Patients should strain their urine to catch a passing stone, which is then sent for analysis (best test for stone type). Serum studies include:

- Calcium (sometimes high in calcium stones); if elevated, check the parathyroid hormone level
- Uric acid (high in most urate stones)

Serum creatinine will be elevated only if there is bilateral obstruction (hydronephrosis), which would be seen on U/S or CT.

Treatment. Analgesia, hydration, and bed rest are the mainstays of treatment. Definitive treatment depends on stone size as determined by radiologic study:

- <5 mm: stones pass spontaneously
- 5–10 mm: ureteral dilation agents, e.g., tamsulosin
- 1–2 cm: lithotripsy (extracorporeal or transurethral)
- >2 cm: surgical excision (percutaneous or transurethral)

Recurrent stones should be treated with increased hydration—especially in warm climates—and medication appropriate to type.

- **Calcium stones:** thiazide diuretics (increases urine Ca reabsorption) or citrate if urine citrate is low
- **Urate stones:** allopurinol or febuxostat (lowers serum uric acid)

CYSTIC KIDNEY DISEASE

Cystic disease of the kidney may be primary or acquired. The most common primary disease is autosomal dominant polycystic kidney disease (ADPKD), which often leads to ESRD and transplantation or dialysis. Acquired disease is most often seen in dialysis patients as an adventitious finding on CT scanning and requires no further management.

Autosomal Dominant Polycystic Kidney Disease

Autosomal dominant polycystic kidney disease (ADPKD) is the most common cystic disease (prevalence 1:200 to 1:1,000). Presentation ranges from asymptomatic to painful to progressive CKD requiring eventual dialysis. Patients are commonly detected in early adulthood during evaluation for a urinary tract infection or flank pain, initially confused with stones.

Clinical presentation includes:

- Flank pain (one or both sides)
- Hematuria (microscopic or gross)
- Progressive loss of GFR
- Recurrent urine infections
- Hypertension
- Extra-renal manifestations: hepatic cysts (40–60%); intracranial aneurysm (10–20%); mitral valve prolapse (25%), colonic diverticula

Diagnosis. The best test is **renal ultrasound or CT scanning**. Many patients are concerned about the risk of rupture of undetected intracranial aneurysms. Without symptoms there is no recommendation to screen ADPKD patients with cranial CT scanning, but this may be individualized for patient preference. Even if detected, there is no indication for neurosurgical intervention without evidence of a bleed.

Treatment is management of the complications (UTI, calculi, and hypertension) and prepare the patient for dialysis if renal function declines. There is no specific treatment. Some patients require nephrectomy for intractable pain.

Simple Cysts

Simple renal cysts are very common and usually of no significance. If they are smooth-walled with no debris inside the cyst, they can be managed without further treatment or diagnostic tests. If they have irregular walls or debris inside, follow closely with repeat scans to exclude malignancy.



HYPERTENSION

An estimated 50 million Americans have high BP. Hypertension may be primary (essential) or secondary to known diseases. Severe hypertension with end-organ damage is termed emergent hypertension.

Complications of uncontrolled hypertension include:

- **Cardiac:** increased risk of myocardial ischemia and infarction, left ventricular hypertrophy with eventual CHF, aortic aneurysm, and dissection
- **Cerebrovascular:** transient ischemic attack (TIA) or stroke
- **Renal:** nephrosclerosis with microscopic hematuria, mild proteinuria, progressive elevation of BUN/creatinine, and eventual dialysis. Hypertension worsens the prognosis of most renal diseases.
- **Retinopathy:** hemorrhages, exudates, arteriolar narrowing, and papilledema; these result in blurred vision, scotomata, and sometimes blindness

Essential Hypertension

Essential hypertension (>95% of all cases of hypertension) is best thought of as a syndrome with many causes, not a single disease. Causes in each patient vary: arterial stiffening, increased sodium sensitivity, or increased renin/angiotensin/aldosterone axis activity. This variability means that each patient will respond differently to a given intervention or medication.

Epidemiologically, essential hypertension is:

- More common with increasing age (found in 50% of those age >60)
- More common in obese patients
- Men > women until after menopause
- More common in black population at all ages, as is incidence of end-organ damage
- Onset usually age 25–55

Clinical Presentation. The most common presentation of essential hypertension is an **asymptomatic patient** in whom an elevated BP is found during a routine examination or evaluation for other medical problems. Much less commonly when symptoms are associated with hypertension, think of them as follows:

- Acute symptoms associated with a hypertensive emergency OR
- Complications from end-organ damage

With a hypertensive emergency, signs and symptoms may include evidence of stroke (neurologic findings, headache, blurred vision, dizziness) or cardiac symptoms (chest pain, dyspnea).

Diagnosis. Hypertension is diagnosed when **systolic BP 140 mm Hg or diastolic BP $\geq$ 90 mm Hg (or both) on repeated examination**. Systolic BP is particularly important and is the basis for diagnosis in most patients. These numbers apply to all adults age >18 (although for those age $\geq$ 80, systolic BP up to 150 mm Hg is now regarded as acceptable).

New 2017 ACC guidelines have recommended diagnostic values and therapy targets of **<130/80 mm Hg for patients with DM, elevated calculated cardiac risk (>10%), or chronic kidney disease**. These more rigid guidelines are controversial, since “tight” treatment increases medication use and increases the risk of falls, especially in elderly patients.

Table 8-6. ACC/AHA Guidelines (New as of 2017)

Normal BP	<120/80 mm Hg
Elevated	SBP 120–129 with DBP <80 mm Hg
Hypertension Stage 1	SBP 130–139 or DBP 80–89 mm Hg
Hypertension Stage 2	SBP >140 or DBP ≥90 mm Hg

As much as 20–25% of mild office hypertension is artifactual, i.e., these initial elevated readings merely represent a manifestation of anxiety on the part of the patient to the doctor/medical environment (known as “white coat hypertension”). These patients rarely have evidence of end-organ damage. Home BP monitoring is the best way around this difficulty, and all hypertensive patients should learn how to take and record their BP. Never label a patient as hypertensive after only a single reading: **repeat the reading 3–6 times over several months** before confirming the diagnosis and initiating therapy.

The physical exam includes evaluation of the heart for murmurs and LVH, auscultation for abdominal bruits seen in renal artery stenosis, and identifying edema seen in chronic kidney disease. A dilated eye exam looking for retinopathy is needed.

Lab testing is done to exclude chronic hypertensive complications and causes of secondary hypertension. Most routine lab testing will be normal. Once done on initial evaluation, repeat testing is unnecessary if the BP is well controlled, except to monitor drug side effects (e.g., hypokalemia with diuretics). Initial basic studies include:

- Urinalysis for protein, RBCs (screen for hypertensive nephrosclerosis and other renal diseases as secondary cause)
- Serum potassium (to exclude hyperaldosteronism as a secondary cause)
- Serum creatinine and BUN (screen for hypertensive nephrosclerosis and other renal diseases as secondary causes)
- Electrocardiogram to evaluate for left ventricular hypertrophy
- Serum glucose and plasma lipid analysis as an indicator of atherosclerotic risk

Treatment is aimed toward reducing BP to levels that will prevent acute and chronic complications. These targets vary depending on other patient risk factors.

- For patients **without** DM, cardiovascular disease, CV risk >10%, or chronic kidney disease, use the following guidelines:
 - Treat confirmed mild and moderate hypertension (DBP 90–100) with nonpharmacologic modifications in lifestyle: weight loss for the obese, dietary sodium restriction, aerobic exercise, reduced alcohol intake, and low-fat diet with increased dietary fiber (DASH “Dietary Approaches to Stop Hypertension” diet includes increased fruits/vegetables, low-fat dairy). For every kilogram of weight lost, there is generally a 0.5–1.0 mm Hg drop in systolic and diastolic BP. Relaxation methods have inconsistent effects.
 - Patients who continue to have diastolic BP >90 mm Hg after 3–6 months of nonpharmacologic therapy should then be started on an antihypertensive drug.

Note

First-line drugs for essential hypertension in patients without other diseases include thiazides, ACE inhibitors/ARB, and calcium channel blockers (CCBs). **Beta blockers should not be given.**



- Treat severe hypertension (diastolic >100 mm Hg) immediately with drug therapy.
- Use 2 medications as initial therapy for those with BP >160/100 mm Hg, since a single drug will not control this level of hypertension.
- For patients **with** DM, cardiovascular disease, elevated CV risk (<10%), or chronic kidney disease, treat more aggressively, with ≥ 1 medications, to achieve BP **both** SBP <130 mm Hg **and** DBP <80 mm Hg.

Medications. There are almost 50 medications approved for the initial treatment of hypertension, not including combination medications. Choice of drug is determined both by guidelines for the general population and by knowledge of drugs to use or avoid in specific patients based on their other medical problems.

Diuretics are still first choice in the absence of a specific indication or contraindication; their mortality benefit is unsurpassed, and chlorthalidone is best of all. If diuretics do not control the BP, add a second medication (an ACE inhibitor/ARB or CCB).

For BP >160/100 mm Hg, use a 2-drug combination: diuretic plus either ACE inhibitor/ARB or CCB.

Consider the following when treating specific hypertensive groups:

- Treat those who have post-myocardial infarction (ischemic heart disease) or systolic CHF with beta blockers.
- Treat those with systolic CHF or chronic kidney disease with ACE/ARB.
- Pregnancy: treat HTN with alpha-methyldopa, labetalol, hydralazine, or CCBs. **ACE inhibitors and ARBs are absolutely contraindicated.** Diuretics are relatively contraindicated.
- African-American patients receive the least BP lowering benefit from ACE inhibitors.

Clinical Recall

A 48-year-old man comes to the clinic with blood pressure 150/95 mm Hg. What is the best initial therapy?

- A. Hydrochlorothiazide
- B. Lifestyle modification and chlorthalidone
- C. Lisinopril
- D. Atenolol
- E. Amlodipine

Answer: B

Secondary Hypertension

Secondary hypertension (5% of all HTN cases) is hypertension due to an identifiable underlying cause. Renal artery stenosis is the most common cause. The following groups should be screened for secondary hypertension:

- Those who become hypertensive age <25 **or** >55
- Those with a key feature of history, physical examination, or lab abnormality consistent with a particular form as described
- Those with “essential hypertension” who remain hypertensive despite increasing dosages and numbers of antihypertensive medications, i.e., those refractory to what should normally be effective therapy

With secondary hypertension, the presentation depends upon the cause.

- Renovascular disease causes an abdominal bruit
- Chronic kidney disease shows edema
- Cushing disease causes weight gain, moon-like facies, striae, and ecchymoses
- Primary hyperaldosteronism causes muscular weakness and polyuria/polydipsia from hypokalemia
- Pheochromocytoma (very rare) causes episodic hypertension associated with headache, palpitations, and sweating

The recommended lab work-up for essential hypertension will screen for the most common forms of secondary hypertension. A more intensive work-up can be done if there is a high clinical suspicion.

There are several types of secondary hypertension.

- **Renal artery stenosis** may be unilateral or bilateral and is caused by atherosclerotic disease in patients with high CV risk or fibromuscular dysplasia in young women. Physical exam may show an **upper abdominal bruit** radiating laterally (50–70% of patients). Radiologic confirmation tests include:
 - **Renal artery duplex U/S** (best screening test)
 - Captopril renogram measures the uptake of a radioisotope before and after the administration of captopril; a positive test is when there is decreased uptake of the isotope (i.e., decreased GFR) after giving the captopril (accuracy is diminished with renal insufficiency)
 - Magnetic resonance angiography (equal to sonography in diagnostic ability but more expensive)
 - Renal arteriography (more invasive and used prior to surgical revascularization to confirm the extent of stenosis)
 - **Treatment.** For **bilateral disease**, the best initial treatment is **percutaneous transluminal angioplasty** with stenting. If stenosis recurs, repeat the procedure. If angioplasty fails, attempt surgical revascularization. ACE inhibitors are effective for BP control; however, since they carry the risk of acute kidney injury in bilateral disease, use with caution.
 - For **unilateral disease**, it is not clear whether angioplasty is superior to ACE inhibitors.



- **Chronic kidney disease (CKD)** is typically associated with hypertension (often severe). Treatment emphasizes the use of ACE inhibitors (or ARB) for their effect in slowing progression of disease and reducing proteinuria. Once on dialysis, effective fluid removal will improve the resistant hypertension seen in these patients.
- **Primary hyperaldosteronism** is caused by a unilateral or bilateral adrenal adenoma (most common) or by bilateral adrenal hyperplasia. Cancer is rarely the cause. The key features are **hypertension in association with hypokalemia**. Diagnose with elevated aldosterone level and aldosterone/plasma renin activity in urine and blood. Treatment is surgical resection (for those with an adenoma) or potassium sparing diuretics such as spironolactone for those with adrenal hyperplasia. If an adenoma is suspected but not seen on radiologic studies, bilateral renal vein sampling for differential aldosterone levels may assist in locating the lesion.
- **Cushing disease** is hypercortisolism, most often due to ACTH hypersecretion by a pituitary adenoma. The key feature is hypertension in association with characteristic cushingoid manifestations such as truncal obesity, buffalo hump, menstrual abnormalities, striae, and impaired healing, etc. Dexamethasone suppression testing, 24-hour urine cortisol, or salivary cortisol are the best initial tests. Treatment is surgical resection of the adenoma.
- **Pheochromocytoma** (rare) is most often a benign tumor of the adrenal gland. The key feature is episodic hypertension in association with headaches, sweating, palpitations, tachycardia, or flushing (but only 50% have these acute features). The best initial tests are urinary vanillylmandelic acid (VMA), metanephrines, and free urinary catecholamines. Plasma catecholamine evaluation is helpful as well. CT and MRI will often localize the site of the tumor. Treatment is alpha-adrenergic blockade followed by surgical removal.
- **Coarctation of the aorta:** the key diagnostic feature is severe hypertension markedly greater in the upper extremities compared with the lower extremities.
- Other endocrine causes: oral contraceptives, acromegaly, and congenital adrenal enzyme deficiencies

Hypertensive Emergency

A hypertensive emergency (replaces the term *malignant hypertension*) is the acute onset of severe hypertension in association with severe and rapidly worsening symptoms of end-organ damage (~1% of hypertensive patients).

Clinical Presentation: Diastolic BP will usually be >120–130 mm Hg.

- **Neurologic:** encephalopathy, headache, confusion, seizures, subarachnoid or intracerebral hemorrhage
- **Cardiac:** chest pain, myocardial infarction, palpitations, dyspnea, pulmonary edema, jugular venous distension, gallops
- **Nephropathy:** acutely progressive hematuria, proteinuria, renal dysfunction
- **Retinopathy:** papilledema, hemorrhage, blurred vision

Lab evaluation is the same as for initial evaluation of essential hypertension, except that a head CT scan may be necessary to exclude hemorrhage. ECG is important as an initial test to exclude infarction.

Treatment. The initial goal is to reduce BP by no more than 25% within the first 1–2 hours.

- IV therapy is indicated: labetalol and nitroprusside are the best agents (nitroprusside carries a greater risk of thiocyanate toxicity when used >24 hrs)
- For those with myocardial ischemia or chest pain, nitroglycerin is indicated; other options are enalaprilat (an IV ACE inhibitor), esmolol, or nicardipine

The most important point in management is **not to lower the pressure too far** (e.g., not <95–100 mm Hg diastolic) so as not to compromise myocardial or cerebral perfusion.

Antihypertensive Medications

First-line agents

- **Thiazide diuretics: chlorthalidone** (preferred in guidelines), hydrochlorothiazide, metolazone, and indapamide are least expensive. Specific indications include CHF, edematous states, calcium kidney stones, nephrogenic DI. Side effects include decreased potassium and magnesium; increased glucose, calcium, uric acid, LDL; and gynecomastia. Relative contraindications include pre-diabetes and diabetes (worsens glucose tolerance), gout, hyponatremia, and hyperlipidemia.
- **ACE inhibitors (ACEi):** benazepril, enalapril, captopril, lisinopril, quinopril, and ramipril
- **Angiotensin-receptor blockers (ARBs):** losartan, candesartan, valsartan, telmisartan, and irbesartan. Use only when intolerant of ACEi (more expensive). Specific indications for ACEi/ARB include chronic kidney disease, diabetics with microalbuminuria (to prevent nephropathy), CHF (afterload reduction), and postmyocardial infarction with low EF. Side effects include cough (ACEi only), angioneurotic edema (ACEi > ARB), neutropenia, hyperkalemia, taste disturbances, anaphylactoid reactions. Relative contraindications include hyperkalemia >5.0, bilateral renal artery stenosis (effective, but may cause AKI). Absolute contraindications include pregnancy.

Note

ARBs are less effective than ACEis in African-American patients.

Calcium channel blockers

- Dihydropyridines: amlodipine, felodipine, isradipine, nicardipine, nifedipine. Non-dihydropyridines: diltiazem and verapamil. Specific indications include angina pectoris (verapamil and diltiazem only), supraventricular arrhythmia, migraine, Raynaud phenomenon, esophageal spasm. Side effects include peripheral edema, constipation, heart block, reflex tachycardia (dihydropyridines). Relative contraindications include atrioventricular conduction defects, CHF from systolic dysfunction, angina pectoris, or CAD (dihydropyridines only).

Second- and third-line agents

- **Beta blockers** include bisoprolol (good in CHF, asthmatics), metoprolol (good in CHF, inexpensive) > acebutolol, atenolol, nadolol, pindolol, and timolol. Labetalol (combined beta and alpha) good for emergent hypertension. Specific indications include **myocardial infarction or ischemic heart disease (first line)**, **diastolic and systolic CHF (first line)**, supraventricular arrhythmias including a-fib, migraine headache, glaucoma, and anxiety (resting tachycardia). Side effects include bronchospasm,

**Note**

Furosemide and other loop diuretics are the most potent agents for diuresis (CHF, renal failure), but they lack the vasodilating capability of thiazides so are **not effective for treating essential hypertension**.

heart block, bradycardia, Raynaud phenomenon, depression, impotence, fatigue, decreased HDL, increased triglycerides, and hyperglycemia. Relative contraindications include asthma, COPD, atrioventricular conduction defects, CHF from systolic dysfunction, and diabetes because of masking signs of hypoglycemia; absolute contraindications include cardiogenic shock and acute asthma attack.

- **Potassium-sparing diuretics**: spironolactone, amiloride, and triamterene. Specific indications include edema, potassium wasting states (all), CHF (spironolactone), and cirrhosis (spironolactone). Side effects include hyperkalemia and gynecomastia (spironolactone). Relative contraindications include hyperkalemia >5 mmol/L. These agents are **often paired with thiazide diuretics**, neutralizing the thiazides' hypokalemic effect.
- **Loop diuretics** include furosemide, bumetanide, and ethacrynic acid. They are used for severe edema, especially pulmonary edema. Side effects include hypokalemia, hypocalcemia, and tinnitus.
- **Central-acting sympatholytics** include clonidine, guanfacine, guanabenz, and methyldopa. Clonidine can be useful in opiate detoxification. Side effects include depression, fatigue, dry mouth, impotence, bradycardia, heart block, and memory loss. Methyldopa gives hepatitis and Coombs-positive hemolytic anemia. Relative contraindications include elderly or depressed patients (orthostasis, falls, confusion).
- **Direct vasodilators** include hydralazine and minoxidil. Hydralazine is used in eclampsia and with nitrates for some patients with systolic CHF. Minoxidil is used topically to treat baldness. Side effects include a lupus-like syndrome (hydralazine) and marked fluid retention, pericardial effusion, and hirsutism (minoxidil). Relative contraindications include angina pectoris (reflex tachycardia).
- **Alpha-adrenergic blockers** include doxazosin, prazosin, and terazosin. They are used for those with lipid disorders (to reduce LDL and increase HDL), prostatic hyperplasia (to reduce obstructive symptoms), and nephrolithiasis (ureteral dilation). Side effects include syncope after the first dose, dizziness, and headache.

FLUID AND ELECTROLYTE DISORDERS

The fluid and electrolyte disorders such as hyponatremia, hypernatremia, hypokalemia, and hyperkalemia are among the most common disorders seen in acute and hospital medicine.

Hyponatremia

Hyponatremia, a potentially lethal condition, is common in hospitalized patients. It is defined as a low serum sodium concentration <135 mEq.

The cause is almost always an excess of free water (some call it "hyper-aquemia"), usually by excessive renal water absorption.

The physiologic effects of hyponatremia do not stem from the sodium per se, but rather from the **low serum osmolality**, which causes cerebral edema. Sodium is the main determinant of the serum osmolality, as about 85–90% of sodium is extracellular. As seen in the formula for calculated osmolality, about 280 mosm/kg of the total serum osmolality of 290 mosm/kg comes from sodium.

$$\text{Serum osmolality} = (2 \times \underset{290}{\text{sodium}}) + \underset{280}{\text{BUN}/2.8} + \underset{5}{\text{glucose}/18} \quad \underset{5}{\text{5}}$$

Therefore, **hyponatremia usually = hypo-osmolality**.

While hyponatremia suggests a disorder of sodium, water is in fact the culprit, and total body sodium may be low, high, or normal. Hyponatremia can be classified by the patient's extracellular volume status (which equals the total body sodium):

- **Hypovolemic hyponatremia:** low extracellular volume (ECV), low total body sodium (dehydration, GI loss)
- **Euvolemic hyponatremia:** clinically normal ECV, normal total body Na (SIADH, thiazides, SSRIs)
- **Hypervolemic hyponatremia:** high ECV, high total body Na (cirrhosis, CHF)

While total body Na may be low, normal, or high, in all cases the **ratio of total body sodium to total body water** is low, therefore causing the hyponatremia.

Clinical Presentation and Diagnosis. Symptoms of hyponatremia are predominantly neurologic, ranging from mild confusion and forgetfulness, to disorientation and obtundation, to seizure (or even coma). Symptoms do not correspond to a specific sodium level because they largely depend on how fast the level dropped (but symptoms are rare, >125 mEq/L). An acute 15–20 point drop in sodium can cause a seizure or coma.

The history should focus on symptoms of malignancy, psychiatric, heart, renal, and liver disease. The drug history should ask about SSRI antidepressants, thiazides, and antipsychotics. The physical exam should determine the patient's **extracellular volume status** (especially orthostasis), hypotension, tachycardia, and edema.

Labs. In addition to the **serum sodium concentration**, the patient may benefit from checking serum osmolality (usually low; if normal–high consider pseudohyponatremia), urine sodium (low [<10 mEq/L] in hypo- and hypervolemic types, high [>40] in euvolemic), and urine osmolality (inappropriately high in face of low serum osmolality, i.e. >200 mosm/kg, often >500 in SIADH).

Pseudohyponatremia

In pseudohyponatremia, serum sodium is low but serum osmolality is normal or high. The patient appears euvolemic and is asymptomatic. No specific hyponatremia therapy is needed.

The common causes of pseudohyponatremia should be excluded before further work-up is done. These causes include **hyperglycemia** (where increased serum osmolality pulls water out of cells, diluting the serum sodium) and **hyperlipidemia** (a lab artifact in which the high lipid fraction “dilutes” the measured sodium concentration despite a normal true serum value).

Hypovolemic hyponatremia

In hypovolemic hyponatremia, hyponatremia develops because of the loss of sodium and water through body fluids, but sodium losses exceed water losses. It may be worsened if pure water is used as fluid replacement, rather than balanced electrolyte solutions. For example, when you sweat during exercise (loss of hypotonic sodium and water) and replace only with free water, serum sodium may drop over time. Causes include GI loss (vomiting, diarrhea, gastric suction), skin loss (burns, sweating, cystic fibrosis), diuretics, and renal sodium loss (salt wasting in Addison disease, cerebral salt wasting after neurosurgical procedures).



Patients show signs of ECV depletion (orthostasis, hypotension, tachycardia, decreased skin turgor). Serum Na is usually >125 mEq/L, so hyponatremic symptoms are uncommon. Urine sodium concentration will be low (<10 mEq/L) reflecting avid renal Na reabsorption due to low ECV.

Treatment is normal saline (**the only time** this is used in hyponatremia).

Hypervolemic hyponatremia

In hypervolemic hyponatremia, hyponatremia is caused by high ADH levels, stimulated by a drop in “effective circulating volume”, i.e., organ perfusion, such as in vasodilated states or CHF where cardiac output drops. The kidney reabsorbs sodium and water in response to the low perfusion, but more water is retained than sodium, leading to hyponatremia. Note that while Na and water reabsorption are usually linked in normal physiology, Na is controlled by aldosterone, water by ADH, so the linkage may not be precise in some patients with low effective circulating volume. This subset develops hyponatremia. Causes include CHF, nephrotic syndrome and low albumin states, and cirrhosis.

Patients will show signs of ECV expansion: edema, ascites, pulmonary crackles, and specific signs of heart, liver, or renal disease. The serum Na is usually >125 mEq/L, so hyponatremic symptoms are uncommon. Urine sodium concentration will be low (<10 mEq/L), reflecting avid renal Na reabsorption due to reduced renal perfusion.

Treatment is of the underlying disorder. Furosemide may help with urinary dilution, so enhance water excretion.

Note

End-stage kidney disease also may show hypervolemic hyponatremia, but from a different mechanism. Here, the failing kidney stops filtering water, yet the patient continues to drink it, leading to hyponatremia. This is often seen in patients prior to dialysis.

Euvolemic (normal ECV) hyponatremia

Patients with euvolemic hyponatremia are hyponatremic—often severely so—yet appear neither volume-depleted nor expanded. ADH levels are often very high. These cases often require specific hyponatremia treatment to avoid neurologic consequences. Causes include:

- High ADH levels released by the posterior pituitary
 - Psychiatric drugs and diseases (especially SSRI antidepressants, **most common cause** in United States)
 - Surgery, stress, endurance exercise (“marathon hyponatremia”)
 - Hypocortisolism
 - Hypothyroidism
- ADH released by other body cells: syndrome of inappropriate antidiuretic hormone secretion (SIADH)
- Excess water intake: psychogenic polydipsia: patients must drink at least 15–20 liters a day of fluid to overwhelm the diluting capacity of the kidney
 - Decreased renal water excretion (non-ADH mediated)
 - Thiazide diuretics: inhibit distal tubule Na reabsorption and generation of free water, limiting ability of kidney to excrete very dilute urine
 - Often occurs in patients doing extreme hiking or exercise; patients on thiazides need to eat and/or drink solute solutions during such exercise

Diagnosis: Patients will show normal clinical volume status. While there is total body water expansion, water is an ineffective clinical volume expander, so no edema results. Serum Na varies, but may be very low (<110), so **hyponatremic symptoms are common**. Urine sodium concentration will be >40 mEq/L, reflecting the kidney's sensing of mild volume expansion from water retention, resulting in sodium diuresis, thus worsening the problem (water retention, sodium excretion). This explains the increased severity of hyponatremia in some patients. Urine osmolality is often >500 mosm/kg, so administered fluids need to be more concentrated than that (i.e., avoid normal saline whose osmolality is 300). Other lab work-up includes:

- Serum uric acid (low in euvoletic hyponatremia due to increased urine loss of UA)
- Serum ADH level: this is the single most accurate test, but is rarely done due to time and expense. Levels are high.
- Thyroid function (TSH) to rule out hypothyroidism
- Serum cortisol and/or ACTH stimulation test (rule out hypocortisolism)

Treatment. In general, patients should limit water intake since water will worsen any other cause. Conversely, solute intake should be increased. Marathon runners and endurance athletes should drink electrolyte beverages (not pure water) and eat regularly. Normal saline should be avoided since patients with this condition will absorb the water and dump the sodium, often worsening the hyponatremia. Medications suspected as causative should be stopped.

- For **symptomatic hyponatremia** (usually serum Na <120 mEq/L), administer hypertonic (3%) saline infusion (high sodium content, osmolality of 1000, much greater than what is exiting in the urine) and consider furosemide (helps dilute urine in euvoletic hyponatremia). Stop acute treatment when the patient becomes asymptomatic (usually when Na >120 mEq/L). Monitor the rate of rise of sodium so as not to cause **central demyelinating syndrome**, which occurs if sodium is corrected too rapidly or is overcorrected. Generally, the rate of rise should not exceed 0.5–1 mEq per hour; this means no more than a 12-point rise in 12–24 hours.
- For **moderate asymptomatic hyponatremia** (usually serum Na >120), increase serum Na slowly. **Educate the patient about limiting water intake.** Also consider ADH antagonists (tolvaptan, conivaptan), demeclocycline (mild ADH antagonist), urea or salt tablets (increase solute without water), or fludrocortisone (used for cerebral salt-wasting after neurosurgery).

Hypernatremia

Hypernatremia is the “flip side” of hyponatremia, and is caused by **free water deficiency**. Causes include non-renal losses (GI, sweating) (**most common**) or DI, where a lack of ADH (or resistance to it) causes persistent polyuria and free water loss.

Non-renal water loss is often seen during summer months, when temperatures rise. Symptoms include low urine output and concentrated urine. Causes include:

- Insensible losses: sweating, burns, fever, exercise, or respiratory infections
- GI loss: osmotic diarrhea (e.g., lactulose, malabsorption), some infectious diarrhea
- Transcellular shift: rhabdomyolysis or seizures causing muscles to avidly take up water from the ECV

Note

Hyponatremia can be corrected as rapidly as 2 mEq per hour if the patient is seizing.

Note

A critical cause in the development of hypernatremia is **lack of water intake**, usually due to trauma, environmental causes (lost in the desert), or mental status changes. It is also seen in patients with DI who are placed NPO in the hospital for surgery and cannot drink their usual liters of water per day.



Renal water loss may be caused by renal ADH resistance (nephrogenic DI), inadequate ADH release from the posterior pituitary (central DI), or drug-induced loss of excess free water. Symptoms include high urine output and dilute urine.

- Nephrogenic DI: **lithium, chronic interstitial renal disease**, hypercalcemia, hypokalemia, sickle cell disease
- Central DI: Idiopathic (most common); **brain surgery**, trauma, infection, tumor, granulomatous, or hypoxia
- Osmotic diuresis with renal water loss: diabetic ketoacidosis (DKA), nonketotic hyperosmolar coma, mannitol, loop diuretics (water lost > sodium)

Clinical Presentation and Diagnosis. Symptoms are primarily neurologic. With severe hyponatremia of any cause, lethargy, weakness, irritability, seizures, and coma are present. There should be a history of limited water access (e.g. loss of consciousness, confusion, falls, lack of water access), since patients with these diseases will normally drink enough water to keep their serum sodium normal.

The physical exam usually demonstrates signs of volume depletion (orthostasis, tachycardia), since water and salt are both lost. Urine output is <1 liter per day in insensible water loss, while 3–20 liters per day in diabetes insipidus.

Lab evaluation will show high serum Na, low urine Na (<10 mEq/L).

- In DI, the urine osmolality will often be <100 mosm/kg, reflecting the dilute urine.
- To **differentiate central from nephrogenic DI**, administer ADH (nasal, IV). The urine osmolality will increase in central DI, but not in nephrogenic DI.

Treatment. Stop or reduce the lithium or other implicated medication. If patients are alert, they can drink water. If patients are hypovolemic (tachycardia, orthostasis), first administer normal saline and then switch to hypotonic saline (0.45% saline or 5% dextrose in water). Once they become alert, switch to oral fluids.

- Correction of sodium should be **<1 mEq/L every 2 hours** or **12 mEq/L per day**. Complications of overly rapid correction include cerebral edema and seizures, possibly causing permanent neurologic damage. A rate of correction as fast as 2 mEq per hour is acceptable only if the patient is seizing.
- In **central DI** also use **vasopressin** (ADH) subcutaneously, intravenously, intramuscularly, or by nasal spray. Central DI is usually transient, esp. post operatively
- In **nephrogenic DI**, reduce or stop the causative drug. For chronic DI, thiazides may be useful (recall that they **cause** hyponatremia but **treat** hypernatremia). NSAIDs may also help, as they inhibit prostaglandins which impair concentrating ability; NSAIDs will increase the action of ADH at the kidney.

Hypokalemia

Hypokalemia (serum potassium <3.5 mEq/L) is relatively common, especially in patients taking diuretics or with poor PO intake. Dietary potassium is high in fruits and meats. Excretion is by renal (controlled by aldosterone) and GI routes.

Unlike most electrolytes, potassium is mainly intracellular, so serum levels may not accurately reflect total body levels. Shifting of K in and out of cells is a major determinant of the serum concentration, in addition to total body K.

Hypokalemia may be caused by the following:

- **K shifting into cells:** beta agonists, insulin, metabolic alkalosis
- **Low K intake:** alcoholism, starvation
- **GI losses:** diarrhea
- **Renal losses:** from diuretics; low magnesium; increased aldosterone states (e.g., hyperaldosteronism, Bartter syndrome, or Cushing disease); vomiting (urine loss of K stimulated by high aldosterone and urine loss of bicarbonate)

Clinical Presentation. Symptoms and signs of hypokalemia predominantly affect the muscles and the heart.

- Muscle weakness, paralysis (when it is severe), and rhabdomyolysis
- Cardiac arrhythmias (which can be fatal)
- Nephrogenic diabetes insipidus: potassium is necessary for ADH effect on the kidney

In emergency cases, the most important diagnostic test is the ECG; abnormalities will include T-wave flattening and U-waves.

Treatment. Correct the underlying cause. Replete potassium as follows:

- Oral: the gut regulates absorption, i.e., there is no maximum rate of oral potassium replacement.
- IV: maximum 10–20 mEq/hour; do not use dextrose containing fluids as they increase insulin release and lower the serum potassium. Too-rapid IV repletion may cause a **fatal arrhythmia**.

Very large amounts of potassium may be necessary to raise the body potassium level by even 1 or 2 points. The best estimate is to give 4–5 mEq per kg per deficit point.

Hyperkalemia

Hyperkalemia (serum potassium >5.5 mEq/L) is common in patients with DM and chronic kidney disease. It is potentially lethal and requires prompt treatment and good prevention. Patients at risk should avoid bananas, citrus, and other high-K foods. Causes include:

- Increased intake (orally or by IV): usually in the presence of impaired excretion
- Shift of K out of cells into ECF:
 - Pseudohyperkalemia (a lab artifact): secondary hemolysis due to mechanical RBC trauma during venipuncture (look for “hemolyzed” specimen)
 - Excessive thrombocytopenia >1,000,000, leukemia (WBCs >100,000)
 - Damaged cells: rhabdomyolysis, seizures, extreme exercise
 - Metabolic acidosis: H⁺ moves into cells, K⁺ moves out; for every 0.1-point decrease in the pH, potassium level will increase by 0.7

Note

Hyperaldosteronism can be caused by adrenal adenomas (low renin and AT), bilateral adrenal hyperplasia (low renin and AT), or renal artery stenosis (high renin and AT). Hyperaldosteronism causes secondary hypertension, hypokalemia, and metabolic alkalosis.

Note

A U-wave is an extra wave after the T-wave that is indicative of Purkinje fiber repolarization.



- Insulin deficiency (type 1 diabetes, DKA)
- Periodic paralysis: mild, brief episodes of muscle weakness with mild increase in K^+ ; diagnosis with recurrent attacks and family history
- Decreased urinary K excretion
 - Chronic kidney disease with GFR $<10\%$ normal
 - Potassium-sparing diuretics: amiloride, triamterene, spironolactone
 - ACE inhibitors and ARBs
 - Type IV RTA
 - Hypoaldosteronism: DM (hyporeninemic), Addison disease, adrenalectomy, adrenalitis, adrenal enzyme deficiency, heparin (inhibits production of aldosterone)
 - NSAIDs

Clinical Presentation. Patients are often asymptomatic despite dangerous hyperkalemia. Muscular weakness is seen with serum K^+ level >6.5 . The most important initial test is the ECG. Abnormal cardiac conduction is the most common cause of death. With worsening hyperkalemia, the ECG shows:

- Peaked T waves
- Flattening of P waves
- Widened QRS and short QT
- Flattening of QRS complexes
- Ventricular fibrillation or tachycardia

Treatment. For asymptomatic patients with normal ECG: Low K diet; diuretics and/or GI binding agents (Kayexalate, patiomer). Patiomer is a newer GI binding agent with fewer GI side effects (including bowel necrosis) than Kayexalate.

For patients with ECG changes, urgent treatment is required. The serum K may be lowered rapidly, but hypokalemia should be avoided. A stepwise approach should be taken. In practice, the steps are often done simultaneously, as some drugs take time to work.

1. First, stabilize the cardiac membrane. Calcium gluconate: membrane stabilization (most emergent treatment in presence of ECG abnormalities); effect is immediate and short-lived
2. Next, shift the K intracellularly
 - Glucose and insulin: drives K^+ intracellular, takes 30–60 min to work
 - Beta agonists (e.g., albuterol)
3. Then remove K from the body
 - Loop diuretics (ineffective in some patients with CKD, low GFR)
 - GI cation exchange resin (Kayexalate or patiomer)
 - Patiomer has lower incidence of bowel necrosis
 - Resin absorbs 1 mEq K^+ per g and releases 1 mEq Na^+
 - Give with sorbitol to prevent constipation
 - Kayexalate available as retention enema for those who cannot take orally
 - Dialysis if above fail or if an ESRD patient

Clinical Recall

Which of the following treatments for hyperkalemia removes potassium from the body?

- A. Calcium chloride
- B. Sodium bicarbonate
- C. Potassium exchange resin
- D. Beta agonists
- E. Insulin

Answer: C

ACID/BASE DISTURBANCES

Acid/base disorders are common and are often seen in hospitalized patients as a consequence of serious illness and medications. They have consequences and sequelae based on changes to the body pH, but also are very useful diagnostically as clues to other diseases.

- **Acidemia** and **alkalemia** are reduced and increased blood pH, due to ≥ 1 causes.
- **Acidosis** and **alkalosis** are specific pathologic processes (≥ 1) that cause the net change.
- A **mixed acid-base disorder** means having ≥ 2 acidoses/alkaloses, e.g., an anion gap metabolic acidosis with a respiratory alkalosis (as in aspirin toxicity).
- A **compensation** is not a disorder; it is the body's normal response to a change in pH caused by an alkalosis or acidosis. For example, during a metabolic acidosis (e.g., DKA), the acidemic pH is sensed by the CNS, which induces pulmonary hyperventilation (the respiratory compensation), lowering the $p\text{CO}_2$ and raising the pH back toward normal. Each acid base disorder has an expected compensation.

Metabolic Acidosis

Metabolic acidosis is a decrease in blood pH [<7.35] caused by either endogenous or exogenous acids accumulating in the blood. It often accompanies serious illness (e.g., lactic acidosis in sepsis).

The pattern seen on the arterial blood gas is:

pH	$p\text{CO}_2$	HCO_3^-
↓	↓	↓

The low bicarbonate reflects the increased serum protons, which lowers the pH. The $p\text{CO}_2$ then falls as a **respiratory compensation**, as the CNS senses the acidosis and stimulates hyperventilation, which raises the pH back toward normal. Note that this reduction in $p\text{CO}_2$ is **not a “respiratory alkalosis”** (which would suggest an actual respiratory disorder, not a compensation as seen here).



An alternative shortcut (but less accurate) is that in metabolic acidosis the expected PaCO_2 is approximately equal to the last 2 digits of the $\text{pH} \pm 2$.

The expected compensation for a given level of HCO_3^- in metabolic acidosis can be predicted from Winters Formula:

$$\text{Expected PaCO}_2 = (1.5 \times \text{serum HCO}_3^-) + 8 \text{ mm Hg } (\pm 2)$$

If the observed pCO_2 is too high or too low compared to this calculated value, a second acid-base disturbance is present (see Mixed Acid Base Disorders).

Formulas such as these become less accurate at extremes of pH. For these, use an acid base nomogram.

The **anion gap** should be calculated once the diagnosis of metabolic acidosis is established so that we can categorize metabolic acidoses into high anion gap or normal anion gap types. The **anion gap** is an estimate of the unmeasured anions present in the bloodstream. The blood is electrically neutral, with a mix of anions and cations that include minerals (Na^+ , H^+ , Ca^{++} , HCO_3^-), proteins (albumin [negative charge]), and immunoglobulins (positive charge). Rather than measure them all, the anion gap is used to estimate the net charge due to abnormal anions or cations that may be present in the blood.

$$\text{Anion gap} = (\text{Na}^+) - (\text{HCO}_3^- + \text{Cl}^-) \\ (\text{normal } 8-12)$$

The normal anion gap of 8–12 means that in normal subjects all the anions, cations, and proteins that are **not** Na^+ , HCO_3^- , or Cl^- , add up to a net negative 8–12 mEq/L. When this number increases (becomes more negative), it indicates an “anion gap” caused by excess anions that are **not normally present in the blood**. These may be exogenous (e.g., oxalic from antifreeze) or endogenous (lactic from sepsis).

Therefore, when there is an elevated anion gap, assume that a **high anion gap acidosis** is present. If instead the patient has a metabolic acidosis with a normal anion gap, a **normal anion gap metabolic acidosis** is present.

Clinical Presentation and Treatment. Patients with metabolic acidosis will have symptoms related to the underlying cause. Acidemia per se does not cause symptoms until very severe (<7.1), when it may cause arrhythmias and decreased cardiac output. Treatment varies by cause, and usually includes some combination of removing the excess acid and administration of bicarbonate.

High anion gap metabolic acidosis

This is a metabolic acidosis caused by excess acid present in the blood, which may be endogenous or exogenous (ingested). The main causes are summarized (note that many of these cause lactic acidosis, which can be measured in routine lab testing).

Use the mnemonic **MUDPILES**:

- **M**ethanol, metformin (cause formic acidosis and lactic acidosis, respectively)
- **U**remia (GFR $<10\%$ of normal)
- **D**iabetic ketoacidosis (DKA): beta hydroxybutyric acid and acetoacetate
- **P**ropylene glycol (causes lactic acidosis)
- **I**NH (cause lactic acidosis)
- **E**thylene glycol, ethanol (cause oxalic acidosis and ketoacidosis, respectively)

Note

The anion gap may become abnormally low without acid-base abnormalities due to excess blood cations or deficient anions:

- Hypoalbuminemia (cirrhosis, nephrotic syndrome)
- Multiple myeloma (excess positive light chains)
- Lithium (excess cations)

- Lactic acid: sepsis, shock, ischemia, drugs, etc.
- Salicylates: aspirin overdose (causes lactic acidosis with combined respiratory alkalosis)

Clinical Presentation varies depending on the cause:

- Methanol: altered mental state, blindness, renal failure
- Uremia: edema, elevated serum creatinine
- Diabetic ketoacidosis (DKA): elevated serum and urine ketones, hyperglycemia, hyperkalemia
- Ethylene glycol: altered mental state, vomiting, hypocalcemia, oxalate crystals in urine, elevated serum osmolality
- Ethanol: vomiting, withdrawal, urine and serum ketones
- Lactic acid: hypotension, fever, causative drugs (metformin, INH, propylene glycol, aspirin); high serum lactic acid level
- Salicylates: tinnitus, nausea, respiratory alkalosis (mixed disorder); high serum lactic acid level

Treatment. Remove the offending acid or prevent its formation. Specific treatments include:

- Dialysis: uremia, methanol, ethylene glycol, propylene glycol, severe aspirin
- Saline and insulin: diabetic ketoacidosis
- Sodium bicarbonate: aspirin, methanol, ethylene glycol, propylene glycol
- Fomepizole: ethylene glycol, methanol (prevents conversion of substrate to toxic acid)

Normal anion gap metabolic acidosis

Metabolic acidosis with a normal anion gap results from either loss of bicarbonate (renal, GI) or deficient renal excretion of acid (renal tubular acidosis).

The kidney normally excretes metabolic acids by secreting protons in the cortical collecting duct (controlled by aldosterone), which are then buffered and excreted by either of the following:

- Filtered buffers (phosphate) called *titratable acid*: reduced when GFR drops (chronic kidney disease)
- Ammonia, secreted in the proximal tubule (regulated by serum pH): increased by acidosis and reduced by hyperkalemia

The main causes of normal anion gap metabolic acidosis are:

- **GI loss of bicarbonate:** Diarrhea and any post-surgical state that causes increased fecal transit may cause non-gap metabolic acidosis, due to loss of bicarbonate. Hypokalemia is usually present due to simultaneous GI potassium loss. The kidney functions normally, excreting acid and lowering pH to <5.5.
- **Proximal (type I) renal tubular acidosis:** This is an inability of the principal cells in the cortical collecting duct to secrete protons, a step needed for net acid excretion. It may be due to a transporter malfunction or to a back-leak of secreted protons back through damaged luminal cell membranes (as in amphotericin toxicity). Causes include chronic renal interstitial disease, Sjogren syndrome, SLE (and other autoimmune diseases), lithium, and amphotericin B.



Diagnosis: Serum HCO_3^- drops modestly, usually to 18–20 mEq/L. Serum K is low. Urine pH is appropriately low (<5.3) for any acidosis, unless the patient has just ingested bicarbonate, in which case the transient bicarbonate diuresis will raise the urine pH.

To confirm diagnosis, show that bicarbonaturia develops with bicarbonate administration, even when the patient is acidotic. Normal subjects do not excrete bicarbonate in the urine until their serum bicarbonate >24 .

Treatment is bicarbonate (large amounts), potassium, and thiazide diuretics.

Distal (type II) renal tubular acidosis

This may be an isolated inability of the proximal tubule to reclaim bicarbonate, or accompanied by global proximal tubule dysfunction (Fanconi syndrome)—the latter would also show glucosuria, phosphaturia, uric acid, and aminoaciduria. The loss of bicarbonate leads to the non-anion gap metabolic acidosis. Patients may develop **osteomalacia**. Causes include multiple myeloma, amyloidosis, and genetic disorders such as cystinosis and galactosemia.

Diagnosis. Serum HCO_3^- may drop to low levels (<15). Serum K is usually low but can vary. Urine pH is inappropriately high (>5.5) for acidosis, due to the lack of free protons secreted into the tubule. There may be associated nephrocalcinosis or renal stones. Associated hypocitraturia may lead to calcium renal stones.

Treatment is bicarbonate and citrate.

Note

Urine anion gap (urine $\text{Na} + \text{K} - \text{Cl}$) estimates the ammonium secreted in the urine, so it can help detect RTAs. A **negative gap** indicates ammonium is **present**, and a positive gap indicates ammonium is not present. Ammonium is the normal renal response to acidosis, so it should be present unless there is an RTA.

- Diarrhea: UAG negative (ammonia present)
- Distal RTA: UAG positive (ammonia absent)
- Type IV RTA: UAG positive (ammonia absent)

Hyperkalemic (type IV) renal tubular acidosis

Hyperkalemic (type IV) RTA (most common RTA) is especially common in diabetics. Its name is a clue to the pathophysiology:

- The initial problem is chronic **hyperkalemia**, often due to hyporeninemic hypoaldosteronism (a common consequence of DM, where patients lack sympathetic regulation of renin).
- The hyperkalemia inhibits the proximal tubule's secretion of ammonia.
- The lack of ammonia limits net acid excretion and causes the acidosis.

Causes (and factors that worsen it) are largely those of hyperkalemia:

- DM (with hyporeninemic hypoaldosteronism) (50%)
- Adrenal insufficiency with mineralocorticoid deficiency
- ACE inhibitors/ARB: reduce aldosterone
- K sparing diuretics: raise serum K
- Sickle cell disease

Diagnosis. Serum HCO_3^- only drops to a moderate level (18–22). The hyperkalemia is uniform. Urine pH is appropriate (<5.3) for acidosis, since distal proton secretion is normal.

Treatment. Lower serum potassium (diet, change medications, diuretics). Add bicarbonate and fludrocortisone (if aldosterone deficient) but use caution because it causes edema.

Table 8-7. Renal Tubular Acidosis

Type	Associations	Serum HCO_3^- (mEq/L)	Serum K	Urine pH	Bones and calcium
Proximal (Type II)	Myeloma, acetazolamide, Fanconi syndrome	18–22	low	<5.3	Osteomalacia
Distal (Type I)	Lithium, amphotericin, rheumatoid disease	12–20	low	>5.5	Calcium stones, nephrocalcinosis, low urine citrate
Type IV	DM	18–22	high	<5.3	None

Metabolic Alkalosis

Metabolic alkalosis is an increase in blood pH (>7.45) caused by loss of body acids (vomiting) or gain of bicarbonate. Because excess bicarbonate is normally excreted rapidly by the kidney, maintenance of metabolic alkalosis usually requires concurrent **volume depletion**, which stimulates Na and HCO_3^- reabsorption.

The pattern seen on the ABG is:

pH	pCO ₂	HCO ₃ ⁻
↑	↑	↑

The respiratory compensation is respiratory—a central hypoventilation, raising pCO₂ and returning the pH toward normal. Hypokalemia is seen in most cases, and K depletion compounds the alkalosis and needs to be corrected to cure the acid base disorder.

Metabolic alkalosis is often classified by **responsiveness to saline infusion**, which is predicted by measuring the **urine chloride concentration**. Those with low urine chloride (e.g., vomiting, volume depletion after diuretics) will correct with saline. Those with a high or normal urine chloride (e.g., hyperaldosteronism) will not. The saline-responsive group is by far the most common.

- Saline-responsive metabolic alkalosis (low urine Cl⁻)
 - GI loss (vomiting, nasogastric suction)
 - Diuretics

Note

Type IV RTA (most common RTA) always shows concurrent hyperkalemia and should be looked for in diabetic patients.

Note

In **diuretic use**, patients are saline responsive but urine chloride is variable.

- It may be high if the patient is still taking the diuretic.
- It may be low if the patient has stopped the diuretic but is still volume-depleted.



- Saline-resistant metabolic alkalosis (high-normal urine Cl^-)
 - Hyperaldosteronism (including Cushing Syndrome)
 - Exogenous steroids
 - Tubular diseases causing K loss (Liddle, Gitelman, Bartter syndromes)
 - Excess bicarbonate administration

Clinical Presentation. Hypokalemia is seen in all the conditions. More specific findings include:

- Saline responsive: volume depletion (orthostasis, tachycardia)
- Saline-resistant: hypertension (in hyperaldosteronism, Cushing, and Liddle syndromes)

Treatment. Potassium repletion for all forms. Saline-responsive alkalosis should receive oral or IV saline to expand the ECV. The endocrine-related saline-resistant causes require treatment of the underlying disorder. Those with high aldosterone may respond to spironolactone.

Respiratory Acidosis

Respiratory acidosis is a decrease in blood pH (<7.35) caused hypoventilation with CO_2 retention. This can be acute or chronic, and due to problems with nervous control of breathing, muscle strength, or intrinsic pulmonary disease. The pattern seen on the ABG is as follows:

pH	pCO_2	HCO_3^-
↓	↑	↑

Note

Severe metabolic alkalosis will enhance calcium binding to albumin, reducing the free (ionized) calcium level, potentially causing hypocalcemic symptoms even with a normal total calcium concentration.

The metabolic compensation is initially the intracellular buffering of protons, then enhanced renal bicarbonate reabsorption, both causing serum HCO_3^- to rise, thus returning the pH toward normal. Causes include hypoventilation of any cause:

- **CNS/Neurological:** opiates; barbiturates/other sedatives; Pickwickian syndrome; sleep apnea; morbid obesity; neuropathy
- **Lung parenchymal disease or pleural disease:** COPD; severe asthma; pleural effusion; aspiration
- **Respiratory muscle weakness:** myopathies; myasthenia gravis; kyphoscoliosis

Clinical Presentation and Diagnosis. Evaluation should initially be directed to an immediate reversible cause, especially opioid overdose. Naloxone should be given unless a clear alternative explanation is present. Other labs include urine or serum toxicology and chest x-ray.

Treatment. Naloxone in uncertain cases; endotracheal intubation if the hypoventilation worsens; draining of pleural effusions

Respiratory Alkalosis

Respiratory alkalosis is an increase in blood pH (>7.45) caused by hyperventilation, which lowers the $p\text{CO}_2$. It can be acute or chronic, and due to psychiatric, pain syndromes, or pulmonary disease.

pH	$p\text{CO}_2$	HCO_3^-
↑	↓	↓

The metabolic compensation is initially due to intracellular buffering, then enhanced renal bicarbonate excretion, both causing the HCO_3^- to fall, thus returning the pH toward normal.

Since hyperventilation is a normal response to hypoxemia, first check the arterial O_2 saturation by pulse oximetry to guide further evaluation.

Hypoxic causes (low pulse oximetry O_2)

- **Hypoxic causes** (low pulse oximetry O_2): asthma; pneumonia; pulmonary embolus (not always hypoxic); sarcoidosis; high altitude
- **Nonhypoxic causes:** anemia (although total O_2 capacity is reduced); anxiety; pain; aspirin toxicity (mixed disorder, precedes the metabolic alkalosis); pregnancy
- Cirrhosis

Clinical Presentation and Diagnosis. Initial evaluation should include pulse oximetry; oxygen should be supplied if patient is hypoxic. Pulmonary embolus should be ruled out in uncertain cases. Other labs include CBC (anemia evaluation) and chest x-ray.

Treatment. Oxygen and support for the specific disorder; acetazolamide (carbonic anhydrase inhibitor, stimulates renal bicarbonate excretion) for headaches and nausea caused by high altitude respiratory alkalosis

Mixed Acid-Base Disorders

Acid-base disorders may not come alone as a single disorder; in other words, patients may develop 2 or more, and the net blood pH reflects the combination of all of them. An example is aspirin toxicity, where there is a combined respiratory alkalosis and high anion gap metabolic acidosis. The net pH may be normal in the face of abnormal $p\text{CO}_2$ and bicarbonate, as shown by these values: blood: pH 7.41, $p\text{CO}_2$ 25 mm Hg, HCO_3^- 16 mEq/L.

Diagnosis. There are several clues to help identify a mixed acid-based disorder:

- **Clue 1:** If there are large changes in $p\text{CO}_2$ and HCO_3^- but a near-normal pH, there is a mixed disorder (as shown in the aspirin toxicity example).
- **Clue 2:** In **all single disorders**, the $p\text{CO}_2$ and HCO_3^- “**move together**”; both either go up or down. If they go in different directions or if one is normal, suspect a mixed disorder.
 - Suppose the values from a patient after cardiac arrest are blood pH 7.15, $p\text{CO}_2$ 60 mm Hg, and HCO_3^- 20 mEq/L. The $p\text{CO}_2$ is elevated while the bicarbonate is depressed, which violates the “move together” rule.
 - Therefore, the patient has a combined metabolic and respiratory acidosis, typical of those who have had a cardiac arrest. The severely acidemic net pH further supports this.

**Table 8-8. Simple Acid Base Disorders**

	pH	pCO ₂	HCO ₃ ⁻
Metabolic acidosis	↓	↓	↓
Metabolic alkalosis	↑	↑	↑
Respiratory acidosis	↓	↑	↑
Respiratory alkalosis	↑	↓	↓

- **Clue 3:** A more refined way to diagnose mixed disorders is to use compensation formulae. In simple disorders, the calculated expected value should align with the measured value. The Winter's Formula (for metabolic acidosis compensation) is an example:

$$\text{Expected PaCO}_2 = (1.5 \times \text{serum HCO}_3^-) + 8 \text{ mm Hg } (\pm 2)$$

Suppose the values from a septic patient are blood pH 7.10, pCO₂ 35 mm Hg, and HCO₃ 10 mEq/L. Using clues 1 and 2 would still support a single disorder (metabolic acidosis).

However, when the Winter's Formula is applied, we see that the predicted pCO₂ in a compensated simple metabolic acidosis should be $(1.5 \times 10) + 8 = 23$ mm Hg, which diverges from the measured value of 35. This patient has a higher than expected pCO₂ and thus a combined metabolic and respiratory acidosis. This double disorder results in a very acidemic pH.

Each of the single acid base disorders has a compensation formula similar to Winter's for metabolic acidosis. Using them in routine acid base analysis (or referring to a nomogram) allows better diagnosis of mixed acid-base disorders.

Learning Objectives

- ❑ Interpret results of pulmonary function testing and chest radiography
 - ❑ Diagnose disturbances of gas exchange
 - ❑ Describe the presentation and management of obstructive lung disease, atelectasis, interstitial lung disease, and acute respiratory distress syndrome
 - ❑ Outline the presentation, diagnosis, and management of sleep apnea
 - ❑ List the types of lung cancer and their epidemiologic associations and prognosis
 - ❑ Present risk factors, diagnosis, and treatment plan for pulmonary thromboembolism
-

PULMONARY PHYSIOLOGY FOR THE CLINICIAN

The respiratory system is responsible for 2 things: obtain oxygen from the environment for the utilization of energy in the form of ATP, and eliminate carbon dioxide, the waste product of cellular respiration.

Obtaining oxygen for cellular respiration can be divided into 2 processes, which illustrate the clinically relevant physiology required in patient management:

- Exchange of oxygen between alveoli and blood in the pulmonary capillaries (“oxygen diffusion,” which applies Fick’s law of diffusion); relevant for the following:
 - Evaluating A-a gradient or the response to supplemental oxygen
 - Determining DLCO
- Transport of oxygen in blood (“oxygen delivery”)

Do not confuse oxygen delivery with total oxygen content and oxygen diffusion.

Total Oxygen Content

Total oxygen content in the blood is the sum of 2 measurable components:

- Amount of oxygen carried in the blood attached to hemoglobin, in RBCs
- Amount of oxygen dissolved in the plasma

Note

- A problem with the diffusion of oxygen is called **hypoxia**.
- A problem with the delivery of oxygen is called **hypoxemia**.

**Note**

The dissolved O_2 value is negligible, therefore is not usually considered in the clinical evaluation of O_2 delivery.

The relationship between these two forms is represented in an oxygen-hemoglobin dissociation curve. The proportion of hemoglobin bound to oxygen (saturated) is seen on the y axis, and the oxygen tension (dissolved oxygen) is seen on the x axis.

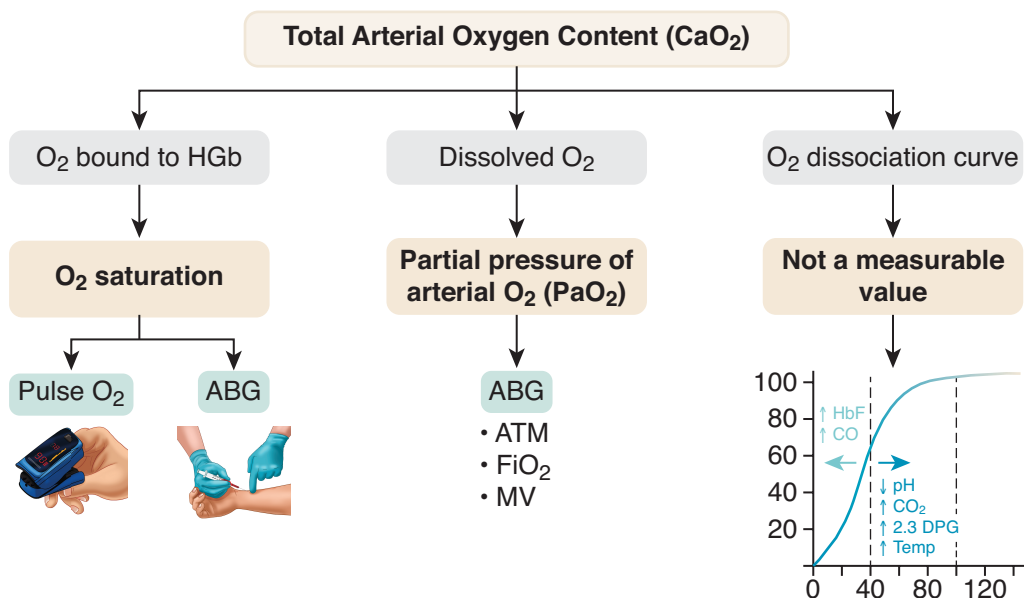


Figure 9-1. Total Arterial Oxygen Content

Table 9-1. Clinical Application of Oxygen Dissociation Curve

	PO ₂	Hb Concentration	O ₂ per g Hb	O ₂ Content
Anemia	Normal	Decreased	Normal	Decreased
Polycythemia	Normal	Increased	Normal	Increased
CO poisoning (acute)	Normal	Normal	Decreased	Decreased

Note

For the exam, there is no need to memorize the oxygen delivery equations.

Oxygen Delivery

Oxygen delivery (DO_2) is the volume of oxygen that the tissues are receiving. CaO_2 is the amount of oxygen within the arterial blood. The following equations are used:

- $CaO_2 = (1.34 \times Hgb \times SaO_2) + (0.003 \times PaO_2)$
- $DO_2 = CO \times CaO_2$ (or $CO \times [(1.34 \times Hb \times HbSat) + (0.0031 \times PaO_2)]$)

where Hgb is hemoglobin level, and SaO_2 is hemoglobin saturation.

Therefore, the oxygen received by the tissues relies on 2 main factors: **CO** ($HR \times SV$) and **hemoglobin level**.

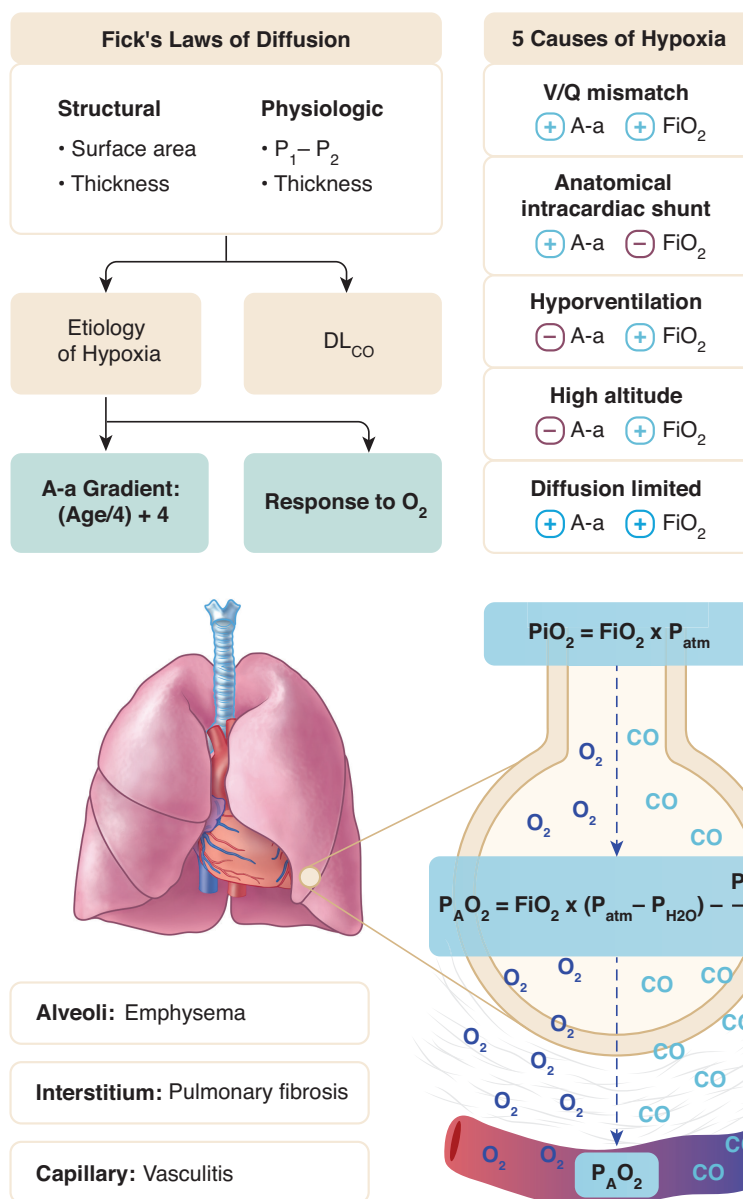
Alveolar-arterial (A-a) Gradient

The alveolar-arterial (A-a) gradient (the difference between $A-aO_2$) indicates the functionality of the alveolar-capillary unit. It increases physiologically with advancing age and pathologically with diseases of the lung.

Normal (healthy) A-aO₂ gradient is **5–15 mm Hg**. With hypoxia, that number is elevated, except when caused by hypoventilation or elevated altitude.

In order to determine the age-appropriate A-aO₂ gradient, use **A-aO₂ gradient ≤ (age/4) + 4**.

- First, calculate the PAO₂
 - PAO₂ = [(Pb - PH₂O) × FiO₂] - [PaCO₂/0.8]
 - Under normal conditions (at sea level): PAO₂ = [(760 - 47) × 0.209] - [PaCO₂/0.8]
 - PAO₂ = 150 - 1.25 (PaCO₂)
- Next, calculate the alveolar-arterial gradient
 - PAO₂ - PaO₂ = [150 - (1.25 × PaCO₂) - PaO₂]



PAO₂ is partial pressure of the air within the alveoli (relatively constant among subjects), while PaO₂ is partial pressure of oxygen within the bloodstream, and usually obtained through the ABC (subject to variation based upon lung problems).

Figure 9-2. Clinical Physiology of the A-a Gradient



Hypoxia

Hypoxia is insufficient oxygen content in the tissues, caused by a pathological condition or a temporary variation in arterial oxygen concentrations (e.g., when exercising). To determine the etiology, one must determine if the patient's A-aO₂ gradient is normal or widened, as well as the response to supplemental O₂.

The causes of hypoxia are classified into categories.

- **Ventilation/perfusion (V/Q) mismatch (most common cause of hypoxia in chronic lung disease)**
 - Seen with alveolar disease (e.g., pneumonia), pulmonary vascular disease (e.g., PE), and atelectasis
 - Responds to O₂ supplementation
- **Right-to-left (R-to-L) anatomical intracardiac shunting**
 - Seen with intra-cardiac defects where deoxygenated blood is shunted from right to left
 - Does not fully respond to O₂ supplementation
- **Hypoventilation**
 - Seen with neuromuscular disease (e.g., ALS), CNS disorders or drug toxicity (e.g., opioids, barbiturates)
 - Usually associated with a high PaCO₂ with normal A-aO₂ gradient
 - Responds well to O₂ supplementation
- **Diffusion-limited ventilation**
 - Seen with pathologies affecting the alveolar-blood interface
 - Widening of A-a gradient
 - Responds to O₂
 - Supplementation
- **High altitude**
 - Low FiO₂— results in a reduced PAO₂
 - Normal A-aO₂ gradient
 - Responds to O₂ supplementation

POSITIVE PRESSURE VENTILATION

Positive-pressure ventilation is an artificial way to help inflate the alveoli in preparation for effective gas exchange and maintenance of patency. A ventilation device replaces the normal mechanisms and restores the functional surface area of the alveoli, leading to an effective gas exchange.

Positive-pressure ventilation is helpful for hypoxia that is not resolved by oxygen administration or for serving as a bridge while resolving the underlying problem. It is used frequently in the ICU. There are 2 classifications, both of which can cause a decrease in systemic venous return.

Noninvasive Ventilation

Noninvasive ventilation (NIV) ventilation with the use of a mask. It is less invasive and at times safer.

- **Continuous positive airway pressure (CPAP)** is used to create a pneumatic splint of the airways (keeping them continuously open, preventing collapse) through a constant air pressure (= 10 cm H₂O)
 - Frequently used to manage OSA
 - Not commonly used for inpatient management of acute respiratory failure
- **Bi-level positive airway pressure (BiPAP)** applies to different pressures during the phases of breathing (e.g., BiPAP 10/5 cm H₂O): a larger pressure is applied during inspiration and a smaller pressure during expiration which is equivalent to PEEP; this helps ventilate the patient and blow off CO₂.
 - Frequently used for acute/chronic respiratory failure, OSA, and obesity hypoventilation syndrome

Invasive Ventilation

Invasive ventilation is mechanical ventilation with endotracheal intubation or tracheostomy.

- Used during acute respiratory failure with the additional benefit of protecting the airway
- Preset with tidal volume (volume-controlled) or pressure range (pressure-controlled)
- Patients are started on 100% FiO₂ and ventilation is titrated based on oxygen saturation and ABG
- **Positive end-expiratory pressure (PEEP)** is a ventilator setting to prevent alveolar collapse; defines pressure at the end of expiration in alveoli; usual starting point is 5 cm H₂O (>5 cm H₂O ie, with ARDS to offset low tidal volumes which induce atelectasis)
- Watch for a drop in the systemic venous return to the right side of the heart (useful in treating CHF)

Note

Modern mechanical ventilation is referred to as **assist-controlled**, meaning the patient only has to trigger the ventilation to receive a tidal volume. Triggering is based on the generation of negative pressure or the flow by the patient. With this new technology, patients can breathe beyond the respiratory rate preset on the ventilator.

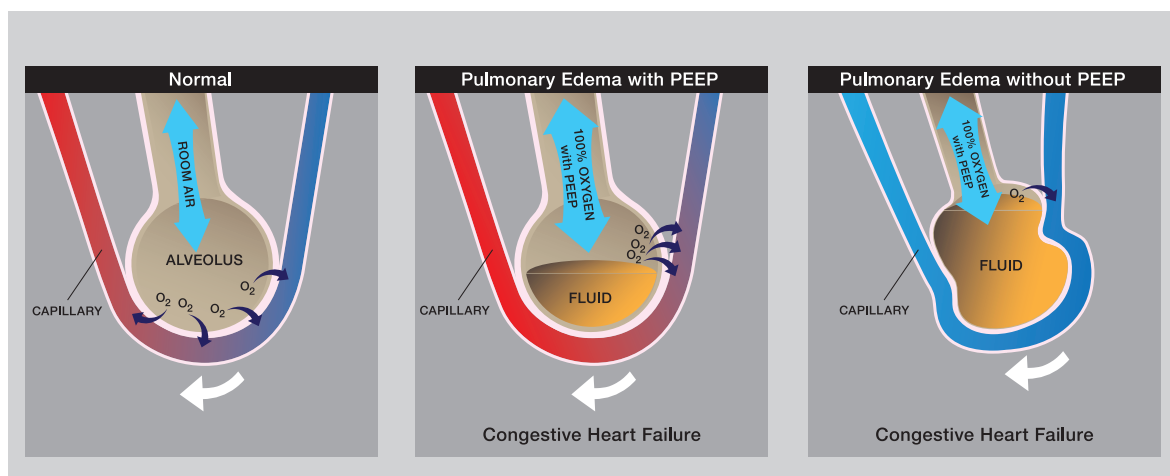


Figure 9-3. Effect of PEEP



Clinical Pearl

Perform PFTs in all patients before they undergo lung resection surgery.

Clinical Correlate

- PFTs with an **obstructive pattern + decreased DLCO**: think emphysema
- PFTs with a **restrictive pattern + decreased DLCO**: think interstitial lung disease (intrapulmonary restriction) or mild left heart failure
- PFTs with **elevated DLCO**: think alveolar hemorrhage, polycythemia, and left-to-right intracardiac shunting (all secondary to the increased blood flow through the pulmonary capillaries or increased hemoglobin available at the level of the pulmonary capillaries)

TESTS FOR PULMONARY DISEASE

Diagnostic tests in pulmonology are used to identify the general condition, and then to investigate the source of the condition.

Pulmonary Function Tests

PFTs are non-invasive tests used to identify restrictive vs. obstructive disease, to assess disease severity (preop evaluation and overall prognosis), and to evaluate post-treatment lung function. The basic tests are spirometry, static lung volumes, and alveolar diffusing capacity of a gas.

- **Spirometry** (most common, can be done bedside/in office)
 - Determines most lung volumes and capacities, as well as expiratory flows and bronchodilator response (asthma evaluation)
 - Measures airflow/air movement by expiratory flow rate
 - When performing spirometry, a flow volume loop is obtained
 - Abnormal is generally **<70% of predicted** in any lung volume or flow rate
- **Static lung volume**
 - Volume measured is residual volume (RV), done in order to calculate total lung capacity (TLC) (defining value for restrictive disease)
 - **$TLC = RV + VC$ or $VC = TLC - RV$** , where TLC is volume of gas in the lungs after maximal inspiration, RV is volume of gas remaining in the lungs after forced maximal expiration (unused space), and VC is volume of gas exhaled with maximal forced expiration
- **Alveolar membrane permeability (DLCO)** measures the alveolar membrane permeability
 - Determines how well (a) oxygen passes from alveolar space of the lungs into the blood, and (b) lungs are able to perform gas exchange
 - Single-breath DLCO test requires patient to inhale CO gas consisting of helium, CO, and room air
 - Diffusing capacity is reduced in following conditions:
 - When alveolar walls are destroyed and pulmonary capillaries are obliterated by emphysema
 - When alveolar-capillary membrane is thickened by edema, consolidation, or fibrosis (as in interstitial lung disease)

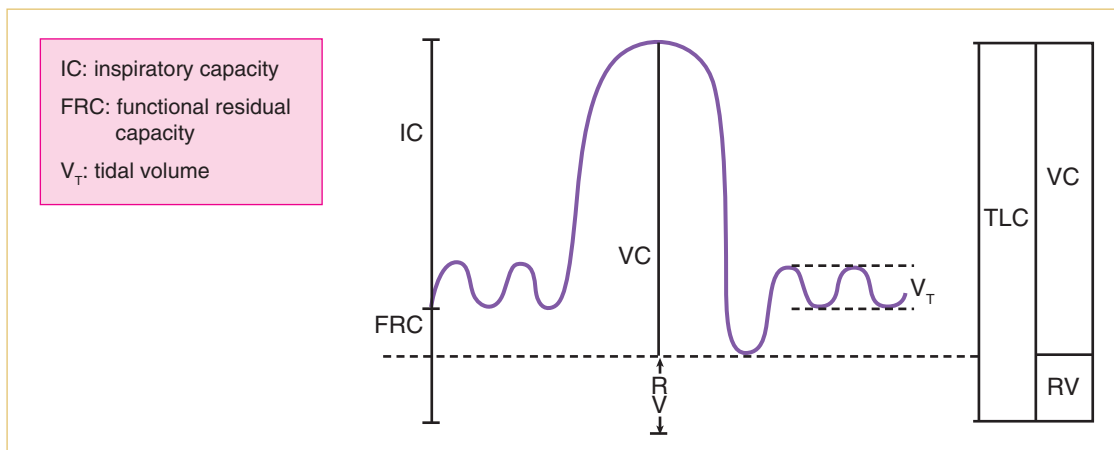


Figure 9-4. Determination of Lung Volumes

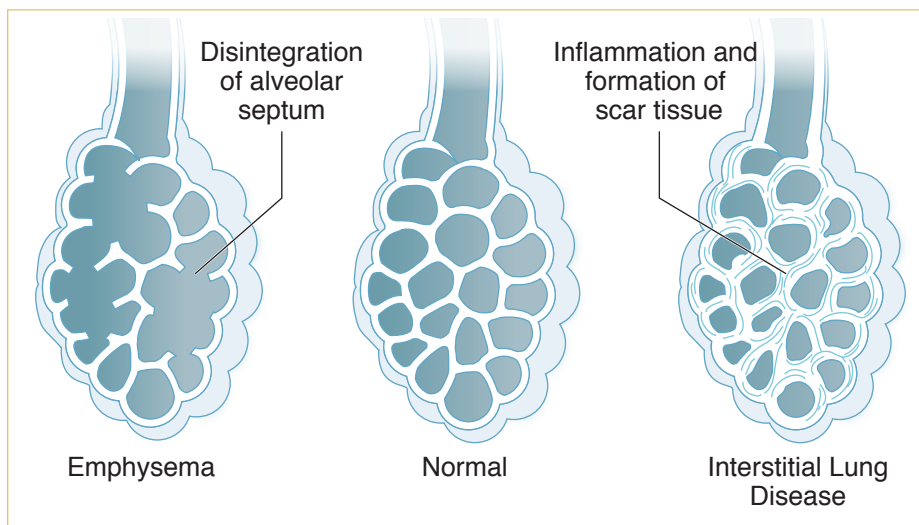


Figure 9-5. Alveolar Diffusing Capacity



Note

Common values obtained from spirometry include:

- **FEV₁**: forced expiratory volume in 1 second
- **FVC**: forced vital capacity

The **FEV₁/FVC ratio** is the defining value for obstructive disease.

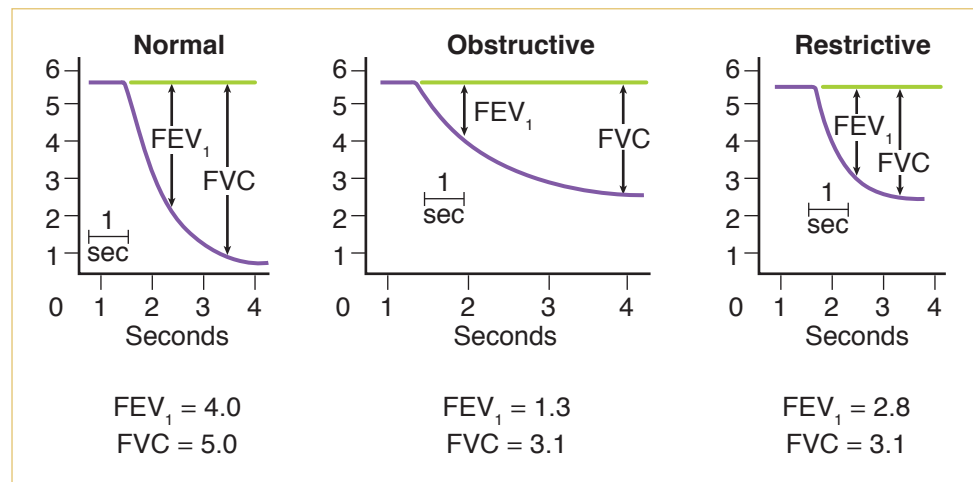


Figure 9-6. Forced Expiratory Volumes

Flow volume loop

Flow volume loop expresses airflow in lung disease, showing the relationship between flow rate and lung volume. It plots volume (x -axis) against flow rate (y -axis) during a maximally forced inspiration and expiration. The x -axis shows **volume** (lung volume increases to the left), and the y -axis shows **flow rate**.

Clinical Pearl

Some patients with asthma may have normal PFTs. In those cases, methacholine challenge will provoke an asthmatic crisis and allow a diagnosis of asthma to be made by PFTs. Thus, perform methacholine challenge only for patients with normal PFTs and in whom asthma is suspected.

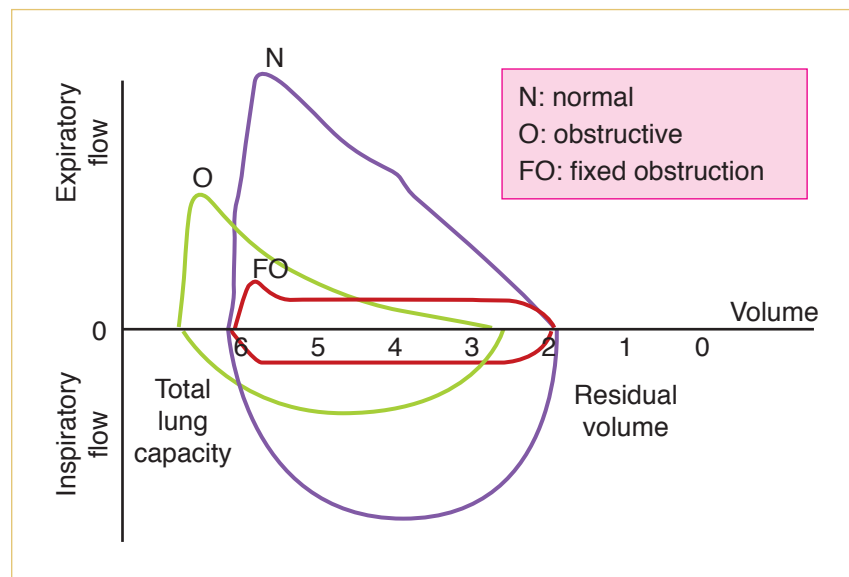


Figure 9-7. Flow Volume Loops

The shape of the loop can characterize the type and distribution of airway obstruction.

- **Restrictive lung disease** alters the size of the loop (a shift to the right of the x -axis), which is related to a reduction in lung volumes.
- **Obstructive lung disease** alters the shape of the loop by causing a reduction of airflow on the y -axis during expiration.
- **Fixed airway-obstruction** (tracheal stenosis after prolonged intubation) flattens the flow volume loop on the top and bottom.

With dynamic extra-thoracic upper airway obstruction, there are 2 main types: obstruction that occurs mostly with inspiration (ex bilateral vocal cord paralysis), and obstruction that occurs mostly with expiration, where there is a flattening of the expiratory part of the loop likely due to damage of the tracheal cartilage (ex tracheomalacia).

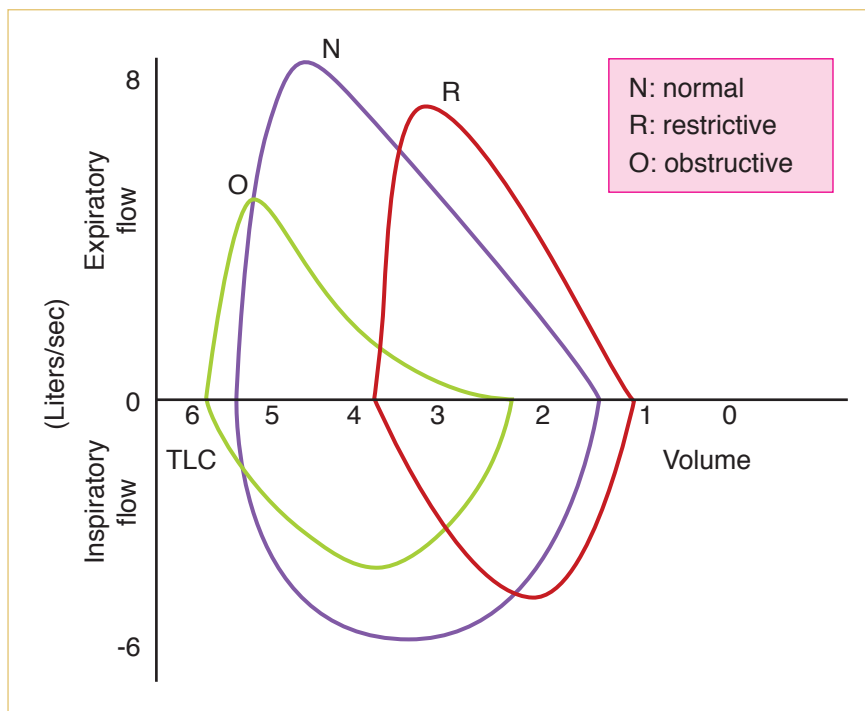


Figure 9-8. Flow Volume Loops

Clinical Pearl

FEO may occur in the setting of a tracheal tumor or foreign object aspiration or tracheal stenosis after prolonged intubation.

Methacholine challenge test

The methacholine challenge test evaluates cough-variant asthma or exercise-induced bronchoconstriction in the presence of normal PFTs and no bronchodilator response (a common scenario with asthmatics).

- Patient inhales methacholine and bronchoprovocation is evaluated
- The results of PFTs performed before and after the inhalation (e.g., spirometry) are used to quantitate the response.
- A **decrease $\geq 20\%$ from baseline FEV1** is considered **positive**

**Note**

In pregnancy, U/S is used instead of CT.

Note

BAL differs from bronchial washings in which secretions are aspirated from multiple parts of the pulmonary tree and not from a specific sub-segment.

Note

Because of its invasive nature, **mediastinoscopy** is now being replaced with endobronchial U/S.

Imaging

Noninvasive Testing

Various non-invasive technologies allow physicians to observe a specific pathology: chest x-ray, chest CT, PET scan, and lung biopsy.

- **Chest x-ray (most common)**
 - Usually the first diagnostic test in the evaluation of pulmonary complaints/respiratory symptoms
 - May also show initial evidence of pulmonary disease in the absence of symptoms, e.g., pulmonary nodule found incidentally on chest x-ray
 - Not a confirmatory test for a diagnosis such as pleural effusion, interstitial lung disease, or nodule
- **Chest CT** (more detailed but there is a negligible risk of cancer)
 - Used to assess the mediastinum, pleura, and parenchyma
 - Cost-effective
 - Can be performed in the presence of metallic equipment (e.g., pacemaker) and is less sensitive to patient's movement
 - CT pulmonary angiography uses a rapid-timed infusion of IV contrast dye to enhance the imaging of the pulmonary vasculature during the bolus phase to assess for PE
 - Low-dose CT is used as a screening tool for lung cancer (USPTF guidelines), while high-resolution CT uses smaller slices and no contrast to assess for interstitial lung disease
- **PET scan** (functional imaging) provides a metabolic profile of lesions. It is usually compared with anatomical imaging (CT) to localize the metabolically active tissues.
 - Used to differentiate some benign lesions (e.g., scars) from pulmonary lesions that are malignant, infectious, or inflammatory
 - Cannot differentiate between malignant, infectious, and inflammatory lesions
 - Good for metabolically active tissue
 - Excellent at detecting disease in its early stages
 - Intensity of the FDG uptake can guide clinical decision-making (paired with CT, can localize FDG avidity by metabolically active cells)

Invasive Testing

- **Lung biopsy** allows microscopic examination and staining of a piece of the lung that may contain pathology.
 - Can be performed percutaneously (CT-guided), via bronchoscopy, or via surgery (open or VATS)
 - Indications include a peripheral pulmonary nodule where traditional bronchoscopy may not be able to reach the intended lesion
 - CT-guided biopsy (percutaneous transthoracic needle biopsy) allows real-time imaging via CT in conjunction with percutaneous needle biopsy to remove samples of lung tissue; has fewer complications than other procedures but caution in those with emphysema due to the increased risk of pneumothorax

- **Bronchoscopy** is an endoscopic technique used to visualize the inside of the airways and to perform procedures and biopsies. A device is inserted through the mouth, nose, or tracheostomy site along the walls of the airways.
 - **Flexible bronchoscopy (most common)** is helpful for the following:
 - BAL (collection of bronchoalveolar washings in the sub-segmental bronchi after infusion of saline into the alveoli); indications include non-resolving pneumonia, diffuse lung infiltrates (especially in immunocompromised patients), diffuse non-infectious pulmonary disease, and suspected alveolar hemorrhage.
 - Bronchial brushing to sample the lung (used most often in infection and malignancy evaluation)
 - Endobronchial biopsy
 - TBB (used to obtain a piece of lung tissue); associated with less morbidity and mortality than open biopsy. Indications are to diagnose lung nodules, pulmonary infections in immunocompromised patients, and acute allograft rejections in lung transplant patients.
 - FNA of a mediastinal lymph node
 - Endoscopic bronchial U/S (U/S in conjunction with a bronchoscope) to visualize the airway wall and surrounding structures; indications include staging of lung cancer, mediastinal lymphadenopathy, intrapulmonary nodules, and endobronchial lesions
 - **Rigid bronchoscopy** (usually performed in the OR) is helpful for foreign body removal and advanced airway management; complications include injury to lips, teeth and tongue, and pneumothorax (rare)
- **Open lung biopsy:** under general anesthesia, excision of lung tissue/lung lobe as needed; performed only after minimally invasive procedures have failed to yield a significant diagnosis; requires hospital stay and has complications
- **VATS:** minimally invasive lung biopsy similar to laparoscopy; indications are similar to those for lung biopsy, plus pulmonary decortication, pleurodesis, and lung/pleural biopsy

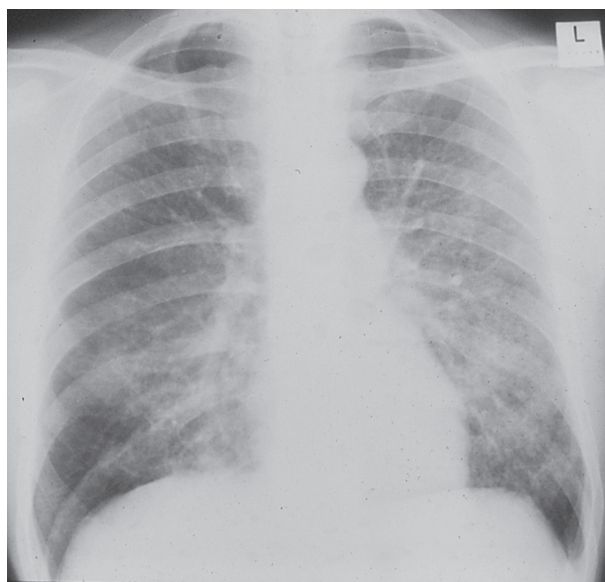


Figure 9-9. Bilateral Interstitial Infiltrates on Chest X-ray

Clinical Correlate

- PET scan is good for metabolically active tissue because this type of tissue needs glucose, and the tracer of a PET scan mimics glucose (hence ¹⁸F-fluorodeoxyglucose). The tracer gets taken up if the tissue is metabolically active.
- This explains why PET scan is used in cancer evaluation and staging.

**To describe a chest x-ray, use ABCDE:**

- **Airway**
 - Is the trachea shifted?
 - Look at the carina and the main stem bronchus.
- **Bone**
 - Fractures
 - Compression fracture of the spine (lateral view)
- **Cardiac and mediastinum silhouette**
 - Cardiomegaly, chamber enlargement
- **Diaphragm**
 - Look under it, through it, and above it
 - Where is the stomach bubble?
- **Everything else**
 - Lines and tubes
 - Lungs (one at a time)
 - Nodules
 - Markings: vascular (more central) and interstitial (more peripheral)

OBSTRUCTIVE LUNG DISEASE

The obstructive disease process leads to expiratory airflow limitation in patients. It may be reversible (asthma) or irreversible (COPD).

Asthma

A 26-year-old woman with a history of asthma presents to the ED with 3 days of progressive wheezing and shortness of breath after an upper respiratory tract infection. She is taking inhaled albuterol and an over-the-counter medication for her cold symptoms. Her respiratory rate is 28/min and pulse 110/min; she is afebrile. Her right nasal turbinate is edematous and erythematous. There is evidence of wheezing throughout both lungs, but no crackles are noted. Supplemental oxygen by nasal cannula is administered.

Asthma is characterized by inflammatory hyperreactivity of the airways (bronchial hyperreactivity) to various stimuli, resulting in reversible airway obstruction. Bronchial obstruction occurs as a result of mucosal inflammation, bronchial musculature constriction, and excessive secretion of viscous mucus plugs. The bronchial hyperreactivity occurs in an episodic pattern secondary to “triggers,” with interspersed normal airway tone.

Asthma can occur at any age but is usually seen in young people; about half outgrow their asthma by adulthood.

There are 2 types of asthma. Many patients have features of both types.

- **Extrinsic (allergic, atopic) asthma (very common)**
 - Results from sensitization
 - Total serum IgE concentration is elevated
 - Precipitated by allergens; other symptoms include allergic rhinitis, urticaria, and eczema
 - Prognosis is good; many new biological agents target moderate-to-severe persistent extrinsic allergic asthma
- **Intrinsic or idiosyncratic asthma (small number of cases)**
 - Bronchial reaction
 - Secondary to nonimmunologic stimuli, such as infection, drugs, irritating inhalants, cold air, exercise, or emotional upset

Asthma is a narrowing of the large and small airways caused by hypertrophy and spasm of bronchial smooth muscle, edema, inflammation of the bronchial mucosa, and mucus production.

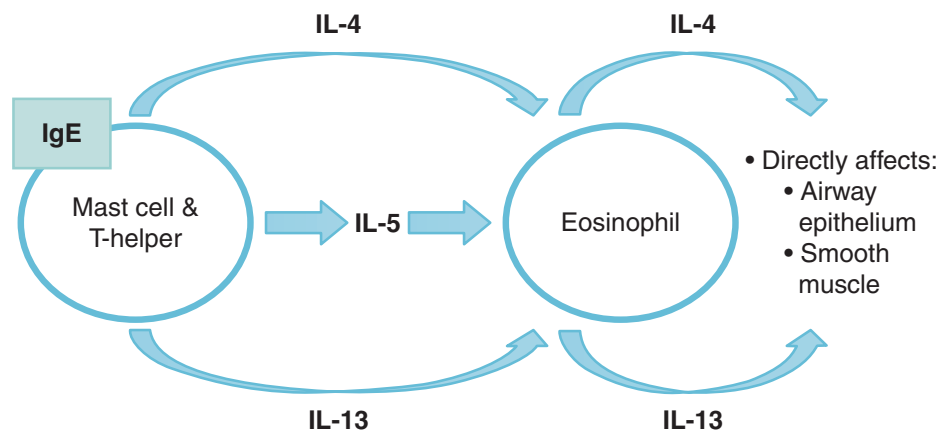


Figure 9-10. Pathway of Allergic Asthma

Clinical Presentation.

- Recurrent episodes of wheezing and chest tightness at night or early morning
- Slight tachypnea (increased respiratory rate), tachycardia, prolonged expirations, and mild, diffuse wheezing (mild attacks)
- Use of accessory muscles of respiration, diminished breath sounds, loud wheezing, hyper-resonance and intercostal retraction (severe attacks)
- Nocturnal cough and exercise-induced bronchospasm (seen in variants of asthma)

Note

Samter's triad includes asthma, nasal polyposis (causing recurrent sinus disease), and sensitivity to aspirin and NSAIDs.

Clinical Correlate

Cells thought to play an important role in the inflammatory response are those in both the innate and adaptive immune systems:

- Macrophages
- Mast cells
- Lymphocytes
- Eosinophils
- Specific interleukins (mainly IL-5, IL-4, IL-13)

**Note**

Variants of asthma include asthma presenting primarily with nocturnal cough and exercise-induced asthma (commonly tested on the exam).

Diagnosis is based primarily on the history and physical examination. Spirometry and/or full PFTs show an obstructive pattern that typically reverses with bronchodilation. Spirometry using FEV1 is not the best indicator of severity without a good history and physical examination.

- PFTs may be normal without bronchial hyperreactivity; in that case, a provocative challenge with methacholine, exercise, or histamine will show decreased FEV1 or FVC >20%
- FEV1 or FVC must show 12% and/or 200 mL reversibility with use of beta-2 adrenergic agonist
- Chest x-ray findings are nonspecific in an asthma exacerbation. They may be helpful in ruling out acute infection as the cause of the exacerbation.
- **Acute asthma:** ABG abnormalities consistent with tachypnea (decreased arterial carbon dioxide tension (PaCO_2), increased pH, normal PaO_2 (may be low with significant airway obstruction)
- **Severe asthma or status asthmaticus:** decreased PaO_2 , increased PaCO_2 , decreased pH
 - In an acute setting, bicarbonate is not usually elevated, but it does elevate with chronic respiratory acidosis.
 - In an acute setting, normal PaCO_2 may indicate the beginning of respiratory muscle fatigue.

Table 9-2. Asthma Classification

Asthma exacerbation: SABA as needed (3 doses/IV x 1 hr), $\text{SpO}_2 > 92\%$, IV fluids, ipratropium bromide, systemic glucocorticoids (impending respiratory failure), MgSO_4 if severity constant even after 1 hr of bronchodilatory therapy				
How to Classify?				Asthma Classification (age ≥ 12)
	Intermittent	Persistent		
		Mild	Moderate	Severe
Symptoms	$\leq 2\text{x/wk}$	$> 2\text{x/wk}$	Daily	Many times/day
Nighttime awakenings	$\leq 2\text{x/mo}$	3-4x/mo	$> 1\text{x/wk}$	4-7x/wk
SABA use frequency	$\leq 2\text{x/wk}$	$> 2\text{x/wk}$	Daily	Many times/day
Limitation of activities	None	Minor	Moderate	Major

Treatment. The foundation of treatment is bronchodilators, oxygen, steroids, and airway protection if unstable, and chronic outpatient therapy if stable.

Medical therapy is as follows:

- **Inhaled corticosteroids (mainstay of chronic asthma therapy in adults)** work by reducing airway inflammation
 - Review with patients the correct technique for inhaler use, including the use of spacers and mouth-rinsing to avoid oral candidiasis
 - Side effects include glaucoma, cataracts, diabetes, muscle weakness, and osteoporosis
- **Beta-adrenergic agonist inhalers** (used in acute and chronic asthma therapy) act on β_2 -adrenergic receptors to cause smooth muscle relaxation (bronchodilation)
 - Inhaled (metered-dose inhalers [MDIs]) are the preferred route because they allow maximal bronchodilation with minimal side effects)
 - Side effects include tremor and tachycardia (consider levalbuterol, especially if patient has Afib)
 - **Short-acting beta agonists (SABA)** (inhaled SABAs such as albuterol are the **mainstay of chronic asthma therapy**, usually used with inhaled corticosteroids)
 - All asthmatics should carry a SABA, to be used “as needed” for SOB or cough, up to 2 puffs every 4 hrs.
 - Use of SABA ≥ 3 days/wk indicates poor control of symptoms, and treatment should be intensified.
 - **Long-acting beta agonists (LABA)** (for moderate to severe persistent asthma, after initial therapy with SABA + inhaled corticosteroids, especially with a significant nocturnal component)
 - Not for use during acute exacerbation or for use alone (i.e., always use in conjunction with inhaled corticosteroids)
 - Inhaled LABAs, such as salmeterol and formoterol, have a sustained effect on bronchial smooth muscle relaxation
 - LABA monotherapy has numerous side effects and is associated with an increase in asthma-related deaths.
- **Anticholinergic drugs** (ipratropium bromide, tiotropium) act as antagonists to M3 receptors of smooth muscle in the airway
 - **Short-acting:** very effective for acute exacerbation of asthma in conjunction with beta 2 agonist
 - **Long-acting:** if symptomatic even after ICS/LABA therapy, add a LAMA
- **Leukotriene modifiers**
 - **Zileuton:** inhibits 5-lipoxygenase, the enzyme involved in leukotriene production (LTC₄, LTD₄, LTE₄)
 - **Montelukast** and **zafirlukast:** cysteinyl leukotriene-1 (CysLT₁) antagonists
 - Approved for severe asthma resistant to maximum doses of inhaled corticosteroids and as a last resort before using chronic systemic steroids
- **MAST cell stabilizers** (cromolyn sodium, nedocromil)
 - Inhibit release of contents of mast cells (mast cell degranulation); used for chronic asthma, not immediate asthma relief
 - Less effective than inhaled corticosteroids at preventing asthma exacerbation and reducing inflammation in adults and children

Note

With asthma, caution with aspirin/NSAIDs (due to possible Samter's Triad) and non-selective beta-adrenergic antagonists. Infections can trigger both intrinsic and extrinsic asthma (classic infections are RSV in children and rhinoviruses in adults).

Note

Neither short-acting nor long-acting beta 2 agonists address the inflammatory component of asthma.

**Note**

If a patient has contraindications to LABAs, LAMAs can be used instead.

Note

Methylxanthines (theophylline, aminophylline) are seldom used in asthma and are usually the wrong answer on the exam.

Note

Bronchodilators do not address the inflammatory component of asthma.

- **Biologics** (reserved for moderate to severe persistent allergic asthma that is refractory to traditional inhalers and patient is oral-steroid-dependent)
 - **IgE antibody:** omalizumab (indicated for elevated IgE in both children and adults); an injectable medication administered in a health care setting due to the risk of anaphylaxis (patient must carry an EpiPen at all times); dosing is based on symptoms (not IgE level), usually every 3–4 weeks
 - **IL-5 inhibitors:** mepolizumab, benralizumab, and reslizumab (indicated for elevated eosinophils noted on patient's CBC); work as antibodies that bind and inactivate interleukin-5, which leads to the activation of eosinophils
 - **IL-4 and IL-13 inhibitors:** dupilumab, an at-home injectable medication indicated for elevated eosinophils on CBC and when patient cannot taper off steroids

Severe persistent allergic asthma refractory to inhalers is treated with monoclonal antibody drugs.

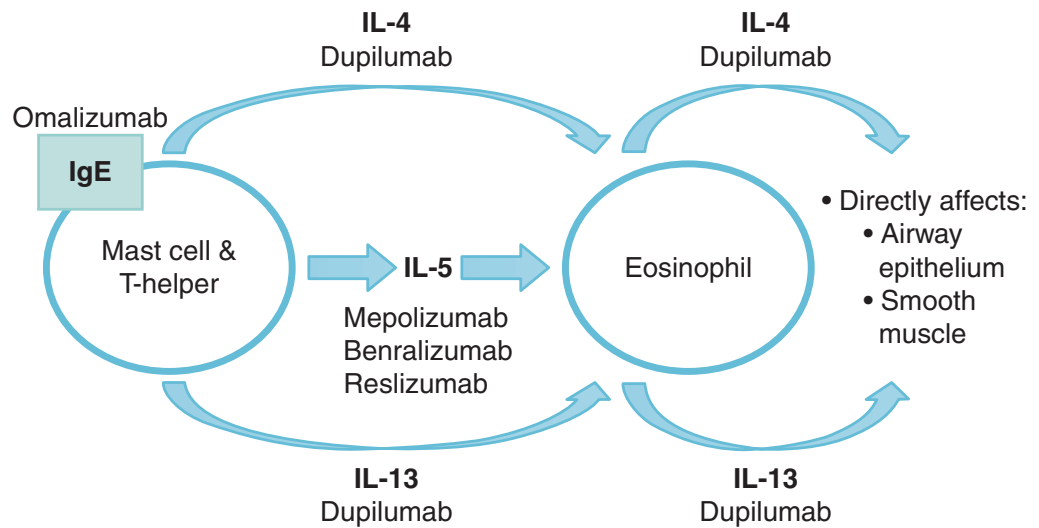


Figure 9-11. Mechanism of Action of Biologic Drugs Used in Persistent Allergic Asthma

Avoid corticosteroids in the management of chronic asthma when possible. Remember the side effects with CUSHINGOID.

- **C:** cataracts/candidiasis (oral, through improper use of ICS)
- **U:** ulcers
- **S:** striae, skin thinning
- **H:** hypertension, hirsutism
- **I:** immunosuppression, infections
- **N:** necrosis of femoral heads
- **G:** glucose elevation
- **O:** osteoporosis, obesity
- **I:** impaired wound healing
- **D:** depression/mood changes

During the exam, you must distinguish whether the question is asking about acute asthma management or chronic asthma. Some general guidelines are as follows:

- Management of **acute exacerbations**
 - Inhaled (preferably nebulized) beta 2 agonist (e.g., albuterol) and anticholinergics (e.g., ipratropium)
 - Oxygen as needed to maintain $\text{SpO}_2 \geq 92\%$
 - IV fluids (normal saline) as needed for hypotension
 - Systemic glucocorticoids (e.g., methylprednisolone, dexamethasone); route of administration depends upon clinical severity
 - If no response to initial treatment, use a one-time infusion of magnesium sulfate (modest evidence of benefit and low likelihood of harm)
 - Transfer all patients to an appropriate care setting based upon clinical presentation, with a low threshold for ICU monitoring
- Management of **chronic asthma**
 - Non-pharmacological/lifestyle measures
 - Avoid triggers (crucial but can be difficult to identify triggers)
 - Remove (or minimize contact with) environmental irritants and allergens, such as pets and dust
 - Involve patients by using an action plan for self-triage: green zone when asthma under control; yellow zone when asthma not well-controlled; and red zone when asthma out of control and needs emergent medical attention



There are 3 pathologies associated with asthma.

- **EGPA** (eosinophilic granulomatosis with polyangiitis)
 - Common in men, age 20–40
 - Small-and-medium vessel vasculitis with rhinosinusitis, asthma (90% of EGPA patients have asthma), and eosinophilia; peripheral neuropathy (mononeuritis multiplex); GI/respiratory tract involvement
 - Labs show elevated IgE, p-ANCA positive (antibodies directed against myeloperoxidase)
 - Treatment: steroids, mepolizumab (newly approved IL-5 blocker)
- **CEP** (chronic eosinophilic pneumonia)
 - Common in women, age 30–40
 - Asthma (50% of cases)
 - Labs show peripheral blood eosinophilia (unlike acute eosinophilic pneumonia, where eosinophils can be normal) and elevated IgE
 - Treatment: steroids (use long taper, as relapse is common)
- **ABPA** (allergic bronchopulmonary aspergillosis)
 - Non-invasive allergic lung reaction to a fungus (commonly *Aspergillus fumigatus*)
 - Rather than invading the lung tissue and destroying it, the fungus colonizes the mucus in the airways of patients with asthma or CF (both conditions have increased mucus) and causes allergic inflammation in the lung
 - Diagnosed with major and minor criteria
 - Bronchiectasis and scarring if extensive damage has occurred
 - Treatment: oral steroids; antifungals (steroid-sparing agents), omalizumab (for patients with elevated IgE and taking steroids)

Diagnostic Criteria for ABPA

- Predisposing conditions (**one must be present**): asthma or CF
- Major criteria (**both must be present**): *aspergillus* skin test positivity or detectable IgE levels against *A. fumigatus* and elevated total serum IgE concentration (typically >1,000 IU/mL, but <1,000 IU/mL may be acceptable if patient meets all other criteria)
- Minor criteria (**≥2 must be present**)
 - Precipitating serum antibodies to *A. fumigatus*
 - Radiographic pulmonary opacities consistent with ABPA
 - Total eosinophils >500 cells/microL in glucocorticoid-naïve patients (may be historical)

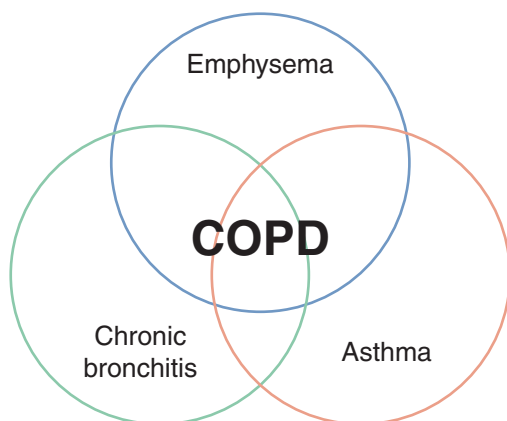
Chronic Obstructive Pulmonary Disease

A 67-year-old woman with COPD is evaluated for dyspnea that occurred the prior day. She denies fever and chills but has noted productive cough. Her medications include ipratropium MDI. Her respiratory rate is 32/min and pulse 106/min; she is afebrile. She looks cachectic and is breathing fast. You note an increased anteroposterior diameter, distant heart sounds, and expiratory wheezing.

Chronic obstructive pulmonary disease (COPD), a common condition with high morbidity and mortality, is an umbrella term to describe emphysema (pink-puffer), an anatomic/histologic diagnosis, chronic bronchitis (blue bloater), a clinical diagnosis (cough, and sputum >3 months in 2 successive years), asthma and COPD overlap syndrome (ACOS), and bronchiectasis.

COPD should be considered in anyone with dyspnea, chronic cough with sputum production, and/or a history of exposure to risk factors for the disease. There are 2 main etiologies:

- **Smoking** (80–90% of cases)
 - COPD symptoms usually begin after 20 pack-years of tobacco exposure; 10–15% of smokers develop COPD
 - Number of pack-years of smoking often correlates to reduction of FEV1
- **Non-smoking** (10–20% of cases)
 - Air pollution, airway infections, and allergies can lead to bronchitis
 - Alpha 1-antitrypsin deficiency, a rare hereditary autosomal recessive disease, can cause emphysema and liver abnormalities



Note

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) has developed a system for categorizing COPD severity according to frequency of symptoms, severity, and risk of exacerbations.

You will not need to memorize these categorizations for the exam.

Note

COPD is the only cause of death among the top 5 in the United States that is increasing in frequency. It is a leading cause of death worldwide.



After long-term exposure to cigarette smoke, inflammatory cells are recruited in the lung.

- The inflammatory cells in turn secrete proteinases, which may lead to destruction of the acinus (lung structures distal to the terminal bronchiole, including alveolar ducts, alveolar sacs, and alveoli).
- Alpha-1 antitrypsin can combat these proteinases, explaining the early emphysema in patients with alpha-1 antitrypsin deficiency.
- Over time, decreased elastic recoil (mainly with emphysema) and increased airway resistance (mainly with chronic bronchitis) occur.
- The chronic inflammation causes structural changes, small airways narrowing, and destruction of lung parenchyma.

Symptoms of COPD include cough, sputum production, and dyspnea on exertion (all common). Daily sputum production may precede the dyspnea by many years.

Diagnosis requires spirometry with post-bronchodilator FEV1/FVC <0.70.

- Chest x-ray is essential in evaluating SOB and other pulmonary symptoms but is neither sensitive nor specific for diagnosing COPD and does not reliably reflect the severity of the disease.
- Classic findings of emphysema include hyperinflation; flattening of diaphragm (lateral view); and widening of retrosternal airspace (lateral view) on PA and lateral chest x-ray).

Treatment begins with education about smoking cessation and COPD, and then as follows:

- **Acute exacerbation**

- Systemic glucocorticoids: oral prednisone when urgent admission not required
- Inhaled short-acting bronchodilator therapy (alternatives include a short-acting anticholinergic agent, e.g., ipratropium alone or in combination with a SABA)
- Antibiotics if bacterial bronchitis or pneumonia is suspected
- Supplemental oxygen titrated to target 90–92% SpO₂ when there is hypoxia due to an exacerbation of COPD
- Noninvasive ventilation (NIV) (e.g., BiPAP); if NIV contraindicated, consider invasive mechanical ventilation

- **Chronic management** (pulmonary rehabilitation improves symptoms, exercise capacity, and quality of life)

- SABA, SAMA, or both to relieve intermittent increases in dyspnea
- If symptoms persist, LABA, LAMA, or both
- If symptoms still persist, inhaled corticosteroids to decrease exacerbations and slow progression of respiratory symptoms (but have little impact on lung function)
 - Start at same time as a LABA if there are signs of inflammation or asthmatic component to the COPD
 - Side effects include dysphonia, skin bruising (elderly patients), oral candidiasis (at higher doses), increased incidence of pneumonia and cataracts, and diminished bone density (at higher doses)

- Long-term oxygen therapy for COPD patients with chronic hypoxemia (resting arterial oxygen tension (PaO_2) ≤ 55 mm Hg or pulse oxygen saturation (SpO_2) $\leq 88\%$)
- Yearly influenza vaccine, pneumococcal polysaccharide vaccine, and conjugate pneumococcal vaccine (for those age >65)
- Roflumilast: phosphodiesterase-4 inhibitor to prevent future exacerbations in severe COPD, particularly in those who experienced ≥ 1 exacerbation in the past year and have predominantly chronic bronchitis phenotype
- Azithromycin to prevent future exacerbations and improve quality of life
 - Use caution, as a side effect of azithromycin is slightly increased risk in cardiovascular death
 - Risk is highest among those with a high baseline risk of cardiovascular disease

The main interventions that have been shown to decrease mortality in COPD are **home oxygen** and **smoking cessation**; however, consider lung volume reduction surgery and lung transplant in selected patients.

- Home oxygen therapy (goal is to maintain O_2 saturation $>90\%$, especially at night when patients desaturate)
 - Use for patients with hypoxemia ($\text{PaO}_2 < 55$ mm Hg or saturation $< 88\%$)
 - Use for patients with cor pulmonale (right-sided heart failure) when $\text{PaO}_2 < 59$ mm Hg
 - Use intermittent oxygen for patients who desaturate with exercise
- Tobacco cessation: slows progression of COPD and slows decrease in FEV1
- Lung volume reduction surgery (proven to prolong survival only in patients with mainly upper-lobe emphysema and poor exercise capacity)
 - Removal of ruined areas of the lung in an attempt to reduce hyperventilation (reduction of dead space) and improve chest wall and diaphragm dynamics
 - Endobronchial valves are newly-approved, minimally-invasive, bronchoscopically implanted devices that permit exhalation and drainage of secretions but prevent air entry during inspiration
- Lung transplant (proven to prolong survival in patients with COPD)
 - Substantial improvement in exercise tolerance and quality of life
 - Transplant recipients are at risk for infection secondary to immunosuppression, toxic effects of immunosuppressant drugs, and acute and chronic rejection of the lung allograft
 - Single or double lung transplants are possible

Returning to our patient in the vignette, she is likely to have a decreased DLCO on her PFTs. Treatment of her acute exacerbation would be with systemic steroids, antibiotics, and bronchodilators, with O_2 as needed. Treatment when she goes home will include an ipratropium inhaler and home O_2 (if she has chronic hypoxemia). The severity of her disease should be assessed by measuring FEV1.



Bronchiectasis

A 17-year-old girl is admitted to the hospital with a right lower lobe pneumonia. She provides a history of recurrent pneumonias, some of which have kept her in the hospital for weeks, and of chronic productive cough that occurs every day. Her parents add that she has had “loose stools” since childhood. On examination she is found to be thin and in distress. There are diminished breath sounds on the right lower lobe with rhonchi.

Note

Bronchi means airways of the lung, and *ectasis* means an organ that is enlarged or dilated.

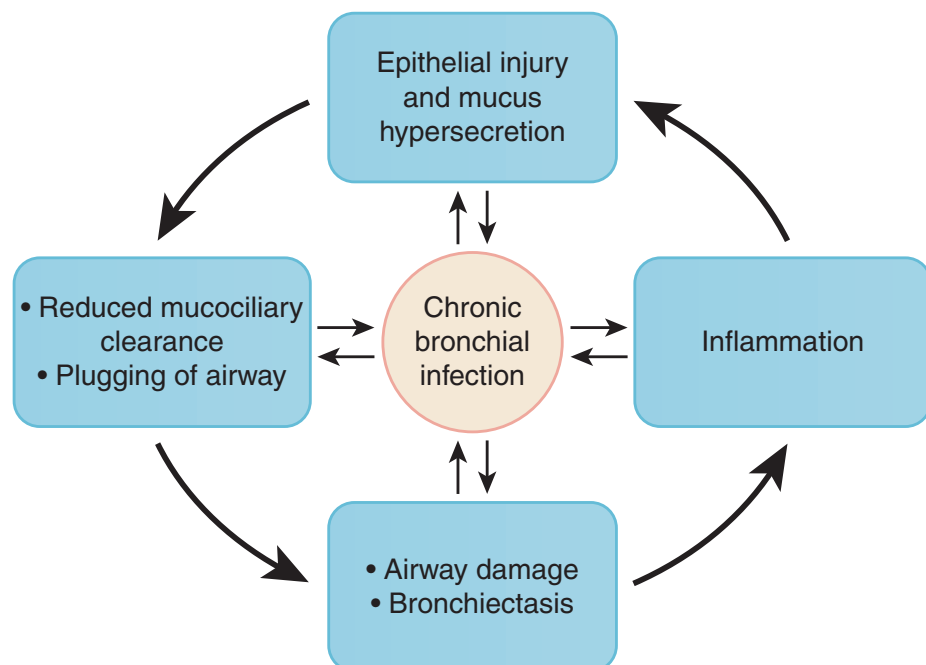
Clinical Correlate

Neutrophil elastase is known as one of the most destructive enzymes in the body.

Bronchiectasis means “dilated airways,” meaning the permanent dilation of small- and medium-sized bronchi resulting from destruction of bronchial elastic and muscular elements with eventual fibrosis of the bronchi. The progressive airway destruction may be related to the unopposed activity of neutrophil elastase (usually balanced by α_1 -antitrypsin activity).

The cause of bronchiectasis is recurrent pulmonary infection. Immune deficiency can play a role. Clinical features include:

- Chronic cough
- Copious, viscid sputum production that is foul-smelling
- Airway dilation (honeycombing)
- Bronchial wall thickening (tram-tracks)
- Significant history of recurrent pneumonia that commonly involves gram-negative bacteria (especially *Pseudomonas species*)



The etiologies of bronchiectasis are CF and non-cystic fibrosis.

Cystic fibrosis bronchiectasis

Cystic fibrosis (CF) is a multisystem disorder caused by mutations of the CF transmembrane conductance regulator (CFTR) gene. A small number of patients present with CF in early adulthood. Pulmonary disease is the most common cause of morbidity and mortality.

- Symptoms include diffuse bronchiectasis; chronic productive cough (especially if there is a history of recurrent sinusitis, nasal polyps, and weight loss); infertility in men
- Symptoms are consistent with CF in ≥ 1 organ system PLUS evidence of CFTR dysfunction (elevated sweat chloride or evidence of disease-causing mutations in CFTR)
- Treatment: CFTR modulators (ivacaftor, tezacaftor-ivacaftor); airway clearance therapies (inhaled airway clearance agents [dornase alfa, hypertonic saline], chest physiotherapy, exercise); bronchodilators (inhaled β_2 agonists, anticholinergics); anti-inflammatory agents (azithromycin, ibuprofen); lung transplant if no response
- Prevention of infection: vaccination (influenza and Pneumococcal), palivizumab (humanized monoclonal antibody against RSV), and other general precautions

Non-cystic fibrosis bronchiectasis

Non-CF is a focal bronchiectasis caused by infection, impairment of drainage, airway obstruction, and a possible defect in host immune response. Causes include:

- Local infection (recurrent gram-negative infection, TB, other mycobacterial infections, fungal infections, *Nocardia*); lung abscess; or pneumonia
- Chronic inflammatory disease, e.g., Sjogren syndrome, SLE, rheumatoid arthritis
- Inadequate clearance of secretions: mucous plugging (primary ciliary dyskinesia, Young syndrome); anatomic bronchial defects; bronchial obstruction: intraluminal obstructing lesion from a cancer or mass; immunosuppression
- Genetic: alpha-1 antitrypsin deficiency (current guidelines recommend testing in patients with bronchiectasis and no other evident etiology)

Diagnosis.

- Chest x-ray: early findings may be normal, while advanced cases may show 1- to 2-cm cysts and thickened airways (tram-tracking, i.e., appear like rings on cross-section); radiologic classifications of bronchiectasis include:
 - Cylindrical
 - Varicose
 - Cystic (or saccular)
- Chest CT to confirm; may show signet-ring appearance, tram-track lines and honeycombing
- A normal sweat chloride result is usually sufficient to rule out CF.

Note

In Young syndrome, patients have no evidence of CF but they do have bronchiectasis, sinusitis, and obstructive azoospermia. Possible causes include childhood exposure to mercury or misidentification of primary ciliary dysfunction.

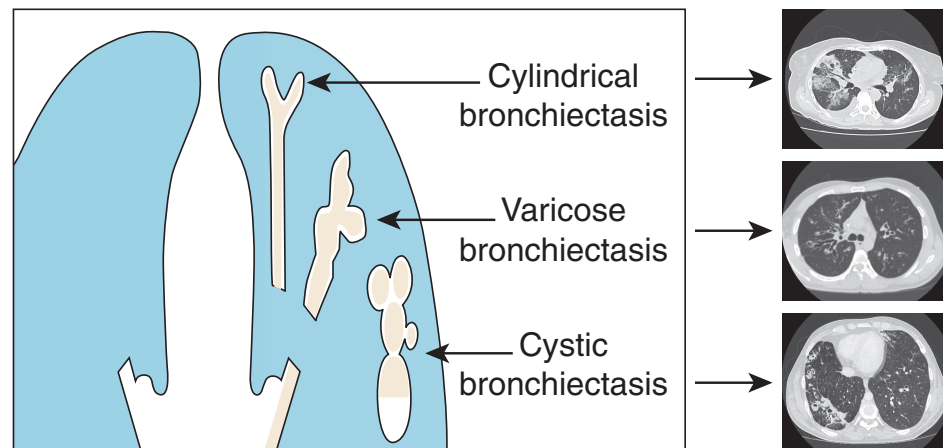


Figure 9-12. Radiology of Bronchiectasis

Treatment is conservative at first, treating the underlying cause and giving antibiotics when sputum production increases or symptoms are mild. Chest physiotherapy and postural drainage can control/improve drainage of bronchial secretions.

- Antibiotics to cover gram-negative bacteria if significant symptoms or pneumonia
- Hemoptysis: CT chest and bronchoscopy may help localize the site of bleeding; for brisk hemoptysis, bronchial artery embolization or resection surgery may be required
- Prevention with annual vaccination for influenza; pneumococcal vaccine (Pneumovax 23 and/or Prevnar 13); long-term, low-dose macrolide for patients who have >2 bronchiectasis exacerbations/year to prevent bacterial infection

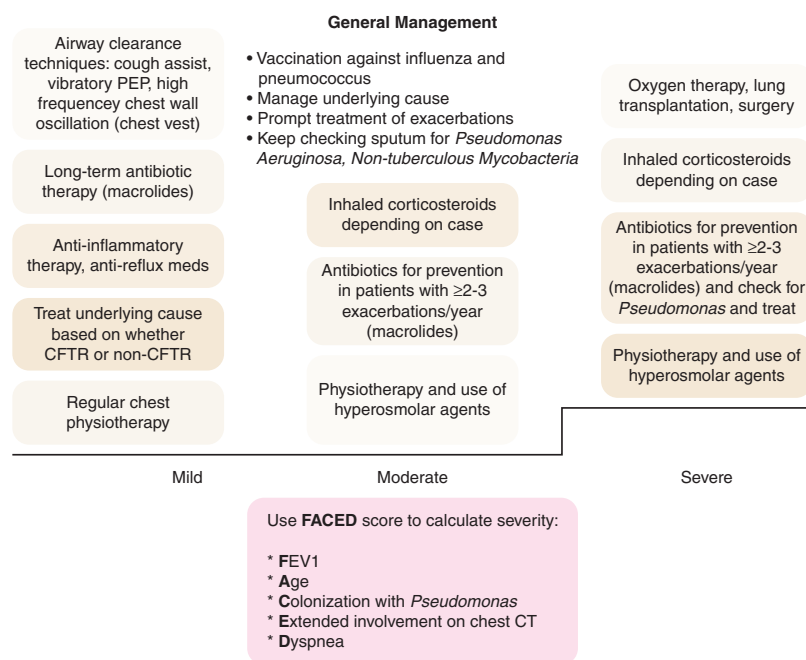


Figure 9-13. Treatment of Bronchiectasis

Going back to our earlier patient, treatment would include antipseudomonal antibiotics (ciprofloxacin, ceftazidime). Based on her history, consider a chloride test to diagnose CF.

Clinical Recall

A 17-year-old boy presents with an acute asthma attack. Which of the following patterns will be seen on an arterial blood gas?

- A. PaCO_2 decreased, pH increased, PaO_2 normal
- B. PaCO_2 decreased, pH decreased, PaO_2 increased
- C. PaCO_2 increased, pH decreased, PaO_2 decreased
- D. PaCO_2 increased, pH increased, PaO_2 increased

Answer: A

RESTRICTIVE LUNG DISEASE

Restrictive lung disease is caused by restriction of lung expansion due to extrinsic (extra-pulmonary) and intrinsic (parenchymal) pulmonary disease. On PFTs, restrictive lung disease is defined as a reduced TLC, a decrease in the forced vital capacity and FEV1 with a normal FEV1/FVC ratio.

A **normal** DL_{CO} implies **extrinsic** restrictive lung disease, while a **decreased** DL_{CO} implies **intrinsic** restrictive lung disease.

- **Extrinsic** restriction
 - Anatomical diseases: pectus carinatum, pectus excavatum
 - Musculoskeletal diseases: ankylosing spondylitis, kyphosis, scoliosis
 - Neuromuscular diseases: myasthenia gravis, Lambert-Eaton syndrome, ALS
 - Diseases restricting volume: obesity, pneumothorax, pleural effusion
- **Intrinsic** restriction (caused by interstitial lung disease)

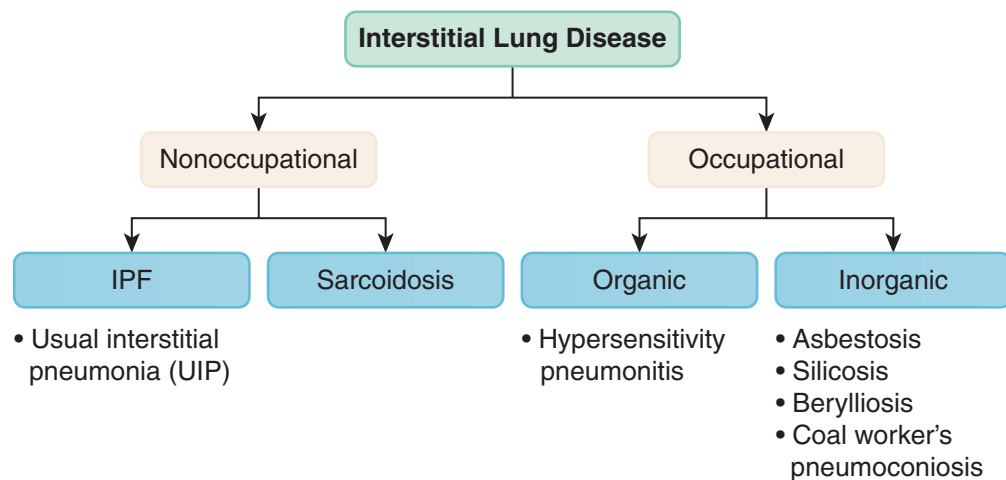


Figure 9-14. Interstitial Lung Disease

Interstitial Lung Disease

Interstitial lung disease (ILD) (or diffuse parenchymal lung disease) inflames or scars the lungs. The scarring can lead to stiffness, which in turn can make it difficult to breathe. The interstitium (supporting structure) of the lung is the tissue around the small blood vessels and alveoli.

The various interstitial lung conditions are characterized by chronic inflammation and fibrosis of the interstitium that eventually extends into the alveoli and disrupts normal gas exchange.

Symptoms include exertional dyspnea (**most common**), nonproductive cough, coarse crackles, evidence of pulmonary hypertension (increased pulmonic sound, right heart failure), and possible clubbing.

Diagnosis.

- Chest x-ray will show reticular, nodular, or reticulonodular pattern
- High resolution CT will show “ground glass” pattern and honeycombing in cases of UIP/IPF and chronic HP
- PFTs will show intrinsic restrictive pattern
- Lung biopsy if needed: bronchoscopy or open lung

Occupational interstitial disease

History is of primary importance in assessing occupational lung disease. Causes include inhalation of dust/fibers (which initiates an inflammatory process that leads to fibrosis of the lung and eventual respiratory insufficiency); organic etiologies; and inorganic etiologies.

Organic etiologies include **hypersensitivity pneumonitis (HP)** (or extrinsic allergic alveolitis), a complex syndrome of varying intensity, clinical presentation, and natural history.

- Symptoms include:
 - **Acute HP:** abrupt onset (hours following exposure) of fever, chills, malaise, nausea, cough, chest tightness, and dyspnea; first step is to remove exposure to the inciting antigen
 - **Subacute HP:** develops gradually with a productive cough, dyspnea, fatigue, anorexia, and weight loss; respiratory impairment more pronounced than with acute HP
 - **Chronic HP:** insidious onset of cough, dyspnea, fatigue, and weight loss; possible irreversible respiratory findings due to PF may be present, which is difficult to differentiate from idiopathic PF
- Pathology: poorly formed granulomas or multinucleated giant cells; chronic cellular pneumonitis with patchy lymphocytic infiltration; in chronic HP, lung pathology may resemble usual interstitial pneumonitis/IPF but with occasional granulomas or multinucleated giant cells
- **Diagnosis:** exposure history, clinical/physiologic findings, and patient's response to removal of the inciting agent; specific antibodies (precipitins) have a high false-negative rate, and positive results can be seen in exposed but asymptomatic patients; high-resolution CT shows characteristic mid-to-upper zone ground-glass or nodular opacities; BAL may confirm the diagnosis of hypersensitivity pneumonitis (a marked BAL lymphocytosis is supportive but not diagnostic)
- **Treatment:** antigen/allergen avoidance and corticosteroids (for acute); supportive care; vaccinations; pulmonary rehabilitation; long-term supplemental O₂; corticosteroids with possible steroid-sparing agents; lung transplantation evaluation (for chronic)

Inorganic etiologies include

- **Asbestosis** (pulmonary disease): parenchymal fibrosis caused by prolonged exposure >10 years to asbestos; latency period can be >30 years
 - Diagnosis: history of exposure; dyspnea on exertion (**most common complaint**); restrictive PFTs with reduced DLCO (**classic pattern**); basilar crackles with or without clubbing; radiographic lower lobe fibrosis
 - Look for ferruginous bodies (or asbestos bodies) but their presence only confirms exposure
 - Lung biopsy usually not required
 - Treatment: no effective therapy
- **Silicosis:** caused by inhalation of silica dust; seen in mining, tunneling, glass/pottery manufacturing; silica causes inflammatory reactions; symptoms are similar to asbestosis and any other pneumoconioses (except acute silicosis, caused by massive exposure, can cause lung failure in months)
 - Pathologic lesion is hyaline nodule
 - Diagnosis is made clinically; bronchoscopy with TBB and lung biopsy are confirmatory tests but are seldom done; chest x-ray will show nodules (1–10 mm) throughout the lungs but mostly in upper lobes; eggshell calcifications (rare); in progressive massive fibrosis, densities are ≥ 10 mm and coalesce into large masses
 - Treatment: no effective therapy; death eventually occurs because of progressive respiratory insufficiency

Note

Do not confuse **asbestosis with asbestos exposure**, which causes bilateral mid-thoracic pleural thickening/plaque/calcification formation.

In **asbestos exposure:**

- Chest x-ray will show diaphragmatic calcifications with sparing of the costophrenic angle, pleural plaques, and pleural thickening (completely benign).
- Benign asbestosis pleural effusion (BAPE) can present with a bloody effusion.
- 35% of cases have eosinophilia of pleural fluid
- Malignant mesothelioma, a tumor arising from mesothelial cells of the pleural plaques (80% of cases are associated with asbestos exposure)



- **Coal worker's pneumoconiosis (CWP)** (or black lung disease): caused by inhalation of large amounts of coal dust
 - Diagnosis: chest x-ray will show small, round densities in parenchyma, usually involving upper half of lungs; in complicated/progressive massive fibrosis, there are larger densities, from 1 cm in diameter to an entire lobe
 - When accompanied by joint inflammation and lung nodules, it is called rheumatoid pneumoconiosis or Caplan syndrome
 - Dust from the grinding of metal/rock enters the lungs, causes inflammation, and forms small lumps, leading to airway disease.
 - When someone breathes in inorganic dust, the immune system is affected and can lead to RA (where body's immune system attacks healthy body tissue by mistake).
 - When someone who already has RA is exposed to mineral dust, it can lead to rheumatoid pneumoconiosis.
 - Treatment: no effective therapy
- **Berylliosis** (or chronic beryllium disease) is a cell-mediated immune response (non-caseating granulomas of the lung) caused by exposure to even slight amounts of beryllium (high tech electronics, alloys, ceramics, pre-1950 fluorescent lights)
 - Clinically looks identical to sarcoidosis
 - Affects the upper lobes (like silicosis, TB, CWP), hilar lymphadenopathy common
 - Diagnosis: beryllium lymphocyte proliferation test (blood or BAL) (also used as surveillance tool for those who are sensitized)
 - Treatment: corticosteroids

Clinical Recall

A 65-year-old man complains of progressive difficulty breathing for 6 months. He has a 30-pack-year smoking history and is suspected of having COPD. Which of the following is the best initial management?

- A. Antibiotics
- B. Chest CT
- C. Pulse oximetry
- D. PFTs

Answer: C

Non-occupational interstitial disease

For the purposes of exam, there are 2 main types of non-occupational disease: idiopathic pulmonary fibrosis and sarcoidosis.

- **Idiopathic pulmonary fibrosis (IPF)**

- Lungs become scarred and over time breathing becomes difficult
- Etiology unknown
- Main risk factors are GERD (up to 90% of patients with IPF have GERD) and chronic micro-aspiration
- Symptoms include progressive exercise intolerance and dyspnea, coarse dry crackles (“Velcro-type rales”) on auscultation, and clubbing
- Chest x-ray will show reticular or reticulonodular disease; high-res CT will show extensive fibrosis with honeycomb pattern (referred to as a classical UIP pattern in which a biopsy is not indicated); PFTs will show restrictive intrinsic pattern; ABG will show A-a gradient widening
- Histopathology: heterogeneous appearance with alternating areas of normal lung, interstitial inflammation, fibroblast foci, and honeycomb changes
- **Diagnosis:** one of exclusion, after ruling out occupational exposure and drugs (bleomycin, amiodarone, methotrexate); tissue biopsy needed only if UIP is probable or indeterminate or if non-IPF diagnosis
- **Treatment:** supportive; consider pirfenidone (small-molecule with anti-fibrotic effects) or nintedanib (inhibitor of receptor tyrosine kinases) (equally effective; do not use both drugs together); lung transplantation (**definitive treatment**)
 - For acute IPF therapy, use a broad-spectrum antibiotic, high-dose glucocorticoid, and a cytotoxic agent (e.g., azathioprine)
 - For chronic IPF therapy, do not use glucocorticoid monotherapy or combination therapy of azathioprine, prednisone, N-acetylcysteine

- **Sarcoidosis**

- Systemic disease characterized by the presence of non-caseating granulomas; in United States, commonly seen in African Americans and those age 20–40; etiology is unknown
 - Lung involvement (**most common**; 90% of cases)
 - Skin manifestations (common): lupus pernio, erythema nodosum, non-scarring alopecia, and papules
- Two distinct sarcoid syndromes
 - **Lofgren syndrome** (acute): erythema nodosum, arthritis, hilar adenopathy
 - **Heerfordt-Waldenstrom syndrome** (subacute to chronic): fever, parotid enlargement, uveitis, facial palsy
- **Diagnosis** begins with exclusion of other granulomatous diseases: hypersensitivity pneumonitis, berylliosis, infectious disease caused by mycobacteria and fungi
 - Hilar and left paratracheal adenopathy (**most common presentations, even in an asymptomatic patient**)
 - Pathology will show demonstrate noncaseating granulomas that are negative for both malignancy and infection

Note

GERD is an important risk factor for the progression of IPF. However, the classic symptoms of GERD are poor predictors of increased esophageal acid exposure seen in those with moderate/severe IPF.



- When indicated, biopsy the most accessible lesion to confirm diagnosis; since many sarcoid patients have lung involvement, this is oftentimes the initial organ to biopsy via bronchoscopy with TBB +/- EBUS
- If patient has pulmonary complaints, start with chest x-ray
- **Treatment:** glucocorticoids (mainstay of treatment for active disease)
 - Three organs always treated are eyes, heart, and CNS
 - The lungs, even though they are the most common organ involved in sarcoidosis, do not always have to be treated; for example, if patient is asymptomatic with mediastinal adenopathy, surveillance is sufficient
 - If patient is unable to taper off steroids or worsens on steroids, use steroid-sparing agents (see Rheumatology chapter)

Sarcoidosis: Clinical Presentation

- Schaumann calcifications
- ACE levels elevated
- Respiratory complications/renal calculi/restrictive cardiomyopathy
- Calcium increase in serum and urine/CD4 helper cells (CD4/CD8 ratio >2 in early disease)
- Ocular lesions
- Immune-mediated noncaseating granulomas
- Diabetes insipidus/1-25 vitamin D increase
- Osteoporosis/Osteopenia early (prednisone therapy) in some patients
- Skin (erythema nodosum, lupus pernio, granulomatous lesions)
- Interstitial lung fibrosis
- Seventh cranial nerve palsy (Heerfordt-Waldenstrom syndrome)

Table 9-3. Medications Used in Sarcoidosis

Medication	Mechanism of action/Side effects
Methotrexate (MTX)	• Works by inhibiting purine synthesis by inhibiting dihydrofolate-reductase • Given orally or intramuscularly (for refractory nausea) • Always check for HBsAg and HCV antibody before initiating • Patient must take folic acid or leucovorin while on MTX
Azathioprine	• Dosing is weight-based • Toxicity is largely related to its metabolites, which are broken down by the enzyme TPMT (thiopurine-S-methyltransferase)
Leflunomide	• Works by inhibiting pyrimidine synthesis • Side effects include nausea, diarrhea, abdominal pain, hepatotoxicity
Antimalarials	• Chloroquine and hydroxychloroquine have immunomodulating properties • Mainly for cutaneous sarcoidosis; also used for hypercalcemia because it decreases 1,25 dihydroxy vitamin D • Always check G6PD level before initiating • Side effects include irreversible retinopathy and blindness (require exam at baseline and q 6–12 mos)
Mycophenolate mofetil	• Inhibitor of lymphocyte proliferation and activity • Used to treat a variety of ILDs associated with rheumatic disease • Side effects include nausea and diarrhea (may be dose limiting)
Corticotropin injection	• FDA-approved for symptomatic refractory sarcoidosis usually after prednisone and one other cytotoxic agent have failed to respond • Works on a steroid-dependent pathway and a non-steroid dependent pathway through melanocortin receptors
TNF-inhibitors	• Only infliximab and adalimumab used for sarcoidosis • Always check for latent TB, hepatitis B, and hepatitis C before initiating

OTHER PULMONARY CONDITIONS

Atelectasis

A 62-year-old man is dyspneic 24 hours after cholecystectomy. His respiratory rate is 22/min and pulse 112/min. He has a mild fever, and decreased breath sounds are noted in the left lower lobe. Complete blood count shows leukocytosis 27,000/mm³.



Atelectasis is the collapse of lung tissue. It can be acute or chronic. It is most commonly seen in the immediate postoperative period, often secondary to poor inspiration or lack of coughing. It can also be caused by a mucous plug, tumor, or foreign body.

Symptoms in acute disease include tachycardia, dyspnea, fever, and hypoxemia. In chronic disease patients may be asymptomatic, with only x-ray abnormalities.

Diagnosis is made with chest x-ray:

- **Upper lobe** atelectasis: tracheal deviation to affected side (occurs secondary to volume loss from atelectasis)
- **Lower lobe** atelectasis: elevation of corresponding part of the diaphragm
- **Massive** atelectasis: mediastinal shift to affected side (atelectatic lobe will appear densely consolidated and smaller than normal lobe)

Treatment is deep breathing and coughing (post-operative phase), plus incentive spirometry and pulmonary hygiene for airway clearance.

For massive atelectasis that cannot be managed with minimally invasive airway clearance, do a bronchoscopy with subsequent removal of the mucous plugs.

Pleural Effusion

A 67-year-old man presents with complaints of dyspnea and pleuritic chest pain that have worsened over the past month. He has also noticed weight loss of 20 pounds and low-grade fever during this time. On physical examination his respiratory rate is 24/min, and you find decreased air entry in the right lower lobe with dullness to percussion. Chest x-ray shows a pleural effusion involving about one-third of the lung field. A decubitus x-ray shows layering of the fluid.

Pleural effusion is the accumulation of fluid in the pleural cavity.

- **Transudative effusion**
 - Caused by increased hydrostatic pressure (e.g., CHF) or decreased oncotic pressure (e.g., nephrotic syndrome or cirrhosis)
 - Because conditions are **systemic**, they cause bilateral and equal effusion
 - No further evaluation needed, as it resolves with adequate treatment of primary disease
- **Exudative effusion** is caused by pneumonia, malignancy, or TB; conditions are **local**, so cause unilateral effusion; further investigation required to treat underlying disease.
 - Caused by pneumonia, malignancy, or TB
 - Because conditions are **local**, they cause unilateral effusion
 - Further evaluation needed to treat underlying disease

Symptoms of pleural effusion include SOB and pleuritic chest pain (sharp pain that worsens with breathing), secondary to the pleural effusion weighing down the diaphragm; most patients are not hypoxic despite a considerable effusion.

Note

- On the exam, a question about pleural effusion may include buzzwords about “positive egophony,” “dullness to percussion,” and “decreased tactile fremitus.” Do not be tempted to diagnose with those symptoms alone. Diagnostic testing is required.
- Because U/S can be easily done bedside and can guide thoracentesis and pleural tube placement, it is often the correct diagnostic test for pleural effusion.

Diagnosis starts with imaging:

- PA and lateral chest x-ray (performed first)
- However, since chest x-ray cannot distinguish a density as effusion vs consolidation, consider other tests:
 - Lateral decubitus x-ray looking for free-flowing fluid which layers in the dependent pleura (however, it is possible to still have an effusion despite the lack of free-flowing pleural fluid if the effusion is loculated)
 - Chest CT (most helpful after pleural fluid is drained, to examine the lung parenchyma)
 - Ultrasound (**best test to confirm diagnosis**)
- Once the presence of fluid is confirmed, sample with thoracentesis and **classify as transudative or exudative based on Light's criteria** (biochemical analysis)
 - Get 2 tests from both the pleural fluid and the serum: lactate dehydrogenase (LDH) and protein
 - Calculate the ratios of effusion to serum to get a diagnosis
 - If even 1 criterion is positive, then it is an **exudative effusion**; all 3 criteria must be negative to be considered a **transudative effusion**

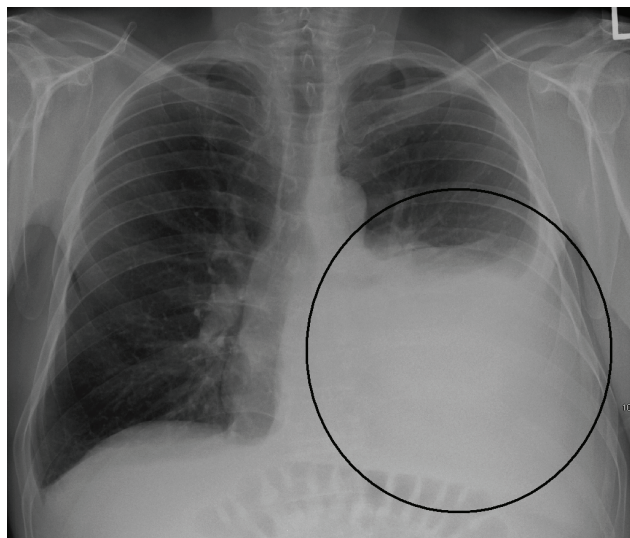
Clinical Correlate

When a patient has a history of CHF, do not assume that new pleural effusions are due solely to the CHF.

Table 9-4. Light Criteria for Exudative Pleural Effusion

	Transudative	Exudative
LDH effusion	<200 IU/mL	>200 IU/mL
LDH effusion/serum ratio	<0.6	>0.6
Protein effusion/serum ratio	<0.5	>0.5

On x-ray, pleural effusion can appear as a white area at the base of the lung.



Wikipedia, James Heilman, MD

Figure 9-15. Pleural Effusion



Treatment. Treat the underlying cause. Some common Step 2 scenarios include:

- **Parapneumonic effusion:** caused by bacterial pneumonia; a thoracentesis is required to rule out a complicated parapneumonic effusion because of the possibility of progression to an empyema (empyema requires chest-tube drainage, while an uncomplicated parapneumonic effusion will respond to antibiotics alone)
 - When a parapneumonic effusion or empyema fails to drain from a well-placed chest tube, consider possible loculations
 - Next step is to administer intrapleural tissue plasminogen activator (TPA) and deoxyribonuclease (DNase), 2×/day for 3 days; when compared with no intrapleural therapy or either agent alone, this combination therapy reduces the need for more invasive procedures
- **Malignant pleural effusion:** causes include lung/breast cancer, lymphoma; if this diagnosis is suspected, the thoracentesis fluid must be sent for cytologic examination
- **Hemorrhagic pleural effusion:** may be seen in mesothelioma, metastatic lung/breast cancer, pulmonary thromboembolism (with infarction), trauma; strongly consider a large-bore surgical tube to allow adequate drainage
- **Lymphocyte-predominant exudative pleural effusion (an exam favorite):** causes include malignancy and possible hypersensitivity reaction to *Mycobacterium tuberculosis* and its antigens
 - Adenosine deaminase is elevated
 - Polymerase chain reaction for tuberculous DNA is positive
 - Acid-fast stain and culture for TB are positive (<30% of cases)
 - Pleural biopsy confirms the diagnosis and is the most sensitive and specific test for pleural TB; however, this is invasive and uncomfortable

Note

PE can cause a transudative or exudative pleural effusion. If a patient has a transudative effusion with no apparent cause, consider PE.

Clinical Recall

Which of the following does not present with an exudative pleural effusion?

- A. Lung cancer
- B. Liver disease
- C. Pancreatitis
- D. Pneumonia
- E. Tuberculosis

Answer: B

Acute Respiratory Distress Syndrome

A 32-year-old man is admitted to intensive care with a presumed diagnosis of gram-negative sepsis. He is placed on double gram-negative antibiotic coverage and remains stable for 24 hours. Blood cultures grow *Pseudomonas*, sensitive to both ceftazidime and ciprofloxacin, both of which have been administered to the patient. The patient seems to improve but suddenly, during day 2 of hospitalization, develops severe dyspnea. Lung examination reveals diffuse crackles; ABG shows hypoxemia and hypercarbia. Diffuse alveolar densities are seen on chest x-ray (the admission chest x-ray was unremarkable).

Acute respiratory distress syndrome (ARDS) is an acute, diffuse, inflammatory form of lung injury that has various etiologies. The classic definition of ARDS by the American-European Consensus Conference has 3 components:

- Ratio of $P_aO_2/FiO_2 < 200$
- Acute bilateral pulmonary infiltrates
- Pulmonary capillary wedge pressure < 18 mm Hg measured by Swan-Ganz catheter, or no clinical evidence of left-heart failure

The causes of ARDS include:

- **Direct causes:** aspiration (**most common**), pneumonia, inhalation injury (toxins), drug overdose, and drowning
- **Indirect causes:** sepsis (**most common**), pancreatitis, transfusion-related acute lung injury, trauma, DIC, Goodpasture syndrome (or any cause of diffuse alveolar hemorrhage), SLE, and most rheumatologic diseases

Direct and indirect ARDS are grouped together due to similarities in clinical presentation, physiology, pathology, and management.

ARDS is characterized by increased permeability of the alveolar-capillary membrane:

- Causes pulmonary edema (non-cardiogenic)
- Leads to severe hypoxemia
- Decreases pulmonary compliance
- Demonstrates accumulation of inflammatory cells and their mediators, leading to diffuse alveolar damage.

Clinical Presentation. There is a 24–72-hour lag time between injury and the development of ARDS. Symptoms include dyspnea, tachypnea, diffuse rales and rhonchi on auscultation, and severe hypoxemia. Other findings include decreased PaO_2 and normal/increased $PaCO_2$ (measured by ABG).

Clinical stages include exudative, then proliferative, then fibrotic.

Clinical Correlate

Healthy lungs regulate the movement of fluid to maintain a small amount of interstitial fluid and dry alveoli. Lung injury interrupts this balance, causing excess fluid in both the interstitium and in alveoli. Consequences include impaired gas exchange, decreased compliance, and increased pulmonary arterial pressure.



Diagnosis. The latest Berlin Definition of ARDS (2012) requires that all of the following criteria be present to diagnose ARDS. **Swan-Ganz catheter is no longer needed.**

- Symptoms must have begun within 1 week of a known clinical insult
- Bilateral opacities consistent with pulmonary edema must be present on chest x-ray or CT
- Respiratory failure must not be explained by cardiac failure or fluid overload

The severity of ARDS is defined by the severity of the hypoxemia.

- **Mild ARDS**
 - $\text{PaO}_2/\text{FiO}_2 >200$ mm Hg but ≤ 300 mm Hg
 - On ventilator settings that include PEEP or CPAP ≥ 5 cm H_2O
- **Moderate ARDS**
 - $\text{PaO}_2/\text{FiO}_2 >100$ mm Hg but ≤ 200 mm Hg
 - On ventilator settings that include PEEP ≥ 5 cm H_2O
- **Severe ARDS**
 - $\text{PaO}_2/\text{FiO}_2 \leq 100$ mm Hg
 - On ventilator settings that include PEEP ≥ 5 cm H_2O

Treatment. Treat the underlying disorder, e.g., antibiotics for sepsis. Optimize cardiopulmonary support and maintain adequate cardiac output.

- Enteral nutrition (via intestines), not parenteral
- Glucocorticoids for early ARDS (reduces duration of mechanical ventilation and length of ICU stay, but weigh risks/benefits of steroids, especially in septic patient)
- Ventilator management (no ventilator mode has proven better than any other)
 - Low tidal volumes: 6–8 mL/kg ideal body weight to prevent barotrauma to lungs; caution that low tidal volumes may lead to elevated PaCO_2 (“permissive hypercapnia”)
 - PEEP: best way to improve oxygenation is to recruit some of the fluid-filled collapsed alveoli
- Positioning: lateral decubitus, with the better functioning lung dependent to maximize perfusion and improve V/Q matching

Pulmonary Nodule

A 26-year-old man is found to have a 2.5-cm calcified nodule in the right middle lung on a routine chest x-ray before starting his residency. He has never smoked and otherwise feels well. The physical examination is unremarkable. What will you recommend for this patient?

The solitary pulmonary nodule that is found incidentally on an x-ray poses a specific problem for the clinician. Around 35% of all solitary nodules are malignant.

Calcification of the nodule points toward a benign diagnosis, e.g., popcorn calcifications usually are caused by hamartomas, whereas bull's-eye calcifications are caused by granulomas.

The **first step** is to look for a **prior x-ray**. Finding the same pulmonary nodule on an x-ray done years ago may save you from doing any further workup. If no prior x-ray is available, then consider whether this patient is high or low risk for lung cancer.

- In **low-risk patients**, age <35, nonsmoker with calcified nodules but no previous history of malignancy; follow with chest x-ray/CT every 3 months for 2 years: stop testing if there is no growth after that time (based on Fleischner Society Radiology guidelines)
- **High-risk patients** age >50, smoking history, previous history of malignancy with a nodule: likely to have bronchogenic cancer

Diagnosis is based upon a multidisciplinary approach.

- Bronchoscopy (traditionally used for central lesions but more recently can reach lesions that are more peripheral)
- CT-guided biopsy or resection of a nodule intra-operatively with a frozen section (for most peripheral lesions)
- PET-CT scan (to evaluate malignancy), especially in those at moderate risk for malignancy and with a pulmonary nodule >0.8 cm
- Possible lobectomy/pneumectomy, based on pathology

Treatment. New Fleischner Society guidelines from 2017 advise a less intensive approach than before for most small pulmonary nodules discovered incidentally on CT scan.

- No follow-up for solitary nodules ≤ 6 mm in low-risk patients age >35 (even if multiple nodules are present)
- Surveillance up to 5 years for (slow-growing) ground-glass nodules (not solid) >6 mm with low risk for malignancy

PET scan is not recommended because these nodules are slow-growing and thus not very metabolically active.

Clinical Pearl

In all patients with a pulmonary nodule, first try to obtain an old chest x-ray.



Note

PE is the third most common cardiovascular cause of death in the United States, and the incidence has not declined in recent years. This may be related to inadequate DVT prophylaxis in hospitalized patients.

Note

Newer research shows that upper extremity DVT is a more frequent cause of PE than previously thought, especially in those with an IV catheter in internal jugular and subclavian veins.

Clinical Correlate

The circulatory system is made up of the heart, arteries, capillaries, and veins.

- The body pumps blood from the heart into the arteries, where it then flows into capillaries.
- Blood returns back to the heart through the veins. As it does this, the blood flow slows down.
- Slowed blood flow has the potential to cause clot formation; blood clotting is a normal process to prevent bleeding.

Pulmonary Embolism and DVT

A 32-year-old woman is brought to the ED with an acute onset of shortness of breath and pleuritic chest pain that occurred while she was shopping. She has never been sick and takes no medications other than oral contraceptives. Her respiratory rate is 26/min and pulse 107/min. Auscultation is clear, and the rest of the examination is normal. ABG shows evidence of mild hypoxemia (7.52/70/25/93%). Chest x-ray is normal.

Pulmonary embolism (PE) and deep vein thrombosis (DVT)—considered one disease—are defined as an obstruction of a pulmonary artery by a particle (usually a blood clot) that has dislodged or moved from another part of the body through the bloodstream.

- **PE** occurs when a clot breaks loose and travels through the bloodstream to the lungs. The clot can block a blood vessel in the lungs, causing damage and interfering with oxygenation. Types (examples) of emboli include:
 - Fat (petechial rash post-long bone fracture)
 - Air (caisson disease [decompression sickness] seen in ascending ocean divers)
 - Thrombus (in pulmonary thromboembolism or stroke)
 - Bacterial (infective endocarditis causing septic emboli)
 - Amniotic fluid (with DIC post-delivery)
 - Tumor
- **DVT** (most common cause of PE) occurs when a blood clot forms in a deep vein of the leg (often after sitting for long periods, since lack of movement slows down blood flow). From the leg, the clot can break off and travel through the bloodstream to another area of the body.

After a proximal DVT dislodges, it travels through the vena cava and into the right side of the heart. As it goes into the pulmonary circulation, obstructing parts of the pulmonary artery, it often breaks into multiple thrombi. The result is increased alveolar dead space, vascular constriction, and increased resistance to pulmonary blood flow.

- When ~50% of the lung vasculature is involved, significant pulmonary hypertension may occur. This is followed by an increase in right ventricular workload and may lead to right-sided heart failure.
- When a PE causes hemodynamic compromise (low systolic BP), this is referred to as a **massive PE**.

Symptoms include the following:

- Sudden onset of dyspnea (shortness of breath) and tachypnea
- Thigh or calf swelling, with or without dyspnea
- Pleuritic chest pain
- Hemoptysis (only with infarction, which is rare because of the dual circulation [bronchial and pulmonary] that supports lung parenchyma)
- Tachycardia and increased pulmonic sound (P2)



Biomedical Communications 2007—Custom Medical Stock Photo

Figure 9-16. Unilateral Right Leg Swelling Due to DVT

Diagnosis.

- DVT

- Serum D-dimer (only if pretest probability of DVT is low; a normal D-dimer safely excludes DVT); note that it is nonspecific in chronically ill and hospitalized patients
- Compression ultrasonography of lower extremity (**procedure of choice for the exam**)
- Venography (invasive and not practical)

- PE

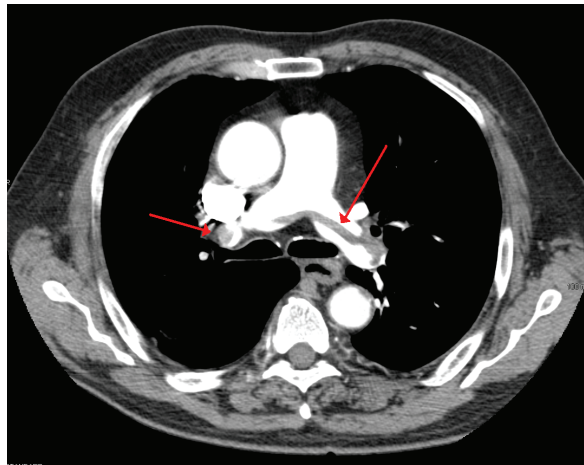
- Chest CT scan with IV contrast (**plus clinical suspicion is best combination to diagnose**)
- Other work-ups include:
 - **ABG** will show hypoxia, widened A-a gradient, and respiratory alkalosis secondary to the tachypnea from the pain (plus discomfort of a PE)
 - **Chest x-ray (done first)** to help rule out other causes in the differential; most often it is normal but some classic findings include “Hampton’s hump” (pleural-based, wedge-shaped defect from infarction just above the diaphragm), “Westermark’s sign” (lack of vascular markings in area downstream of the embolus), and “Fleischner lines” (atelectasis, pleural effusions)
 - **ECG usually done for anyone with chest pain:** right-axis deviation S1, Q3, T3 (deep S in lead I, Q wave in lead III, inverted T wave in lead III); sinus tachycardia (**most common**)



- **V/Q lung scan** (only if PE is suspected but patient cannot receive contrast): tagged albumin is injected into pulmonary circulation and then patient inhales a tagged gas that is distributed into the airways; results are not positive or negative but rather normal, low probability, moderate probability, or high probability; results must be combined with history, physical exam, pre-test probability, and other clinical information such as D-dimer and U/S results for DVT
- **Venous studies:** PE and DVT are 2 manifestations of the same disease process; once a DVT is diagnosed, assume that a PE has been diagnosed as well, because management will not change in the **acute** setting; U/S of the lower extremities is commonly ordered when tests such as CT pulmonary angiogram cannot be done in acute setting. A negative lower extremity U/S does not rule out a PE.
- **Serum D-dimer** (only for those with low pre-test probability of a PE; has a very high negative predictive value): **fibrin degradation product** (small protein fragment) present in the blood after a blood clot is degraded by fibrinolysis (main enzyme is plasmin); predicts recurrent disease after stopping anticoagulant therapy for unprovoked VTE
- **CT pulmonary angiogram (non-invasive “gold standard” in evaluation)**, now often used in place of V/Q scan; requires contrast (renal failure is probably a contraindication in the setting of a suspected PE)
- **Echocardiogram** to determine right ventricular strain and evaluate other etiologies for symptoms; not indicated for diagnosis of PE
- **Pulmonary angiogram** (not commonly ordered in the acute setting due to the specificity and sensitivity of CT angiography for PE); invasive

Hypercoagulable workup is indicated if thrombosis is in an unusual site, is recurrent, is seen age <40, or patient has a family history. Perform 2 wks after anticoagulation has been discontinued.

- If patient clots at the hepatic or portal vein (unusual sites), evaluate for JAK2 mutations and paroxysmal nocturnal hemoglobinuria by checking CD 55 and CD 59 markers.
- If patient has thrombosis and develops warfarin-induced skin necrosis, evaluate for protein C deficiency.
- Any arterial thrombosis is unusual; one main thing to evaluate for is antiphospholipid syndrome.



Wikipedia, James Heilman, MD

Figure 9-17. Pulmonary Embolism CT

Treatment. Treatment is dictated by whether the cause is **provoked (reversible)** or **unprovoked (nonreversible)**. This is determined clinically by evaluating the patient's risk factors, which include:

- Pregnancy (increased risk for thromboembolism continues until 2 months post-delivery)
- Smoking
- Oral contraceptives (risk increases even more if patient currently smokes)
- Paroxysmal nocturnal hemoglobinuria
- Perioperative status (knee replacement surgery carries a 70% risk for DVT)
- Prolonged immobility (perioperative, extended travel)
- DM
- Age >60
- Obesity
- Nephrotic syndrome (loss of proteins C and S; antithrombin III in the urine)
- Occult cancer
- Coagulation factor abnormality ("hypercoagulable workup")
 - Factor V Leiden mutation (**most common**) (protein C resistance, not deficiency)
 - Protein C deficiency
 - Protein S deficiency
 - Antithrombin III deficiency
 - Elevated homocysteine
 - Antiphospholipid antibodies: lupus anticoagulant, anticardiolipin; β_2 -microglobulin

Clinical Correlate

In patients with patent foramen ovale, venous thromboembolism may result in embolization involving the systemic circulation. This frequently presents as CVA.

Clinical Correlate

- Consider PE if the patient has dyspnea and normal chest x-ray.
- Consider PE if the patient has a transudative effusion with no apparent cause. PE can cause a transudative or an exudative pleural effusion.



To determine the pretest probability of a PE, use the Wells' criteria, which have been validated in both inpatient and emergency settings. Do these after the chest x-ray is complete. Start heparin in patients at high risk while completing the diagnostic evaluation. Exclude PE with normal CT plus D-dimer or Doppler U/S.

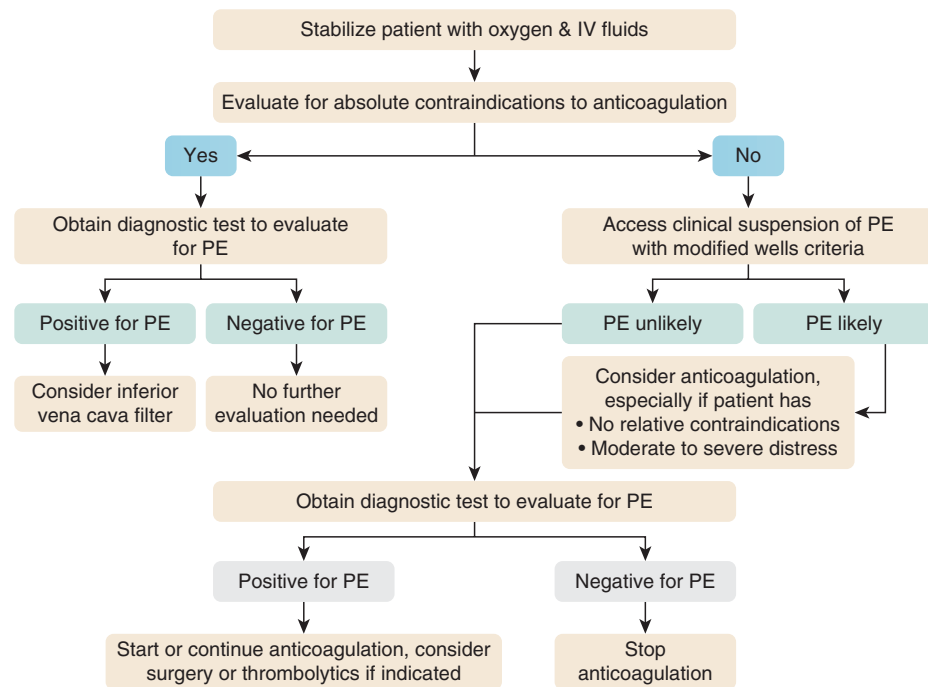


Figure 9-18. Triage Management of PE

Note

For each patient, weigh the risk of morbidity and mortality without anticoagulation against the risk of bleeding with anticoagulation.

Treatment is anticoagulation. VTE encompasses DVT and PE. The risk of recurrent thrombosis and embolization is highest in the first few days and weeks following diagnosis; therefore, initial anticoagulation on days 0–10 is critical to prevent recurrence and VTE-related death.

- Indications include patients with U/S-proven proximal DVT (popliteal, femoral, or iliac vein), most cases of symptomatic distal DVT (below the knee), and PE
- Initial anticoagulation: unfractionated heparin, low-molecular-weight heparin (high success rate), fondaparinux, or oral factor 10a inhibitors
 - Traditional treatment
 - Unfractionated heparin or low-molecular-weight heparin (you can see “HIT” with both) and monitor platelets
 - Warfarin (begin on day 1 and overlap with heparin for 5 days to maintain INR = 2–3); for warfarin-induced skin necrosis (factor 7 has shortest half-life), initiate treatment with heparin (UFH/LMWH)
 - New oral anticoagulants (direct oral anticoagulants [DOACs])
 - Factor Xa inhibitors (e.g., apixaban, rivaroxaban): often used for initial therapy because no “bridge” with heparin is required, as in the case of dabigatran
 - Direct thrombin inhibitors (e.g., dabigatran)
 - IVC filter: if anticoagulation contraindicated, if there is recurrence despite adequate anticoagulation, or if bleeding requires discontinuation of anticoagulation

- For massive PE (hemodynamic instability in the setting of a PE/DVT and persistent hypotension/severe hypoxemia despite maximum oxygen therapy)
 - Systemic thrombolytic therapy (e.g., tPA)
 - Mechanical thrombectomy if contraindications to systemic thrombolytics: catheter-directed via interventional radiology or surgical (invasive and associated with high mortality)

Bleeding Risk of DOACs vs. Heparin/Coumadin

- DOACs have lower risk of intracranial hemorrhage than warfarin
- DOACs have higher risk of GI bleed than warfarin (except apixaban, which has same risk as warfarin)
- Dabigatran has highest risk of GI bleed

Tools such as the **HAS-BLED** score can facilitate estimating the risk of bleeding in anticoagulated patients (note that no tool has been validated in anticoagulation for VTE). Prophylaxis must be weighed against bleeding risk. For the exam you will **not** have to calculate the score.

- Hypertension
- Abnormal liver/renal function
- Stroke
- Bleeding
- Labile INRs
- Elderly age >65
- Drugs or alcohol

Score >3 indicates the need for regular follow-up, but it is not an indication for termination of anticoagulation. Consider alternatives if available, e.g., IVC filter.

Clinical Recall

A 36-year-old woman presents to the ED with a sudden onset of difficulty breathing. She has a significant smoking history and is suspected of having a pulmonary embolism. Which of the following is the gold standard test?

- ABG
- Chest x-ray
- D Dimer
- Pulmonary angiogram
- PFTs

Answer: D



Clinical Pearl

Chronic elevation of serum bicarbonate may be seen in patients with sleep apnea. This is a response to respiratory acidosis.

Note

Apnea means $> 90\%$ decrease in airflow for ≥ 10 seconds. **Hypopnea** is $> 30\%$ decrease in airflow for ≥ 10 seconds with an associated decrease in oxygen saturation or an arousal.

Sleep-Disordered Breathing

Sleep-disordered breathing often includes “apnea,” a pause in breathing that lasts at least 10 seconds.

Sleep apnea

- **Obstructive** sleep apnea (OSA) (**common**) is caused by an upper airway obstruction secondary to the patient’s anatomy. Patients are usually obese, but that is not a necessary clinical feature. Treatment begins with lifestyle modification such as weight loss and exercise, but CPAP is the gold standard. When noninvasive measures are not effective, surgical procedures are considered.
- **Central** sleep apnea ($< 5\%$) is caused by inadequate ventilatory drive. Treatment is focused on addressing the underlying causes, which can include heart failure and medications such as opioids.

Diagnosis is done with polysomnography, at a sleep clinic or at home. Airflow is monitored, effort belts are evaluated, etc. The frequency of apnea/hypopnea determines severity of disease (adult criteria):

- **Normal** $< 5/\text{hr}$
- **Mild** 5–15/hr
- **Moderate** 15–30/hr
- **Severe** $> 30/\text{hr}$

Obesity hypoventilation syndrome

Previously known as Pickwickian syndrome, obesity hypoventilation syndrome is a breathing disorder affecting people suffering from obesity (BMI > 30) with hypercapnia (PaCO_2 high, paO_2 low) even while awake.

Patients may have this condition independent of OSA. Having both conditions portends a worse prognosis.

Treatment is lifestyle modification, weight loss (consider bariatric surgery evaluation), and BiPAP (essential to treat the hypercapnia which cannot be accomplished with CPAP).

LUNG CANCER

A 65-year-old man is seen in the ED with headache and blurry vision for several days. On examination neck vein distension and darker skin color over the face and neck are noted. The patient seems confused. Chest x-ray reveals a right upper lobe lung mass. Blood tests indicate significant hypercalcemia.

Lung cancer (or bronchogenic carcinoma) is the **most common cause of death among all cancers in both males and females**, surpassing breast cancer in females and prostate cancer in males. The overall 5-year survival rate is $< 10\%$.

For the sake of staging, treatment, and prognosis, lung cancers are categorized into 2 categories: **small-cell lung carcinoma** (SCLC) and **non-small-cell lung carcinoma** (NSCLC).

- **SCLC**: faster growing than NSCLC but more responsive to chemotherapy
- **NSCLC (far more common)**
 - **Adenocarcinoma** (a very common lung cancer in the United States for both men and women)
 - **Adenocarcinoma in situ** (formerly known as bronchoalveolar carcinoma), seen primarily in non-smokers; does not have to be a solid nodule or mass
 - **Squamous cell carcinoma** (SCC), 25% of all lung cancers
 - **Large cell carcinoma**

Risk factors for any lung cancer include:

- Smoking (**most common**) and exposure to second-hand smoke
- Asbestos exposure (75× greater risk over those not exposed); mesothelioma (rare but aggressive) is caused by inhaled asbestos fibers
- Radon, arsenic, vinyl chloride, and air pollution exposure (all often overlooked)
- Genetic factors
- Infectious agents, like *Mycobacterium tuberculosis*

Pathology.

- **SCLC** (formerly known as oat-cell carcinoma due to its neurosecretory granules; recall it is derived embryologically from neural crest cells): usually centrally located (thus a common cause of veno-caval obstruction syndrome); rapidly growing tumor with early distant metastasis to extrathoracic sites such as liver/adrenal glands/bone; associated with Eaton-Lambert syndrome, SIADH, and other paraneoplastic syndromes
- **Adenocarcinoma**: usually peripherally located, metastasizes widely (to same sites as other bronchogenic tumors)
- **SCC**: usually centrally located; associated with cavitary lesions more than other bronchogenic tumors; often associated with hypercalcemia from secretion of a parathyroid hormone-like substance (paraneoplastic syndromes)
- **Large-cell carcinoma**: usually peripherally located; typically a diagnosis of exclusion based on pathologic biopsy lacking the features of adenocarcinoma, SCC, or small cell carcinoma

Clinical Presentation.

- Cough (**most common symptom at time of diagnosis**)
- Weight loss (common)
- Dyspnea
- Hemoptysis, chest wall pain, and repeated pneumonic processes (caused by postobstructive pneumonia)
- Hoarseness (indicates a non-resectable bronchogenic carcinoma)

**Note**

On the exam it is never wrong to order sputum cytology but clinically, it is low-yield in confirming a diagnosis.

Note

Of the bronchogenic tumors, SCC most often invades the bronchus and results in atelectasis.

Note

Lung cancer staging is beyond the scope of the exam.

Diagnosis.

- CT-guided biopsy or resection of the mass intra-operatively with a frozen section; consider lobectomy or pneumectomy based upon pathology
- Sputum cytology (minimally invasive): tumor must be invading the main airway in order to get a positive test
- Bronchoscopy with trans-bronchial biopsy and intra-bronchoscopic U/S (traditionally used for central lesions, but more recent navigational technology allows it to reach more peripheral lesions)
- If a pleural effusion is present based upon imaging, the next step is thoracentesis and cytologic evaluation of the pleural fluid; if no diagnosis is obtained, consider a biopsy of the pleura.
- Atelectasis on imaging may suggest airway obstruction; tumors in the airway are usually considered stage IV, except for a carcinoid tumor (classically in the bronchiole and usually has a good prognosis)
- Clinical staging requires extensive imaging. Earlier stages have better prognosis for cure with surgical resection, while later stages often require chemotherapy, radiation, and surgery.

Treatment requires a multi-disciplinary approach; hopefully patient can tolerate complete surgical resection of the primary tumor, with negative ipsilateral and contralateral lymph node biopsies (only definitive cure).

- **SCLC:** chemotherapy (etoposide and platinum-based therapies are current treatments of choice)
- **NSCLC:** most common mutations include EGFR mutation; ALK translocation; BRAF gene mutation; and PD-L1
 - Adenocarcinoma: new targeted therapy for non-resectable disease has significantly changed the clinical course for patients
 - SCC: chemotherapy (prognosis is very poor)

In general, prognosis is good after surgical resection of early-stage NSCLC and poor for small-cell carcinoma.

Screening for Lung Cancer

As per USPSTF guidelines, screen annually for patients who have **both of the following criteria**. Use low-dose, non-contrast CT.

- Age 55–80 with a 30 pack-year smoking history
- Currently smokes or quit <15 years ago

No screening is needed if patient age >80; quit smoking >15 years ago; or has another medical problem that significantly limits life expectancy or the ability to undergo surgery.

The **risk of smoking on lung cancer is directly related to the number of pack-years**. Active smokers have significantly greater risk than nonsmokers.

Learning Objectives

- ❑ List the steps to follow in basic life support (cardiopulmonary resuscitation)
- ❑ Interpret ECG strips to diagnose cardiac dysrhythmias and present the appropriate emergency management
- ❑ Answer questions about principles of toxicology and initial management with specific management for poisoning or overdose
- ❑ Describe direct and indirect complications and emergency management of acute/chronic alcohol use
- ❑ Describe the emergency management of head trauma, anaphylaxis, subarachnoid hemorrhage, burns, radiation injuries, drowning, and venomous bites/stings



BASIC LIFE SUPPORT (CARDIOPULMONARY RESUSCITATION)

A 54-year-old man is at the opera when he suddenly jumps up, clutches his chest, and falls into the lap of the woman sitting next to him.

Basic life support is the initial management algorithm of any patient who seems to have become unresponsive. Etiology is a cardiac, neurologic, or toxicologic event leading to markedly diminished responsiveness or loss of pulse.

Most causes of cardiac arrest are related to ventricular rhythm disturbance. The most common etiology of serious cardiac dysrhythmia is ischemia-related, particularly with coronary artery disease or another cardiac anatomic abnormality (especially cardiomyopathy).



Clinical presentation is any patient with diminished responsiveness that is usually sudden in onset.

- At first this is a clinically determined diagnosis. The initial step is to assess the patient's responsiveness, to make sure he is truly unresponsive and not just asleep. Call to or gently shake him (but be careful about shaking a patient who might have serious traumatic injury, particularly of the cervical spine).
- After determining that the patient is truly unresponsive, call for help (dial 911). Although it is natural to reach down to check a pulse, this is not the action that the USMLE or the American Heart Association wants you to build as a reflex. Without the ECG, defibrillator, and cardiac medication, there is very little a rescuer can do for a patient with a serious dysrhythmia beyond chest compressions and opening the airway.
- If a patient has a serious dysrhythmia such as asystole or ventricular fibrillation, there is virtually no survival if the heart has not been restarted within 10 minutes. Chest compressions just perfuse vital organs; they will not convert the arrhythmia back to normal sinus. AHA guidelines emphasize **high-quality CPR with uninterrupted chest compressions of adequate depth (5 cm, 2 in.) at 100/min and decreased intervals between stopping the chest compression and shock delivery.**
- Avoid excessive ventilation as it can be detrimental. ABC, according to new guidelines, is now **CAB** (excluding newborns). **Removing the 2 rescue breaths allows chest compressions to be delivered sooner. Earlier chest compressions and defibrillation are critical elements of CPR.**
 - Do **not** look, listen, feel for breathing.
 - Do check for pulse (for 10 seconds); if there is no pulse, start chest compressions (after calling 911).
 - Do not give rescue breaths first, as that has been shown to delay vital chest compressions and leads to an increase in mortality.
 - Do not perform jaw thrust, which just delays chest compression.
- After calling for help, position the patient on a firm, flat surface, and roll to be face up. Check for a pulse by feeling for 5–10 seconds at the carotid artery. If there is no pulse, perform chest compressions at 100/min, “push hard and push fast.”
 - In **adults**, provide 30 compressions and then 2 ventilations, whether 1 or 2 rescuers is present.
 - In **children**, if 1 rescuer is present, perform 30 compressions and then 2 ventilations; if 2 rescuers are present, give 15 compressions and then 2 ventilations. Depth of chest compression is 2 inches or 5 cm.

Advanced Cardiac Life Support Algorithms

Note

The key to successful CPR is excellent chest compressions without interruption.

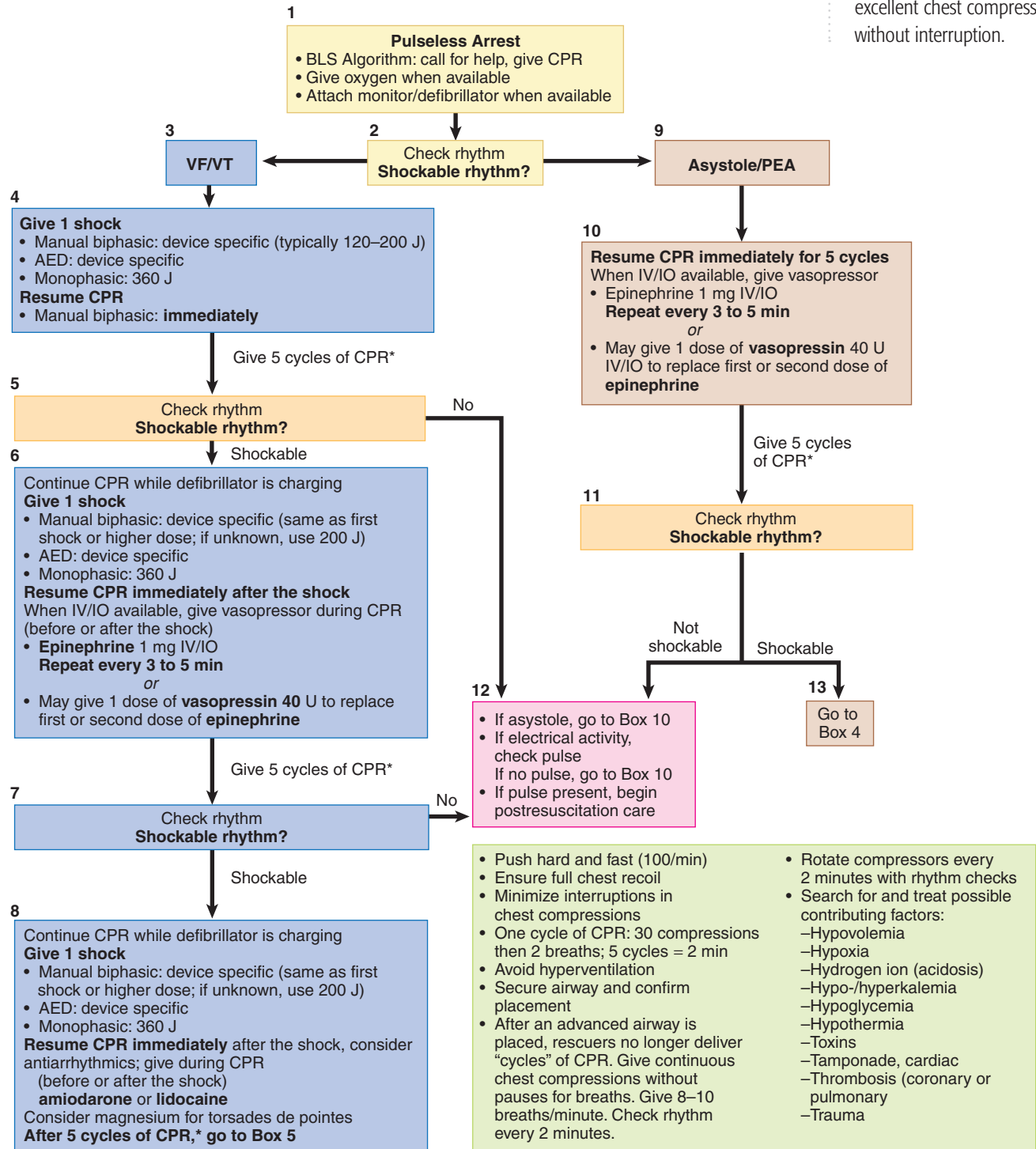


Figure 10-1. ACLS Pulseless Arrest Algorithm



CARDIAC DYSRHYTHMIAS

Asystole

A 54-year-old man is at the opera when he suddenly jumps up, clutches his chest, and falls into the lap of the woman sitting next to him. After confirming that he is unresponsive, a nearby physician performs chest compressions and ventilations. An ECG reveals no evidence of electrical activity.

Asystole is the complete absence of electrical activity in the heart. (This does not necessarily mean a completely flat line on an ECG because there may be slight variability on the rhythm strip.) Causes include:

- Ischemia and severe underlying cardiac disease (**most common causes**)
- Metabolic derangements, drug overdose, and trauma

Clinical presentation includes an unresponsive person with asystole on ECG; there is no pulse. Always confirm asystole by observing the rhythm in more than one lead on ECG.

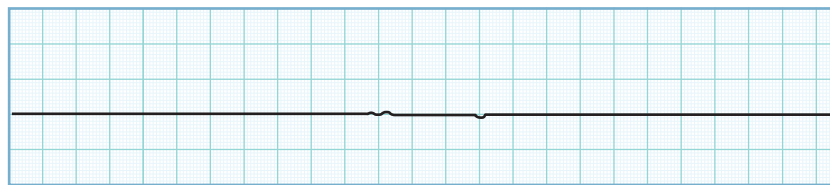


Figure 10-2. Asystole

Treatment. As you continue CPR, obtain IV access and prepare the patient for intubation.

1. Consider transcutaneous pacing only for very slow bradycardia (perform as early as possible). Pacing is not for asystole.
2. Next, administer 1 mg epinephrine via IV push every 3–5 minutes. (Atropine is no longer recommended for asystole.)
3. If asystole persists, withhold resuscitative efforts in order to evaluate the presence of atypical clinical features or cease-effort protocol.

When you see asystole on the monitor, make sure of the following:

- There are no loose or disconnected leads
- The power to ECG machine and monitor is on
- There is not a low signal gain on the monitor

Bicarbonate is useful if asystole is caused by a preexisting acidosis (except hypercarbic acidosis), tricyclic antidepressant overdose, aspirin overdose, hyperkalemia, or diabetic ketoacidosis.

Note

For asystole and other arrhythmias in this chapter, remember the “Hs and Ts”:

Hypoxia

Hyper/Hypokalemia

Hypothermia

Hypoglycemia

Hypovolemia

Trauma

Toxins (including overdose)

Tamponade

Tension pneumothorax

Thrombosis (coronary and pulmonary)

Note

Atropine is no longer indicated in asystole.

Note

Transcutaneous pacemaker is not useful for asystole.

Ventricular Fibrillation

A 54-year-old man is at the opera when he suddenly jumps up, clutches his chest, and falls into the lap of the woman sitting next to him. He is not breathing. After confirming that he is unresponsive, a nearby physician performs chest compressions and ventilations. An ECG is done and reveals ventricular fibrillation. He has no spontaneous respirations.

Ventricular fibrillation is significant electrical activity on ECG with no signs of an organized pattern. The most common causes are ischemia, myocardial infarction, cardiomyopathy, and severe underlying cardiac disease. Remember the “Hs and Ts.”

Presentation is a dead person with ventricular fibrillation on ECG. Diagnosis is entirely based on the ECG.

Treatment. The differences between defibrillation and cardioversion are very important.

- **Defibrillation** is a nonsynchronized delivery of shock at any phase of cardiac cycle. It is used in VF and pulseless VT. During defibrillation you depolarize all of the myocytes simultaneously, hoping that the SA node will start up normal sinus rhythm.
- **Cardioversion** is a synchronized shock with the QRS complex. When performing cardioversion, the defibrillator will not shock until the QRS complex appears. You will be able to see spikes over the QRS complexes on the monitor. If you shock on the T-wave when ventricular repolarization is taking place, you may induce VF.

Make sure that the SYN button is pushed when performing cardioversion. Use UNSynchronized shock (defibrillation) for VF or pulseless VT only.

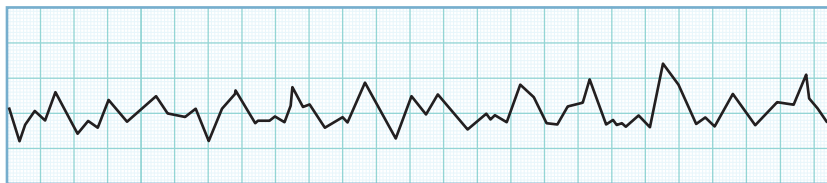


Figure 10-3. Ventricular Fibrillation

Post-Resuscitation Care. Most patients who survive resuscitation have anoxic brain injury. Therapeutic hypothermia reduces the risk of this type of severe neurologic injury. Initiate it if a patient is not following commands or showing purposeful movements. The goal of the protocol is to reach core temperature 32–34 C (90–93 F) within 6 hours and maintain for 12–24 hours. This can be done with ice packs, cooling blankets, or cold IV fluids.

Absolute contraindications for induced hypothermia are active bleeding and do-not-resuscitate order.

Note

The exact mechanism of cardiovascular collapse in an individual is often impossible to establish since patients rarely have cardiac electrical activity monitored. Research has shown that VT or VF accounts for most sudden cardiac death cases, with bradycardia or asystole accounting for the remainder.

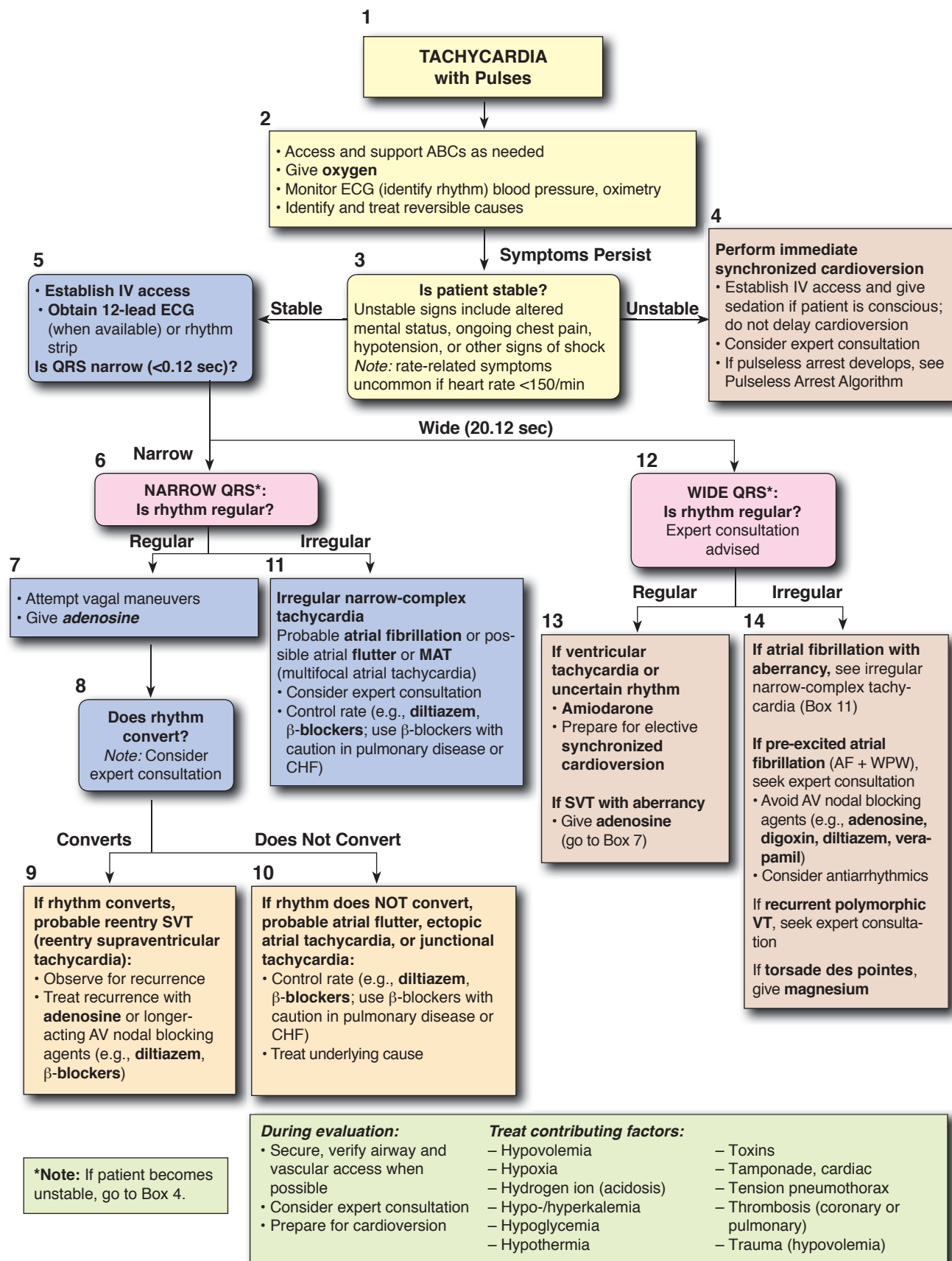


Figure 10-4. Algorithm for Tachycardia with Pulses

Ventricular Tachycardia

A 54-year-old man is at the opera when he suddenly jumps up, clutches his chest, and falls into the lap of the woman sitting next to him. He is awake but disoriented and confused, complaining of dyspnea and lightheadedness. His exam reveals jugulovenous distention and blood pressure 114/80 mm Hg. ECG shows ventricular tachycardia at rate 180 beats/min.

Ventricular tachycardia (VT) is a wide complex tachycardia with an organized, uniform pattern on the ECG. No P-waves are visible. It is most commonly caused by ischemia, myocardial infarction, and anatomic cardiac disease. Other possible etiologies include quinidine, tricyclics, phenothiazines, and long QT syndromes.

The dysrhythmia originates from an ectopic focus in the myocardium or from the AV node. When the impulse originates from around the AV node, this is from reentry. The electrical impulses must travel throughout the myocardium, from myocyte to myocyte, without the benefit of the more rapidly conducting normal pathways such as the bundle branches or His-Purkinje fibers.

The slowness of the conduction produces the slower and therefore wider complexes on ECG. The rate most often varies 160–240/min. **Torsade de pointes** is a form of VT in which the morphology varies with an undulating amplitude, making it seem that it “twists around a point.” Torsade may be associated with hypomagnesemia and preceded by **long QT interval**.

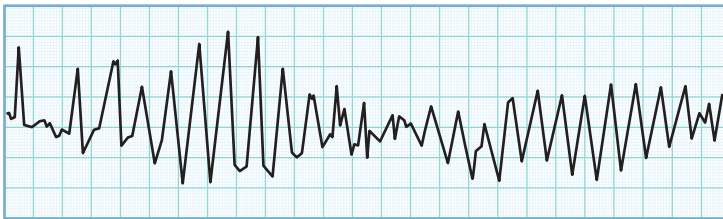


Figure 10-5. Torsade (Polymorphic VT)

Symptoms are often related to duration of the dysrhythmia. Short bursts of a few seconds may produce no symptoms at all. VT lasting >30 seconds is referred to as sustained VT. Symptoms include lightheadedness, hypotension, CHF, syncope, and death.

Diagnosis. The ECG shows the VT. For those patients presenting with syncope suspected to be of cardiac origin and in whom an arrhythmia is not visible on the initial ECG, an electrophysiologic study can be done to try to elicit the VT.

Note

Medications that prolong QT interval

- TCAs
- Antipsychotics
- Macrolides
- Methadone
- Fluoroquinolones
- Amiodarone
- Quinidine
- Class III: sotalol, ibutilide, dofetilide
- Procainamide

Causes of prolonged QT and Torsade

- Hypothyroidism
- Hypokalemia
- Hypocalcemia
- Congenital or prolonged QT syndrome

Note

Amiodarone is superior to lidocaine for VF/VT.

**Note**

If patient has sustained monomorphic VT and is hemodynamically stable after recording a 12-lead ECG, consider giving an IV anti-arrhythmic agent (amiodarone, lidocaine) and reserving electrical cardioversion for refractory patient who becomes unstable.

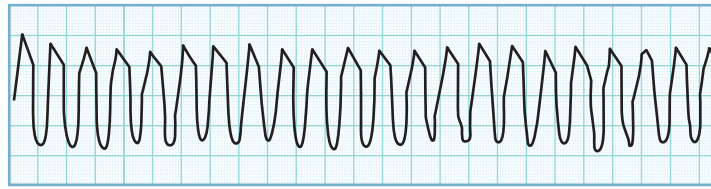


Figure 10-6. Ventricular Tachycardia (Monomorphic)

Treatment. For those with sustained VT and with a pulse who are hemodynamically unstable, immediate synchronized cardioversion is required. Signs of hemodynamic instability requiring cardioversion include hypotension, chest pain, altered mental status, and CHF. A lower dose of electricity, starting at 100 J, can be used at first for monomorphic VT. The cardioversion should be synchronized. Conscious patients should be sedated with midazolam, fentanyl, or morphine before cardioversion.

VT for those without a pulse should be managed in the same way as ventricular fibrillation (unsynchronized shock). Stable VT (wide, monomorphic, regular) without serious hemodynamic compromise can be treated medically with antiarrhythmics.

Magnesium may be useful in general but it is most useful for Torsade de pointes; if it fails to treat Torsade, then try isoproterenol or lidocaine. Overdrive pacing can be used if pharmacologic treatment fails. Patients undergoing cardioversion should be sedated first with medications like midazolam, fentanyl, or morphine. Long-term therapy is most effective with BBs. VT that produces sudden death or that is sustained through initial drug therapy may require the placement of an implantable cardiac defibrillator (ICD) or catheter ablation technique. All patients with ejection fraction <35% should have ICD due to increased risk of VT and VF.

Pulseless Electrical Activity

Pulseless electrical activity (PEA) is hypotension to the point of losing one's pulse; there is still some type of electrical activity on the ECG that may even be normal or a simple tachycardia. More than the other dysrhythmias, knowing the etiology PEA is the key to the therapy because the specific therapies are so divergent.

Essentially, the heart may still be beating, but there is no blood in the heart, and therefore there is no cardiac output. Causes of PEA are severe hypovolemia, cardiac tamponade, tension pneumothorax, massive pulmonary embolism, and a massive myocardial infarction. Other causes in which there may not be actual muscular contraction are hypoxia, hypothermia, potassium disorders, acidosis, and drug overdoses with tricyclics, digoxin, BBs, or CCBs.

The patient appears to be dead with no pulse. Other symptoms are based on the specific nature of what led to the PEA, such as those described. Diagnosis is made with a pulseless patient who has significantly organized, and occasionally normal, activity on ECG.

Treatment. The most important action is to maintain CPR while determining the specific origin of the PEA. General therapy includes CPR, IV access, intubation, and epinephrine. Do not shock PEA arrest. The most important therapy is repair of the cause. Bicarbonate is useful if a known acidosis has caused the arrest; it can also be used in a prolonged resuscitation if severe lactic acidosis develops and causes the refractory state of arrest.

Clinical Recall

Which of the following disorders is not an indication for cardioversion?

- A. Atrial fibrillation
- B. Atrial flutter
- C. Electromechanical dissociation
- D. Ventricular tachycardia

Answer: C

Atrial Dysrhythmias

A 24-year-old medical student is brought to the ED because of palpitations. He has been studying vigorously for the USMLE Step 2 exam and has been up for the last 24 hours. He has had 5 cups of coffee, 4 beers, 3 stimulant tablets, 2 cheeseburgers, and 1 sildenafil (Viagra). Electrocardiogram reveals an atrial dysrhythmia.

Atrial fibrillation (Afib), atrial flutter, and supraventricular tachycardia (SVT) are all characterized by an ectopic focus in the atrium or re-entry at the AV node.

- All have normal conduction in the ventricular myocardium once the impulse successfully passes the AV node and travels down the normal ventricular conduction system.
- All have a normal or narrow QRS complex and the absence of a normal P-wave.
- Afib is caused by chronic hypertension (most common), but valvular heart disease (most often mitral valve pathology), left ventricular hypertrophy, cardiomyopathy, atrial fibrosis, atrial dilation, CAD, and CHF are other causes. Another cause is toxicity causing overstimulation of the heart, i.e., hyperthyroidism, pheochromocytoma, caffeine, theophylline, alcohol, and cocaine. Drug toxicity (such as digoxin), pericarditis, pulmonary embolism, surgery, chest wall trauma, or ischemia can also cause atrial dysrhythmias.
- SVT is caused by a re-entrant mechanism around or within the AV node.

Clinical Presentation. Symptoms vary on the basis of the duration of the disorder, the ventricular rate, and the underlying health of the heart.

- With a normal heart, only 10–20% of cardiac output is directly derived from the contribution of atrial systole.
- With a dilated or postinfarction heart or with significant valvular disease, this contribution may rise to 30–40%, in which case more severe symptoms arise: from complete absence of palpitations to lightheadedness, hypotension, disorientation, CHF, and syncope.
- Rate-related symptoms are unlikely in those with heart rate <150 per minute in atrial dysrhythmia.

Note

Afib, atrial flutter, and SVT are discussed as a group because their initial management has considerable overlap.



Narrow complex tachycardia is always atrial in origin (QRS <0.12 sec). Wide complex tachycardia can be atrial or ventricular. For example, it is very difficult to distinguish Afib in the presence of LBBB and VT. The key is that in Afib with LBBB, the rate is irregular on ECG, whereas in VT it is regular. If in doubt, treat as VT.

Diagnosis. Initially, the diagnosis is based entirely on the ECG. Other patients may need a 24–72 hour Holter monitor to detect brief paroxysms of the dysrhythmia not seen on the initial brief ECG.

Note

- Narrow complex tachycardia is *always* atrial in origin (QRS <0.12).
- Wide complex tachycardia can be atrial or ventricular in origin.



Figure 10-7. Normal Sinus Rhythm



Figure 10-8. Atrial Tachycardia

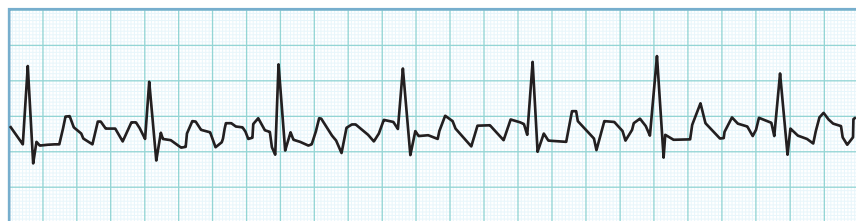


Figure 10-9. Atrial Flutter



Figure 10-10. Atrial Fibrillation

Treatment. Initial therapy is based on whether there are signs/symptoms of severe hemodynamic compromise, such as hypotension, confusion, CHF, or chest pain. If there are signs, perform immediate synchronized cardioversion.

If the patient is hemodynamically stable, then the first step is to control the ventricular rate. For SVT, a vagal maneuver such as carotid sinus massage, Valsalva, or ice water immersion is most effective.

- The modified Valsalva maneuver is more effective than the standard technique: **do Valsalva followed by supine repositioning and immediate passive leg raise.**
- Do not do carotid sinus massage bilaterally.
- Do not do carotid massage on patients with carotid bruits.

If vagal maneuvers do not work, treat SVT with several rapid IV infusions of adenosine. (Do not use adenosine in patients with asthma or COPD, as it can cause bronchospasms.)

If adenosine is not effective, use a CCB (diltiazem or verapamil), BB, or digoxin to slow the heart rate.

- Try to avoid verapamil in patients with severe left ventricular dysfunction and low ejection fraction.
- Be cautious using BBs if there is a history of reactive airway disease.

After the rate has been lowered <110/min, conversion of the rhythm to normal sinus does not need to be routinely done. Chronic rate control with anticoagulation with warfarin to INR 2–3 is superior to converting the patient into sinus rhythm. Returning the patient to a normal sinus rhythm is preferable because chronic Afib can result in embolic stroke (5–7% of patients per year).

Amiodarone, ibutilide, propafenone, and dofetilide can all convert a minority of patients to sinus rhythm. (At the level of the Step 2 exam, you will not need to know much about the specific indications for each, though you will need to know that elective cardioversions should be preceded and followed by several weeks of anticoagulation with warfarin.)

Avoid adenosine in asthma and COPD, as it can cause bronchospasms.

Rate Control vs. Rhythm Control. When patients present in Afib with rapid ventricular response, hemodynamic stability must first be determined.

- If hemodynamically stable: rate-control with AV nodal blocking agents
- If unstable, do immediate synchronized cardioversion

With long-term management, rate control and anticoagulation are preferred over rhythm control. Consider **rhythm control** for the following:

- Symptomatic patients on rate control (poor exercise tolerance)
- Younger patients with normal heart structure and function
- Patients unable to be rate controlled with AV nodal blocking agents

It is very difficult to keep patients with structural heart disease in normal sinus rhythm. Several studies have shown an increase in overall mortality with rhythm control. Catheter-directed ablation of the AV node or accessory pathway may be used when pharmacological treatment fails to control rate.

Note

Palpitations and lightheadedness are not signs of hemodynamic compromise.

Note

For patients with **Afib and flutter**, give **rate control treatment plus anticoagulation** (aspirin, warfarin, etc.). When warfarin is used, optimal INR therapeutic range is 2.0–3.0.

**Note****CHADS₂–VASc score**

CHF: 1 point

HTN: 1 point

Age ≥ 75 : 2 points
(age 65–74: 1 point)

DM: 1 point

Prior stroke/TIA: 2 points

Female sex: 1 point

Vascular disease (CAD, PAD):
1 point**Note**

For anticoagulation, use warfarin, dabigatran, or rivaroxaban.

Note

If a patient doesn't want to check INR or has difficulty staying in therapeutic range, give a newer agent.

Note

Patients with Afib and thyrotoxicosis always get anticoagulation until euthyroid and back in NSR.

The **rate control** goal is HR < 110 /min. Diltiazem, BBs, verapamil, and digoxin may help.

- Most patients require combined therapy: BBs with digoxin have been shown to be best combination.
- In patients with decompensated CHF: use digoxin first and amiodarone as second-line therapy; start BBs once patient is euvolemic on exam but use caution.

Agents for chemical cardioversion in Afib include amiodarone, dofetilide, flecainide, ibutilide, propafenone. In CHF patients, use amiodarone and dofetilide only.

Agents for maintaining sinus rhythm include flecainide, propafenone, sotalol, dronedarone, dofetilide, and amiodarone. To maintain normal sinus rhythm in CHF patients, use only amiodarone or dofetilide. In patients with coronary artery disease and normal EF, dofetilide, dronedarone, and sotalol are first line over amiodarone.

The CHADS₂–VASc score is used to determine if a patient with non-valvular Afib needs anticoagulation.

- **Score 0**: no treatment
- **Score 1**: aspirin or anticoagulation
- **Score ≥ 2** : anticoagulation

Dabigatran, rivaroxaban, and apixaban are newer agents that produce similar or lower rates of both ischemic stroke and major bleeding compared with warfarin.

- Dabigatran is an oral direct thrombin inhibitor shown to reduce the incidence of ischemic stroke compared with warfarin, with similar rates of bleeding.
- Rivaroxaban is an oral factor Xa inhibitor.
- Apixaban, another oral factor Xa inhibitor, may be used instead of warfarin for stroke prophylaxis in patients with Afib and high risk of stroke (CHADS₂ score ≥ 2).

Advantages of the newer agents include convenience (no requirement for routine testing of the international normalized ratio), 50% less intracranial bleed than warfarin, and less susceptibility to dietary and drug interactions. Disadvantages include lack of an antidote and the potential that new side effects may be seen over time.

For patients undergoing elective cardioversion, first determine if they have been in Afib for > 48 hours. If they have, there are 2 options:

- Transesophageal echo can be done to exclude a clot; then, cardioversion (electrical or chemical). Cardioversion should be followed by 6 weeks of warfarin.
- Warfarin can be administered for 3 weeks before electrical or chemical cardioversion. Cardioversion should be followed by another 6 weeks of Coumadin.

It is very difficult to maintain patients with structural heart disease in NSR, and most convert back into Afib. Atrial flutter is managed the same way as atrial fibrillation.

For patients in Afib with Wolff-Parkinson-White syndrome, administration of drugs that slow AV node conduction (Ca-channel blockers, digoxin) is strongly contraindicated, as they can induce VT. Procainamide, ibutilide, flecainide, or amiodarone can be used in such cases.

If none of the medications described can successfully convert the patient to a normal sinus rhythm, then elective electrical cardioversion can be attempted. This too must be preceded and followed by several weeks of anticoagulation if the Afib has been present for >48 hours. Transesophageal echo can be done to exclude a clot and allow the cardioversion without preconversion anticoagulation. Neither medical nor electrical cardioversion can permanently maintain the majority of patients on sinus rhythm. Most convert back into atrial fibrillation.

Bradycardia

A 48-year-old manager comes for advice about vaccinations and travel medicine before traveling overseas. He feels well and has no symptoms. He takes no medications. On examination you find blood pressure 118/76 mm Hg and pulse 40/min.

Bradycardia is a slow heart with rate <60 beats/min.

- **Sinus bradycardia** can be a normal phenomenon, particularly in trained athletes. Medications such as BBs can cause it without serious sequelae. Symptomatic sinus bradycardia from sinus node disease can be from degeneration of the node or from ischemia.
- More **serious types of bradycardia** can be from Mobitz type II second-degree heart block and third-degree (complete) heart block. These can occur secondary to ischemic damage of the AV node. Other causes are myocarditis, infiltrative disease such as amyloidosis or sarcoidosis, or neoplasms.

Clinical presentation can range from the lifelong absence of symptoms to severe symptoms of hypotension and decreased cardiac output. Diagnosis is made with ECG.

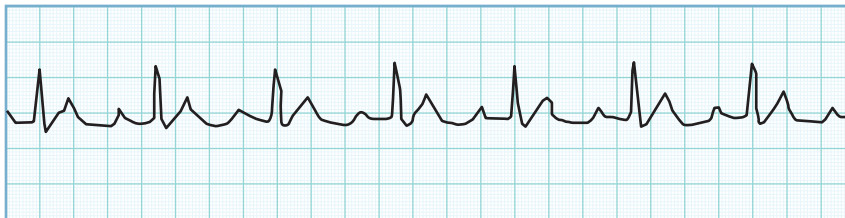


Figure 10-11. First-Degree Heart Block

**Note**

Mobitz type I second-degree block is characterized by **progressive** P-R lengthening, whereas **Mobitz type II** is characterized by a **constant** P-R interval.

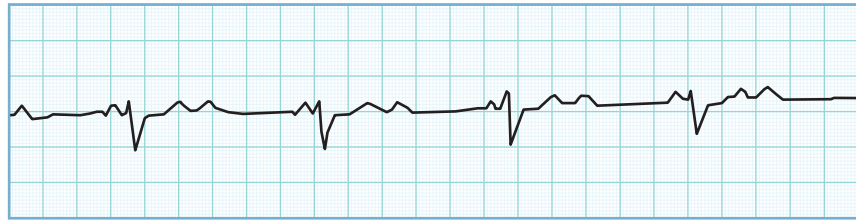


Figure 10-12. Second-Degree Heart Block



Figure 10-13. Complete Heart Block

Note

In the acute setting, transcutaneous pacing is always preferred over transvenous pacing.

Note

If the patient is on a BB, give glucagon. If the patient is on a CCB, give calcium.

Treatment. Asymptomatic sinus bradycardia, first-degree AV block, and Mobitz type I (Wenckebach) second-degree AV block often need no specific therapy. Any form of severe symptomatic bradycardia is treated initially with atropine and then a pacemaker, if there is no improvement in symptoms.

Mobitz type II second-degree block and third-degree block require the placement of a pacemaker, even in the absence of symptoms. Dopamine or epinephrine is used to improve blood pressure if there is still hypotension after the use of atropine.

For symptomatic sinus bradycardia, treatment is atropine. If atropine fails, then use transcutaneous pacing.

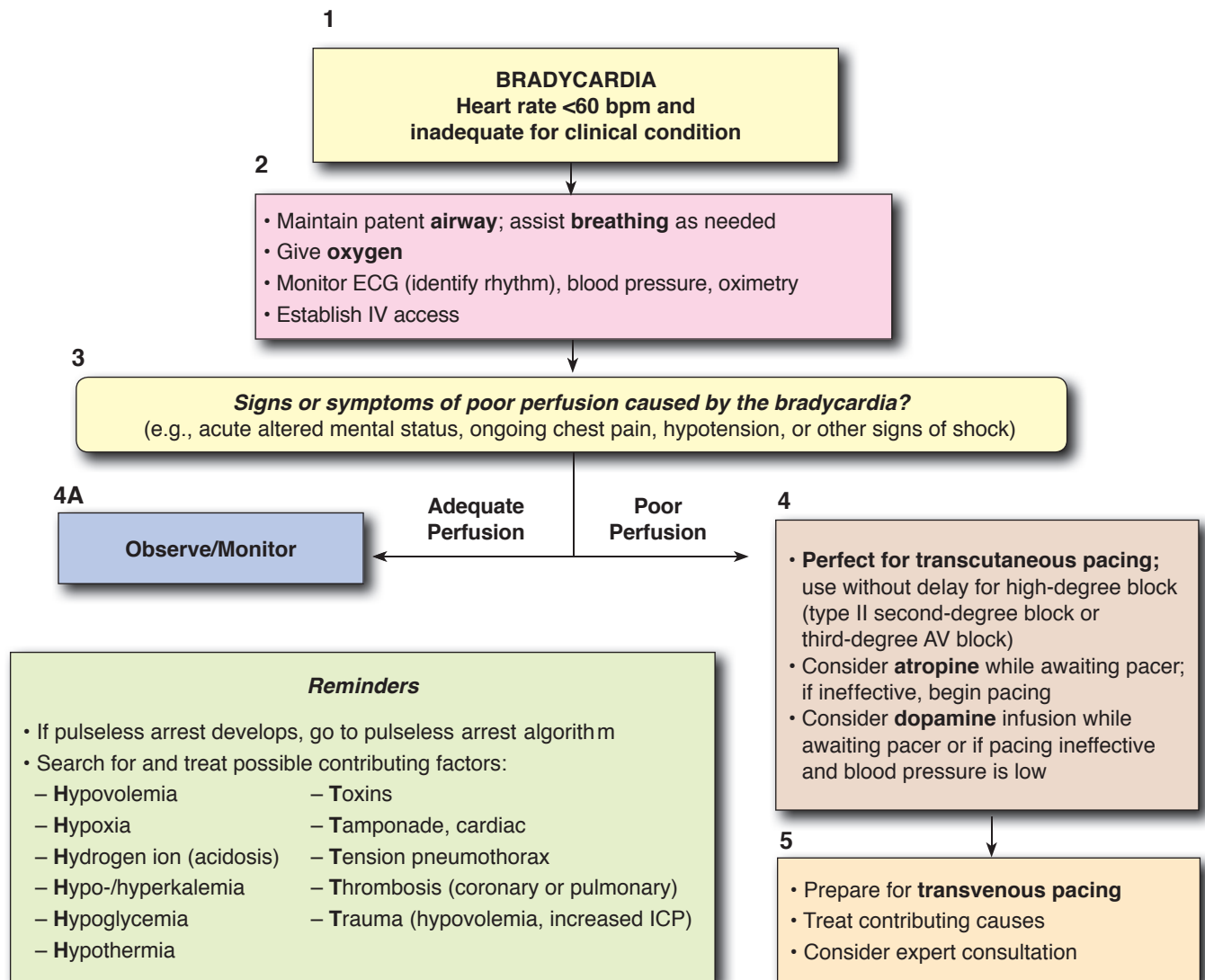


Figure 10-14. Algorithm for Bradycardia



Clinical Recall

Which of the following medications causes a prolongation of QT interval?

- A. Amoxicillin
- B. Erythromycin
- C. Isoniazid
- D. Vancomycin

Answer: B

TOXICOLOGY

A 25-year-old medical student goes home after class and finds no phone messages from his girlfriend. In a fit of despair he takes a full bottle of pills in an attempt to commit suicide. He takes the label off the bottle to prevent any attempt to reverse the poisoning through the identification of the specific agent. A few minutes later his girlfriend calls, after which time he runs to the nearest ED and states that he has changed his mind and wants to live after all. He says that he took the pills 30 minutes ago but won't tell you the specific name of what he took.

The initial evaluation of a patient who has been poisoned involves attempting to find out the nature of the toxin ingested. At the same time, history and physical examination can provide clues. In this case, the key issue is the short time between the ingestion and the arrival at the ED. The patient is awake.

Toxidromes

Toxidromes (*toxic + syndromes*) are groups of “common symptoms” associated with exposure to a particular class of poison. They are useful in that they help clinicians to narrow down the possible poisons involved.

Table 10-1. Common Toxidromes

Class	Physical Finding
Clonidine, barbiturates, opiates, cholinergics, pontine stroke	Miosis
Sympathomimetics, anticholinergics	Mydriasis
Anticholinergics	Dry skin
Cholinergics	Wet skin
Barbiturates, carbon monoxide poisoning	Blisters

Note

Use caution with toxidromes, as many symptoms are common in more than one class (or can even be absent).

Toxic Ingestion or Overdose

Gastric emptying is rarely, if ever, utilized. In ingestion of an unknown type, perform a urine or blood toxicology screen, but do not delay the administration of antidotes, charcoal, or gastric emptying (rarely needed).

- Activated charcoal (**mainstay of therapy**) every 2–4 hours to block further absorption of the substance and accelerate removal of toxins already absorbed by the body; charcoal is safe for all patients
- Induced vomiting with ipecac syrup, useful for ingestions in the home where the time period since ingestion is short and there are no other effective modalities available (must be done within 1–2 hours so it has no use in the hospital setting); ipecac is never recommended for children
- Lavage, i.e., gastric emptying with a large-bore (37–42 French) oropharyngeal hose (e.g., Ewald tube) only if there is altered mental status because of possible aspiration. Endotracheal intubation beforehand is typically required.
 - Lavage decreases absorption by 52% at 5 min, 26% at 30 min, and 16% at 60 min.
 - The exact indications for lavage are not clear, but the contraindications are very clear: useful only within the first hour after ingestion, and contraindicated with the ingestion of caustic substances such as acid or alkalis.
- Whole bowel irrigation, for large-volume pill ingestion where the pills can be seen on x-ray. A gastric tube is placed and high-volume (1–2 liters per hour) GoLYTELY (polyethylene glycol) is administered until the bowel movements run clear.
- Dialysis (rarely needed) only with profoundly serious symptoms such as coma, hypotension, or apnea, especially when renal/hepatic failure limits the usual means of excreting substances from the body. Hemodialysis is 20× more efficacious at removing drugs from the body than peritoneal dialysis.
- Cathartics
 - Use with charcoal administration; otherwise, they are almost never helpful.
 - On the exam, if cathartics appear as an answer choice, they are generally the wrong answer.
- Forced alkaline diuresis to eliminate salicylates and phenobarbital
 - Otherwise, simply making the patient urinate in high volumes is not helpful.
 - On the exam, forced diuresis is generally the wrong answer—except for salicylates and phenobarbital.
- Naloxone/dextrose/thiamine (**first-line** when there is altered mental status [particularly confusion] or coma)
 - Naloxone has almost no side effects and works instantly; because of its rapid response, it is both therapeutic and diagnostic.
 - Dextrose is very effective at preventing permanent brain damage from hypoglycemia.
 - It does not matter whether the dextrose or thiamine is given first.
- Benzodiazepines (**first-line for any toxin-related seizure**). If no response, use barbiturates next. Phenytoin and fosphenytoin are not indicated or even effective for this type of seizure.

Note

- Ipecac syrup is never used by physicians. It must be used within the first 2 hours of ingestion, and very few people arrive within the first hour.
- Lavage has almost no utility.

Note

Charcoal does not bind to some substances (**PHAILS**):

Pesticides

Heavy metals

Acid/alkali/alcohol

Iron

Lithium

Solvents

Note

Substances/drugs that may require hemodialysis for removal include (**I STUMBLE**):

Isopropanol

Salicylates

Theophylline

Uremia

Methanol

Barbiturates

Lithium

Ethylene glycol



Toxicology screen

Toxicology screen can determine the approximate amount and type of legal and/or illegal drug a person has taken. It is used to screen for drug abuse, monitor a substance abuse problem, and evaluate drug intoxication for overdose.

- The **best initial test** in toxicology screen is the urine immunoassay (qualitative test). Typically screened are alcohol, cocaine, PCP, amphetamines, and cannabinoids.
- The **confirmatory test** is gas chromatography/mass spectrometry, which provides qualitative analysis and allows identification of the specific drug or its metabolites.

Toxicology screen must be done within a certain amount of time after the drug is taken or while metabolites can still be detected in the body. Some examples of clearance time are:

Alcohol	3–10 hrs
Amphetamines	24–48 hrs
Barbiturates	up to 6 wks
Benzodiazepines	up to 6 wks with heavy use
Cocaine	2–4 days; up to 10–22 days with high level use
Codeine	1–2 days
Heroin	1–2 days
Hydromorphone	1–2 days
Methadone	2–3 days
Morphine	1–2 days
Phencyclidine (PCP)	1–8 days
Tetrahydrocannabinol (THC)	6–11 wks with heavy use

DRUG OVERDOSE

Drugs of Abuse

Opiates

Opiate toxicity is predominantly respiratory related, via depressant effects upon the respiratory centers in the brainstem. Death can occur through acute respiratory acidosis. In addition to their analgesic and euphoric effects, opiates also cause pupillary constriction, constipation, bradycardia, hypothermia, and hypotension.

Opiates can be rapidly reversed by naloxone. Since opioids decrease gastric emptying by relaxation of smooth muscle, gastric lavage may be used in cases of overdose with oral agents.

Although withdrawal of opiates is uncomfortable, it is not fatal. It is usually treated with methadone or buprenorphine.

Opiate withdrawal symptoms are the following.

- **3–4 hours:** fear, anxiety, drug craving
- **8–14 hours:** insomnia, yawning, rhinorrhea, diaphoresis, mydriasis, anxiety
- **1–3 days:** tremor, muscle spasms, vomiting, diarrhea, tachycardia, chills, piloerection

Cocaine

Cocaine blocks the reuptake of norepinephrine and other catecholamines at the synapse. This leads to a wide variety of euphoric and toxic effects. Amphetamines work in a similar way but are less likely to produce severe toxicity or death. Severe toxicity from cocaine is far more likely with smoked (“crack”) or injected cocaine rather than snorted (inhaled).

Clinical Presentation. Toxic effects of cocaine are related to a very significant alpha-adrenergic stimulatory effect, resulting in the following (may lead to death):

- Very high BP
- Hemorrhagic stroke
- Subarachnoid hemorrhage
- Myocardial infarction
- Arrhythmia
- Seizures
- Metabolic acidosis, rhabdomyolysis, and hyperthermia in some cases
- Pulmonary edema (specific to smoked cocaine)

Treatment. There is no specific drug to reverse cocaine toxicity. Benzodiazepines such as diazepam are used to control acute agitation. Combined alpha/beta agents such as labetalol or alpha-blockers such as phentolamine are useful to control hypertension. Avoid pure beta-blockers because they lead to unopposed alpha stimulatory effects.

Cocaine withdrawal can cause depression as a result of the norepinephrine depletion. There is limited physiologic withdrawal from cocaine.

Benzodiazepines

Benzodiazepines (BZDs) produce somnolence, dysarthria, ataxia, and stupor. Very infrequently, they lead to death from respiratory depression; most deaths are associated with ethanol or barbiturate ingestion.

Patients receiving prolonged parenteral administration of BZDs are at risk for propylene glycol poisoning (used in parenteral formulations of diazepam and lorazepam). Rarely, this may cause hypotension, cardiac dysrhythmias, lactic acidosis, seizures, or coma.

Treatment. Good supportive care and monitoring are the foundation of treatment. As with any overdose, the first step is to stabilize the patient’s airway, breathing, and circulation.

- Flumazenil is a specific antidote for BZD poisoning, although its use in acute BZD overdose is controversial.
- In long-term BZD users, flumazenil may precipitate withdrawal and seizures.
- In BZD use for a medical condition, flumazenil may exacerbate the condition.



BZD withdrawal can be similar to the symptoms of alcohol withdrawal. Although rare, deaths have been reported from severe withdrawal. The recommendation for treatment of severe forms of withdrawal is the administration of BZDs.

Barbiturates

Barbiturates are a class of drugs with various long- and short-acting agents. Massive overdose can result in death from respiratory depression or CNS depression.

- Can cause hypothermia, loss of deep tendon reflexes, and loss of corneal reflexes
- Could result in a coma simulating brain death
- May lead to absent EEG activity
- Withdrawal may result in seizures similar to alcohol or benzodiazepine withdrawal
- Have no specific antidote, although urinary excretion of phenobarbital can be increased with the use of bicarbonate (similar to treatment for salicylate intoxication)

Hallucinogens

Hallucinogens include a variety of agents such as marijuana, LSD, mescaline, peyote, and psilocybin. Although they may cause delirium and bizarre behavior, the adverse effects are often limited to their anticholinergic effects: flushed skin, dry mouth, dilated pupils, and urinary retention.

The only hallucinogen associated with a potentially fatal outcome is the artificially created, dissociative, anesthetic phencyclidine (**PCP** or “angel dust”), which may cause seizures.

Treatment for severe hallucinogen intoxication is with benzodiazepines.

Clinical Recall

A 19-year-old man is brought to the ED in an unconscious state after consuming an unknown substance at a party. What is the next best step in management?

- A. CT scan of the brain
- B. Intubation
- C. IV insulin
- D. Naloxone/dextrose/thiamine
- E. Video EEG

Answer: D

Lithium

Lithium is a commonly used medication for the treatment of bipolar disorder and acute mania. Although effective, it has a narrow therapeutic window and is associated with toxicity.

- In **acute poisoning**, patients do not have a lithium burden
 - Symptoms are primarily GI, with nausea, vomiting, cramping, and possible diarrhea
 - Progression can involve neuromuscular signs: tremulousness, dystonia, hyperreflexia, and ataxia
 - Most common electrocardiographic finding is T-wave flattening
- In **chronic poisoning**, patients have a large body burden of lithium
 - Symptoms are primarily neurologic, with mental status often altered
 - Progression can lead to coma and seizures if diagnosis is unrecognized
 - May be difficult to treat
 - Usually precipitated by introduction of new medication that may impair renal function or cause hypovolemic state

Three major drug classes have been identified as **potential precipitants of lithium toxicity**:

- Diuretics which promote renal sodium wasting
- ACE inhibitors, which reduce glomerular filtration rate (GFR) and enhance the tubular reabsorption of lithium
- NSAIDs, which reduce the GFR and interrupt renal prostaglandin synthesis

Systemic effects include renal toxicity:

- Nephrogenic DI (most severe manifestation)
- Impaired sodium and water absorption, caused by inhibition of action of antidiuretic hormone on distal renal tubule
- Renal tubular acidosis, chronic tubulointerstitial nephritis, and nephrotic syndrome

The most common endocrine disorder secondary to chronic toxicity is hypothyroidism. Lithium is taken up by thyroid cells and blocks thyroid hormone release from thyroglobulin, which inhibits adenylate cyclase and prevents TSH from activating thyroid cells via the TSH receptor. Acute exposure to lithium can cause leukocytosis, whereas chronic exposure can produce aplastic anemia.

Elevated lithium in the blood will confirm toxicity, although levels may not correlate with clinical symptoms. Serial levels may be warranted in cases of sustained-release tablets.

Treatment. Supportive therapy is the mainstay of treatment. Gastric lavage may be attempted if patient presents within 1 hour of ingestion.

- Airway protection is crucial due to emesis and risk of aspiration.
- Seizures can be controlled with BZDs, phenobarbital, or propofol.
- Fluid therapy is crucial to restore GFR, normalize urine output, and enhance lithium clearance.



Lithium is readily dialyzed because of water solubility, low volume of distribution, and lack of protein binding. Thus, hemodialysis is indicated for patients who have renal failure (and unable to eliminate lithium) and patients who cannot tolerate hydration (e.g., those with CHF, liver disease, or severe toxicity meaning neurologic symptoms >4 mEq/L).

Lithium is a monovalent cation that does not bind to charcoal, so activated charcoal has no role.

Salicylates (Aspirin)

An older woman with osteoarthritis comes to the ED with dyspnea, intractable nausea, vomiting, and tinnitus. She is fully alert and able to give a good history. Her only other problem is hypertension. She is on a wide variety of medications to reduce her pain. Her husband says she was in so much pain lately that she took half a bottle of extra pills 30 minutes ago.

Salicylate intoxication results from the ingestion of a large amount of aspirin and other salicylate-containing medications, resulting in a complex, systemic toxicity.

Salicylates are complex metabolic poisons. The most common presentation is GI distress such as nausea, vomiting, and gastritis. Tinnitus is one of the more specific complaints and is one of the best ways to identify the case, so as to answer the question: “Which of the following is the most likely diagnosis?”

Salicylates affect respiratory function in 2 ways:

- Directly stimulate the respiratory centers in the brainstem to cause a centrally mediated hyperventilation and hyperpnea
- Are directly toxic to the lungs themselves and can cause a noncardiogenic pulmonary edema similar to ARDS

Hyperthermia is possible. CNS toxicity such as confusion, coma, seizures, and encephalopathy can also occur, with possible death.

Salicylates also interfere with Krebs cycle and lead to a metabolic acidosis through the reversion to anaerobic glycolysis as a method of energy production in the body. In other words, salicylates lead to significant lactic acid production with metabolic acidosis and elevated anion gap. This ultimately results in a compensatory respiratory alkalosis.

The most specific test for diagnosis is **aspirin level**.

- Suggestive findings are **elevated anion gap with metabolic acidosis**. However, respiratory alkalosis may be the predominant defect, especially in early stages. Thus, blood gas can show low, high, or normal pH.
- Elevated prothrombin time and hypoglycemia may occur.
- Chest x-ray may be normal or show pulmonary edema.

Treatment. If the patient comes within 1 hour post-ingestion, attempt gastric decontamination. Charcoal may be useful, as it is in many types of ingestion. The mainstay of therapy, however, is increasing urinary excretion by alkalinizing the urine and administering aggressive

fluid resuscitation. When urinary pH rises, that will charge the salicylate molecule (a weak acid) and will block the reabsorption of the substance at the kidney tubule.

Dialysis is sometimes necessary. Indications for dialysis include:

- Renal failure
- CHF
- ARDS
- Persistent CNS symptoms (confusion/seizures)
- Hemodynamic instability
- Severe acid/base or electrolyte imbalance
- Hepatic failure with coagulopathy
- Salicylate level >100 mg/dL

Acetaminophen

A 38-year-old man comes to the ED with complaints of vomiting and right upper quadrant pain. He explains that 4 days ago he ingested a full bottle (60 tablets) of acetaminophen (500 mg each). Bilirubin, AST, and prothrombin time are all elevated.

Acetaminophen is one of the few toxins about which precise toxicity levels are known; the ingestion of ~140 mg per kg is usually sufficient to cause serious toxicity. In other words, in an average-sized, 70-kg (154-lb) person, ~7–10 grams is enough to produce toxicity, and fatalities can occur >12–15 grams. In those with liver disease or concomitant alcohol abuse and thus depleted glutathione stores, the hepatotoxic dose is less (4 grams/day).

Clinical Presentation.

- **Stage I (first 12–24 hrs):** nausea and vomiting, due to a gastritis caused by irritation from the pills
- **Stage II (24–72 hrs):** asymptomatic period, as the acetaminophen is metabolized and part of the drug is converted to a toxic metabolite
 - At 24–48 hrs, subclinical elevation of the transaminases and bilirubin begins
 - At 48–72 hrs post-ingestion, clinically symptomatic signs of liver damage begin: more nausea, jaundice, abdominal pain, and signs of hepatic encephalopathy, renal failure, and death

Diagnosis. A clear history of a large volume of acetaminophen ingestion is initially sufficient to establish a diagnosis that warrants therapy with N-acetyl cysteine (NAC). Starting at 4 hours after ingestion, when most of the drug has been absorbed, drug levels are reliable. A nomogram based on relating the drug level to the time of ingestion is necessary to determine who will develop toxicity. In other words, a level by itself is not enough to determine who will

Note

Acetaminophen is rapidly and completely absorbed from the GI tract. Serum concentration can peak in 2 hours after oral ingestion at a therapeutic dose.

Note

Unlike most other cases of hepatitis, acetaminophen-induced hepatitis is acute in onset, progresses rapidly, is characterized by marked elevation of plasma aminotransferases (often >3,000 IU/L), and is associated with a rise in PT/INR.



Note

NAC is now used for non-acetaminophen drug-induced liver injury, e.g., amoxicillin/clavulanate. It can be given IV or orally.

Note

Arrhythmia is the most dangerous manifestation of digitalis poisoning.

develop toxicity. A certain level at 5–6 hours may not be toxic, but the same level at 10–12 hours post-ingestion may lead to the development of liver failure.

- Elevated AST is more common than elevated ALT. If a patient is known for alcohol abuse and presents with AST and ALT >1,000 U/L, the diagnosis is more likely to be acetaminophen toxicity than alcoholic hepatitis. Give NAC in such cases.
- Elevated bilirubin and prothrombin time indicate severe toxicity and hepatic necrosis. Studies show that NAC administration within the first 8 hours of severe drug poisoning improves liver microcirculation and prevents the need for liver transplant.

Treatment.

- NAC
 - Give within 8 hours of ingestion, when it is most effective
 - If >24 hours has elapsed, no specific therapy can reverse the toxicity (but still give NAC)
 - Avoid gastric emptying, as it would delay the administration of NAC as a specific antidote.
- Activated charcoal in repeated doses

Digoxin

Toxicity of digoxin is seen with suicide attempts and accidental therapeutic overdosage. Toxicity is more common with renal failure because 60% of digoxin is normally excreted renally, and it will accumulate.

The most common precipitating cause of digitalis toxicity is the reduction of potassium stores, often seen in patients with heart failure due to diuretic therapy or secondary hyperaldosteronism. **Hypokalemia** predisposes to toxicity because potassium and digoxin bind to the same site on the sodium–potassium ATPase pump, leading to increased intracellular calcium, thus leading to increased cardiac contractility. Drugs that have been implicated in digoxin toxicity include amiodarone, beta blockers, diltiazem, cyclosporine, macrolide antibiotics, indomethacin, spironolactone, and furosemide.

Clinical Presentation. GI symptoms are most common: nausea, vomiting, diarrhea, and anorexia. Neurologic and visual symptoms include blurred vision, color vision abnormality, hallucinations, and confusion. Cardiac disturbance is predominantly secondary to arrhythmia.

ECG abnormalities are common. Bradycardia, premature contractions, ventricular tachycardia, and any other arrhythmia may be seen (paroxysmal atrial tachycardia is most common). Hyperkalemia occurs acutely from inhibition of Na^+/K^+ ATPase by digoxin. Order a serum digoxin level if you suspect toxicity (due to history, etc.).

Treatment. For GI decontamination, give repeated doses of **charcoal**. For electrolyte abnormality correction, correct the **potassium**.

- Digoxin-specific antibodies (Digibind®) are useful for life-threatening toxicity, particularly with arrhythmias.
- Pacemaker placement may be necessary for bradycardia or third-degree AV block refractory to atropine.

Tricyclic Antidepressants

A 28-year-old man with a history of depression comes to the ED 1 hour after a suicide attempt with his tricyclic antidepressants and benzodiazepines. He is stuporous with respiratory rate 7/min. ECG shows a wide QRS. What is the next step?

Tricyclic antidepressants (TCAs) are characterized by a number of anticholinergic and sodium channel blocker side effects. This is the predominant cause of their cardiac and CNS toxicity.

Clinical Presentation.

- Anticholinergic-mediated findings (**most common**): dry mouth, tachycardia, dilated pupils, flushed skin
- Quick onset with rapid deterioration (common)
- Cardiac dysrhythmia with widening of the QRS complex (most serious side effect), leading to ventricular tachycardia and first-degree conduction blocks
- CNS effects: altered mental status, confusion, and seizure

Serum drug levels are the most specific test for diagnosis, but ECG with abnormalities is more important to determine who will have serious toxicity. ECG may be normal or show any range of ventricular or atrial arrhythmias or conduction delays.

Treatment. TCA overdose has anticholinergic side effects, which include impaired peristalsis and delayed gastric emptying. TCAs block sodium channels and can cause ventricular tachycardia.

- Charcoal in (first-line in the acute setting)
- Bicarbonate to protect the heart from the TCAs.
 - Give immediately if QRS >100 msec
 - Will not increase urinary excretion (as opposed to the treatment of aspirin overdose)

Anticholinergics

A 65-year-old man is brought to the ED by his wife with lethargy and confusion. She says that he has had a cold and has taken over-the-counter cold preparations for the last few days. On examination he is confused and does not recognize his wife. His temperature is 39.2 C (102.6 F), pulse is 130/min and blood pressure is 100/60 mm Hg. The skin is flushed, dry, and warm. The eyes are dilated.

Anticholinergic drugs competitively inhibit binding of the neurotransmitter acetylcholine to muscarinic acetylcholine receptors and are commonly called “antimuscarinic agents.” Muscarinic receptors are found on peripheral postganglionic cholinergic nerves in smooth muscle (intestinal, bronchial, and cardiac), in secretory glands (salivary and sweat), on the ciliary body of the eye, and in the CNS. Anticholinergic agents do not antagonize the effects at nicotinic acetylcholine receptors, such as at the neuromuscular junction.

**Note**

The role of physostigmine as an antidote is controversial. It may be considered in moderate to severe toxicity. If used, the patient should be placed on a cardiac monitor and atropine should be readily available.

Note

With anticholinergic poisoning, do not use phenytoin or fosphenytoin for seizures that may occur.

Note

Remember **DUMBELSS** syndrome to recall the muscarinic effects:

- Defecation
- Urinary incontinence
- Muscle weakness/miosis
- Bradycardia/bronchospasm
- Emesis
- Lacrimation
- Salivation
- Seizure

Overdose may occur in any age group with high dose, but most commonly presents in the elderly.

The onset of anticholinergic toxicity varies depending on the particular toxin, but usually occurs within 1–2 hours of oral ingestion. Some drugs may take up to 12 hours to have an effect. Be aware with patients on psychotropic agents.

The following medications may cause anticholinergic effects:

- Diphenhydramine
- Scopolamine and hyoscyamine
- TCAs
- Cyclobenzaprine
- Benztropine
- Belladonna

Clinical Presentation. Patients will present with the following characteristics:

- “Red as a beet”: flushed, red skin due to cutaneous vasodilation
- “Dry as a bone”: dry skin (anhidrosis) due to inability to sweat
- “Hot as a hair” anhidrotic hyperthermia
- “Blind as a bat”: mydriasis
- “Mad as a hatter”: delirium, psychosis, hallucinations, and seizures
- “Full as a flask”: urinary retention and absent bowel sounds
- Tachycardia

Treatment is the ABCs, supportive care, and ECG monitoring.

- Sodium bicarbonate to stabilize the myocyte membrane and prevent ventricular tachycardia if there are prolonged QRS and QT intervals
- Benzodiazepines for possible seizure; do not use phenytoin or fosphenytoin

POISONING**Organophosphate Poisoning**

Organophosphates are chemicals used widely as insecticides/pesticides. They inhibit cholinesterase and have muscarinic and nicotinic effects. Patients tend to be farmers and gardeners.

- **Nicotinic effects:** weakness and decreased respiratory drive
- **Muscarinic effects:** defecation, urinary incontinence, muscle weakness/miosis, bradycardia/bronchospasm, emesis, lacrimation, salivation, seizure

To diagnose, check RBC cholinesterase levels. Do not delay treatment while waiting for results.

Treatment. The first step is for the physician to put on protective clothing, as organophosphates are absorbed by the skin. Then, have patient remove clothing immediately. Start atropine immediately to treat the bradycardia. Start pralidoxime (2-PAM), which restores cholinesterase activity and reverses both the nicotinic and muscarinic effects.

Toxic Alcohol Poisoning

All of the toxic alcohols—methanol, ethylene glycol, ethanol, and isopropyl alcohol—can produce intoxication. They are found in many household and commercial settings.

Methanol and ethylene glycol are metabolized by alcohol dehydrogenase.

- **Methanol** (wood alcohol) is found in paint thinner, photocopier fluid, solvents, and windshield washer solution.
 - Metabolized to formaldehyde and formic acid
- **Ethylene glycol** is found in automotive antifreeze.
 - Metabolized partially to oxalic acid and oxalate, which leads to kidney damage

Clinical Presentation.

- **Methanol ingestion:** visual disturbances (even blindness), due to the production of formic acid
- **Ethylene glycol ingestion:** renal failure, oxalate crystals, and stones in the urine
- **Isopropyl alcohol ingestion:** distinguished only after a specific drug level is done by the history or after acidosis has developed in the absence of an elevated anion gap

Diagnosis. Determining specific levels of each alcohol is the most specific test.

- **Methanol and ethylene glycol:** increased serum osmolar gap and metabolic acidosis with elevated anion gap
- **Ethylene glycol:** oxalate crystals in the urine, increased BUN/creatinine, or urine fluorescence (add fluorescein to the urine and observe with ultraviolet Wood's lamp); possible hypocalcemia
- **Isopropyl alcohol:** increased serum osmolar gap without an elevated anion gap

Treatment.

- Fomepizole (alcohol dehydrogenase inhibitor) (**drug of choice**) to inhibit the production of toxic metabolites without leading to intoxication
- Dialysis for those with severe anion gap metabolic acidosis or signs of end-organ damage (coma, seizures, renal failure)

Carbon Monoxide Poisoning

You are the chief resident at a metropolitan training program at the time of a fire at a large office building. A total of 2,500 people come to the ED for treatment of smoke inhalation. Among them is a 68-year-old man with a history of aortic stenosis who had to walk down 90 flights of stairs.

Note

Methanol, ethylene glycol, and isopropyl alcohol ingestion will all result in an osmolar gap, usually >25 mOsm.

Note

Charcoal will not inhibit the absorption of alcohols. Do not use.

Note

In the past, methanol and ethylene glycol intoxication were treated with ethanol infusion (to prevent the production of the toxic metabolites), followed by hemodialysis to remove the substance from the body.

Note

In Northern climates, space heaters during wintertime are a common cause of carbon monoxide poisoning. The most common symptom is headache, along with nausea.

**Note**

Low levels of CO poisoning are present in most tobacco smokers.

Note

There are some similarities to the initial presentations of CO poisoning and hypoglycemia. If fingerstick glucose is normal, that should raise your suspicions.

Poisoning with carbon monoxide (CO) occurs by exposure to burning materials (gasoline, wood, natural gas) and by entrapment in fires and smoke inhalation. CO itself is odorless and tasteless. CO poisoning is common, potentially fatal, and underdiagnosed because of its non-specific clinical presentation.

- CO binds to hemoglobin 200× more avidly than oxygen.
- Carboxyhemoglobin decreases release of oxygen to tissues and inhibits mitochondria, resulting in tissue hypoxia and anaerobic metabolism (similar to what would occur with anemia).

Clinical Presentation.

- Pulmonary symptoms include dyspnea, tachypnea, and shortness of breath.
- Cardiac symptoms include chest pain, arrhythmia, and hypotension.
- Early neurologic symptoms include headache (most common), nausea, blurry vision, and dizziness, while late symptoms include confusion, seizures, impaired judgment, and syncope.

Carboxyhemoglobin (COHb) levels indicate the severity of the exposure.

- **COHb level <10%** may occur in city dwellers who are smokers
- **COHb level 20–30%** mild symptoms
- **COHb level 30–50%** moderate to severe symptoms
- **COHb level >50–60%** may be fatal

Carbon monoxide pulse oximetry (a co-oximeter) is the initial diagnostic test for suspected CO poisoning, as it provides a way to measure carboxyhemoglobin. Routine pulse oximetry is not helpful.

Influenza is the most common misdiagnosis because most people present during wintertime. When an entire family presents with “flu” symptoms without fever, think CO poisoning.

- Arterial or venous blood gases: metabolic acidosis is present from the failure of carboxyhemoglobin to release oxygen to tissues; pO₂ will be normal
- CPK may be elevated.

Treatment.

- Remove the source of exposure and give 100% oxygen
- For severe cases, give hyperbaric oxygen
 - COHb >25% (pregnant women >15%)
 - Myocardial ischemia
 - ECG changes
 - CNS abnormalities other than headache or chest pain

In room air, carbon monoxide has a half-life of 4–6 hours. On 100% oxygen, it decreases to 40–80 minutes. On hyperbaric oxygen, it decreases to 15–30 minutes.

Corrosives

The oral ingestion, inhalation, or cutaneous/ocular contact with corrosive substances is commonly seen in emergency medicine, especially with children.

- The most common household **acids** are toilet bowl cleaners, drain openers, swimming pool chemicals, and metal cleaner.
- The most common **alkali** ingestions are from dishwasher detergent, hair relaxer, and oven cleaner.

In most circumstances, **alkali exposures are more serious than acid exposures**, since alkaline substances are more destructive to tissues.

Symptoms from ingestion injury include the following:

- Oral pain
- Drooling
- Odynophagia
- Abdominal pain
- Possible esophageal injury with subsequent stricture formation (from acid or alkali ingestion)
- Possible gastric perforation

The history of exposure with subsequent characteristic injury is sufficient to establish the diagnosis. Upper endoscopy is critical for determining the extent of the injury.

Treatment.

- Wash out the mouth immediately with large volumes of cold water.
- Irrigate ocular exposures with large volumes of saline or water, followed by fluorescein staining to determine if there is significant corneal injury.
- Do not induce emesis with acid or alkaline ingestion because it can worsen the injury. Simply give water.
- Do not try to neutralize the acid with a base or a base with an acid because a heat-producing reaction can occur, which would destroy more tissue.
- Charcoal is not useful, nor are steroids or prophylactic antibiotics.

Lead Poisoning

Up to 12 million preschool children per year may be affected by lead in the United States. Lead is ingested from paint, soil, dust, drinking water, and in the past from gasoline. Lead poisoning is primarily a chronic condition, not acute.

- Can be absorbed by inhalation, from the skin, or from the GI tract (increased by deficiencies of zinc, iron, and calcium)
- Is primarily excreted through urine (80–90%), with the remainder through stool

Note

Corrosive describes a chemical that will dissolve the structure of an object (can be acids or bases). In other words, when it comes into contact with a surface, the surface will deteriorate.

Caustic is sometimes used as a synonym for corrosive but really only refers to strong bases, not acids.

Note

The most common serious injury is the oral ingestion of liquid drain cleaner.

Note

Corrosives/caustics are immediately dangerous to tissues they contact, while **poisons** may have systemic effects which require time to be evident.

Note

Lead is primarily excreted in urine and bile.



Note

Think **lead** in patients who have both microcytic anemia and abdominal pain.

Clinical Presentation

- Adults: abdominal pain, anemia, renal disease, azotemia, neurologic manifestations such as headache and memory loss; possible hypertension
- Children:
 - Acute: abdominal pain, anemia, lethargy, seizures, coma
 - Chronic: irreversible neurologic damage such as mental retardation and poor cognitive/behavioral function

Blood lead level is the key to diagnosis, with **<10 µg/dL** considered acceptable. In children, “lead lines” are densities seen at the metaphyseal plate of the long bones, indicating long-term exposure.

Treatment. Treatment includes chelation with calcium EDTA, dimercaprol (BAL), penicillamine, or succimer (oral therapy). Urine output should be maintained at 1–2 mL/kg/hr to aid in maximal excretion.

Management of lead toxicity/poisoning should be done according to blood lead level:

- **Mild (5–44 mcg/dL):** no treatment needed; repeat level in 1 month
- **Moderate (45–69 mcg/dL):** 2,3 dimercaptosuccinic acid (DMSA)
- **Severe (≥70 mcg/dL):** DMSA + EDTA (calcium disodium edetate)

ALCOHOLISM

A 35-year-old man is brought to the ED by his wife after he had a seizure. He is agitated and combative. He is yelling and trying to hit the nurses, and tells you that he is in France. He is also yelling at his mother, who is not in the room. His wife tells you that he drinks a liter of whiskey a day, though he has not had any in the last few days because he didn't have the money. His pulse is 130/min, blood pressure 160/90 mm Hg, and respirations 24/min. He is diaphoretic and extremely irritable. His temperature is 38°C (100.4°F). The rest of the exam is unremarkable.

Alcoholics may present with any one of the following symptoms:

Mild withdrawal: tremors, tachycardia, anxiety; seizures may be seen 6–12 hours after last drink

Delirium tremens (DT) (manifests 48–72 hours after last drink but can last up to 10 days): mental confusion, autonomic hyperactivity, visual hallucinations, severe agitation, diaphoresis

Alcoholic hallucinosis (may be confused with DT) (starts 12–24 hours after last drink but can last days to weeks)

- Paranoid psychosis without tremors and confusion
- Normal vital signs (no hypertension or tachycardia)

Note

The diagnosis of all alcohol withdrawal-related syndromes is made clinically, not by lab values.

- No agitation
- Normal appearance except for auditory (most common), visual, or tactile hallucinations

Wernicke encephalopathy: confusion, ataxia, and ophthalmoplegia (nystagmus)

Korsakoff psychosis: amnesia and confabulations

Treatment. Alcohol withdrawal has a very high mortality rate (5%). Benzodiazepines can be life-saving (**taper dose slowly**). Diazepam and chlorthalidone are common, due to their long half-life. Hydrate with isotonic fluids and electrolyte replacement.

- Anticonvulsants have no role.
- Avoid antipsychotics such as haloperidol, as they can lower the seizure threshold and cause prolonged QT interval.

Symptom-triggered therapy is recommended. A work-up for alternative diagnosis is also very important.

- Be careful when using benzodiazepines for cirrhosis
- CT head to look for intracranial bleed
- Lumbar puncture to rule out meningitis if there is a fever
- Chest x-ray: look for aspiration pneumonia
- High doses of thiamine IV for Wernicke and Korsakoff; treatment for alcoholic hallucinosis is benzodiazepines and haloperidol (there is no risk of seizures, so it can be used here)

Clinical Recall

A 17-year-old woman who drank from her grandfather's whiskey bottle is brought to the ED with intermittent blurring of vision and vomiting. Which of the following is the treatment of choice?

- Activated charcoal
- Ethanol
- Fomepizole
- Thiamine

Answer: C

Note

Benzodiazepines are dosed and administered using a validated assessment tool, the most common of which is Clinical Institute Withdrawal Assessment for Alcohol (CIWA-Ar) scale. This requires formally assessing the patient at regular intervals.

HEAD TRAUMA

A 20-year-old man is playing football when he is struck in the head and loses consciousness for a few minutes. He awakens and has some motor weakness of his left arm, which seems to slowly worsen over the course of the next hour as he is brought to the ED.



Head trauma is any degree of traumatic brain injury resulting in a range of injuries, from scalp laceration to headache to loss of consciousness or focal neurologic deficits. The term does not imply a specific mechanism of injury. The injury can result in concussion, contusion, epidural hematoma, subdural hematoma, or traumatic subarachnoid hemorrhage. Cerebral contusion can progress to intraparenchymal hemorrhage.

Clinical presentation is often only suggestive of the degree of injury. The specific injury can only be determined with CT scan.

- All forms of head trauma can result in headache, amnesia, and loss of consciousness. The degree of amnesia is loosely associated with the degree of head trauma, i.e., the worse the trauma, the more memory one loses.
- Memory loss starts from the time of injury and stretches both forward (**anterograde**, in which one doesn't remember events since the time of the injury) and backward (**retrograde**, in which one forgets past events).
 - Retrograde amnesia (more common) starts from the time of the injury and moves further back in time depending on the severity of the injury. The more severe the injury, the further back in time you forget.
 - Recovery of memory starts with recollection of the most distant progressing to the most recent memories.
- Loss of consciousness, although possible in any form of head trauma, is not always present, even with relatively severe forms of brain injury. There can be very severe intracranial bleeding (e.g., subdural hematoma) without a loss of consciousness. This is particularly true of chronic subdural hematoma.
- Concussion is generally not associated with focal neurologic findings, such as motor or sensory deficits. The presence of focal findings, starting in order of highest frequency, is most commonly associated with epidural and subdural hematomas and contusion.

Diagnosis. CT scan of the head is the mainstay of diagnosis of brain injury. Contrast enhancement is not necessary because blood does not enhance with contrast.

- Hemorrhage should be visible instantly if present at the time of the initial presentation.
- **Subdural hematoma is crescent-shaped and epidural hematoma is lens-shaped.**

Follow-up scanning is also done with CT, as needed.

- Skull x-ray is never used for diagnostic purposes.
- Normal x-ray does not exclude hemorrhage, and abnormal x-ray does not confirm the presence of a hemorrhage.
- Cervical spine x-rays should be obtained if there are focal findings consistent with cervical radiculopathy or if spinal tenderness is present. Even without these findings, you should have a very low threshold for obtaining cervical spine x-rays.

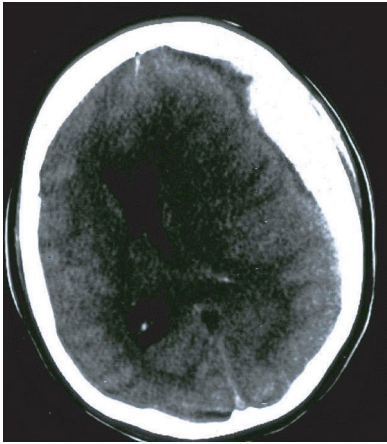


Figure 10-15. Subdural Hematoma
(venous in origin; may be acute or chronic and may or may not result in midline shift)

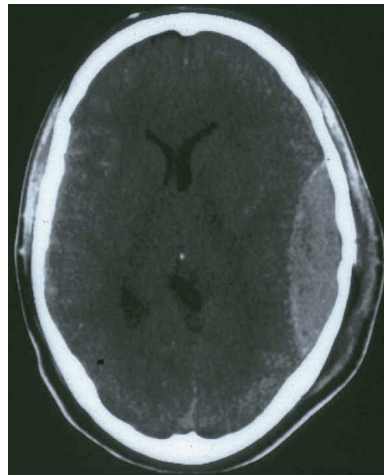


Figure 10-16. Epidural Hematoma
(usually arterial and associated with skull fractures)

Note

A concussion is diagnosed by a history of loss of consciousness plus a negative CT scan of the head.

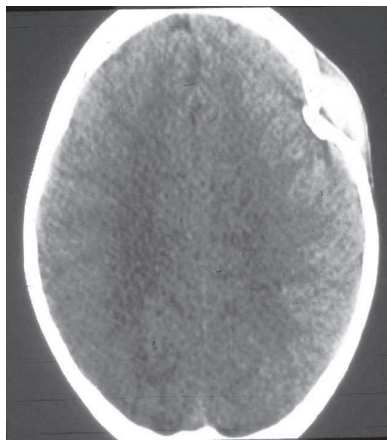


Figure 10-17. Depressed Skull Fracture

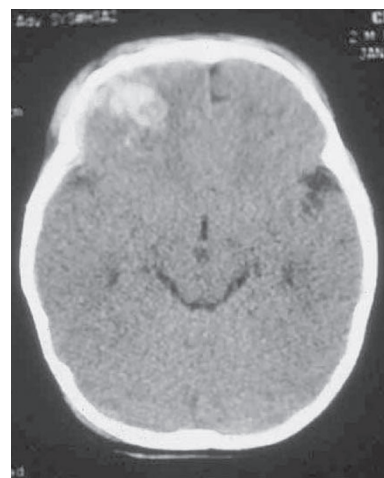
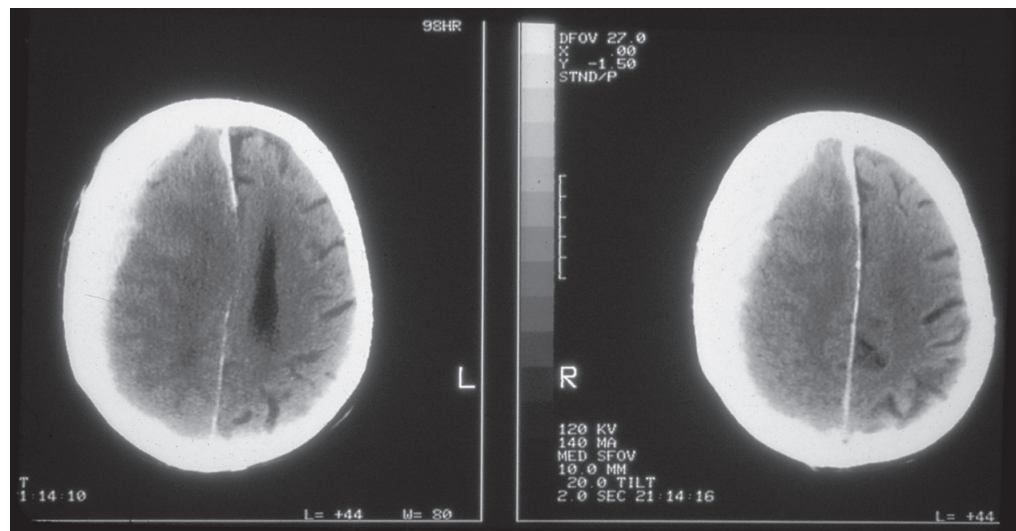


Figure 10-18. Cerebral Contusion
(petechial hemorrhage and/or edema, which may worsen over days)



Dr. Conrad Fischer

Figure 10-19. CT Scan Demonstrating Subdural Hematoma with a Midline Shift

Treatment. Severe intracranial hemorrhage should be managed by lowering the intracranial pressure.

- For acute response, use hyperventilation to $p\text{CO}_2$ of 30–35, which will cause vasoconstriction of cerebral vessels and then a drop in intracranial pressure; use in moderation and for limited amount of time.
- Osmotic diuretics such as mannitol and elevation of the head of the bed are also helpful for lowering intracranial pressure. This is in preparation for surgical evacuation. Elevate the head of the bed to 30 degrees and maintain systolic BP to 110–160 mm Hg. This slight degree of hypertension assures that the cerebral perfusion pressure is adequate.
- Steroids are not effective for head trauma.

Cerebral perfusion pressure is best when mean arterial pressure ≥ 60 mm Hg above the intracranial pressure. Stress ulcer prophylaxis with medications such as PPIs and H₂ blocker is given after all severe head trauma and after intubation for >72 hours.

Subarachnoid Hemorrhage

A 52-year-old woman is at her office when she develops the sudden onset of a severe headache, stiff neck, photophobia, and loss of consciousness. She awakens within the hour that she arrived in the hospital. She is noted to have a severe headache, nuchal rigidity, photophobia, and temperature 38.5 C (101.3 F).

Subarachnoid hemorrhage (SAH) is the sudden onset of bleeding into the subarachnoid space. It most often occurs spontaneously.

- Aneurysm formation is the most common etiology. The aneurysms can be saccular or fusiform, and are most commonly around the circle of Willis. The most common sites are anterior communicating artery, middle cerebral artery, and posterior communicating artery.
- There is an association with polycystic kidney disease, Ehlers-Danlos syndrome, and some other connective tissue diseases.
- Head trauma is rarely a cause.

Clinical Presentation. Sudden onset of severe headache is the hallmark of SAH. Other features include:

- Loss of consciousness due to sudden rise in intracranial pressure (up to 50% of patients)
- Focal neurologic symptoms (>30%), most commonly from compression of the oculomotor cranial nerve
- Other possible neurologic defects, due to the pressure of the bleed dissecting into surrounding tissues
- Nuchal rigidity, photophobia, headache, and papilledema due to meningeal irritation
- Fever 3–4 days after the initial hemorrhage; this can simulate meningitis because SAH is a form of chemical meningitis from irritation by the blood
- Seizures (extremely common); 1-year mortality can be up to 50%, with half of the patients dying upon immediate occurrence of the bleed



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Figure 10-20. Subarachnoid Hemorrhage on CT Scan



Note

A spinal headache may occur after a lumbar puncture in some patients. This is treated with a blood patch.

Clinical Pearl

Traumatic lumbar puncture may cause RBC in the CSF, but xanthochromia is absent.

Longer-term manifestations include the development of focal deficits, seizures, rebleeding, and hydrocephalus. Vasospasm after the bleed results in hypoperfusion to portions of the brain parenchyma and the development of stroke. Rebleeding occurs when the clot falls off of the original site of bleeding. Up to half of the people who rebleed will die. Hydrocephalus occurs when the blood cells clog up the arachnoid granulations through which CSF normally drains.

Diagnosis. The initial test is the CT scan, which is more sensitive than MRI for the diagnosis of SAH. The CT, done without contrast, has a sensitivity of 90–95% within the first 24 hours after the onset of the bleed. With time, the diagnostic sensitivity of the CT actually diminishes, as the red cells within the CSF hemolyze and are resorbed and converted into the yellowish coloring (described on CSF examination as **xanthochromia**).

- If the initial CT is normal and SAH is still suspected, do a **lumbar puncture**. The lumbar puncture is the most sensitive diagnostic test, i.e., an absence of red cells and xanthochromia on lumbar puncture essentially excludes an SAH. Xanthochromia is due to lysis of RBCs and formation of bilirubin (straw-colored CSF). Xanthochromia needs 4–6 hours to develop.
- Angiography is used to determine the specific anatomic site of the vascular defect and the site of the bleed. ECG abnormalities such as inverted or enlarged T-waves are often associated with the development of SAH and are not a cause for alarm.

Treatment. Initial steps are to maintain systolic BP at 110–160 mm Hg. Pressure higher than that can provoke more bleeding, while pressure lower can provoke cerebral ischemia through hypoperfusion (given the increased intracranial pressure).

- Use nimodipine, a calcium-channel antagonist, to lower the risk of spasm in the blood vessel, thus lowering the risk of subsequent stroke.
- Do **angiography** to determine the anatomic site that will need catheter or surgical correction. It is important to perform this so that surgical correction (usually with embolization or clipping of the AVM) can occur before rebleeding develops. If hydrocephalus occurs, then shunting will be needed. Embolization is superior to surgical clipping.

BURNS AND RADIATION INJURY

Burns

A 32-year-old fireman is caught in a fire and briefly trapped under a burning staircase. He is quickly extracted and brought to the ED fully alert. His respiratory rate is 14/min and weight is 220 pounds. There is soot in his mouth and nose and on his face, and his sputum is not carbonaceous. The nasal hairs are singed. He has no stridor or hoarseness, and the lungs are clear to auscultation. He has first-degree burns on his right leg and second- and third-degree burns on his right arm and chest.

Injury due to burns can be divided into several types. The most common causes of death from fire are **smoke inhalation** and **carbon monoxide poisoning**. Thermal injury is most dangerous when it is respiratory related.

Skin injury is labeled *first-degree* when the skin is fully intact, even though it may be discolored.

- **First-degree** burns are not associated with blister formation and appear “sunburn-like.” The skin may be red or gray, but capillary refill remains normal.
- **Second-degree** burns result in blister formation.
- **Third-degree** burns are deeper and destroy skin appendages such as sweat glands, hair follicles, and sometimes pain receptors. This leaves patients with third-degree burns insensate; any pain they perceive is from surrounding structures where pain receptors are intact.

Although not apparent at first, respiratory injury can be the most life-threatening injury.

- Soot in the mouth or nose, stridor, wheezing, altered mental status, burned nasal hairs, and burns involving closed spaces are all clues to impending pulmonary and laryngeal edema.
- Shock occurs not only from direct skin loss but also from release of a host of mediators that cause **diffuse capillary leak** for the first 18–24 hours. Serious capillary leak occurs when the percentage of serious body surface area burn >20–25%.

Clinical Presentation. Altered mental status, dyspnea, headache, and chest pain are clues to severe carbon monoxide poisoning. Laryngeal edema can result in stridor, hoarseness, and dyspnea. Soot in the nose and mouth can imply impending airway compromise.

The “**Rule of Nines**” is used to determine the body surface area that has been burned, and thus assess fluid resuscitation needs:

- **Head and arms:** 9% each
- **Chest, back, and legs:** 18% each
- Patchy burns can be estimated by using one hand’s width as an estimate of 1% of body surface area burned.
- Circumferential burns are critical in the assessment because as they heal, they tighten and cut off circulation, leading to limb compromise and the need for escharotomy.

Diagnosis. Besides the obvious burn, carboxyhemoglobin levels are essential in severe burns. Severe burns are defined as combined second- and third-degree burns >20% in adults, or >10% in the very old or very young, or third-degree burns >5% of body surface area (BSA). Chest x-ray and bronchoscopy help determine the exact extent of respiratory injury when it is uncertain. Bronchoscopy can reveal severe thermal injury to the lungs even when the initial chest film is normal. Foley catheter placement helps determine the adequacy of fluid resuscitation.

Treatment.

- If patient has signs of severe respiratory injury, the first step is to intubate before more severe laryngeal edema can occur and make the intubation difficult.
- If carboxyhemoglobin level is significantly elevated (>5–10%), administer 100% oxygen.
- Fluid resuscitation over the first 24 hours is based on a formula of 4 mL per % BSA burned per kg. Use second- and third- degree burns in your calculation.
 - Use Ringer’s lactate as the preferred fluid; give 50% of the fluid in the first 8 hours, 25% in the second 8 hours, and 25% in the final 8 hours. (This is known as the **Parkland formula**.)
 - Afterward, when the diffuse capillary leak improves, give enough fluid to maintain urine output >0.5–1 mL per kg per hour.

Note

The **Rule of Nines** differs between adults and children. Refer to the Pediatrics book for more information on burns in children.



- Give stress ulcer prophylaxis with H2 blocker or PPI.
- To prevent infection, use topical treatment with silver sulfadiazine.
- Do not break blisters and do not use steroids.
- Escharotomy is useful in circumferential burns.
- Skin grafting is done on the basis of the size and severity of the injury.
- Patients with burn injuries are at increased risk for pseudomonal and staphylococcal infections; if there is concern for infection, give IV antibiotics that cover these organisms.

Radiation Injury

- **Ionizing radiation** damages tissues primarily through destructive changes to DNA molecules. Ionizing radiation is lethal and can often cause cancer. Longer exposures give worse injury.
- **Nonionizing radiation** is less destructive to tissue and causes injury primarily as burns. Examples include infrared, ultraviolet, and microwave radiation.

Clinical Presentation. To give a sense of scale, mortality is almost zero with <2 Gy (or Sv) of exposure. This rises almost to 100% mortality with >10 Gy (or Sv). (10 Gy = 1,000 rad.)

Any cell can be damaged by ionizing radiation, but the more rapidly the cell divides, the more vulnerable it is to radiation. This is because more DNA damage can be done during the time of division.

Common sites of radiation injury include the following:

- **Bone marrow:** As little as 2–3 Gy (200–300 rad) can depress lymphocyte count. Neutrophils are the next most sensitive cell, while erythrocytes are the least sensitive.
 - Leukemia (**earliest and most common cause of cancer from radiation exposure**)
 - Thrombocytopenia, with possible death from bleeding
 - Infection and bleeding from depressed bone marrow function (**most common causes of death in acute exposure**)
- **Gonads:** 2–3 grays result in temporary aspermatogenesis, while 4–5 grays can make men permanently sterile. Testes are more sensitive than ovaries.
- **GI:** Nausea and vomiting are the most common early symptoms of radiation exposure (50% of cases with 2 Gy [200 rad] exposure and 100% of patients with >3 Gy exposure). Also, the rapidly reproducing intestinal lining ulcerates, leading to bleeding and infection later.
- **Other common sites of radiation injury:** the skin, salivary glands, respiratory epithelium, and thyroid glands

Treatment. Management is supportive. There is no specific therapy to reverse radiation injury.

- Antiemetics, given that nausea is such a common feature of radiation sickness
- Blood products, i.e., platelets and RBC transfusions; WBC transfusions do not help
- Colony-stimulating factors (G-CSF, GM-CSF) to help restore marrow function
- Antibiotics, used as needed when infection develops
- Bone marrow transplantation (occasionally useful)

THERMOREGULATORY DISORDERS

Heat Disorders

Heat disorders are classified as exertional disorders, common in younger individuals doing strenuous activity (“exertion”) in hot environments, or nonexertional disorders, common in the elderly, the very young, and the chronically ill.

Exertional disorders

- **Heat cramps** (mild exertional disorder) can happen to any healthy person who develops fluid and electrolyte depletion
 - Patient develops painful muscular contractions lasting a few minutes, with muscle tenderness present. Body temperature is normal.
 - Patient is able to sweat. There are no neurologic abnormalities.
 - Treatment is rest, oral rehydration, and salt replacement.
- **Heat exhaustion** (more severe)
 - Patient is weaker with more systemic symptoms. Body temperature may be slightly elevated.
 - Patient is able to sweat and remove heat from the body. There may be mild neurologic symptoms such as headache, nausea, and anxiety, but severe confusion is rare.
 - Death is very unlikely, but the disorder can progress to heat stroke if not treated.
 - Treatment is oral fluid and electrolyte replacement. For severe weakness, IV hydration may be needed.
- **Heat stroke** (very severe and potentially life-threatening)
 - Patient has lost the ability to remove heat from the body because of an impaired ability to sweat; 50% of patients retain some capacity to sweat but in insufficient amounts to keep up with heat generation.
 - Body temperature may become severely elevated ($>41^{\circ}\text{C}$), resulting in confusion, disorientation, nausea, blurred vision, and seizures.
 - Numerous lab abnormalities may occur, including hemoconcentration, rhabdomyolysis, and elevated BUN, creatinine, and white cell count.
 - Anuria, DIC, and lactic acidosis may develop.
 - Treatment for **non-exertional heat stroke** is IV fluid replacement and external evaporative cooling of the body (place in cool environment and spray with water, then fan to evaporate the fluid). Treatment for young athletes with **exertional heat stroke** is immersion in ice water. In the elderly, chlorpromazine and diazepam can be used to control shivering.

Nonexertional disorders

- **Malignant hyperthermia** occurs as an idiosyncratic reaction to an anesthetic such as halothane or succinylcholine. Virtually any anesthetic may cause it.
 - Rhabdomyolysis may develop.
 - Treatment is dantrolene, which directly relaxes muscles by inhibiting calcium release from the sarcoplasmic reticulum,



- **Neuroleptic malignant syndrome** occurs as an idiosyncratic reaction to a phenothiazine or butyrophenone such as haloperidol. It is postulated that dopamine blockade or depletion can lead to abnormal regulation of body temperature and Parkinsonian features.
 - Muscular rigidity and rhabdomyolysis may occur; also, altered mental status, muscle rigidity, and autonomic dysfunction
 - Treatment, besides stopping the drug, is bromocriptine and dantrolene.
- **Serotonin syndrome** (common and potentially life-threatening) is a drug reaction that often occurs when 2 medications affecting the body's level of serotonin are taken together, such as SSRI, SNRI, meperidine, and tramadol.
 - Symptoms can range from mild to severe: agitation, confusion, muscle rigidity, and heavy sweating
 - No single test can confirm serotonin syndrome, and a number of other conditions have similar symptoms
 - Treatment is supportive care and cyproheptadine (serotonin antagonist)

Hypothermia

Hypothermia is a medical emergency that occurs when the body loses heat faster than it can produce heat, causing a dangerously low core body temperature $<35^{\circ}\text{C}$ ($<95^{\circ}\text{F}$) (normal 37°C or 98.6°F). Core temperature is measured with a rectal probe or through the esophagus. It is often seen with alcohol intoxication, particularly in the elderly.

Severe hypothermia is core temperature $<30^{\circ}\text{C}$ ($<86^{\circ}\text{F}$).

Clinical Presentation. Symptoms of severe hypothermia commonly relate to the CNS. Lethargy, confusion, and weakness may occur. Death is most commonly a result of arrhythmia (Osborne wave or J-wave), from the effect of the cold on altering cardiac conduction. Other complications include metabolic acidosis, respiratory acidosis, kidney injury, and hyperkalemia.

Diagnosis. The ECG can show a wide variety of serious arrhythmias, including ventricular fibrillation or ventricular tachycardia. The most characteristic finding is an elevated J-point, known as Osborne waves. J-wave elevation may mimic ST-segment elevation.

Treatment. Most patients respond well to common-sense treatment such as a warm bed, bath, and heated blanket. For very severe cases, use warmed IV fluid or humidified oxygen. Use caution, though, because overly rapid rewarming can cause arrhythmias; if life-threatening arrhythmias occur, it is important to continue resuscitative efforts until body temperature $>35^{\circ}\text{C}$ ($>95^{\circ}\text{F}$). If the patient is cold but not shivering, active measures should be used:

- **Active external rewarming:** only to truncal areas; warm blankets; heat lamps; hot-water bottles
- **Active internal rewarming:** warm IVFs (45°C [113°F]), warm humidified oxygen (45°C [113°F]), warmed gastric lavage via NGT, warmed hemodialysis

Hypothermia is one of the few times in which a patient can be resuscitated from pulselessness beyond the usual 10 minutes of efforts.

Note

Hypothermia must be worked up for precipitant factors:

- Hypoglycemia (most common cause)
- Hypothyroidism
- Sepsis

Clinical Recall

A 65-year-old woman is brought to the ED after a fall in the shower. On examination, there is a contusion on the posterior aspect of the skull. On examination of the eye, there is mild dilation of the right pupil with evidence of papilledema in both eyes. Which of the following would not be considered in the management of this condition at this time?

- A. Administer IV steroids
- B. Elevate head end of bed
- C. Hyperventilate the patient
- D. Maintain systolic blood pressure >110 mm Hg
- E. Mannitol infusion

Answer: A

DROWNING

Drowning is a significant worldwide public health concern. It is a major cause of disability and death, particularly in children. At least 35% of survivors sustain moderate-to-severe neurologic sequelae.

- Alcohol and drug use are strongly associated with an increased risk of death by drowning.
- Muscular exhaustion, head and spinal trauma, or acute myocardial infarction are predispositions to drowning and near drowning.
- 10–20% of drowning victims may have suffered dry drowning, in that there is no water aspirated into the lungs. Dry drowning is secondary to laryngospasm.

Drowning from aspiration of water can be divided into 2 types:

- **Freshwater** (hypotonic) alters pulmonary surfactant, resulting in unstable alveoli which then collapse.
 - The hypotonic water is absorbed into the body, leading to **acute hypervolemia, hemodilution, and intravascular hemolysis**.
 - At autopsy, the lungs may contain little water.
- **Seawater** (hypertonic) draws water out of the body into the lung, causing **systemic hypovolemia and hemoconcentration**.
 - The lungs become even more heavy and fluid-filled because the surfactant is essentially washed out.

Presentation. Only the presentation of near drowning is important to discuss because drowned victims are dead. Presentation can vary from coma to agitation. Cyanosis, coughing, and signs of pulmonary edema, such as tachypnea, tachycardia, and blood-tinged sputum are common. Rales and rhonchi can be found on the exam. Hypothermia is also common.

Note

Near drowning is survival after immersion, at least for some time. Morbidity is high and death may occur later. The exact definition is still the topic of much debate.

Drowning is defined as death within 24 hours after submersion in water.

Note

Young children are more likely to drown in freshwater (e.g., swimming pool) than in seawater.



Laboratory Findings. Arterial blood gases show hypoxia and hypercarbia, as well as metabolic acidosis from anaerobic metabolism. Hyperkalemia may be present if there is significant hemolysis. Renal insufficiency on the basis of hypoxia is a rare finding.

Treatment. The first task is to remove the patient from the water and do ABCs (airway/breathing/circulation) of resuscitation.

- Endotracheal intubation as needed
- Supplemental oxygen

After removal from water, the most important initial step is to **establish an adequate airway**. Continuous positive airway pressure (CPAP) is the most effective treatment and gives the best correction of hypoxia and acidosis. Even if the patient appears comfortable initially, observe for 24 hours because ARDS (acute respiratory distress syndrome) may develop as a late finding.

The following treatments **do not help and may be harmful**:

- **Abdominal thrusts** may lead to aspiration of gastric contents.
- **Antibiotics** are indicated only if pneumonia develops.
- **Steroids** have no benefit.

ALLERGIC REACTIONS

Anaphylaxis

Anaphylaxis is a syndrome of histaminergic release in which there are signs of severe injury such as urticaria, angioedema, hypotension, tachycardia, and respiratory compromise. As an idiosyncratic reaction, patients can develop anaphylaxis from any medication, food, insect bite, or antigenic substance entering the body by oral or parenteral route.

- Penicillin, phenytoin, contrast agents, and allopurinol allergy are common.
- Chocolate, peanuts, and strawberries are common.
- Bee stings are common.

Clinical Presentation. Mild symptoms include a rash known as “hives.” More severe symptoms include dyspnea, stridor, tachycardia, hypotension, and hemodynamic collapse.

Treatment. Treatment is epinephrine (intramuscular or IV) and inhaled albuterol.

Venomous Bites and Stings

Cat and dog bites

Dog bites (most common bites in United States) are usually ripping and tearing in nature, whereas cat bites are usually a puncture wound.

Note

Antihistamines and corticosteroids have not been proven to improve outcomes in anaphylaxis (and neither agent would work quickly enough). Steroids are sometimes given to prevent a delayed recurrence of symptoms, but this is not supported by strong evidence.

Clinical Presentation. Infection is more likely in patients with a delay in treatment, extremes of age and extremity injuries. Infections are most often polymicrobial.

- Cat bites are highly associated with *Pasteurella multocida*.
- Dog bites are associated with *Pasteurella*, *Eikenella*, hemolytic streptococci, *Staph aureus*, and *Capnocytophaga canimorsus*.

Treatment. Treatment is exploration, debridement, irrigation, and proper wound care. If prophylactic antibiotics are indicated, the drug of choice is amoxicillin and clavulanate (with penicillin-allergy, use a combination of clindamycin or metronidazole plus ciprofloxacin or trimethoprim/sulfamethoxazole or doxycycline).

Indications for antibiotic prophylaxis:

- Any cat bite
- Any bite on hand, face, joint, or genitals
- Immunocompromised status
- Asplenic patient (high risk of overwhelming sepsis from *Capnocytophaga canimorsus*)

Most wounds should be left unsutured except for facial wounds for cosmetic reasons. Never suture the hand.

Human bites

Human bites can occur as a result of incidental or purposeful injury. They carry an infection rate of 15%, which is greater than cat and dog bites together. The most common organisms are anaerobic and aerobic bacteria, specifically, *Eikenella corrodens*. Hepatitis B and HIV can also be transmitted through bites but are much less common.

Treatment. Clean and irrigate wound well. If bite <12 hours old, close loosely.

- Tetanus, hepatitis B, and prophylaxis counseling
- 5–7 day course of prophylactic antibiotics
- There is no place for cultures on fresh bites.

Rabies

Rabies (bite) is a viral disease that affects the CNS. It is carried by bats, dogs, cats, raccoons, rats, skunks, and foxes; transmission occurs through their **saliva** a few days before death, when the animal “sheds” the virus. Since it affects the nervous system, most rabid animals behave abnormally.

The incubation period of rabies is up to 1 year. It is nearly 100% fatal once the disease has been contracted.

Clinical Presentation. Prodrome of 2–10 days, including fever and paresthesias at the bite site. Neurologic changes include aphasia, paralysis, hypersalivation, and myoclonus. Diagnose with viral cultures from saliva, CSF, or serum.

Note

All human and monkey bites should receive prophylactic antibiotics.



Note

All venomous snakes are capable of biting a person without injecting venom. They may deliver a “dry bite” rather than waste their venom on a creature too large for them to eat.

Note

Identification of the snake is very important in planning treatment, but it is not always possible. However, in North America, polyvalent antivenoms are available, so snake identification is not high priority.

Treatment. Ribavirin has been used in confirmed cases. Prophylaxis with human rabies immunoglobulin (HR16), which gives immediate passive immunity, and human diploid cell vaccine (HDCV) should be given. The current guidelines for rabies vaccination are as follows:

- **Preventive vaccination** (no exposure) (usually 3 doses)
 - Those at high risk of exposure to rabies (veterinarians, animal handlers, rabies lab workers, etc.) should be offered the vaccine.
 - Those in frequent contact with rabies virus or potentially rabid animals (e.g., an international traveler who is likely to come into contact with animals in a region where rabies is common) should be offered the vaccine.
- **Vaccination post-exposure**
 - Those who have been bitten by an animal or may have been exposed to rabies should receive wound cleaning and started on vaccine.
 - **If never vaccinated against rabies previously:** 4 doses (1 dose right away and additional doses on days 3, 7, and 14); give rabies immune globulin at first dose
 - **If vaccinated against rabies previously:** 2 doses (1 dose right away and another on day 3); no need to give rabies immune globulin

Snakebites

Although 50,000 snakebites are reported per year worldwide, only about 8,000 are poisonous. There are <5–10 deaths per year, with rattlesnakes accounting for almost all fatalities.

Snake venom contains numerous potentially dangerous substances such as hemolysis toxin, cardiotoxin, neurotoxin, and proteolytic enzymes. Some of these substances can result in neuromuscular blockade.

Factors which affect the severity of the bite:

- **Body size:** The smaller the body, the worse the effect; thus, bites tend to be worse in children.
- **Location of bite:** Trunk and face bites are worse than extremity bites.
- **Exercising after bite:** Muscular activity helps spread the venom through the lymphatics (so minimize physical activity).
- **Depth of injury:** No poisoning occurs in 20–50% of bites because they are too superficial.

Treatment. Transport the patient immediately to the nearest medical facility.

- **Immobilize:** will help decrease the spread of venom through the lymphatics, which increases with muscular contraction
- **Apply compression bandage:** will help to decrease lymph flow; be sure not to apply so tightly that it decreases venous flow
- **Antivenin:** be cautious of anaphylactic reaction that may occur to the horse serum
- **Supportive:** manage hypotension with fluids; ventilatory support may be necessary

Ineffective therapy includes incision and suction of the bites. Tourniquets and ice immersion do not help and might be harmful.

Learning Objectives

- ❑ Outline the presentation, diagnosis, and management of diseases of the spinal cord including spinal cord compression, syringomyelia, subacute combined degeneration, anterior spinal artery occlusion, ALS, and Brown-Sequard syndrome
 - ❑ Describe the epidemiology, classification, and treatment of seizures and epilepsy
 - ❑ Describe the presentation, diagnosis, and management of movement disorders including benign essential tremor, restless leg syndrome, Huntington disease, and Parkinson disease
 - ❑ Present the diagnosis and management of autoimmune neurological diseases, including Guillain-Barre syndrome, MS, and myasthenia gravis
 - ❑ Provide a differential diagnosis and work-up of patients presenting with headache, vertigo, or dizziness
 - ❑ List the criteria for prevention of cerebrovascular accident in patients with TIA, and outline the management of patients with acute cerebrovascular accident
 - ❑ Describe the epidemiology of dementia and typical course and complications
-

DISEASES OF THE SPINAL CORD

Spinal Cord Compression

A 63-year-old African-American man is brought to the ED with back pain that started gradually 3 days ago. The patient describes the pain as “band-like” around the abdomen, but not radiating. His past medical history is significant for prostate cancer 3 years ago, which was treated with radiation.

Spinal cord compression (**neurologic emergency**) is an acute syndrome of back pain, associated with compression of the spinal cord. Common causes include cancer, herniated disk, epidural abscess, hematoma, and trauma.

Note

Spinal Cord Compression

Acute: trauma

Subacute: neoplasm most common cause

Chronic: herniation



Symptoms include:

- Pain (**earliest symptom**) which may intensify with actions that increase intrathoracic (and thus CSF) pressure
- Insidious onset of mild sensory disturbance
- Lower extremity weakness
- Sphincter or sexual dysfunction

Acute spinal cord compression has to be suspected on the basis of the history and neurologic exam; that is essential for instituting appropriate treatment early on. Cancer, fever, or bowel/bladder incontinence/retention in the clinical history would strongly suggest this diagnosis. Also, neurologic exam will show:

- Dermatomal sensory level with bilateral lower extremity weakness
- Increased lower extremity muscle tone
- Upper motor neuron signs below the level of compression

The thoracic cord (**most common site of compression, 70%**) is frequently involved because the spinal cord is narrowest at that point. Symptoms may progress quickly.

Diagnosis.

- MRI of the spine (**test of choice**)
- Abnormal plain x-ray (very common but rarely done)
- CT myelogram if MRI is contraindicated

Treatment. Once the diagnosis is suspected, start high-dose dexamethasone immediately. After the specific etiology is identified more clearly by MRI, initiate specific therapy:

- **For a radiosensitive tumor, e.g., lymphoma or multiple myeloma:** radiation therapy as soon as possible
- **For herniated disk, epidural abscess, or hematoma:** surgical decompression

Prognosis depends mainly on the functional status of the patient at the time of presentation. Up to 80% of patients who are initially able to ambulate retain that ability after treatment. Only 5% of patients without antigravity leg strength are able to ambulate after treatment.

Syringomyelia

Syringomyelia is cavitation of the spinal cord. It occurs as communicating (with the CSF pathways) or noncommunicating.

- **Communicating** syringomyelia is usually associated with the congenital Arnold Chiari malformation.
- **Noncommunicating** syringomyelia is typically secondary to trauma or tumors of the spinal cord.

In the cervical vertebrae of both gray and white matter, there is typically sensory dissociation with impaired pain and temperature and intact sensation to light touch. The loss of pain and temperature occurs in a cape-like distribution across the neck and arms. There is sparing of tactile sensation, position, and vibratory sense. Reflexes are lost.

As the lesion enlarges, there may be lower motor neuron manifestations at the level of the lesion with upper motor neuron signs below the lesion. Cavitation most commonly occurs at the level of the cervical cord. MRI is the most accurate diagnostic test. Treatment is surgical, but often unsatisfactory.

Note cavitation of spinal cord in shaded area

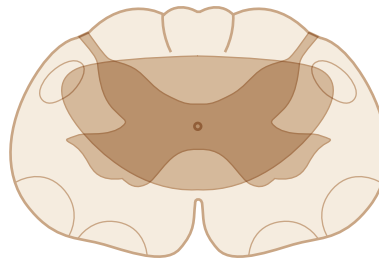


Figure 11-1. Syringomyelia

Subacute Combined Degeneration

Subacute combined degeneration occurs with vitamin B12 deficiency. Patients will complain of distal paresthesias and weakness of the extremities followed by spastic paresis and ataxia. On exam there is a combined deficit of vibration and proprioception with pyramidal signs (plantar extension and hyperreflexia).

Diagnosis is made with low vitamin B12 level. Treatment is vitamin B12 replacement.

Anterior Spinal Artery Occlusion

Anterior spinal artery occlusion presents with acute onset of flaccid paralysis that evolves into a spastic paresis over days to weeks. Additionally, there is loss of pain and temperature sensation with sparing of vibration and position sense as the posterior columns are supplied by the posterior spinal artery. Everything (motor, sensory, autonomic) is lost below the level of the infarction with the striking exception of retained vibration and position sense.

Treatment is supportive.

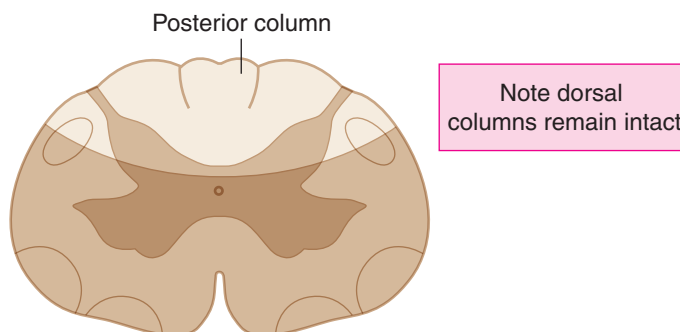


Figure 11-2. Anterior Spinal Artery Occlusion



Brown-Séquard Syndrome

Hemisection of the cord results in a lesion of each of the 3 main neural systems:

- Principal upper motoneuron pathway of the corticospinal tract
- One or both dorsal columns
- Spinothalamic tract

Presentation of 2 ipsilateral signs and 1 contralateral sign is the **hallmark sign** of a lesion.

- A lesion of the corticospinal tract results in an ipsilateral spastic paresis below the level of the injury.
- A lesion to the fasciculus gracilis or cuneatus results in an ipsilateral loss of joint position sense, tactile discrimination, and vibratory sensations below the lesion.
- A lesion of the spinothalamic tract results in a contralateral loss of pain and temperature sensation starting 1 or 2 segments below the level of the lesion.

At the level of the lesion, there will be an ipsilateral loss of all sensation, including touch modalities as well as pain and temperature, and an ipsilateral flaccid paralysis in muscles supplied by the injured spinal cord segments.

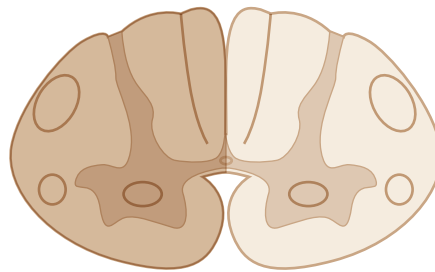


Figure 11-3. Hemisection: Brown-Séquard Syndrome

Clinical Recall

Which of the following is not a symptom of spinal cord compression?

- A. Sensory disturbance
- B. Back pain
- C. Visual disturbance
- D. Sexual dysfunction
- E. Sphincter dysfunction

Answer: C

Epidural Abscess

Epidural abscess is a rare but serious infection, usually in the spinal epidural space.

Symptoms include:

- Fever
- Leukocytosis
- Back pain
- Spinal cord dysfunction (weakness or even paralysis)
- Bladder/bowel dysfunction
- Hyperreflexia
- Possible discitis (infection of the spinal discs)

Diagnosis. Prompt evaluation with MRI is critical. Blood cultures and sampling of the abscess for the pathogen are crucial.

The bacteria most likely to be seen is *Staphylococcus aureus*, but other pathogens are also seen. MRSA is not uncommon and should be considered.

TB, as well as geographic fungi (and even brucellosis), may be causal.

Treatment should be directed at the pathogen diagnosed, with early antimicrobial therapy. On occasion surgical drainage and laminectomy are required.

Note

As *Staphylococcus aureus* is such a common cause of epidural abscess, risk factors include:

- IV drug use
- Tattoos, acupuncture
- Staph bloodstream infections, e.g., endocarditis

CEREBRAL DISORDERS

Cerebrovascular Accident (Stroke)

A 56-year-old woman is brought to the ED by her daughter with sudden onset of right upper extremity weakness that began while watching television earlier. The daughter became concerned when her mother was unable to talk in response to questions. Neurologic exam shows right upper extremity weakness with pronator drift and right facial nerve palsy. When questioned, the patient seems to understand what is being said but cannot clearly respond.

Cerebrovascular accident (CVA), or stroke, is the sudden onset of a focal neurologic deficit. The principal mechanisms by which stroke occurs are:

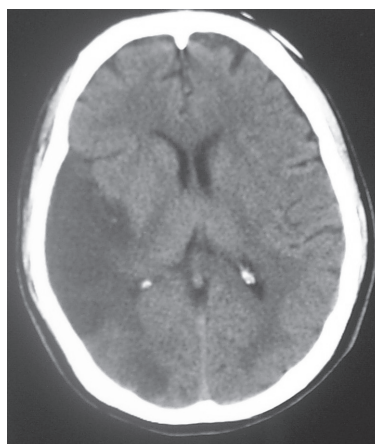
- Large artery thrombosis
- Small artery thrombosis (lacunar)
- Embolic (cardiogenic or artery-to-artery)
- Vascular dissection
- Systemic hypertension
- Bleeding



Clinical Presentation. Stroke should be considered in any patient who presents with acute onset of a focal neurologic deficit. The specific clinical syndrome is determined by the mechanism and vascular territory affected.

The blood supply to the brain is divided into 2 systems: the carotid (anterior) circulation and the vertebrobasilar (posterior) circulation. The major blood vessels comprising the anterior circulation include the anterior cerebral artery (ACA) and middle cerebral artery (MCA).

- **Occlusion of the ACA** presents with contralateral weakness and sensory loss in the leg more than in the upper extremity. Urinary incontinence, confusion, and behavioral disturbances are common. Lower extremity weakness exceeds upper extremity weakness.
- **Occlusion of the MCA** presents with contralateral hemiplegia, hemisensory loss, and homonymous hemianopia with eyes deviated toward the cortical lesion. Dominant hemisphere involvement results in aphasia. Nondominant hemisphere involvement results in preserved speech, comprehension with confusion, and apraxia with spatial and constructional deficits.



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Figure 11-4. CT Scan of a Right MCA Infarction

The posterior circulation provides blood supply to the cerebellum, brainstem, occipital lobe of the cortex, and pons. The major blood vessels that comprise the posterior circulation are the posterior cerebral artery (PCA), basilar artery (BA), and vertebral arteries.

Table 11-1. Posterior Circulation Syndromes

	Ipsilateral	Contralateral
Weber	CN III	Hemiplegia
Benedikt	CN III	Ataxia
Wallenberg	Facial sensory loss	Body sensory loss

Specific syndromes associated with occlusion of basilar artery branches include the “locked-in syndrome” (paramedian branches), presenting as quadriparesis with intact vertical eye movements; and Wallenberg syndrome (posterior inferior cerebellar artery), which presents as ipsilateral facial sensory loss, contralateral body sensory loss, vertigo, ataxia, dysarthria, dysphagia, and Horner syndrome.

Occlusion of the major cerebellar arteries produces vertigo, vomiting, nystagmus, and ipsilateral limb ataxia.

Diagnosis.

- Noncontrast CT of the head (**initial test of choice**) to distinguish between hemorrhagic and ischemic stroke; it is often negative for ischemia within first 48 hours
- Diffusion-weighted MRI (**most accurate test for detecting cerebral ischemia**)

For acute ischemic stroke, the work-up involves searching for embolic sources (echocardiogram, carotid duplex, and 24-hour Holter monitor). Also consider a work-up for inherited hypercoagulability.

Subarachnoid hemorrhage is associated with ECG abnormalities such as ischemia or inverted T-waves (“cerebral T-waves”). A “bubble study” is done on the echocardiogram to detect the presence of a patent foramen ovale or other cardiac defect.

Treatment.

- Tissue plasminogen activator (tPA) if patient presents within 3 hours of symptoms; contraindications for tPA include:
 - Stroke or serious head trauma within 3 months
 - Hemorrhage (GI or GU) within 21 days
 - Surgery within 14 days
 - History of intracranial hemorrhage
 - BP >185/110 mm Hg
 - Current use of anticoagulants
 - Platelets <100,000/mm³
 - Coagulopathy (PT >15 seconds)
- Antiplatelet therapy for secondary prevention of ischemic stroke
- Aspirin (**first-line**); start 24 hours after tPA
 - When there is known allergy to aspirin or recurrent cerebrovascular events on aspirin alone, add dipyridamole or switch to clopidogrel to enhance antiplatelet therapy.
 - **Do not combine** aspirin and clopidogrel for a stroke.
- Ticlopidine is no longer used because the rates of thrombotic thrombocytopenic purpura and leukopenia are unacceptably high.
- Nimodipine for subarachnoid hemorrhage, to reduce the risk of ischemic stroke
- Early surgical intervention (within several days) to clip off aneurysm or embolize the vessel with a catheter, for good operative candidates
 - Do not wait for unrepaired aneurysm to rebleed
 - Repair unruptured aneurysms found incidentally if >10 mm in size

Note

Noncontrast CT is the most sensitive test for detecting blood in the brain.

Note

Patients who receive tPA in an appropriate manner have better neurologic function 3 months after CVA, as compared with those who do not receive it.

**Note**

Combination of antiplatelet agents is used in coronary disease but **not in cerebral disease**.

Note

Heparin has no clear benefit with stroke. That is because of the increased risk of bleeding. Any benefit is offset by adverse events associated with treatment. For every stroke prevented, one intracranial hemorrhage is caused.

- For **symptomatic** carotid stenosis when occlusion >70% of the arterial lumen, endarterectomy is recommended (the more severe the disease, the greater the benefit). Carotid stenting is an alternative. For **asymptomatic** carotid stenosis, the effectiveness of endarterectomy is not clear; it may benefit when >60% stenosis in men age <60, but is less clear in women because they have a lower risk of stroke.

Endarterectomy is better than carotid angioplasty and stenting for symptomatic patients with >70% stenosis. Angioplasty and stenting should be considered only for those who cannot undergo surgical endarterectomy.

Transient ischemic attack

TIA (transient ischemic attack), or "mini-stroke," is a sudden finding of neurological dysfunction (blood supply to the brain is temporarily blocked) that resolves within 24 hours. It is likely of the same pathogenesis as a true stroke, and the risk of recurrent events—including completed strokes—is very high.

Therefore, full evaluation is recommended:

- Cardiac evaluation
- Visualization of the carotids

Treatment of TIA is prompt initiation of antiplatelet agents. If patients begin improving within a few hours, there is no benefit to thrombolytic therapy.

Seizures and Epilepsy

A 29-year-old man is brought to the ED after being found convulsing in his bedroom. His mother says that during the episode, her son was unable to respond to her frantic cries. She describes jerking movements that became more frequent and then stopped after a minute. Then, for at least 20 minutes after the episode, he seemed tired and lethargic.

A seizure is a paroxysmal event due to abnormally discharging CNS neurons. Epilepsy is a condition involving recurrent seizures, due to a chronic underlying process.

Causes of seizure can be remembered with the acronym "VITAMINS":

- **V**ascular (stroke, bleed, arteriovenous malformation)
- **I**nfection (meningitis, abscess, encephalitis)
- **T**rauma (especially penetrating)
- **A**utoimmune (CNS vasculitis)
- **M**etabolic (hyponatremia, hypocalcemia, hypomagnesemia, hypoglycemia, hypoxia, drug overdose/withdrawal)
- **I**diopathic
- **N**eoplasm
- **P**Sychiatric

A seizure is essentially a paroxysmal, involuntary event (associated with abnormal movement or change of consciousness or both).

- Sudden in onset, with or without an aura
- Disorientation, sleepiness, and aching muscles for minutes to hours after the event
- Incontinence, tongue-biting, and headache as a result of the seizure

Classification of seizures according to their clinical features is important in that it will determine the medications used for treatment.

The first classification is **partial** versus **generalized**. The next classification is **simple** versus **complex**.

- **Partial** seizure occurs within discrete portions of the brain. Symptoms include involuntary jerking of a finger or hand.
 - If consciousness is maintained for the duration of the seizure, that is a **simple** partial seizure. If there is a *change in consciousness* for the duration of the seizure, that is a **complex** partial seizure.
 - When a partial seizure progresses to a generalized seizure, that is a **partial seizure with secondary generalization**. Typically, the seizure will begin focally and become generalized as seizure activity involves both cerebral hemispheres.
- **Generalized seizure** arises from both cerebral hemispheres spontaneously without any detectable focal onset.
 - **Generalized tonic-clonic (grand mal)** seizure is characterized by tonic contraction of muscles throughout the body followed by intermittent relaxation of various muscle groups (clonic phase).
 - **Absence (petit mal)** seizure (children > adults) is characterized by sudden, brief loss of consciousness without loss of postural tone. EEG will show a generalized, symmetric 3-Hz spike-and-wave discharge pattern. **Atonic** seizure is characterized by sudden loss of postural tone lasting 1–2 seconds. **Myoclonic** seizure is characterized by sudden, brief muscle contraction.

Status epilepticus is defined as recurrent or continuous seizures (lasting at least 5–30 min).

Diagnosis. For idiopathic seizure, diagnosis is made only after secondary precipitating factors have been ruled out. For epilepsy, diagnosis is done with EEG. However, an abnormal EEG alone is not diagnostic, as 2–18% of the population has an abnormal EEG. Always check serum electrolytes, glucose, toxicology, and arterial blood gas to rule out hypoxia as a cause of a patient's seizure. CT scan or MRI of the head is usually indicated to rule out a structural lesion as the cause of seizure. Think of any seizure as a symptom, much like shortness of breath or chest pain, that has an extensive differential diagnosis. The evaluation of any seizing patient is to rule out reversible causes of seizure.

Treatment of seizure can be divided into management for the acutely seizing patient (status epilepticus) and the chronic epileptic patient.

Clinical Correlate

It may be difficult to differentiate **seizure** from **syncope**. Be sure to obtain a history from anyone who witnessed the event.

- Syncope does not often present with significant postictal symptoms.
- Patients recover consciousness within several minutes.
- There is no incontinence or tongue-biting afterward.

**Note**

There is no superior drug for seizures during pregnancy. Valproic acid is clearly more dangerous in pregnancy.

In the acutely seizing patient:

- Secure the airway, breathing, and circulation.
- Once an airway is established, breathing is assured, and patient is hemodynamically stable, then simultaneously evaluate and treat any precipitating cause of seizure. If a reversible cause is identified, treat aggressively.
- If patient continues to seize, then give a benzodiazepine (lorazepam or diazepam) (**drugs of choice**), which will potentiate GABA receptor function. Side effects of phenytoin include CNS (diplopia, dizziness, and ataxia) and systemic (gum hyperplasia, lymphadenopathy, hirsutism, and rash).
- If patient continues to seize, add phenytoin or fosphenytoin, which will inhibit sodium-dependent action potentials.
- If patient continues to seize, add phenobarbital. Side effects include sedation, ataxia, and rash.
- If, despite all of the treatments, patient continues to seize, add midazolam or propofol.

In patients with first-time seizure, start anticonvulsant therapy *only* if patient has:

- Abnormal neurologic exam
- Presented with status epilepticus
- Strong family history of seizure
- Abnormal EEG

Otherwise, first-time seizure is generally not treated with long-term anticonvulsant therapy.

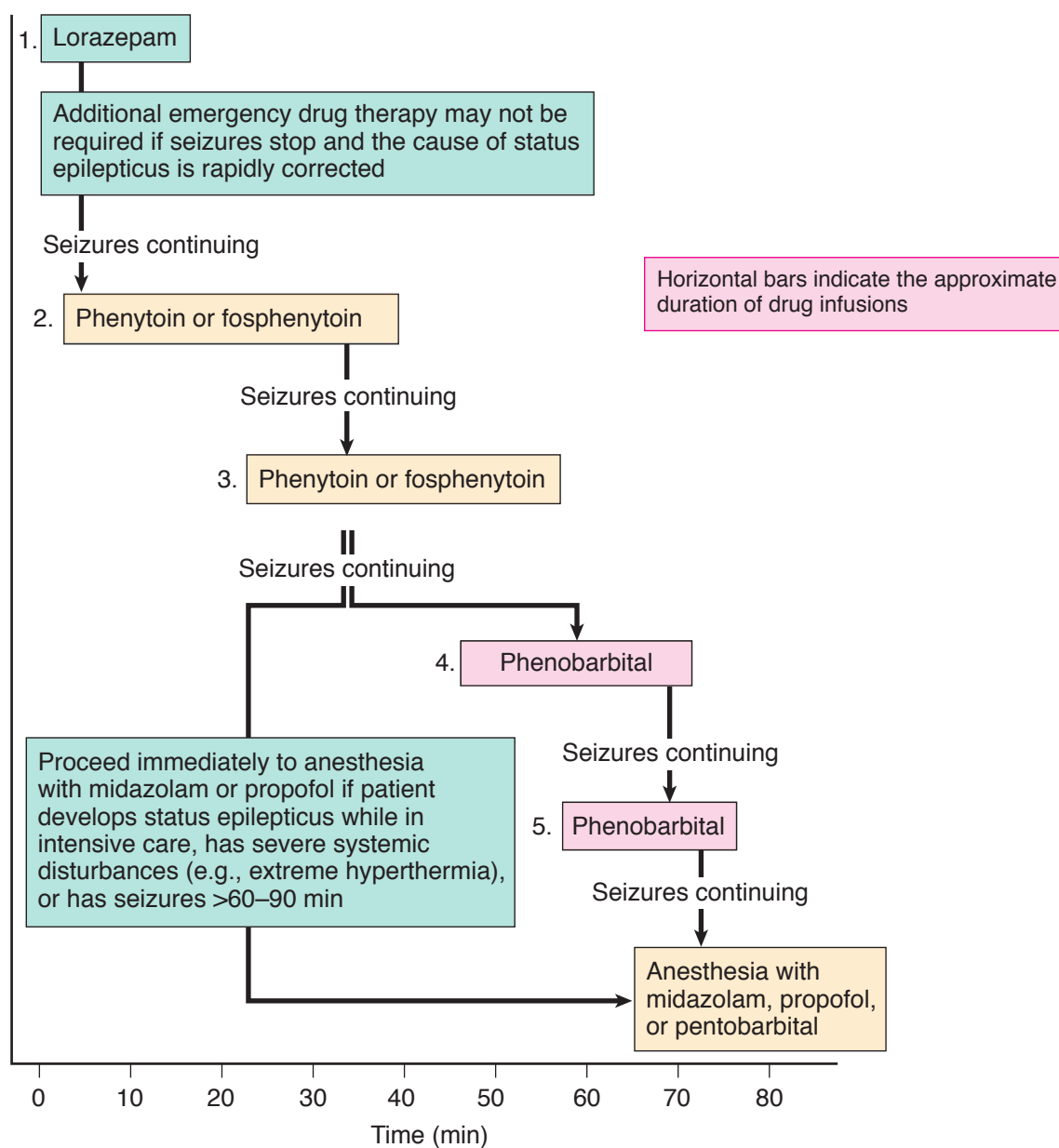


Figure 11-5. Development of Status Epilepticus

Treatment. There is no single antiepileptic drug that is superior to the others. Valproic acid, phenytoin, levetiracetam, and carbamazepine are nearly equal in efficacy.

- **Primary generalized tonic-clonic seizure** is treated with valproic acid, phenytoin, lamotrigine, carbamazepine, or levetiracetam. Lamotrigine works by decreasing glutamate release. Side effects include Stevens-Johnson syndrome.
- **Absence seizure** is treated with ethosuximide (**first-line**). Valproic acid is an alternative.



- **Myoclonic and atonic seizure** is treated with valproic acid (**first-line**).
- **Partial seizure**—whether complex or simple, and whether progressed to secondary generalized seizure—is treated with carbamazepine and phenytoin (**first-line**). Valproic acid, lamotrigine, and levetiracetam are alternatives.

Knowing when to stop treatment is difficult for the clinician.

- One option is to stop if the patient has been free of seizures for 2–3 years.
- Another option is to do a sleep-deprivation EEG to evaluate the patient's risk of recurrence. A normal test means a lower likelihood of seizures.

Clinical Recall

Which of the following symptoms are seen in Wallenberg syndrome?

- A. CN III palsy with contralateral ataxia
- B. Quadriparesis with intact vertical eye movements
- C. Vertigo, nystagmus, and ipsilateral limb ataxia
- D. Weakness and sensory loss of lower extremities
- E. Facial nerve palsy, dysarthria, dysphagia, and Horner syndrome

Answer: E

Dementia

A 67-year-old woman is brought to the clinic with complaints of forgetfulness. She explains that she has been forgetting common phone numbers and the name of her mailman, whom she has known for 25 years. Her past medical history is significant for hypertension, coronary artery disease, and high cholesterol. Her physical examination is unremarkable.

Cognitive function is measured by various mental functions, including memory, concentration, language, praxis, visuospatial functioning, and executive functions. “Dementia” refers to loss of memory with impairment of any other cognitive function sufficient to interfere with social or occupational functioning.

There are more than 100 identifiable causes of dementia in the elderly.

- **Reversible causes** include hypothyroidism, vitamin B12 deficiency, hepatic or uremic encephalopathy, CNS vasculitis, syphilis, brain abscess, brain tumor (primary or metastatic), medications (especially anticholinergics), obstructive sleep apnea, central sleep apnea, trauma, subdural hematoma, normal pressure hydrocephalus (NPH), and depression.
- **Irreversible causes** include progressive multifocal leukoencephalopathy, **Alzheimer disease (60–80% of all cases)**, dementia with Lewy bodies, frontotemporal degeneration including Pick disease, vascular dementia including multi-infarct dementia and Binswanger disease, and Creutzfeldt-Jakob disease (CJD).

Note

- By age 65–69, the prevalence of dementia is 1–5%.
- By age 100, the prevalence of dementia is 45%.
- Only 5% of Alzheimer disease is inherited.

Clinical Presentation. The most common cause of dementia is Alzheimer disease. Typically, patients will present with problems in memory and visuospatial abilities that generally occur early in the course of the disease. Social graces can be retained despite significant loss of cognitive decline. Hallucinations and personality changes typically occur late in the course of the disease.

Mild cognitive impairment refers to memory loss without dysfunction of other cognitive domains. These patients have a higher risk of developing Alzheimer disease later in life but do not have Alzheimer disease. The rate of progression is 15–20% per year.

Alzheimer disease is, by definition, the loss of memory as well as other cognitive disturbances such as aphasia, agnosia (the failure to identify entities despite intact sensory function), apraxia, or the loss of the ability to make plans and execute them. There is no single diagnostic test for Alzheimer disease.

Patients with frontotemporal dementias such as Pick disease will typically present with personality changes early in the course of their disease, with relative sparing of their visuospatial function. Social, interpersonal, and emotional abnormalities precede memory impairment. Frontotemporal dementia is often noted primarily by the family because the patient lacks insight into their condition. There is no proven therapy for this condition.

Dementia with Lewy bodies (DLB) can be confused with delirium and is characterized by fluctuating cognitive impairment.

Dementia secondary to Parkinson disease should be accompanied by clinical findings consistent with that disease. Recurrent visual hallucinations are also characteristic.

Dementia secondary to CJD is characterized by a shorter (weeks to months), more aggressive course than Alzheimer disease. Patients with CJD will present with dementia and myoclonus. Variant CJD is bovine spongiform encephalopathy (BSE). BSE is from the ingestion of prions from affected cattle. The diagnosis of CJD is by rapidly progressive dementia, myoclonus, ataxia, and the presence of 14-3-3 protein in the CSF. EEG may also help diagnose. These criteria can eliminate the need for brain biopsy.

Vascular dementia is divided into multi-infarct dementia, which typically has a stepwise progression associated with discrete cerebrovascular events, and Binswanger disease, involving the subcortical white matter, which presents with a slowly progressive course.

Normal pressure hydrocephalus will present with prominent gait abnormalities early in the course of the disease that usually precede the onset of cognitive impairment. There will also be associated urinary incontinence.

Diagnosis. All patients with cognitive impairment should be assessed with a Mini Mental Status Examination (MMSE) to identify the areas of cognitive impairment.

Initially, the work-up should focus on ruling out reversible causes of the dementia. If a reversible cause is identified it should be treated, with the hope that cognitive function can be recovered. Laboratory studies should include a complete blood count (CBC), electrolytes, calcium, creatinine, liver function studies, glucose, thyroid-stimulating hormone (TSH), vitamin B12, RPR, and HIV.

Brain imaging is most useful for patients who have a focal neurologic exam, seizures, gait abnormalities, and an acute or subacute onset of their symptoms. EEG and CSF evaluation are not necessary except for NPH-opening pressure. No CSF marker is proven beneficial, with the exception of 14-3-3 protein in CJD.



Treatment. Treatment of dementia revolves around ensuring that the family and the patient have the proper medical and emotional support to cope with the disease. Caregivers are at an increased risk for depression and anxiety. Their concerns and frustrations should be addressed at frequent intervals.

Raising the level of acetylcholine in CSF benefits patients with Alzheimer disease. Pharmacotherapy with donepezil has been shown to improve cognitive function in mild to moderate dementia. Other anticholinesterase inhibitors (rivastigmine, galantamine) appear to have similar efficacy.

Memantine is a disease-modifying drug used in advanced disease, either alone or with a cholinesterase inhibitor. Memantine seems to be neuroprotective and reduces the rate of progression of disease.

Subdural Hematoma

Subdural hematomas (also see Emergency Medicine) are venous bleeds that form between the dura and arachnoid membranes. They are caused by bleeding from small veins in this areas after trauma.

Diagnosis is (easily) made with CT scan without contrast.

Treatment.

- **Small hematomas with minimal neurologic impairment:** nonsurgical management
 - Consider reversing anticoagulation
 - Monitor neurologic status and repeat CT imaging to see if hematoma is expanding
- **Large hematomas or evidence of severe neurologic dysfunction:** prompt surgical drainage

Note

With subdural hematoma, corticosteroids are not helpful.

PAIN AND SENSORY DISORDERS

Vertigo and Dizziness

A 53-year-old woman presents at the ED with complaints of dizziness. She describes walking to the bathroom and experiencing a sudden feeling of nausea. She then vomited and fell to the floor. She was unable to get up but was able to call 911. The patient describes a feeling of the room “spinning” around her, even though she realizes she was not moving.

Vertigo is a false sensation of movement, i.e., the sensation of movement in the absence of actual movement. It may be caused by Ménière disease, labyrinthitis, positional vertigo, traumatic vertigo, perilymphatic fistula, and cervical vertigo. Other causes include vascular disease of the brainstem, arteriovenous malformation, brain tumor, MS, drug overdose, and vertebrobasilar migraine.

With the dizzy patient, the first step is to determine the nature of the patient’s complaints. “Dizziness” is a nonspecific term that provides no meaningful information about what is occurring to the patient. Simply by taking a complete history, it is possible to determine whether the patient is experiencing vertigo or presyncope.

Patients who experience vertigo will describe a sensation of movement without actually moving. They often describe their environment “spinning around them.” Sensations of tilting, swaying, or falling forward or backward are all consistent with vertigo. Acutely, these episodes are commonly associated with nausea and vomiting.

Patients who complain of presyncope will describe their symptoms as “lightheadedness” or “feeling like I’m going to black out.” Associated symptoms include generalized weakness, palpitations, and shortness of breath. It is essential to differentiate vertigo from presyncope because vertigo is usually a manifestation of neurologic disease, whereas presyncope is a cardinal manifestation of cardiovascular disease.

Once you are convinced by the history that the patient is indeed experiencing vertigo, determine whether the vertigo is **secondary to peripheral** or **central vestibular disease** (management will differ). Several points on history and physical examination will help to distinguish them.

Table 11-2. Vertigo

	Central Vertigo	Peripheral Vertigo
Onset	Gradual	Usually sudden
Tinnitus, hearing loss	Absent	Present
Neighborhood signs (diplopia, cortical blindness, dysarthria, extremity weakness/numbness)	Present	Absent
Nystagmus	Pure, vertical, does not suppress with fixation, and multidirectional	Mixed, horizontal, suppresses with fixation, and unidirectional

Once you have determined that the patient has peripheral vertigo, there is a wide differential diagnosis that should be considered.

- **Ménière disease** is characterized by tinnitus, hearing loss, and episodic vertigo. Each episode lasts 1 to 8 hours. Symptoms wax and wane as the endolymphatic pressure rises and falls. The most common are syphilis and head trauma.
- **Benign paroxysmal positional vertigo** is a cause of peripheral vertigo that characteristically is exacerbated by head movement or change in head position. It may be associated with nystagmus, perhaps caused by calculi on the semicircular canals. There is a latency of several seconds after head movement before the onset of vertigo, and the vertigo usually lasts up to 60 seconds. Episodes occur in clusters which persist for several days.
- **Labyrinthitis** presents with sudden onset of severe vertigo that lasts for several days with hearing loss and tinnitus. The disease frequently follows an upper respiratory tract infection.
- **Perilymphatic fistula** is a form of peripheral vertigo related temporally to head trauma (blunt trauma to the ear, e.g., a slap to the ear) or extreme barotrauma during air flight, scuba diving, or vigorous Valsalva maneuver. Explosions deafen people.
- **Central vertigo** is caused by any cerebellar or brainstem tumor, bleed, or ischemia. Drug toxicity/overdose is a common cause. In the young patient with unexplained central vertigo, consider MS.



Note

Patients may be taught to do a modified Epley maneuver at home.

Note

Any patient who presents with headache and the following should be considered to have a secondary headache syndrome:

- “Worst headache of my life”
- Worsening symptoms over days to weeks
- Abnormal neurologic exam
- Fever
- Vomiting preceding the headache
- Headache induced by coughing, bending, lifting, or onset age >55

Treatment. Symptomatic treatment for peripheral vertigo includes meclizine or, in severe cases, diazepam.

- **Ménière disease:** low-salt diet and diuretics; if no response, consider surgical decompression
- **Benign paroxysmal positional vertigo:**
 - Dix Hallpike and Barany maneuvers, positional maneuvers that attempt to move the otolith out of the circular canals
 - Epley maneuver, which attempts to reposition the head by dislodging the calculi; the examiner holds the (seated) patient's head and rotates it to the side as he moves the patient into a lying position
- Vertigo secondary to **labyrinthitis:** meclizine and diazepam when symptoms are severe; steroids are helpful

Headache

A 32-year-old woman presents with headache for 2 days. She says it is at the right side of her head and it is throbbing. Things that seem to worsen the pain include walking up stairs or around the block, bright light, and loud noise. She experiences nausea but denies vomiting.

Headache is defined as pain located in the head, neck, or jaw. There are many causes.

- **Primary headache syndromes** include migraine (15% of the general population), cluster, and tension headache.
- **Secondary causes of headache** include intracranial hemorrhage, brain tumor, meningitis, temporal arteritis, and glaucoma.

The most important question to answer with a complaint of headache is whether a serious underlying cause exists for the symptoms. Do this with a thorough history and physical examination.

- Is this the patient's first episode of headache? A history of recurrent symptoms suggests a primary headache disorder, while a first-time headache—especially severe and rapidly peaking—suggests a serious underlying pathology.
 - Headache with fever and nuchal rigidity suggests meningitis.
 - Headache described as “the worst headache of my life” and/or “thunderclap” at onset, accompanied by nuchal rigidity without fever, suggests an intracranial hemorrhage.
 - Headache described as a deep, dull, aching pain and that disturbs sleep suggests a brain tumor.
 - A history of vomiting that precedes the onset of headache by a number of weeks, or a history of headache induced by coughing, lifting, or bending, suggests a posterior fossa brain tumor.

- Unilateral pounding headache associated with visual changes described as dull and boring with superimposed lancinating pain suggests temporal arteritis.
 - Commonly seen age >50
 - Symptoms also include polymyalgia rheumatica, jaw claudication, fever, weight loss, and scalp tenderness (difficulty combing hair/lying on a pillow) (scalp tenderness is due to pain over the temporal artery).
 - Causes sedimentation rate to elevate
 - Diagnosed with biopsy of the temporal artery
 - Do not wait for the biopsy results to initiate therapy with steroids.
- History of eye pain preceding the onset of headache suggests glaucoma.
- Once serious underlying pathology is excluded by history and physical examination, consider a primary headache syndrome: migraine, tension, or cluster headache.

Migraine headache

Migraine headache is a benign and recurrent syndrome of headache, nausea/vomiting, and other varying neurologic dysfunction.

- Pulsatile, throbbing, unilateral, and aggravated by minor movement
- Present with photophobia and phonophobia
- Time to maximal pain is 4–72 hours

Migraine is a likely diagnosis when a typical trigger can be identified. Alcohol, chocolate, certain cheeses, monosodium glutamate, hunger, and irregular sleep patterns are common triggers.

- **Migraine without aura (more common)** is a migraine without a preceding focal neurologic deficit.
- **Migraine with aura (classic migraine)** is accompanied by a preceding aura that consists of motor, sensory, or visual symptoms. Focal neurologic symptoms usually occur during the headache rather than as a prodrome. The pathognomonic aura for classic migraine is the scintillating scotoma. Visual auras are also described as stars, sparks, and flashes of light. Migraine equivalent is defined as focal neurologic symptoms without the classic complaints of headache, nausea, and vomiting.
- Complicated migraine is migraine with severe neurologic deficits that persist after the resolution of pain.
- Basilar migraine is migraine associated with symptoms consistent with brainstem involvement (vertigo, diplopia, ataxia, or dysarthria).

Tension headache

Tension headache is a tight, band-like headache that occurs bilaterally. The pain is “vise-like,” and possibly associated with tightness of the posterior neck muscles. The pain builds slowly and may last for several days with or without fluctuations. Movement does not generally exacerbate the headache.



Cluster headache

Cluster headache (men > women) begins without warning.

- Excruciating, unilateral, periorbital
- Peaks in intensity within 5 minutes of onset
- Rarely pulsatile in nature
- Lasts from 30 minutes to 3 hours, and occurs 1–3× day for 4–8 weeks
- Symptoms include rhinorrhea, reddening of the eye, lacrimation, nasal stuffiness, nausea, and sensitivity to alcohol.
- Horner syndrome may be seen.
- Emotion and food will rarely trigger a cluster headache.

Patients with severe, sudden onset of a first-time headache accompanied by strong evidence for an underlying cause should have a head CT scan to rule out any secondary causes.

Treatment.

- **Migraine headache**

- **Acute episode** (abortive therapy)
 - Triptans, serotonin receptor agonists (**sumatriptan is first-line**)
 - Dihydroergotamine
 - Ergotamine, used in combination with caffeine, for acute abortive therapy
 - Dopamine antagonists such as metoclopramide: given orally they help absorption of other medications, and when given parenterally they provide fast-acting relief for migraine
- **Prophylaxis** (for acute migraine headache >3–4/month)
 - Beta blocker: propranolol, valproic acid, and topiramate (**all first-line**)
 - Verapamil and tricyclics (require 2–6 weeks for full effect)
 - SSRIs such as sertraline and fluoxetine

- **Tension headache**

- Relaxation methods
- NSAIDs and acetaminophen
- If no response, add a muscle relaxant

- **Cluster headache**

- Triptan or 100% oxygen
- CCB (prophylaxis); prednisone and lithium are alternatives

Note

Triptans are contraindicated in known cardiovascular disease, uncontrolled hypertension, and pregnancy.

For migraine treatment, caution with the following medications:

- Methysergide, because of the serious side effects associated with prolonged use (valvular and retroperitoneal fibrosis)
- Opioid analgesics, because of their potential for addiction; use only for severe, infrequent migraines that are unresponsive to other therapy

Table 11-3. Migraine Therapies

Abortive	Prophylactic
• NSAIDs, aspirin, acetaminophen • Triptans • Ergotamine derivatives	• Beta blockers • Calcium blockers • Tricyclics • SSRIs • Valproic acid • Topiramate

Pseudotumor Cerebri

Pseudotumor cerebri (or benign intracranial hypertension) is an idiopathic increase in intracranial pressure. Women > men by 10×.

Often there is no identified cause and the disorder resolves spontaneously after several months. There is an association with obesity, chronic lung disease, Addison disease, oral contraceptives, tetracycline use, and vitamin A toxicity.

Symptoms include:

- Headache
- Visual disturbances such as diplopia and papilledema; enlargement of the blind spot on visual field testing
- Sixth cranial nerve (abducens) palsy
- Normal CT, MRI, and CSF beyond an increase in pressure

Treatment.

- Weight loss
- Removal of the offending agent, e.g., oral contraceptives
- Diuretics such as acetazolamide and furosemide
- Steroids such as prednisone
- For urgent cases, repeated lumbar punctures
- If there is no response, possible placement of a surgical shunt between the ventricles and peritoneum

Trigeminal Neuralgia

Trigeminal neuralgia (or tic douloureux) is an idiopathic pain syndrome that causes sudden, sharp pain starting near the side of the mouth and progressing to the ear, eye, or nostril. Attacks can be triggered by touch or small movements such as talking or eating. The pain lasts for a few seconds and disappears, but it can be extremely severe, and even incapacitating.



Trigeminal neuralgia is felt to be secondary to compression of the trigeminal nerve root by a blood vessel. Occasionally it can be a manifestation of MS or a posterior fossa tumor.

- Despite the pain, the sensory examination will be normal.
- With the exception of MS or the posterior fossa tumor, all imaging and neurologic testing will be normal.

Treatment is carbamazepine (standard of care). If there is no response, try phenytoin, baclofen, or gabapentin.

If still no response, surgery or radiofrequency lesioning into the affected nerve may work.

Clinical Recall

Which of the following are the characteristic features of labyrinthitis?

- A. Syphilis induced vertigo, hearing loss, and tinnitus
- B. Perilymphatic fistula as a result of head trauma
- C. Sudden onset of vertigo following upper respiratory tract infection
- D. Vertigo that occurs with changes in head position
- E. Central vertigo following toxicity with gentamicin

Answer: C

AUTOIMMUNE DISORDERS

Multiple Sclerosis

A 32-year-old woman presents at the ED complaining of numbness and tingling in her right hand. The symptoms began several days ago and have worsened over the last several hours. Three years ago she had an episode of “seeing double” for 2 days but it resolved on its own. Physical examination is significant for hyperreflexic reflexes bilaterally in her lower extremities. Increased spasticity is also noted in the lower extremities.

Multiple sclerosis (MS) is an autoimmune inflammatory disease of the CNS white matter with a relapsing or progressive course. The cause is thought to be multifactorial:

- Genetic susceptibility has been proven.
- Environmental triggers (infectious, climatic, dietary) are suspected, as MS occurs primarily in women of Northern European descent and of child-bearing age, respectively.

Clinical Presentation. Commonly, patients complain of weakness, numbness/tingling, or unsteadiness of a limb. Urinary urgency/retention and blurry/double vision are also seen in early disease. Symptoms may persist for several weeks or just a few days.

Pathologically, focal areas of demyelination are characteristic of the disease.

There are several forms of the disease that may change the course of management. Most patients have a disease-free period (from months to years) after their first exacerbation.

- **Relapsing-remitting disease:** progression is characterized by relapses of active disease with incomplete recovery during the periods of remission
- **Secondary progressive disease:** progression becomes more aggressive so that a consistent worsening of function occurs
- **Primary progressive disease:** symptoms are progressive from the onset of disease with the early onset of disability (least common form)

Infections or trauma may acutely worsen the disease. Pregnancy, especially the 2 to 3 months post-birth, may also exacerbate symptoms. (During the pregnancy itself, there are fewer attacks.) Uncomplicated MS typically has no adverse effects on the outcome of the pregnancy.

Diagnosis. To diagnose MS you have to rely on clinical criteria supplemented with radiologic and laboratory confirmation. Clinically, a young patient (age <55) presents with a history of multiple neurologic complaints that cannot be explained by the presence of one CNS lesion, i.e., when there are multiple neurologic deficits **separated by time and space (anatomy)**.

- MRI of the brain (**most accurate test**) has nearly 95% sensitivity in symptomatic persons.
- Increased T2 and decreased T1 intensity represent the increased water content of demyelinated plaques in the cerebrum and spine.
- Enhancement of lesions with gadolinium indicates active MS lesions that may enhance for up to 2–6 weeks after an exacerbation.
- Evoked response potentials detect slow or abnormal conduction in response to visual, auditory, or somatosensory stimuli (**rarely used** because many other neurologic diseases can cause an abnormal result).
- CSF analysis usually reveals a mild pleocytosis (<50 cells/ μ L) and total protein that is mildly elevated.
- Elevated IgG index (oligoclonal bands) (up to 90% of patients) but is nonspecific, so CSF for oligoclonal banding recommended only when MRI is nonconfirmatory yet clinical suspicion for MS remains high.

Treatment. Treatment of MS can be divided into disease-modifying therapies, treatment of complications, and treatment for symptomatic relief during an acute exacerbation.

- **Disease-modifying therapies** (interferon β 1a and β 1b; glatiramer acetate [or copolymer I]) are used for relapsing-remitting disease to reduce the number of clinical exacerbations, decrease MRI activity, and delay the onset of significant disability.
 - For **primary** progressive disease: no approved disease-modifying treatment

Note

MS is an unusual disease in that the best initial test for diagnosis is also the most sensitive test, namely **MRI of the brain and spine**.

Note

In MS, protein >100 mg/dL is unusual and should be considered as evidence *against* the diagnosis of this condition.

Note

All disease-modifying therapies are relatively **contraindicated in pregnancy**. Interferon and glatiramer should both be stopped for a pregnancy.



- For **secondary** progressive disease: interferon- β 1b and mitoxantrone
 - Methotrexate, mitoxantrone, cyclophosphamide, IV immunoglobulin, or azathioprine if patients with relapsing-remitting or secondary progressive disease cannot tolerate interferon β 1a/ β 1b or glatiramer acetate
 - Side effects of mitoxantrone include dose-related cardiotoxicity, so give only to those with normal ejection fraction.
 - Natalizumab is associated with progressive multifocal leukoencephalopathy.
 - Do not use mitoxantrone, cyclophosphamide, or natalizumab for a first episode of disease.
 - ACTH is no longer used.
- **Treatment of complications**
 - Glucocorticoids to reduce the length and intensity of an acute exacerbation
 - Give intense IV steroids for 3 days, followed by a course of oral medication tapered over 4 weeks
 - If no response and disease is severe, consider plasma exchange
 - Baclofen for spasticity (tizanidine and diazepam are helpful in nocturnal spasticity but are limited for daytime symptoms because they cause intense somnolence)
 - Carbamazepine, gabapentin, phenytoin, pregabalin, or tricyclic antidepressants for pain secondary to trigeminal neuralgia and dysesthesias
 - Oxybutynin for bladder hyperactivity
 - Bethanechol for urinary retention
 - Amantadine or fluoxetine for fatigue
 - Sildenafil acetate for erectile dysfunction

Note

Mitoxantrone is not first-line to prevent disease progression of MS because of its cardiotoxicity.

Fingolimod is an oral disease-modifying medication that decreases rates of MRI progression. It prevents lymphocytes from proliferating outside of lymph nodes. Cardiac toxicity can be severe.

Dalfampridine is an oral disease-modifying medication that increases walking speed. It is a unique potassium channel blocker for which the precise mechanism of action (for improved walking speed) is not clearly known.

Myasthenia Gravis

A 35-year-old woman comes to the clinic complaining of double vision that seems to worsen near the end of the day. She also complains of difficulty chewing meat and other hard foods. Her symptoms seem to improve after a good night's sleep. On neurologic examination you note a snarling appearance when the patient is asked to smile, and a nasal tone is heard in her voice. You also note a weakness in the upper extremities when she is asked to clench her fist around your finger repeatedly.

Myasthenia gravis (MG) is a disease of the neuromuscular junction characterized by weakness and fatigability. In MG, an autoimmune process characterized by acetylcholine-receptor antibodies leads to a decreased number of active and functional acetylcholine receptors at the postsynaptic membrane.

Clinical Presentation. The major features in a patient's history that help to diagnose MG are muscle weakness and fatigability.

- **Early disease:** diplopia/ptosis/difficulty swallowing, speech with a “mushy” or nasal quality, facial weakness that manifests as a “snarl” when smiling
- **Later disease:** generalized weakness involving proximal muscles in an asymmetric pattern, intact deep tendon reflexes, normal pupillary responses, no sensory abnormalities
- **Very severe disease:** muscles of respiration

Diagnosis.

- Acetylcholine-receptor antibody test will be positive (close to 90% of patients).
 - In the presence of fatigable muscle weakness, a positive antibody test is specific and virtually diagnostic.
 - Antibodies are present in only 70% of those with disease limited to the eyes.
- Edrophonium (Tensilon) test is sensitive but not specific for diagnosis. Additionally, patients may experience nausea/diarrhea, fasciculations, syncope (rare), or bradycardia during the test, which are cholinergic symptoms.
- X-ray and CT of the chest to detect a thymoma (found in 10–15% of patients); thymic hyperplasia is found in 65% of patients
- Electromyography (EMG) is the most accurate test; a decremental decrease in muscle fiber contraction on repetitive nerve stimulation is the characteristic finding.

Treatment.

- Anticholinesterase medications such as pyridostigmine (**preferred**, as it is longer-lasting) or neostigmine
- If no response with anticholinesterase medications, consider thymectomy for patients who are postpubertal but age <60.
 - Thymectomy can prevent the use of potentially toxic medication such as systemic steroids.
 - Thymectomy can help to prevent the spread of malignancy thymic disease when a thymoma is present.
- If no response to anticholinesterase medications or thymectomy, consider immunosuppressive therapy to improve weakness.
 - Plasmapheresis and IV immunoglobulin have a rapid effect; reserve for those in acute myasthenic crisis
 - Glucocorticoids, but take 1–3 months for a clinical benefit
 - Steroids (initial immunosuppressive of choice); if no response, add azathioprine (take 3–6 months for a clinical benefit); alternatives to azathioprine are cyclosporine and cyclophosphamide, but they are more toxic.
 - Mycophenolate, a newer immunosuppressive drug that has fewer side effects than steroids or cyclophosphamide

Aminoglycoside antibiotics may exacerbate MG and should be avoided. (In fact, many medications may worsen MG.)

Note

Eaton-Lambert myasthenic syndrome (rare) is characterized by **increasing** muscle strength on repetitive contraction. It is associated with malignancy—especially small-cell carcinoma of the lung. Botulism may cause a myasthenic-like illness, but the pupils are usually dilated, and repetitive nerve stimulation (on EMG) shows an incremental increase in muscular fiber contraction (**opposite of MG**).



Clinical Recall

What is the best initial test in the diagnosis of myasthenia gravis?

- A. Tensilon (Edrophonium) test
- B. EMG
- C. Chest CT
- D. Acetylcholine receptor antibody test
- E. Muscle biopsy

Answer: D

Guillain-Barré Syndrome

A 46-year-old man presents with “rubbery legs” for 2 days. He explains that the only other health issue has been several episodes of diarrhea 3 weeks ago, but those resolved spontaneously. On neurologic examination, bilateral lower-extremity weakness and a loss of reflexes are noted.

Guillain-Barré syndrome (GBS) is an acute, often severe polyradiculopathy, whose underlying pathophysiology is an autoimmune destruction of myelin. Evidence suggests that the etiology is a misdirection of the immune response, where the body’s immune system attacks self-antigens mistaken for foreign antigens (molecular mimicry).

Approximately 75% of patients will have a history of an infection 1-3 weeks before the onset of symptoms, typically in the respiratory or GI system (*Campylobacter jejuni*). This might be an infection with human herpesvirus, cytomegalovirus, or Epstein-Barr.

The condition is seen more frequently in those with HIV, SLE, and lymphoma.

Clinical Presentation. Most patients present with rapidly developing weakness that typically begins in the lower extremities and moves upward. Symptoms will develop over hours to days, with the legs affected more often than the arms or face.

- Motor weakness
- Poor reflexes (in muscle groups affected)
- Sensory disturbances in the form of pain or tingling dysesthesia (due to loss of large sensory fibers, which leads to loss of reflexes and proprioception)
- Severe disease: autonomic instability (profuse sweating, postural hypotension, labile BP, cardiac dysrhythmias) requiring intensive care

Fever, constitutional symptoms, or bladder dysfunction are rare and should raise the possibility of alternate diagnoses.

Diagnosis lies principally in recognizing the typical pattern of weakness with the absence of reflexes, fever, and constitutional symptoms.

Note

The only association between immunizations and GBS occurred in 1976, with the introduction of the swine influenza vaccine. More recent formulations of influenza vaccine are associated with one case of GBS per million patients immunized.

- Lumbar puncture for protein and cell count is the best initial test.
- The characteristic finding is elevated protein without an associated rise in cell count on CSF (only seen 48 hours after the onset of symptoms).
- The most accurate test for diagnosis is electromyography (EMG), which can detect evidence of demyelination of the peripheral nerves.

Treatment is IV immunoglobulin or plasmapheresis (equally effective). There is no benefit to combination therapy.

- Treatment becomes ineffective about 2 weeks after the onset of symptoms, so initiate therapy immediately.
- Vital capacity must be monitored in those with GBS, and early respiratory support must be given to prevent death from respiratory failure.

Glucocorticoids are not effective for acute GBS.

MOVEMENT DISORDERS

Parkinson Disease

A 56-year-old man is evaluated for a resting tremor that his wife noticed recently. She explains that her husband has been moving “very slowly” as of late. The patient says he feels fine and does not know why his wife is dragging him here. His past medical history is significant for mild hypertension that has been treated with a thiazide diuretic. Physical examination is significant for a resting tremor noted in the right hand. When walking, the patient is stooped forward, taking small steps. You note cogwheel rigidity in his right upper extremity with a positive Myerson sign.

Parkinson disease is a neurologic syndrome resulting from the deficiency of the neurotransmitter dopamine as a consequence of degenerative, vascular, or inflammatory changes in the basal ganglia. There are numerous causes.

- Drugs, including neuroleptic agents (haloperidol, chlorpromazine), antiemetics (metoclopramide), alpha-methyldopa, and reserpine
- Poisoning from MPTP, carbon monoxide, cyanide, and manganese
- Any structural lesion around the basal ganglia (trauma, tumor, abscess, infarct)
- Survivors of encephalitis can develop *postencephalitic Parkinsonism*.

Clinical Presentation. Cardinal symptoms are:

- Bradykinesia (manifested by slow movements, mask facies, reduction of automatic movements)
- Cogwheel rigidity
- Postural instability
- Resting tremor

Note

A useful mnemonic is to think of Mr. Parkinson as a fine **BRIT**ish gentleman.

- **B**radykinesia
- **R**igidity (cogwheel)
- **I**nstability (postural)
- **T**remor (resting)



Clinical Correlate

There are a number of “Parkinson plus” syndromes, which are characterized by their relative lack of response to therapy with levodopa/carbidopa.

- Parkinsonism + vertical gaze palsy = **supranuclear palsy**
- Parkinsonism + prominent ataxia = **olivopontocerebellar atrophy**
- Parkinsonism + prominent orthostatic hypotension = **multiple-system atrophy** (previously called Shy-Drager syndrome)

Note

For those Parkinson’s patients whose functional status is intact, treatment does not start with carbidopa/levodopa.

Other diseases that can imitate Parkinsonism:

- **Severe depression** can cause a paucity of spontaneous movement that can mimic Parkinsonism.
- **Essential tremor** can be mistaken for the tremor of Parkinson disease, but the lack of other neurologic symptoms and a positive family history of tremor and its amelioration with alcohol distinguish them.
- A **normal pressure hydrocephalus** can present with ataxia and gait disturbances, which can be mistaken for Parkinson disease. The presence of dementia and urinary incontinence with dilated ventricles on head CT scan can help identify this disorder.
- **Huntington disease** can present with akinesia and chorea. The positive family history and dementia usually suggest the correct diagnosis.

Diagnosis. The diagnosis of Parkinson disease is a clinical one. Identify any secondary causes of a patient’s Parkinsonism that are potentially reversible.

There are no diagnostic tests that can identify patients with Parkinson disease.

Treatment. The underlying pathophysiology causing Parkinson disease is the imbalance of dopaminergic (too little) and cholinergic (too much) tone on the basal ganglia. Thus, medical treatment revolves around increasing dopaminergic tone or decreasing cholinergic tone on the basal ganglia. Specifically, they do one of the following:

- Directly stimulate dopamine receptors (carbidopa/levodopa, dopamine agonists)
- Indirectly increase the amount of dopamine available (COMT inhibitors, selegiline, amantadine)
- Block acetylcholine stimulation of the basal ganglia (benztropine, trihexyphenidyl)

Direct-acting dopamine agonists such as pramipexole or ropinirole can be used alone as initial therapy or in combination with small doses of levodopa/carbidopa. Two other dopamine agonists are bromocriptine and cabergoline. All of them are less effective than levodopa.

Dopamine agonists have fewer dyskinetic side effects. Bromocriptine and pergolide are ergot derivatives and can cause cardiac toxicity.

The first step when considering which medication to start with is evaluating the patient’s functional status.

- **Intact functional status** (less bradykinesia)
 - Age <60: anticholinergic medication, particularly when tremor is predominant symptom
 - Age >60: amantadine (because side effects of anticholinergics are relatively contraindicated in the elderly, e.g., dry mouth, urinary retention, constipation, confusion/hallucinations)
 - Anticholinergics, e.g., benztropine and trihexyphenidyl, to relieve tremor and rigidity (avoid with BPH and glaucoma)

- **Compromised functional status** (more significant bradykinesia)
 - Carbidopa/levodopa (**best initial therapy**) to inhibit extracerebral dopa-decarboxylase, allowing more of the levodopa to reach the CNS, where it is needed.
 - Levodopa is the precursor to dopamine.
 - Carbidopa protects the levodopa from breakdown in the periphery, ensuring its secure delivery to the CNS.
 - Late complications to carbidopa/levodopa therapy include dyskinesia (abnormal movements), akathisia (restlessness), and “on-off” phenomena (all are called “response fluctuations”); management is a sustained release form of carbidopa/levodopa plus a dopamine agonist, selegiline, or COMT inhibitor (tolcapone or entacapone), or restricting the main protein meal to the night.

Selegiline, which was once thought to slow progression of the disease, can offer mild symptomatic benefit in early disease. It can be used when there is a declining or fluctuating response to levodopa. Rasagiline is a newer version.

When there is no response to medical therapy, surgery is a last resort, i.e., pallidotomy, thalamotomy, or placement of deep brain stimulators in the globus pallidus or subthalamic nuclei.

Huntington Disease

A 34-year-old man presents for an evaluation of strange spontaneous movements he has been having. Recently, while sitting at a family dinner, he experienced uncontrolled grimacing with grunting. His father died at age 41 from “dementia.”

Huntington disease is a genetic degenerative brain disorder caused by the presence of the HD gene located on chromosome 4p. The gene contains a CAG trinucleotide repeat expansion that codes for a protein called *huntingtin*. The HD mutation leads to abnormal cleavage of the huntingtin protein, interfering with nuclear mechanisms and causing cell death.

The disease is inherited in an autosomal dominant fashion. Successive generations tend to have the disease occurring at an earlier age. This is called *anticipation*.

Clinical hallmarks of the disease include chorea and behavioral disturbance. Onset is usually in decade 4 or 5 of life, and can begin with chorea or behavioral change.

- Chorea changes may begin as fidgeting that progresses to sudden movements of the trunk or limbs. Gait is poorly coordinated and has a choreic quality. Memory is usually preserved until late in the disease, but lack of judgment, disinhibition, and inattention are early manifestations. There is frequently an associated depression. Dementia becomes severe later in the disease.
- Behavioral (personality) changes consist of irritability, anger, paranoia, depression, and even antisocial behavior.

Diagnosis is made by genetically testing for the presence of the CAG trinucleotide DNA repeat expansion. There is a 50% chance of passing it on to children. CT scanning shows cerebral atrophy. Atrophy of the caudate nucleus is severe later.

Note

COMT inhibitors have no effect alone. Always use in conjunction with levodopa to help reduce side effects.



Treatment is tetrabenazine to help the movement disorder of Huntington (but it will not reverse or cure the underlying disease process). Death occurs 15–20 years after the diagnosis. Haloperidol or clozapine can be used to control behavioral changes.

Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis (ALS) is an idiopathic disorder of both upper and lower motor neurons. The disease has a unique presentation. Symptoms include muscle weakness plus upper motor neuron loss, cranial nerve palsies, respiratory involvement, and lower motor neuron destruction. At the same time, bowel, bladder sensory, cognitive, and sexual function are preserved.

- Dysphagia, difficulty chewing, decreased gag reflex, dysarthria (difficulty in articulating words), and difficulty in handling saliva, due to the cranial nerve, or bulbar, palsies
- Recurrent aspiration pneumonia (**most common cause of death**) due to respiratory muscle involvement
- Weak cough (**common**), which only worsens the respiratory problem
- Head ptosis due to the extensor muscles of the neck becoming too weak to keep the head up
- Significant spasticity that can lead to pain, due to the upper motor neuron involvement
- Both upper and lower motor neuron weakness (**hallmark sign**)
 - Upper motor neuron manifestations: weakness with spasticity and hyperreflexia
 - Lower motor neuron manifestations: weakness with muscle wasting, atrophy, and fasciculations, including tongue atrophy
- The most accurate confirmatory test is the electromyogram, which will show diffuse axonal disease. CPK levels are sometimes mildly elevated, and the cerebrospinal fluid and MRI scans are normal.

This is entirely a motor neuron disease, so there is no pain from abnormal sensory neuropathy. Mentation, bowel, bladder, and sexual function remain intact for the same reason. In other words, a fully mentally alert patient loses nearly all motor control while still being able to think and perceive. The patient becomes fully aware of being trapped in a body that does not function.

Treatment. The only treatment that may slow down progression of the disease is riluzole, which inhibits glutamate release. Death typically results in 3–5 years. Spasticity is treated with baclofen and tizanidine.

Many of the exam questions regarding ALS will be **ethical questions on issues of the withholding of care**. Since ALS has no impact on cognitive function, the patient is felt to retain the capacity to make medical decisions.

- The patient has the right to refuse potentially life-saving therapy such as antibiotics, nasogastric tube placement, tracheostomy, or mechanical ventilation.
- The patient should not be allowed to commit suicide nor should the physician assist with suicide. (Withholding intubation or antibiotics is not considered assisting a suicide.)
- Every adult patient with the capacity to understand the implications of his or her choice is allowed to refuse any unwanted therapy.

Restless Leg Syndrome

Restless leg syndrome (RLS) is an idiopathic condition resulting in a sensation of creeping and crawling dysesthesia within the legs, leading to involuntary movements during sleep. Often the condition is brought to attention because of multiple bruises sustained by the sleep partner. The condition can be familial and is exacerbated by sleep deprivation, caffeine, and pregnancy. There is also an association with uremia, iron deficiency, and peripheral neuropathy.

There is no specific diagnostic test for this disorder. Treatment is a dopamine agonist such as pramipexole or ropinirole, although some patients may need levodopa/carbidopa. Other therapies are narcotics and benzodiazepines.

Clinical Recall

Which of the following is a characteristic feature of Creutzfeldt-Jakob disease?

- A. Memory loss without dysfunction of other cognitive domains
- B. Gradual loss of memory with other cognitive disturbances
- C. Memory impairment with social, interpersonal, and emotional problems
- D. Stepwise progression of cognitive decline
- E. Rapidly progressive dementia with myoclonic jerks

Answer: E

Benign Essential Tremor

Benign essential tremor is an idiopathic disorder of an isolated tremor in the hands or head (or both). The lower extremities tend to be spared.

- Worsened with caffeine or beta agonists
- Improves with alcohol (**characteristic sign**); patients describe shaky hands that improve with 2–3 drinks
- Examination reveals no other abnormalities
- Manual skills such as the ability to write may be affected (but level of disability is limited)

There is no specific diagnostic test for this disorder.

Treatment is propranolol. If no response, try primidone, alprazolam, and clozapine.

If still no response, consider thalamotomy.

Learning Objectives

- ❑ Describe the mechanism of bullous and blistering diseases and approaches to treatment
- ❑ List the common dermatologic parasitic diseases, treatments, and common side effects
- ❑ Outline the treatment of skin and ulcer infections, including decubitus (pressure) ulcers and acne
- ❑ Describe the presentation and management of scalp, hair, and scaling disorders (eczema), and papulosquamous dermatitis
- ❑ Provide an overview of toxin-mediated diseases, hypersensitivity, and toxin-mediated diseases
- ❑ Describe benign lesions, precancerous lesions, and malignant diseases of the skin and their treatment and prognosis

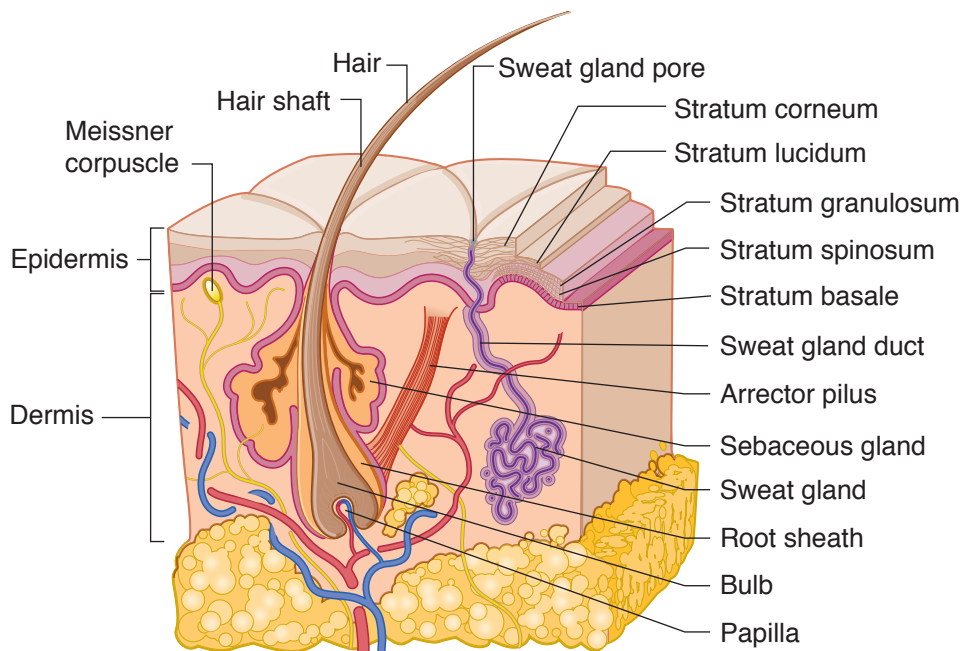


Figure 12-1. Skin

**Note**

"Pemphix" is from the Greek word for bubble, which is what a bulla looks like before it is broken.

Note

Pemphigus vulgaris is a much more serious and potentially life-threatening disease than pemphigoid.

Note

The **Nikolsky sign** (easy removal of skin with a little pressure from the examiner's finger, pulling the skin off like a sheet) is seen in pemphigus vulgaris, staphylococcal scalded skin syndrome, and TEN.

Note

Before the invention of steroids, pemphigus vulgaris was often fatal, with patients dying of sepsis and dehydration—just like a burn patient.

BULLOUS/BLISTERING DISEASES**Pemphigus Vulgaris**

Pemphigus vulgaris is an autoimmune disease of unclear etiology in which the body essentially becomes allergic to its own skin. Antibodies are produced against antigens in the intercellular spaces of the epidermal cells. They attack the "glue" that holds the epidermal cells together. Pemphigus vulgaris is most often idiopathic, but ACE inhibitors or penicillamine can occasionally cause it.

- Seen in decades 3-4
- Occurs prominently in the mouth and starts there
- Oral lesions are erosions, not bullae.
- The bullae are very thin and flaccid and can break easily, causing loss of large volumes of skin surface area and acting like a burn. (This is because the bullae occur from destruction within the epidermis, making them thinner and more fragile.)
- Presence of the **Nikolsky sign** (the easy removal of skin by just a little pressure from the examiner's finger, pulling the skin off like a sheet) is seen in pemphigus vulgaris, staphylococcal scalded skin syndrome, and toxic epidermal necrolysis.
- Lesions are painful, not pruritic.

The most accurate diagnostic test is to biopsy the skin and to use immunofluorescent stains, which will detect intercellular deposits of IgG and C3 in the epidermis.

Treatment.

- Systemic glucocorticoids, such as prednisone (topical steroids are not strong enough)
- When no response with steroids, use azathioprine, mycophenolate, or cyclophosphamide
- Rituximab and IVIG are also effective.

Bullous Pemphigoid

Pemphigoid is 2× as common as pemphigus vulgaris and occurs in elderly persons age 70s and 80s. It can also be drug-induced with sulfa drugs, including furosemide, penicillamine, and others.

The defect occurs at the **dermo-epidermal junction**, so the layer of skin that separates off is much thicker. Because the fracture of the skin causing the blisters is deeper, the bullae are thicker walled and much less likely to rupture. Oral lesions are rare. Because the bullae are tense and intact, the skin is better protected. There is no dressing for skin as good as skin itself. Hence, there is much less fluid loss, and infection is much less likely as compared with pemphigus vulgaris. Mortality is much less likely in bullous pemphigoid.

The most accurate diagnostic test is a biopsy with immunofluorescent antibodies at the dermo-epidermal junction (basement membrane).

Systemic steroids, such as prednisone, are the standard means of treatment. Tetracycline or erythromycin combined with nicotinamide is the alternative to steroids. Use topical steroids only if no oral lesions are present.

Porphyria Cutanea Tarda

Porphyria cutanea tarda is a disorder of porphyrin metabolism. Deficiency of the enzyme uroporphyrinogen decarboxylase results in an abnormally high accumulation of porphyrins, which then leads to a photosensitivity reaction.

On the exam, the patient may have a history of HIV, liver disease, or chronic hepatitis C, or may be taking oral contraceptives. The liver disease may be from any cause but is most likely to involve chronic infectious hepatitis or hemochromatosis, because porphyria cutanea tarda is associated with increased liver iron stores. Diabetes is found in 25% of patients.

Clinical Presentation. Fragile, nonhealing blisters are seen on the *sun-exposed* parts of the body, such as the backs of the hands and the face. This leads to hyperpigmentation of the skin in general and hypertrichosis of the face.

Diagnosis. The diagnostic test is a level of urinary uroporphyrins. Uroporphyrins are elevated 2–5× above the coproporphyrins in this disease.

Treatment.

- Stop alcohol intake and discontinue estrogen use
- Add sun protection, including protective clothing, because most sunscreens do not seem to block the wavelength of light causing the dermal reaction
- If no response, consider phlebotomy to remove iron
- Deferoxamine if phlebotomy is not possible
- Chloroquine to increase excretion of porphyrins

DRUG ERUPTIONS/HYPERSENSITIVITY

Urticaria

Acute urticaria is a hypersensitivity reaction most often mediated by IgE and mast cell activation, resulting in evanescent wheals and hives. It is a type of localized, cutaneous anaphylaxis, but without the hypotension and hemodynamic instability. The most common causes of acute urticaria are allergic reactions to medications, insect bites, and foods, and occasionally, the result of emotions. The most common medications are aspirin, NSAIDs, morphine, codeine, penicillins, phenytoin, and quinolones. ACE inhibitors are also associated with urticaria, as well as angioedema. The most common foods are peanuts, shellfish, tomatoes, and strawberries. Contact with latex in any form can also cause urticaria.

Clinical Presentation. Itching is prominent.

- **Acute urticaria** lasts <6 weeks, and 70% of cases are self-limited. Wheals and hives are seen within 30 minutes and last <24 hours.
- **Chronic urticaria** lasts >6 weeks, and is associated with pressure on the skin, cold, or vibration. If >6 weeks, investigate the etiology.



Note

Pressure on the skin resulting in localized urticaria is also known as dermatographism.

Note

For urticaria, **never use astemizole or terfenadine** (no longer marketed), as they can cause potentially fatal rhythm disturbances.

Note

For urticaria:

Answer **“terfenadine”** or **“astemizole”** only when the test question asks what will kill the patient or which is the most dangerous medication.

Answer **“desensitization”** when the trigger cannot be avoided, e.g., a bee sting in a farmer. Beta blocker medications must be stopped prior to desensitization because they inhibit epinephrine, which may be used if there is an anaphylactic reaction.

Treatment. Urticaria is treated with H₁ antihistamines.

- **Severe, acute urticaria:** older medications, such as diphenhydramine, hydroxyzine, or cyproheptadine; if life-threatening, use H₂ antihistamines when H₁ antihistamines fail and add systemic steroids
- **Chronic urticaria:** newer, nonsedating antihistamines, such as loratadine, desloratadine, fexofenadine, or cetirizine



Wikipedia, James Heilman, MD

Figure 12-2. Urticaria

Morbilliform Rashes

A morbilliform rash is a milder version of a hypersensitivity reaction compared with urticaria. This is the “typical” type of drug reaction and is lymphocyte mediated.

The rash resembles measles and is usually secondary to medications that the patient is allergic to, such as penicillin, sulfa drugs, allopurinol, or phenytoin. It is a generalized, maculopapular eruption that blanches with pressure. The reaction can appear a few days after the exposure and may begin even after the medication has been stopped.

Antihistamines are effective, and steroids are rarely necessary.

Erythema Multiforme

Although erythema multiforme (EM) may be caused by the same types of medications that cause urticaria and morbilliform rashes (penicillins, phenytoin, NSAIDs, and sulfa drugs), the most common cause of EM is a reaction to infection. The majority of cases follow infection with herpes simplex or *Mycoplasma*.

The most characteristic feature of EM is target-like lesions that occur especially on the palms and soles. These lesions can also be described as “iris-like.” Bullae are not uniformly found. EM of this type usually does not involve mucous membranes.

Treatment is antihistamines and treatment of the underlying infection.



Wikipedia, James Heilman, MD

Figure 12-3. Erythema Multiforme

Stevens-Johnson Syndrome

Stevens-Johnson syndrome (SJS) (sometimes called *erythema multiforme major*) can be difficult to distinguish from toxic epidermal necrolysis (TEN) and, in fact, the two diseases may be considered a spectrum of severity of the same disorder.

All of these disorders may arise as a hypersensitivity response to the same set of medications, such as penicillins, sulfa drugs, NSAIDs, phenytoin, and phenobarbital.

Clinical Presentation.

- Involves <10–15% of total body surface area
- Overall mortality rate <5–10%
- Mucous-membrane involvement in 90% of cases; most often the oral cavity and conjunctivae, but frequently the respiratory tract

Treatment is early admission to a burn unit, withdrawal of the offending drug, and supportive care. Respiratory tract involvement may be so severe as to require mechanical ventilation. Death occurs from a combination of infection, dehydration, and malnutrition.

For severe disease, the best initial therapy is IV immunoglobulins. Other therapies of unclear value are cyclophosphamide, cyclosporine, and thalidomide.

There is no proven benefit for steroids.



Clinical Pearl

Always do a chest x-ray on a patient with EN, to exclude sarcoidosis.

A biopsy of EN lesions will show nonspecific inflammation.

Toxic Epidermal Necrolysis

Toxic epidermal necrolysis (TEN) is the most serious version of a cutaneous hypersensitivity reaction. Mortality may be 40–50%.

- Involves 30–100% of total body surface area
- Nikolsky sign is present, and the skin easily sloughs off
- Has some features similar to staphylococcal scalded skin syndrome, but is drug-induced and not caused by a toxin coming from an organism

Diagnosis of TEN is usually clinical. The most accurate diagnostic test is a skin biopsy, which will reveal full thickness epidermal necrosis. Skin biopsy is usually not necessary.

Treatment. Sepsis is the most common cause of death, but prophylactic systemic antibiotics are not indicated. Systemic steroids are not effective and may, in fact, decrease survival.

Fixed Drug Reaction

Fixed drug reaction is a **localized** allergic drug reaction that recurs at precisely the **same anatomic site** on the skin with repeated drug exposure. It is not known why the reactions are anatomically localized and do not become generalized morbilliform rashes. The most commonly implicated drugs include aspirin, NSAIDs, tetracycline, and barbiturates.

Fixed drug reactions are generally round, sharply demarcated lesions that leave a hyperpigmented spot at the site after they resolve.

Discontinue the offending drug, and treat the reactions with topical steroids.

Erythema Nodosum

Erythema nodosum (EN) is a localized inflammatory condition of the skin or panniculitis. It is secondary to recent infections or inflammatory conditions. It is also associated with pregnancy. The most common causes of EN are recent streptococcal infections, coccidioidomycosis, histoplasmosis, sarcoidosis, inflammatory bowel disease, syphilis, TB, and hepatitis. Enteric infections such as *Yersinia* also cause the disorder.

EN consists of multiple painful, red, raised nodules on the anterior surface of the lower extremities. They are extremely tender to palpation. They do not ulcerate, and they generally last about 6 weeks.

Diagnosis. ASLO titers can help determine who has recently had a streptococcal infection if there is no other etiology apparent from the history.

Treat the underlying disease and use analgesics and NSAIDs. Potassium iodide solution can be used when patients do not respond to symptomatic therapy. EN is usually a self-limiting condition.

Clinical Recall

A 23-year-old woman from Bangladesh presents with seizure disorders. Prior to initiating treatment, which of the following should you check to avoid Stevens-Johnson syndrome?

- A. HLA-B27
- B. HLA-B57
- C. HLA-B1502
- D. HLA-B5801

Answer: C

INFECTIONS

Fungal Infections

Tinea pedis, cruris, corporis, versicolor, capitis, and onychomycosis

All of the superficial fungal infections of the body share a number of common characteristics leading to the same answer on the test for similar questions for each of these diseases. “Superficial fungal infections” refer to those infections limited to the skin, nails, and hair. Remember, though, that these answers would not be valid for more deep-seated, life-threatening infections, such as fungal endocarditis, meningitis, or abscesses.

Clinical Presentation and Diagnosis. All superficial fungal infections of the skin, hair, and nails are primarily diagnosed by their *visual appearance* and confirmed by a potassium hydroxide (KOH) test of the skin. The leading edge of the lesion on the skin or nails is scraped with a scalpel to remove some of the epithelial cells or some of the nail and hair. KOH has the ability to dissolve the epithelial cells and collagen of the nail, but does not have the ability to melt away the fungus. Hence, a KOH preparation gives an immediate diagnostic answer by revealing fungal hyphae. This is particularly characteristic in tinea versicolor, where the *Malassezia furfur* (*Pityrosporum orbiculare*) organism appears in a “spaghetti and meatballs” pattern.

The most accurate test is to culture the fungus. This is usually not clinically practical because molds that grow on the skin (dermatophytes) take up to 6 weeks to grow even on specialized fungal media. A specific species usually does not need to be isolated in most cases, unless it is an infection of the hair or nails. In the case of nail and hair infections, oral therapy is necessary, and it is important to be precise because there are fewer medications that can be used to effectively treat onychomycosis. Tinea tonsurans is the cause of >90% of cases of tinea capitis.

Treatment. For onychomycosis (nail infection) or hair infection (tinea capitis), the medications with the greatest efficacy are oral terbinafine or itraconazole. These medications are used for at least 6 weeks for fingernails and 12 weeks for toenails. Terbinafine is potentially hepatotoxic, and it is important to periodically check liver function tests. Griseofulvin must be used for 6 to 12 months in the treatment of fingernails and has much less antifungal efficacy than terbinafine. Griseofulvin is no longer recommended in the treatment of onychomycosis of the toenails. In the treatment of tinea capitis, griseofulvin is recommended for 6 to 8 weeks.

**Note**

Drug of choice for oral antifungal treatment:

- Tinea capitis and onychomycosis
 - Terbinafine or itraconazole

The other fungal infections of the skin that don't involve hair or nails may be treated with any of the following topical medications: ketoconazole, clotrimazole, econazole, terbinafine, miconazole, sertaconazole, sulconazole, tolnaftate, or naftifine. There is no clear difference in efficacy or adverse effects between them when used topically. Ketoconazole has more adverse effects when used systemically, such as hepatotoxicity and gynecomastia. This is why ketoconazole is not a good choice for onychomycosis. There is no topical form of fluconazole. Fluconazole is also less efficacious for dermatophytes of the nails when used systemically.

Antifungal medications generally should not be used in combination with topical steroids, unless a diagnosis has been confirmed. Steroids in a cream can relieve redness and itching and give the appearance of improvement even in impetigo and contact dermatitis.

Tinea versicolor

Tinea versicolor is a skin infection characterized by multiple macules (usually asymptomatic), varying in color from white to brown. It is caused by *Pityrosporum orbiculare* (*Malassezia furfur*).

Clinical Correlate

Tinea versicolor has some additional features that are important in its management. It presents with lesions of different colors from tan to pink (hence the name *versicolor*). The lesions often do not tan, and they present with pale areas in the middle of a normal tan. This can be distinguished from vitiligo by the fact that vitiligo has *no* pigmentation, whereas tinea versicolor presents with *altered* pigmentation. The organism may also be contagious. A KOH preparation and fungal culture are used in the same manner as for the other dermatophytes. The main therapeutic difference is the use of topical selenium sulfide every 2 to 3 weeks versus oral therapy with itraconazole or fluconazole. This is not because of antifungal resistance; it is because tinea versicolor is much more likely to involve large amounts of body surface area so it is difficult to cover this volume of skin with an ordinary topical cream or lotion.

Clinical Presentation. Tan, brown, or white scaling macular lesions that tend to coalesce; found on chest, neck, abdomen, or face. Lesions do not tan.

Diagnosis. Skin scrapings examined with 10% KOH under a microscope. The classic description is of "spaghetti and meatballs," which refers to the hyphae and spores that can be seen in the KOH prep.

Treat with topical selenium sulfide, clotrimazole, ketoconazole, or oral itraconazole. Consider local or systemic therapy based on the amount of surface area involved.

Candidiasis

Candidiasis is a yeast infection usually involving skin and mucous membranes, but it can also be systemic. It is caused by *Candida albicans*. It usually spreads in patients with decreased host defenses, i.e., those with increased susceptibility due to systemic antibacterial therapy, obesity, DM, corticosteroid or antimetabolite therapy, pregnancy, debilitating disease and blood dyscrasias, or HIV.

Clinical Presentation

- Intertriginous infection: well-demarcated, erythematous, itchy, exudative patches, usually rimmed with small red-based pustules that occur in the groin, gluteal folds (diaper rash), axilla, umbilicus, and inframammary areas
- Vulvovaginitis: white or yellowish discharge with inflammation of the vaginal wall and vulva common in pregnant women and patients with DM
- Oral candidiasis (thrush): white patches of exudates on tongue or buccal mucosa
- Candidal paronychia: painful red swelling around the nail

Diagnosis. Potassium hydroxide on slide to visualize fungal forms. Culture is definitive.

Treatment

- Topical nystatin, clotrimazole, miconazole, ciclopirox, econazole, or terconazole
- Systemic amphotericin in serious invasive infections. Fluconazole in less serious infections. *Candida paronychia* requires systemic therapy.

Bacterial Infections

Antistaphylococcal antibiotics

The most common bacterial organisms to cause skin infections of any kind are *Staphylococcus* and *Streptococcus*. Antibiotics used to treat *Staphylococcus* are dicloxacillin, cephalixin (Keflex™), or cefadroxil (Duricef™). Cefadroxil, cefazolin, or cephalixin are the preferred agents. If a patient is allergic to penicillin, but the reaction is only a rash, then cephalosporins can be safely used. There is far less than 5% cross-reaction between penicillins and cephalosporins. The IV equivalents of oral dicloxacillin include oxacillin and nafcillin. The IV equivalent of cefadroxil is cefazolin.

If the penicillin reaction is anaphylaxis then cephalosporins cannot be used. The alternative antibiotics that will treat the skin are macrolides, such as erythromycin, azithromycin, clarithromycin, or the newer fluoroquinolones (levofloxacin or moxifloxacin). Ciprofloxacin will not adequately cover the skin. Vancomycin is only for IV use for skin infections, and oral vancomycin is not absorbed. Oral therapy for MRSA is with clindamycin, TMP/SMX, or doxycycline. The ultimate form of oral MRSA therapy is linezolid.

Impetigo

Impetigo is a superficial, pustular skin infection, seen mainly in children (ecthyma is an ulcerative form of impetigo), with oozing, crusting, and draining of the lesions. It is a superficial bacterial infection of the skin largely limited to the epidermis and not spreading below the dermal-epidermal junction. It is caused by group A beta-hemolytic *Streptococcus* and *S. aureus* (*bullous impetigo*).

- Because it is limited to the epidermis, the purulent material is easily able to express itself through the surface; therefore, the patient history will describe the infection with words such as “weeping,” “oozing,” “honey colored,” or “draining.”
- Occurs more often in warm, humid conditions, particularly when there is poverty and crowding of children. This is because it is both contagious and autoinoculable.



Note

Group A *streptococci* and *S. aureus* are the most common causes of impetigo.

Note

Retapamulin is a topical antibacterial that is more active against staph and strep than mupirocin or bacitracin.

- More common on arms, legs, and face
- May follow trauma to skin
- Begins as maculopapules and rapidly progresses to vesicular pustular lesions or bullae. The crusts are described as having a golden or yellow appearance and if untreated can progress to lymphangitis, furunculosis, or cellulitis, and acute glomerulonephritis.
- May cause glomerulonephritis, but it will not cause rheumatic fever

Treatment

- Oral first-generation cephalosporin or semisynthetic penicillin, e.g., oxacillin, cloxacillin, dicloxacillin (for severe or widespread cases)
- Topical mupirocin, bacitracin, or retapamulin for mild cases of impetigo
- Penicillin-allergic patients can be treated with macrolides such as clarithromycin or azithromycin.
- TMP/SMZ, clindamycin, or doxycycline for MRSA

Erysipelas

Erysipelas is a bacterial infection of a deeper layer of the skin than impetigo. Erysipelas involves both the dermis and epidermis and is most commonly caused by group A *Streptococcus* (*pyogenes*).

- Because it involves lymphatic channels in the dermis, erysipelas is more likely to result in fever, chills, and bacteremia.
- Often involves the face, giving a bright red, angry, swollen appearance
- Usually bilateral, shiny red, indurated edematous tender lesions on the face, arms, and legs
- Lesions often sharply demarcated from the surrounding normal skin
- Differentiate from herpes, contact dermatitis, and angioneurotic edema

Treatment. Semisynthetic penicillin or first-generation cephalosporin if you cannot distinguish it from cellulitis; penicillin (if *Streptococcus* is certain).

Cellulitis

Cellulitis is a bacterial infection of the dermis and subcutaneous tissues with *Staphylococcus* and *Streptococcus*. Cellulitis is characterized by redness, swelling, and warmth and tenderness of the skin. Because it is **below the dermal-epidermal junction**, there is no oozing, crusting, weeping, or draining.

Treatment. Cellulitis is treated with the antibiotics prescribed for erysipelas on the basis of the severity of the disease. If there is fever, hypotension, or signs of sepsis or if oral therapy has not been effective, then the patient should receive IV therapy. Oxacillin, nafcillin, or cefazolin is the best therapy. Treatment is generally empiric because injecting and aspirating sterile saline for a specific microbiologic diagnosis has only a 20% sensitivity. Oral therapy for MRSA is with clindamycin, TMP/SMX, or doxycycline.

Folliculitis, furuncles, and carbuncles

Folliculitis, furuncles, and carbuncles represent 3 degrees of severity of staphylococcal infections occurring around a hair follicle. Occasionally, folliculitis can be the result of those who contract *Pseudomonas* in a whirlpool or from a hot tub.

As folliculitis worsens from a simple superficial infection around a hair follicle, it becomes a small collection of infected material known as a furuncle. When several furuncles become confluent into a single lesion, the lesion becomes known as a carbuncle, which is essentially a localized skin abscess. Folliculitis is rarely tender, but furuncles and carbuncles are often extremely tender.

Treatment. Folliculitis mainly can be treated with warm compresses locally without the need for antibiotics. If antibiotics are required, mupirocin is the best choice. Furuncles and carbuncles require treatment with systemic antistaphylococcal antibiotics, and in the case of carbuncles, should be administered intravenously. Treatment with dicloxacillin, cephalexin, or cefadroxil is acceptable. A large furuncle or carbuncle will also require surgical drainage.

Necrotizing fasciitis

Necrotizing fasciitis is an extremely severe, life-threatening infection of the skin. It starts as a cellulitis that dissects into the fascial planes of the skin. *Streptococcus* and *Clostridium* are the most common organisms because they are able to produce a toxin that further worsens the damage to the fascia. Diabetes increases the risk of developing fasciitis.

The features which distinguish necrotizing fasciitis from simple cellulitis are a **very high fever**, a portal of entry into the skin, pain out of proportion to the superficial appearance, the presence of **bullae**, and **palpable crepitus**.

Laboratory evidence of necrotizing fasciitis is an elevated creatine phosphokinase and an x-ray, CT, or MRI that show **air in the tissue or necrosis**. All of these lab methods of establishing a diagnosis lack both sensitivity and specificity. Surgical debridement is the best way to confirm the diagnosis and is also the mainstay of therapy.

Treatment. Surgery is the mainstay of therapy. The best empiric antibiotics are the beta-lactam/beta-lactamase combination medications such as ampicillin/sulbactam (Unasyn™), ticarcillin/clavulanate (Timentin™), or piperacillin/tazobactam (Zosyn™). If there is a definite diagnosis of group A *Streptococcus* (*pyogenes*), then treat with clindamycin and penicillin. Without adequate therapy, necrotizing fasciitis has an 80% mortality rate.

Paronychia

Paronychia is an infection loculated under the skin surrounding a *nail*. It is generally treated with a small incision to allow drainage and with antistaphylococcal antibiotics. The antistaphylococcal antibiotics are dicloxacillin, cefadroxil, or cephalexin orally, or oxacillin, nafcillin, or cefazolin intravenously.

Clinical Pearl

Necrotizing fasciitis is commonly associated with varicella infection, where the skin lesions are infected by *Streptococcus* or *Staph*.

Note

If an exam question presents an obvious clinical case with crepitus, pain, high fever, and a portal of entry, you should answer “surgery” (not a test, such as an x-ray) as the best initial step.



Viral Infections

Herpes simplex

Herpes simplex infections of the genitals are characterized by multiple, painful vesicles. The vesicles are usually obvious by examination, and antibiotic therapy should be initiated immediately without waiting for results of the tests.

Diagnosis is made with the **direct fluorescent antibody (DFA)** test or **HSV PCR**. Tzanck test and culture are no longer used. Serology is not useful for diagnosing herpes infections.

Immediate therapy is with oral acyclovir, famciclovir, or valacyclovir. Topical acyclovir has extremely little efficacy; it will slightly improve resolution in primary lesions and will do absolutely nothing for recurrent herpes simplex lesions. Topical penciclovir has some use for oral herpetic lesions, but it must be applied every 2 hours. The treatment of acyclovir-resistant herpes is with foscarnet.



Centers for Disease Control and Prevention

Figure 12-4. Herpes Simplex Lip

Herpes zoster/varicella

Chickenpox is primarily a disease of children. Complications of varicella are pneumonia, hepatitis, and dissemination. Episodes of dermatomal herpes zoster, also known as shingles, occur more frequently in the elderly and in those with defects of the lymphocytic portion of the immune system (i.e., leukemia, lymphoma, HIV, or those on steroids).

The vesicles are 2–3 mm in size at all stages of development and are on an erythematous base.

Diagnosis. Diagnostic testing is generally not necessary because little else will produce a band of vesicles in a dermatomal distribution besides herpes zoster.

Treatment. Chickenpox is generally not treated with antivirals. If the child is immunocompromised or the primary infection occurs in an adult, then acyclovir, valacyclovir, or famciclovir should be given.

Steroid use is still not clearly beneficial, although the best evidence for efficacy is in elderly patients with severe pain. The rapid administration of acyclovir still has the best efficacy for decreasing the risk of postherpetic neuralgia.

Other treatments for managing the pain are gabapentin, tricyclic antidepressants, and topical capsaicin. The most effective analgesic specific for postherpetic neuralgia is gabapentin. Nonimmune adults exposed to chickenpox should receive varicella zoster immunoglobulin within 96 hours of the exposure in order for it to be effective.

Molluscum contagiosum

Molluscum contagiosum is skin-colored, waxy, umbilicated papules. It is caused by poxvirus. It is commonly seen in children; frequency is increased in patients infected with HIV.

Small papules appear anywhere on the skin (genital and pubic area), usually by venereal contact, and are asymptomatic. The lesions have a central umbilication. They can be transmitted by skin-to-skin contact or sexually.

Diagnosis is made mainly on appearance. Lab testing is rarely, if ever, necessary. Giemsa stain will show large cells with inclusion bodies.

Treat with freezing, curettage, electrocautery, or cantharidin.

Clinical Recall

What is the most appropriate management for onychomycosis of the toenails?

- A. PO griseofulvin
- B. PO terbinafine
- C. Topical itraconazole
- D. PO griseofulvin and topical corticosteroids
- E. Topical itraconazole and PO corticosteroids

Answer: B

PARASITIC INFECTIONS

Scabies

Scabies is a parasitic skin infection characterized by superficial burrows, intense pruritus, and secondary infections. It involves vesicular eruptions resulting from the females of the *Sarcoptes scabiei* (*hominis*) burrowing into the skin. It is caused by the itch mite *Sarcoptes scabiei*. Transmission is by skin-to-skin contact.

Scabies primarily involves the web spaces of the hands and feet. It also produces pruritic lesions around the penis, breasts, and axillary folds. Itching can be extreme. Because *Sarcoptes scabiei* is quite small, all that can be seen with the naked eye are the burrows and excoriations



around small pruritic vesicles. Scabies often spares the head. Immunocompromised patients, such as those with HIV, are particularly vulnerable to an extremely exuberant form of scabies with severe crusting and malodorousness, known as Norwegian scabies.

Diagnosis in all cases is confirmed by scraping out the organism after mineral oil is applied to a burrow; however, skin scrapings are usually not necessary and are not routinely done.

Treat with permethrin. Lindane (Kwell) has equal efficacy, but also greater toxicity. Lindane should not be used in pregnant women. Ivermectin is a suitable alternative and is given as oral therapy if the disease is extensive. Treat Norwegian scabies with a combination of permethrin and ivermectin.

Pediculosis

Pediculosis is skin infestation by lice. It is caused by the following:

- Head: *Pediculus humanus capitis*
- Body: *Pediculus humanus corporis*
- Pubic area: *Phthirus pubis* (“crab louse”)

Patients present with itching, excoriations, erythematous macules and papules, and sometimes secondary bacterial infection. Diagnosis is made by direct examination of the pubic area, axillae, scalp, and other hair-bearing surfaces for the organism (louse or nits). Treat with permethrin or lindane (Kwell).

TOXIN-MEDIATED DISEASES

Toxic Shock Syndrome

Toxic shock syndrome (TSS) is a systemic reaction to a toxin produced from *Staphylococcus* attached to a foreign body. The majority of cases now are not from a menstrual source, such as a tampon or vaginal packing. Nasal packing, retained sutures, or any other form of surgical material retained in the body can promote the growth of the type of staphylococci that produces the toxin.

Because there is no single specific test, cases are matters of definition.

TSS is defined as the presence of 3 or more of the following findings:

- Fever $>102^{\circ}\text{F}$
- Systolic BP <90 mm Hg
- Desquamative rash
- Vomiting
- Involvement of the mucous membranes of the eyes, mouth, or genitals
- Elevated bilirubin
- Platelets $<100,000$

In addition, TSS is a systemic disease:

- Raises creatinine, creatine phosphokinase, and liver function tests
- Lowers platelet count
- Can cause CNS dysfunction such as confusion
- Often produces hypocalcemia (usually because of a diffuse capillary leak syndrome that drops the albumin level)

Streptococcal toxic shock syndrome is essentially the same.

To treat, remove the source of the infection and give vigorous fluid resuscitation, pressors (e.g., dopamine), and antibiotics. Empiric treatment is with clindamycin plus vancomycin until cultures return. In confirmed cases of methicillin-sensitive strains, treat with clindamycin plus an antistaphylococcal medication (oxacillin, nafcillin). In methicillin-resistant strains (MRSA), use vancomycin or linezolid.

Staphylococcal Scalded Skin Syndrome

Staphylococcal scalded skin syndrome (SSSS) is transmitted through physical contact with surroundings. It most commonly occurs in infants, young children, and the immunocompromised.

SSSS is mediated by a toxin from *Staphylococcus*. The major presentation is the loss of the superficial layers of the epidermis in sheets. Nikolsky sign is present. It is markedly different from toxic shock syndrome in that there is normal BP and no involvement of the liver, kidney, bone marrow, or CNS.

Patients should be managed in a burn unit and given oxacillin or other antistaphylococcal antibiotics. Consider vancomycin because of possible MRSA.

BENIGN AND PRECANCEROUS LESIONS

The predominant method of distinguishing between benign and malignant lesions is by the shape and color of the lesion.

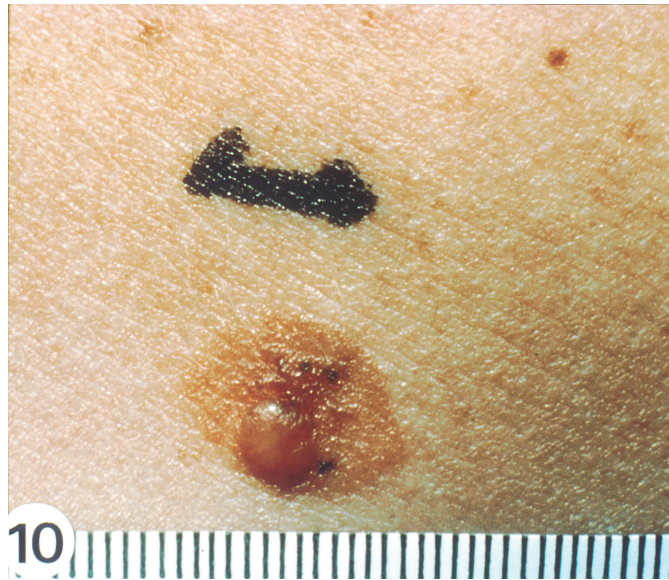
Benign lesions, such as the junctional or intradermal nevus, do not grow in size and have smooth, regular borders with a diameter usually <1 cm. In addition, they are homogenous in color, and this remains constant. Biopsy is the most accurate method of making a diagnosis, and benign lesions need to be removed only for cosmetic purposes.

Note

Differential Diagnosis

SSSS: from an infection; splits off only the superficial granular layer of skin

TEN: from drug toxicity; splits off the full-thickness of skin



visualsonline.cancer.gov

Figure 12-5. Dysplastic Nevus

Seborrheic Keratosis

Seborrheic keratosis is a benign condition with hyperpigmented lesions occurring in the elderly. It has no malignant potential and no relation to either actinic keratosis or seborrheic dermatitis. Lesions have a “stuck on” appearance and are most common on the face, shoulders, chest, and back.

Lesions are removed only for cosmetic purposes with liquid nitrogen or curettage.



Wikipedia, James Heilman, MD

Figure 12-6. Seborrheic Keratosis

Actinic Keratosis

Actinic keratosis presents with precancerous lesions occurring on sun-exposed areas of the body in older persons. Lesions occur more often in those with light skin color. They contain chromosomal abnormalities, and although only 1:1,000 lesions progresses to squamous cell cancer, an individual patient may have dozens of them. Hence, the rate of transformation to squamous cell cancer is 0.25% per patient.

Although the lesions are usually asymptomatic, they can be tender to the touch and lighter in color.

Lesions should be removed with cryotherapy, topical 5 fluorouracil (5-FU), imiquimod, topical retinoic-acid derivatives, or even curettage. Advise patients to use sunscreen to prevent progression and recurrence.

MALIGNANT DISEASES

Melanoma

Superficial spreading melanoma is the most common type of malignancy, accounting for 70% of cases. The rate of occurrence of melanoma is rising faster than any other cancer in the United States.

Malignant lesions grow in size, have irregular borders, are uneven in shape, and have inconsistent coloring. Lentigo maligna melanoma arises on sun-exposed body parts in the elderly. Acral-lentiginous melanoma arises on the palms, soles of feet, and nail beds.

Biopsy diagnosis is best performed with a full-thickness sample because tumor thickness is by far the most important prognostic factor.

Table 12-1. Ten-Year Survival Rates for Melanoma

Lesion Size (mm)	Survival Rate
<0.76	96%
0.76–1.69	81%
1.7–3.6	57%
>3.6	31%

Melanoma is removed by excision. Huge 5-cm margins are not routinely indicated. The size of the margin is determined by tumor thickness.

- Melanoma in situ needs only 0.5-cm margin
- Lesions <1 mm in thickness get 1.0-cm margin
- Lesions 1- to 2-mm in depth get 2-cm margin
- Lesions >2 mm in depth get 2- to 3-cm margin



There is no definitive chemotherapy for any form of skin cancer. Interferon seems to reduce recurrence rates.



National Cancer Institute

Figure 12-7. Melanoma

Squamous Cell Carcinoma

Squamous cell carcinoma makes up 10–25% percent of all skin cancers. It develops on sun-exposed skin surfaces in elderly patients. It is particularly common on the lip, where the carcinogenic potential of tobacco is multiplicative.

Ulceration of the lesion is common. Metastases are rare (3–7%).

Diagnosis is confirmed with biopsy. Treatment is surgical removal. Radiotherapy can be used for lesions that cannot be treated surgically.

Basal Cell Carcinoma

Basal cell carcinoma makes up 65–80% of all skin cancers. It has a shiny or “pearly” appearance. Metastases are very rare (<0.1%).

Diagnosis is confirmed with shave or punch biopsy. Treatment is surgical removal. Mohs micro surgery has the greatest cure rate; instant frozen sections are done to determine when enough tissue has been removed to give a clean margin.

5-FU can be used in the treatment of superficial lesions.



Wikimedia, John Hendrix

Figure 12-8. Basal Cell Carcinoma

Kaposi Sarcoma

The causative organism of Kaposi sarcoma is Human herpes virus 8. These are purplish lesions found on the skin, predominantly of patients with HIV and $CD4 < 100/mm^3$.

Treatment is antiretroviral therapy to raise CD4 count. When that does not occur, the specific chemotherapy for Kaposi sarcoma is liposomal doxorubicin hydrochloride or vinblastine.

Clinical Recall

What is the margin of excision of a suspected melanoma that has an in-depth thickness of 1.5 mm?

- A. 0.5 cm margin
- B. 2 cm margin
- C. 3 cm margin
- D. 4 cm margin

Answer: B

SCALING DISORDERS (ECZEMA)/PAPULOSQUAMOUS DERMATITIS

Psoriasis

The etiology of psoriasis is unknown. Silvery scales develop on the extensor surfaces, either locally or extensively. Nail pitting is a common accompaniment. The Koebner phenomenon is the development of lesions with epidermal injury.



Treatment. Salicylic acid is used to remove heaped-up collections of scaly material so that the other therapies can make contact. If the disease is relatively localized, topical steroids are used. Severe disease also needs coal tar or anthralin derivatives. To avoid the long-term use of steroids, which can cause skin atrophy, and to avoid coal tars, which are messy to use, substitute topical vitamin D and vitamin A derivatives. The vitamin D derivative most frequently used is calcipotriene. Tazarotene is a topical vitamin A derivative.

All patients should use emollients such as Eucerin™, Lubriderm™, or mineral oil. When >30% of the body surface area is involved, it is difficult to routinely use topical therapy to control disease. Ultraviolet light in that case is the most rapid way to control extensive disease. The most severe, widespread, and progressive forms of the disease can be controlled with methotrexate; however, it has the highest toxicity and may cause liver fibrosis.

The newest therapy is immunomodulatory biologic agents, such as alefacept, efalizumab, etanercept, and infliximab. These are monoclonal antibodies that target defects in the immune system, such as tumor necrosis factor.



Wikipedia, James Heilman, MD

Figure 12-9. Psoriasis

Atopic Dermatitis

Atopic dermatitis is an extraordinarily pruritic disorder characterized by high IgE levels. Red, itchy plaques appear on the flexor surfaces. In children, lesions are common on the cheeks and scalp. Adults present with lichenification.

Active disease is managed with topical steroids, antihistamines, coal tars, and phototherapy.

- Use antistaphylococcal antibiotics if there is impetiginization of the skin
- Use topical immunosuppressants such as tacrolimus and pimecrolimus to decrease dependence on steroid use
- Every effort must be made to avoid scratching; the topical tricyclic doxepin can be used to help stop pruritus

Preventive therapy is achieved by keeping the skin moist with emollients, avoiding hot water and drying soaps, and using only cotton clothes, as patients with this condition are extremely sensitive to drying.

Seborrheic Dermatitis

An oversecretion of sebaceous material and a hypersensitivity reaction to a superficial fungal organism, *Pityrosporum ovale*, underlie seborrheic dermatitis. Patients present with “dandruff,” which may also occur on the face. Scaly, greasy, flaky skin is found on a red base on the scalp, eyebrows, and in the nasolabial fold.

Treatment is low-potency topical steroids such as hydrocortisone, or topical antifungals in the form of shampoo such as ketoconazole or sulfide. Zinc pyrithione is also used as a shampoo.

Stasis Dermatitis

Stasis dermatitis is a hyperpigmentation built up from hemosiderin in the tissue. It occurs over a long period, from venous incompetence of the lower extremities leading to the microscopic extravasation of blood in the dermis. There is no way to reverse this problem. Prevention of progression is with elevation of the legs and lower-extremity support hose.

Contact Dermatitis

Contact dermatitis is a hypersensitivity reaction to soaps, detergents, latex, sunscreens, or neomycin over the area of contact. Jewelry is a frequent cause, as is contact with the metal nickel from belt buckles and wristwatches. It can occur as linear, streaked vesicles, particularly when it is from poison ivy.

A definitive diagnosis can be determined with patch testing. Once the causative agent has been identified, treat with antihistamines and topical steroids.



phil.cdc.gov

Figure 12-10. Contact Dermatitis Due to Poison Ivy



Pityriasis Rosea

Pityriasis rosea is a pruritic eruption that often begins with a “herald patch,” a single, pink, oval scaly patch before a full eruption of widespread rash is seen.

It is erythematous, salmon-colored, and looks like secondary syphilis, except that it spares the palms and soles. The lesions on the back appear in a pattern like a Christmas tree.

This condition is mild, self-limited, and usually resolves in 8 weeks without scarring.

This is a clinical diagnosis. VDRL/RPR is negative. Treat very itchy lesions with topical steroids.

DECUBITUS (PRESSURE) ULCERS

Decubitus ulcers are chronic sores that occur in the pressure areas of the body, where bone is closer to the skin. They are often associated with patients who are immobilized or bedridden.

Clinical presentation is in stages.

- Stage I lesions consist of **nonblanchable redness**.
- Stage II lesions result in **destruction of the superficial epidermis or partial destruction of the dermis**.
- Stage III lesions have **destroyed the full thickness of the skin but not the fascia**.
- Stage IV lesions show **destruction all the way to the bone**.

Diagnosis. Never culture a swab of the superficial ulcer or drainage from the ulcer. It will be impossible to determine whether it is a genuine infection or simply colonization. A definitive microbiologic diagnosis is often obtained only in the operating room after debridement.

The major theme of treatment is to relieve pressure. If the lesions are definitely infected, then antibiotics are useful.

HAIR

Alopecia Areata

Alopecia areata is an autoimmune disease in which antibodies attack the hair follicles and destroy hair production. Most cases will resolve spontaneously over time. Immediate treatment is localized steroid injection into the area of hair loss.

Telogen Effluvium

Telogen effluvium is the loss of hair in response to an overwhelming physiologic stress, such as cancer or malnutrition. Treatment is correction of the underlying stress or disease.

ACNE

The contributing organism for acne is *Propionibacterium acnes*. Pustules and cysts occur, which rupture and release free fatty acids, which in turn causes further irritation. Acne is more common in girls, but boys have more severe disease.

Patients present both with closed comedones (which are white) and open comedones (which are black). The discharge, although purulent, is odorless.

Treat mild disease with a topical antibiotic (clindamycin, erythromycin, sulfacetamide) plus the possible addition of the bacteriostatic agent benzoyl peroxide. If the attempts to control the load of bacteria locally are ineffective, use topical retinoids.

Treat moderate disease with benzoyl peroxide plus a retinoid (tazarotene, tretinoin, adapalene).

Treat severe cystic acne with an oral antibiotic (minocycline, tetracycline, clindamycin, oral isotretinoin). Oral retinoic-acid derivatives are a strong teratogen.

Clinical Recall

Which of the following treatment strategies is used to control extensive psoriasis (>30% BSA)?

- A. Topical emollients
- B. Topical vitamin A
- C. Topical vitamin D
- D. Phototherapy
- E. Topical steroids

Answer: D

Learning Objectives

- ❑ List the indications and common abnormal findings for chest x-ray, abdominal x-ray, PET scan, bone scan
- ❑ Answer questions about different approaches to visualizing the CNS

.....

This concise section should help you understand the types of tests offered in radiology.

CHEST X-RAY

The most basic radiologic examination is a chest x-ray. Standard x-rays are based on the degree of density of tissue and how much x-ray energy each type of tissue will absorb.

- The closer a bone structure is in density, the greater the energy it will absorb.
- Therefore, because bones block the most amount of x-ray energy, they will come out white on the film.
- Conversely, air absorbs or blocks the least amount of energy and thus will appear darkest.

Chest x-rays are **not routine** screening tests. There is no routine screening of the general population for cancer or tuberculosis. You can do a chest x-ray if the PPD skin test is positive, but that is not the same thing as just doing a general screening.

Most x-rays are **posterior-anterior (PA)** films. The x-ray plate is placed in front of the chest, and the patient leans forward against the plate. The x-ray beam is directed from posterior to anterior. The patient must be able to stand for a PA film to be performed.

Anterior-posterior (AP) films are less accurate but must be done if the patient is too ill or unstable to stand up.

- All patients with central venous lines or chest tubes
- Unstable patients, such as those in intensive care

The single greatest difference between the film types is heart size:

- AP films will show a heart size that is artificially enlarged; that is because the heart is more anterior in the chest and will therefore cast a wider shadow.
- **AP films** will show a heart >50% of the total transthoracic diameter, while normal **PA films** will show a heart <50%.

Note

The phenomenon produced by **AP film** is no different than holding your hand in a light shined against a wall. The farther your hand is away from the wall, the larger your hand's shadow will appear.



Technical Aspects of Normal Film Quality

- When examining a chest x-ray, first assess the film for its technical quality. If the patient's body is abnormally rotated, the film will be less accurate. You can determine this by seeing if the trachea and the spinous apophysis are midway between the clavicles.
- Perform chest x-ray when the patient is holding in a full inhalation. There should be at least 10 ribs visible, counting from top to bottom.
- An underexposed film will have the structures appearing too white, while an overexposed film will have the blood vessels appearing too dark (preventing one from accurately assessing the blood vessels).
- Note that on a PA film, the right hemidiaphragm is typically higher than the left. That is because the liver is underneath the right hemidiaphragm, pushing it up.

Expiratory Film

Expiratory film is used when one is looking for a pneumothorax. The lungs will appear smaller because less air will remain in the lungs on expiration. Because a pneumothorax is air outside the lungs in the pleural space, this air will appear relatively larger. The volume of air in the pleural space does not decrease on exhalation.

Lateral Chest X-ray

Lateral chest x-ray will determine whether a structure in the chest is more anterior or posterior. For example, it can determine whether a mass that is visible in the center of the mediastinum on a PA film is posterior, making it more likely to be a neurally derived tumor attached to the spinal cord or an anterior mass. Anterior mediastinal masses are from the thymus, thyroid, lymph nodes, or a teratoma.

Lateral x-ray also has a greater sensitivity for the detection of small pleural effusions.

- On a PA film, at least 100-200 mL of fluid need to be present to even begin to see an effusion. Each hemithorax can contain 3 liters of fluid if it is filled to capacity.
- Lateral chest x-ray can detect as little as 50 mL.
- These figures represent the amount of fluid needed to barely begin seeing "blunting," or obliteration, of the costophrenic angle.

On a lateral x-ray, the right hemidiaphragm is the one crossing the heart shadow.

Decubitus Film

Decubitus film helps detect the presence of a pleural effusion. It is taken with the patient lying on his side, and is employed when blunting or obscuration of the costophrenic angle is seen on a PA or lateral x-ray.

Effusions will move and form a layer on the side of the chest wall. Infiltrates from alveolar disease do not move with gravity. You cannot determine if an effusion is infected just from its appearance on an x-ray.

Note

The right hemidiaphragm will appear higher on a lateral x-ray and a PA film because the liver pushes it upward.

Common Disorders Seen on Chest X-ray

COPD/Emphysema

The most common appearance of COPD on a chest x-ray is related to **hyperinflation of the lung**. This leads to an increased anterior/posterior diameter (“barrel chest”).

- Leads to a darkening of the lung fields because more air is present
- Trapped air flattens the diaphragm and gives the impression of an elongated or tubular-shaped heart because it has been stretched down
- Bullae may be seen (large, air-filled cavities that can give thin, white lines on a chest x-ray as walls of the cavities press up against each other)

Pneumonia

Lobar pneumonia causes a whitening of each individual lobe of the lung because of greater density of the lung.

- “Silhouette” sign is present (border between the affected lobe and surrounding denser structure is obscured).
- Density of the lung increases because of alveolar infiltration to the point where it takes on the density of the nearby heart or diaphragm; thus, one can no longer tell where the lung ends and the nearby denser structure begins.
- **Lower lobe** pneumonia gives a silhouette over each half of the diaphragm. **Right middle-lobe** pneumonia obscures the right heart border and will not pass the minor or horizontal fissure seen on a PA chest x-ray. **Upper-lobe** infiltration will not pass the major fissure, and this is more easily seen on a lateral x-ray. You cannot determine a specific microbiologic etiology from the x-ray alone.
- Diseases of the lung outside the airspace but in the interstitial membrane give a fine, lacy appearance visible in most, if not all, of the lobes. Disorders which give interstitial infiltrates include *Pneumocystis* pneumonia, *Mycoplasma*, viruses, chlamydia, and sometimes *Legionella*. Noninfectious etiologies of an interstitial infiltrate are pulmonary fibrosis secondary to silicosis, asbestosis, mercury poisoning, berylliosis, byssinosis (from cotton), or simply idiopathic pulmonary fibrosis. As the long-standing disorders become worse and more chronic, a greater degree of fibrosis occurs and leads to greater thickening of the membrane (described as *reticular-nodular* and, later, *honeycombing*).

Note

Interstitial Syndromes of the Lung include:

Sarcoidosis

Histiocytosis X

IPF (interstitial pulmonary fibrosis)

Tumor

Failure

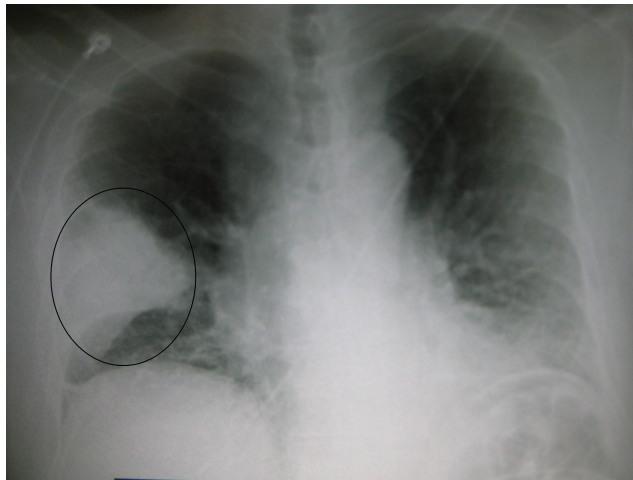
Asbestosis

Collagen disorders

Environmental

Dust

Drugs



Wikipedia, James Heilman, MD

Figure 13-1. Pneumonia

Congestive Heart Failure

The majority of pulmonary vascular flow is normally at the base of the lungs because of gravity. When there is fluid overload, the blood vessels toward the apices become fuller (called pulmonary vascular congestion or “cephalization” of flow). The term *cephalization* is used because more flow is moving toward the head.

The other findings associated with CHF are cardiomegaly, effusions, and Kerley B lines.

Kerley B lines are the least important. They are small, horizontal lines at the bases that represent fluid in the interlobular septa. Each lung has several lobes. When fluid builds up outside the lobes, this is known as a pleural effusion. When fluid builds up within each lobe, in between the lobules, this is known as a Kerley B line.

Position of Lines and Tubes

Chest x-ray is routinely used to determine the appropriate position of central venous lines and both endotracheal and chest tubes. The proper position of the tip of an endotracheal tube is 1 to 2 cm above the carina.

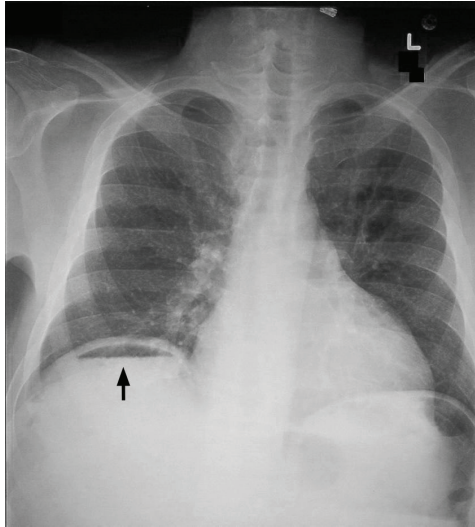
- Keep some space above the carina to make sure the tube doesn’t push into it when the head moves forward. That would be extremely uncomfortable and will provoke coughing.
- The tip of central venous lines is at the junction of the superior vena cava and the right atrium, at the point where the right mainstem bronchus is seen.
- The tip of the line should not be fully inside the atrium because this can irritate the heart and may provoke an arrhythmia.

Note

The subtle radiologic finding with a Kerley B line is less important today in the evaluation of congestive heart failure, since the advent of echocardiography.

Air under the Diaphragm

When there is perforation of an abdominal hollow organ, such as the duodenum, air is released and is visible under the diaphragm. The proper film to detect this is a chest x-ray taken in the upright position. This will allow the air to collect under the diaphragm, which should be easily visible. Abdominal x-rays do not always visualize the top of the diaphragm because of differences in body size. Chest x-rays always visualize the top of the diaphragm.



Wikimedia, Clinical Cases

Figure 13-2. Pneumoperitoneum

Imaging Tools for Lung Parenchyma

High resolution CT scan provides greater detail than a chest x-ray or CT scan because of 1 mm cut. This has a sensitivity of 95% and a specificity of close to 100% for lung parenchymal disease. High resolution CT scan is indicated in the following conditions:

- Symptomatic patients with a normal chest x-ray
- Detecting metastatic lesions, solitary nodules, bullae, bronchiectasis, and diffuse parenchymal disease (i.e., idiopathic lung diseases)
- To determine the type of lung biopsy required and site of biopsy



Clinical Recall

Which of the following is an indication for getting an expiratory chest x-ray?

- A. Pleural effusion
- B. Tuberculosis
- C. COPD
- D. Pneumothorax
- E. Congestive heart failure

Answer: D

ABDOMINAL X-RAY

Compared with chest x-rays, standard abdominal films without barium contrast provide far less information.

- Beneficial only in the detection of an abdominal obstruction, such as an ileus or a volvulus
- **Do not** reliably detect mass lesions, polyps, cancer, ascites, IBD

Use the following guidelines for detection:

- Mass lesions in all abdominal organs are best detected with CT scan or MRI of the abdomen.
- Polyps are best detected by colonoscopy.
- Ascites are visualized by U/S or CT scan.
- IBD, diverticulosis, and cancer are best detected by endoscopy or barium study of the bowel.
- Although 80–90% of kidney stones (nephrolithiasis) can be seen on abdominal films, they are also best detected by U/S or CT scan. Only 10–15% of gallstones can be detected on an abdominal film because most of them do not calcify.
- Pancreatic calcifications can be detected in 30–50% of patients with chronic pancreatitis.

Sonography (U/S)

Sonography is used for evaluation of abdominal and pelvic pathology. Sonograms should be employed first for evaluation of the biliary tract because of their accuracy in evaluating dilation and obstruction of the ducts. The majority of cholelithiasis should be detected with sonography because cholesterol gallstones should be easily visible by sonography. The majority of nephrolithiasis is visible by sonography, although there is less accuracy in detecting stones in the ureters because they become retroperitoneal structures.

Sonography is useful in the evaluation of masses in the liver, spleen, pancreas, and pelvis, as well as for evaluating the presence of ascites. Despite this accuracy, CT scanning tends to have a greater sensitivity and specificity for the abdomen and pelvis. Sonography is particularly valuable in the evaluation of pregnant patients because it avoids radiation exposure to the fetus. Although less accurate, sonography is also practical in patients who have an absolute contraindication to the use of IV contrast. A total of 1:10,000 patients have a life-threatening reaction to the use of iodinated contrast agents.

There is very little utility of sonography in the evaluation of thoracic structures because the ribs block the sound waves. Also, sonography in the evaluation of intracranial structures, such as the brain, is not recommended because the skull blocks the sound waves.

Endoscopic U/S involves introducing a sonographic device into the abdomen at the end of an endoscope. Endoscopic U/S is extremely accurate in evaluating pancreatic pathology that is not easily visualized on CT scanning, such as a gastrinoma. Pancreatic lesions can also be effectively evaluated in this way.

Endoscopic Retrograde Cholangiopancreatography

Endoscopic retrograde cholangiopancreatography (ERCP) is an endoscopically introduced contrast procedure designed to visualize the biliary tract and pancreatic structures. ERCP is for therapy. The endoscope is introduced into the small bowel, and a catheter is placed through the sphincter of Oddi. Contrast is injected through the catheter. This allows extremely accurate visualization of the pancreatic ductal and biliary systems. ERCP is excellent for detecting strictures, stones, and neoplastic causes of obstruction. The other advantages of ERCP are the ability to perform therapy with the removal of these stones, to dilate strictures, and to perform biopsies. The scope does not routinely go up the sphincter of Oddi because it is too large to pass.

MRCP is an MRI alternative to ERCP. It is less invasive than ERCP but does not allow an intervention.

The most common complication of ERCP is acute pancreatitis (around 10% in some series). Most of the time the pancreatitis is mild.

Barium Studies

Barium studies of the large bowel are never as accurate for colonic pathology as is endoscopy. In addition, you cannot biopsy with barium studies or perform therapeutic procedures, such as cautery or epinephrine injection for bleeding. The upper GI series is never as accurate as is upper endoscopy for the same reasons.

However, barium studies of the esophagus are a good test to start with for the evaluation of esophageal pathology. Barium esophagogram is particularly good for the detection of strictures, rings, and webs, or Zenker diverticulum. Barium is not as accurate as an upper endoscopy for the detection of esophageal cancer because a biopsy is required. (Endoscopy is far superior for the detection and therapy of esophageal varices as well.) Barium is not as accurate as manometry for the confirmation of the diagnoses of achalasia or muscular disorders, such as diffuse esophageal spasm and nutcracker esophagus.

Note

MRCP: diagnosis

ERCP: treatment



Clinical Pearl

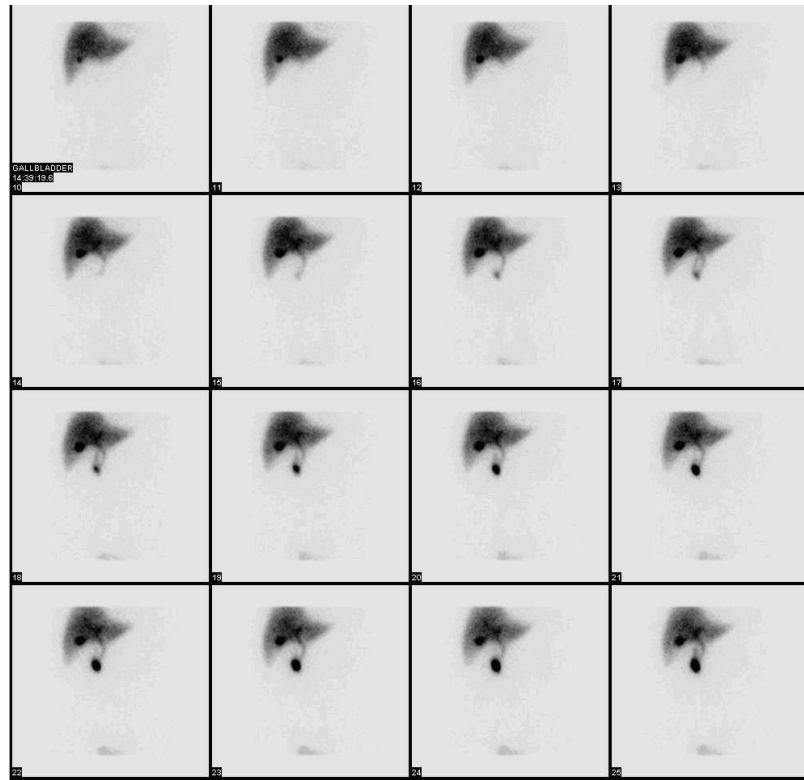
Capsule endoscopy is not a screening test to detect colon cancer. Perform capsule endoscopy to evaluate obscure small bowel GI bleeding.

Capsule Endoscopy

The ileum and jejunum are the hardest parts of the bowel to visualize by radiologic studies or endoscopy. In the past, a “push enteroscopy” was performed by introducing an extremely long, thin scope into the small bowel. Capsule endoscopy is a new technology that allows direct visualization of the small bowel by swallowing a camera that electronically relays thousands of photographic images from the small bowel to a receiver outside the body. The drawback of this procedure is that it is not possible to perform therapeutic interventions in this way. If a patient has GI bleeding that is serious and both upper and lower endoscopy do not reveal the source, then answer “capsule endoscopy” on the exam.

HIDA Scanning

This is a nuclear medicine scan useful only in the detection of acute cholecystitis. HIDA scanning is most useful in patients in whom the diagnosis of cholecystitis is not clear. An abnormal or positive test is the lack of visualization of the gallbladder. This is because the neck of the gallbladder or cystic duct becomes too edematous to allow the passage of the nuclear material. A normal scan will visualize the gallbladder. An abnormal scan will not visualize or fill the gallbladder.



Wikimedia, Myo Han

Figure 13-3. HIDA Scan

Virtual Colonoscopy

This procedure uses CT scan or MRI to provide a computer-simulated bidimensional or tridimensional image of the air-filled, distended colon.

PET SCAN

Positron emission tomography (PET) scans are useful in the detection of cancer. They are particularly useful in determining whether lesions that are visible on a CT scan of the chest are malignant or benign. Cancer is typically associated with the increased uptake of fluorodeoxyglucose. PET scanning is used after chemotherapy to assess for the presence of residual cancer in some patients and can also be used to determine whether a patient is an operative candidate to remove a primary cancer. If the PET scan does not reveal malignancy, then the resection of certain primary cancers, such as lung cancer, is more likely to be successful.

Remember that slow-growing cancers (e.g., bronchoalveolar) may have a negative PET scan. Be careful when evaluating pulmonary nodules with PET scanning.

Clinical Pearl

Always check the patient's glucose before doing a PET scan. If the glucose is elevated, the PET scan can be falsely negative.

CENTRAL NERVOUS SYSTEM VISUALIZATION

In general, the most accurate test for evaluating the CNS is the MRI. The MRI is superior for the detection of stroke, cancer, MS, and infections and in the evaluation of the posterior fossa, such as the cerebellum and brainstem.

The CT scan does not visualize the brainstem well. For example, a stroke is visible on an MRI in >90% of cases within the first 24 hours after its onset, whereas the CT scan needs 3 to 4 days before >90% are visible. This is because the MRI is based on the water content of tissues rather than on the calcium content or simple density of tissue. Within a few hours after the onset of a stroke, the cells begin to swell and increase their water content. This is immediately visible on an MRI, whereas for a CT scan to detect an abnormality, the cells must die to decrease the density of visible cells.

The single exception in which a CT scan is superior to an MRI is in the detection of blood. As soon as bleeding occurs, it is visible on a CT scan. Therefore, the two cases in which a CT scan is a better study are to evaluate head trauma and to exclude hemorrhagic stroke. When a patient arrives within 3 hours of the onset of the symptoms of a stroke, a CT scan is first performed to exclude hemorrhage. This is to see if a patient is eligible for the use of thrombolytic therapy within these first 3 hours.

CT scan is also used first for the detection of subarachnoid hemorrhage. On the first day after the stroke's onset, the CT scan has 95% sensitivity. The sensitivity diminishes by about 5% per day as the blood is hemolyzed and removed.

Contrast on a scan of the head is indicated primarily for the detection of cancers and infection. When an abscess or neoplastic process is present, there is some disruption of the blood-brain barrier, causing some extravasation of the contrast, which is visible as a contrast, or "ring"-enhancing lesion around the mass.



BONE IMAGING

An x-ray is certainly the first study to implement when evaluating trauma and fracture. Unfortunately, the bone scan has much less specificity and does not reliably distinguish between bone infection and infection of the overlying soft tissue. The MRI is 90–95% sensitive and 90–95% specific.

Osteomyelitis

When there is the suspicion of osteomyelitis, an x-ray is done first. Although plain x-rays lack sensitivity for the first 1 to 2 weeks, the specificity for osteomyelitis is excellent. More than 50% of the calcium content of bone must be lost for osteomyelitis to be visible. The earliest finding of osteomyelitis on an x-ray is elevation of the periosteum. If the film returns normal and there is still suspicion of osteomyelitis, then the best test is an MRI. The MRI and technetium nuclear bone scan have the same sensitivity (90–95%); however, the MRI's specificity is far greater (90–95%). Both studies should become abnormal within 2 days of the onset of osteomyelitis. Therefore, a negative bone scan is very useful if it is normal; it means that there is no osteomyelitis. If it is abnormal, you may still need to perform an MRI.

Clinical Recall

Which of the following findings on chest x-ray will be seen with a perforated peptic ulcer?

- A. Kerley B lines with vascular cephalization
- B. Blunting of the costophrenic angles with a clear meniscus sign
- C. Pneumoperitoneum
- D. Flattening of the diaphragm with a tubular shaped heart
- E. Interstitial hyperdensities with hilar lymphadenopathy

Answer: C

Learning Objective

- ❑ Describe the presentation and treatment of glaucoma, cataracts, keratitis, uveitis, periorbital cellulitis, retinal diseases, and conjunctival diseases
-

RETINAL DISEASES

Diabetic Retinopathy

The etiology of diabetic retinopathy is based on damage to the endothelial lining of the small blood vessels of the eye. The endothelial lining of the retinal vessels becomes damaged, leading to progressive occlusion on a microscopic level. The occlusion leads to obstruction and increased pressure.

- The earliest form of this adverse effect on the retina is called **nonproliferative** (or **background**) retinopathy. It is characterized by dilation of veins, microaneurysms, retinal edema, and retinal hemorrhages. Hemorrhages into the retina are not as damaging as intravitreal hemorrhages because they do not obstruct sight.
- **Proliferative** retinopathy is a more advanced form of the disease and is markedly more serious, meaning it progresses more rapidly to blindness.
 - As the microvascular damage to the vessels worsens, the vessels secrete increased amounts of an angiogenesis factor (thus, “nutrition” to the retina decreases).
 - In an effort to deliver more nutrition and oxygen to the retina, the vessels exert an increased effort to have more of them produced.
 - This “neovascularization,” or new blood vessel formation, leads to the optic nerve getting covered with abnormal new vessel formation. In addition, hemorrhages protrude into the vitreous chamber.

Clinical Correlate

The etiology of diabetic retinopathy is identical in pathogenesis to the damage that diabetes causes to all blood vessels in the body, such as in the heart, kidney, brain, and peripheral nervous system.

**Note**

Vitreous hemorrhage is much more serious than a microaneurysm or intraretinal hemorrhage because it is much more sight-threatening.

Symptoms are highly variable. There may be very advanced disease occurring with no symptoms. Vision may decrease slowly or rapidly. Vitreous hemorrhages may develop suddenly, and patients will complain of “floaters” in their vision.



Retina-Vitreous Surgeons of Central New York

Figure 14-1. Features of Diabetic Retinopathy

Diagnosis. Screening for the presence of retinopathy should be performed on an annual basis by an ophthalmologist. This is how candidates for fluorescein angiography and laser photocoagulation are found. Fluorescein helps identify which vessels should undergo laser photocoagulation. The laser selectively destroys focal areas of the retina and diminishes the production of the angiogenesis factor, which causes the proliferative retinopathy.

Treatment of both stages of diabetic retinopathy is tight control of glucose, BP, and lipid levels. For proliferative retinopathy, add immediate laser photocoagulation.

The more tightly the glucose is controlled within the normal range, the slower the progression of the retinopathy. Control BP to a level <130/80 mm Hg.

Aspirin, clopidogrel, and other platelet-inhibiting medications have shown no benefit.

Retinal Detachment

A 71-year-old woman presents with blurry vision in her left eye since that morning. She says it was as if “a curtain came down.” She has had floaters in the periphery of her left eye over the past few weeks but has had no pain or erythema. She has a history of stage I hypertension but is otherwise healthy.

Note

The term *rhegmatogenous*, which describes the detachment, is from the Greek word for “tear.”

Retinal detachment is usually spontaneous, but it may result from trauma. The most common predisposing factors are myopia and surgical extraction of cataracts. Traction on the retina can also occur from proliferative retinopathy from diabetes, retinal vein occlusion, and age-related macular degeneration.

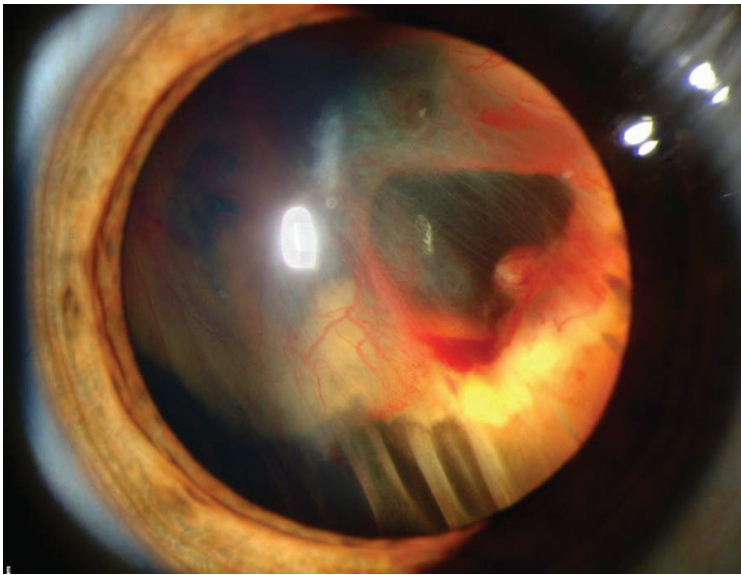
Symptoms include:

- Blurry vision in one eye without pain or redness (**most common**)
- Visualization of “floaters” in the eye, and flashes at the periphery of vision (sometimes described as a “curtain coming down,” as the retina falls off the sclera behind it)

Diagnosis is made by ophthalmologic examination.

Treatment. Try to reattach the retina. Most uncomplicated rhegmatogenous retinal detachments can be cured with one operation, and a few require a second operation.

- Leaning the patient’s head back, to promote the chance that the retina will fall back into place
- Surgical reattachment of the retina to the sclera, with laser photocoagulation, cryotherapy, or injection of expansile gas into the vitreal cavity (the gas will press the retina back into place)
- A “buckle,” or belt placed around the sclera to push it forward so that it makes contact with the retina
- If no response to any method, consider removing the vitreous and surgically attach the retina to the sclera.



National Eye Institute/National Institutes of Health

Figure 14-2. Retinal Detachment

Age-Related Macular Degeneration

Age-related macular degeneration (ARMD) is the most common cause of legal blindness in older persons in the Western world. The etiology is unknown. ARMD is characterized by the formation of deposits of extracellular material collecting into yellowish deposits seen on ophthalmoscopy. These deposits are known as “drusen.” They are small, granular, subretinal deposits that are age related.



There are 2 types of ARMD:

- **Dry**, or atrophic, form
 - Slowly progressive visual loss in the elderly
 - Leads to visual loss that is slow and gradual
 - Diagnosis is confirmed by finding clearly visible drusen on dilated eye exam
- **Wet**, or exudative, form
 - Abnormal growth of vessels from the choroidal circulation into the subretinal space
 - The vessels leak, leading to collections of subretinal fluid and a localized, exudative retinal detachment
 - Rapid distortion of vision over weeks to months
 - Diagnosis is confirmed with fluorescein angiography

Treatment.

- **Dry** form: nothing is proven to stop progression, but zinc, antioxidant vitamins C and E, and beta-carotene may slow progression
- **Wet** form: VEGF inhibitors ranibizumab and bevacizumab

Retinal Occlusions

Central Retinal Artery Occlusion

There are various etiologies of central retinal artery occlusion: carotid artery embolic disease, temporal arteritis, cardiac thrombi or myxoma, or any of the usual causes of thrombophilia such as factor V Leiden mutation.

Patients present with a sudden, painless, unilateral loss of vision. There is no redness of the eye. Ophthalmoscopy reveals a pale retina, with overall diminished perfusion and a “cherry-red” spot at the fovea. There is also “box-car” segmentation of the blood in the veins.

Diagnostic tests include carotid artery imaging, echocardiography, and evaluation for thrombophilia.

Treatment is similar to that of a stroke (cardiovascular accident or transient ischemia attack).

- Lay the patient flat
- Supply oxygen and ocular massage in an attempt to unobstruct the vessel
- Consider acetazolamide and thrombolytics
- Anterior chamber paracentesis may decompress the eye pressure and dislodge the embolus

Central Retinal Vein Occlusion

Patients with retinal vein occlusion are at particularly high risk for developing glaucoma. They should be monitored for the possible use of laser photocoagulation. Younger patients should be investigated for inherited causes of thrombophilia, such as factor V mutation, protein C deficiency, and antiphospholipid syndromes.

Presentation is similar to retinal artery occlusion: sudden loss of vision without pain, redness, or abnormality in pupillary dilation. Ocular examination by funduscopy reveals disk swelling, venous dilation, tortuosity, and retinal hemorrhages.

Retinal hemorrhage is the main way to distinguish **venous obstruction from arterial obstruction**. You can't have a hemorrhage in the retina if you don't have blood getting into the eye.

There is no specific treatment for retinal vein obstruction.

Clinical Recall

Which of the following fundoscopic findings is representative of proliferative diabetic retinopathy?

- A. Dilation of veins, microaneurysms, retinal edema, and retinal hemorrhages
- B. Vitreal hemorrhages with optic nerve concealment by neovascular growth
- C. Floaters, red cells in the vitreous with a wrinkled, detached retina
- D. Yellowish, small, and granular extracellular subretinal deposits
- E. A pale retina with diminished perfusion and a cherry-red spot at the fovea

Answer: B

GLAUCOMA

Glaucoma is an irreversible eye disease associated with increased eye pressure and vision loss. The precise etiology is unknown.

Open-Angle Glaucoma

In open-angle glaucoma (**most common**, 90% of cases), there is a decrease in the outward flow/drainage of aqueous fluid from the anterior chamber, causing increased ocular pressure.

Patients are asymptomatic for a long time, explaining why it is important to screen older patients.

The first clue to the diagnosis is a **cup-to-disk ratio** >0.5 , which should be confirmed by repeated elevation in intraocular pressure as determined by tonometry.

Treatment is to decrease the production of aqueous humor and increase its drainage.

- To **decrease the production of aqueous humor**: beta-blockers (timolol, betaxolol, levobunolol), alpha-adrenergic agonists (apraclonidine, brimonidine), and carbonic anhydrase inhibitors (dorzolamide and brinzolamide)
- To **increase the outflow of the humor**: prostaglandin analogs such as topical latanoprost, travoprost, and bimatoprost (side effects include causing the eyes to change color and darkening of the eyelids); pilocarpine (a miotic agent) constricts the pupil to allow greater outflow of the aqueous humor
- If no response to medical therapy, consider surgery, e.g., laser trabeculoplasty and surgical trabeculectomy.



Closed-Angle Glaucoma

Closed-angle glaucoma is often an ophthalmologic emergency precipitated by the use of medication with anticholinergic properties.

- Eye is red, painful, hard to palpation
- Associated with a fixed midpoint pupil
- Cornea has a hazy cloudiness
- Marked diminishment of visual acuity

Treatment is urgently needed.

- IV acetazolamide, urea, and osmotic diuretics such as mannitol and glycerol
- Pilocarpine to open the canal of Schlemm
- Beta-blockers to decrease humor production
- If no response, laser trabeculoplasty

CATARACTS

Cataracts are opacifications of the lens. They are slowly progressive, with a blurring of vision occurring over months to years. Glare from the headlights of cars is particularly a problem when driving at night. Color perception is reduced in general. The etiology of cataracts is unknown, although there is an association with cigarette smoking.

Mature cataracts can be easily seen on physical examination. Earlier-stage disease is seen with a slit lamp.

There is no medical therapy for cataracts. Surgical removal with the placement of an intraocular lens is the standard of care.

CONJUNCTIVAL DISEASES

Conjunctivitis

Conjunctivitis can occur from any infectious agent, including bacteria, viruses, and fungi. It is highly contagious.

- **Bacterial** conjunctivitis is often unilateral and presents with a marked purulent discharge from the eye.
 - Most symptomatic in the morning, when patient's eye has developed a significant crust overnight (can make it hard to open the eye)
 - Less itching with bacterial than with viral
 - Eye is red but there is a normally reactive pupil and normal ocular pressure
 - Visual acuity is not impaired
- **Viral** conjunctivitis is often bilateral, with enlarged preauricular adenopathy.
 - Severe ocular itching
 - Eyes are red but the pupils are normally reactive without photophobia (light sensitivity)

Treatment is as follows:

- **Bacterial** conjunctivitis: topical antibiotic such as erythromycin ointment, sulfacetamide drops, or topical fluoroquinolones
- **Viral** conjunctivitis: symptomatically with topical antihistamine/decongestants; there is no specific microbiologic treatment

Subconjunctival Hemorrhage

Subconjunctival hemorrhage is more dangerous in its appearance than in its actual damage to vision or even the eye itself. The most common cause is trauma, particularly in the presence of thrombocytopenia. The collection of the hematoma stops at the limbus, which is the anatomic connection between the conjunctiva and the cornea. Because this prevents the blood from covering the cornea, there is no impairment of vision.

There is no intraocular or intravitreal damage and hence no impairment of vision. No specific therapy is necessary.

KERATITIS

Keratitis refers to any infection or inflammation of the cornea. Usually, keratitis happens as a result of trauma to the cornea with the inoculation of bacterial or fungal elements into the cornea.

Herpes Simplex Keratitis

Herpes simplex keratitis is characterized by severe pain in the eye and a sensation that something is caught under the eyelid.

Diagnosis is based on finding a characteristic dendritic pattern over the cornea on fluorescein staining of the eye with examination under a blue light.

Treatment is oral acyclovir, famciclovir, or valacyclovir, plus topical trifluridine 1% solution or idoxuridine.

PERIORBITAL CELLULITIS

Cellulitis is caused by *Staphylococcus aureus* or *Streptococcus* invading the dermis and subcutaneous tissues surrounding the eye.

Treatment is an antistaphylococcal penicillin such as oxacillin or nafcillin. In cases of penicillin allergy, use a first-generation cephalosporin such as cefazolin.

UVEITIS

Uveitis occurs when the structures of the uveal tract (the iris, ciliary body, and choroid) become inflamed. It is caused by various systemic inflammatory conditions, such as psoriasis, sarcoidosis, syphilis, Reiter syndrome, and IBD.

Note

Subconjunctival hemorrhage looks more dangerous than it is.

Note

Never use oral and topical steroids to relieve the inflammation of herpes simplex keratitis. That can markedly worsen the growth of the virus, acting as "fertilizer."



Uveitis leads to a painful, red eye with marked photophobia. One clue to diagnosis is pain that occurs even when shining a light in the unaffected eye. This is because of the consensual light reflex in which the affected pupil will constrict even when light is shined in the normal eye.

Diagnosis is made by slit lamp examination. Inflammation of the iris, ciliary body, and choroid is visible. Inflammatory cells may accumulate on the inside of the cornea after they precipitate out of the aqueous humor, rather like an accumulating snowfall. These focal collections are called keratic precipitates.

Basic management, despite the varied underlying conditions, is to treat with topical or systemic steroids.

Clinical Recall

A 32-year-old man presents with redness of his eyes, marked photophobia, and normal conjunctiva. Which of the following is the best initial treatment?

- A. Topical corticosteroids
- B. Topical oxacillin
- C. Topical acyclovir
- D. Oral idoxuridine
- E. Topical trifluridine

Answer: A

Medical Abbreviations

AAA	abdominal aortic aneurysm
ABG	arterial blood gas
ACE	angiotensin-converting enzyme
ACTH	adrenocorticotrophic hormone
ADH	antidiuretic hormone
AFB	acid-fast bacilli
Afib	atrial fibrillation
AIDS	acquired immune deficiency syndrome
AKI	acute kidney injury
ALS	amyotrophic lateral sclerosis
ANS	autonomic nervous system
ARB	angiotensin receptor blocker
ARDS	acute respiratory distress syndrome
ASA	aspirin
AST	aspartate transaminase
ALT	alanine transaminase
ANS	autonomic nervous system
ATP	adenosine triphosphate
AV	atrioventricular
AVM	arteriovenous malformation
BAL	bronchoalveolar lavage
BM	bowel movement
BMD	bone mineral density

(Continued)



BMI	body mass index
BP	blood pressure
BPH	benign prostatic hypertrophy
BSA	body surface area
BUN	blood urea nitrogen
C-ANCA	cytoplasmic antineutrophil cytoplasmic antibody
CABG	coronary artery bypass grafting
CAD	coronary artery disease
CBC	complete blood count
CCB	calcium channel blocker
CF	cystic fibrosis
CHF	congestive heart failure
CKD	chronic kidney disease
CLL	chronic lymphocytic leukemia
CML	chronic myelogenous leukemia
CMV	cytomegalovirus
CN	cranial nerve
CNS	central nervous system
CO	carbon monoxide (or cardiac output)
COPD	chronic obstructive pulmonary disease
CPAP	continuous positive airway pressure
CPK	creatine phosphokinase
CPPD (also called pseudogout)	calcium pyrophosphate deposition
CPR	cardiopulmonary resuscitation
CSF	cerebrospinal fluid
CT	computed tomography
CVA	cerebrovascular accident
CVP	central venous pressure
DI	diabetes insipidus

DIC	disseminated intravascular coagulation
DLCO	diffusing capacity (of lung) for carbon monoxide
DM	diabetes mellitus
DOACs	direct oral anticoagulants
DO ₂	oxygen delivery
DTR	deep tendon reflexes
DVT	deep vein thrombosis
ECG	electrocardiogram
EEG	electroencephalogram
ED	emergency department
ERCP	endoscopic retrograde cholangiopancreatography
ESBL	extended spectrum beta-lactamases
ESR	erythrocyte sedimentation rate
FEVs	forced expiratory volumes
FNA	fine needle aspiration
FSH	follicle stimulating hormone
GERD	gastroesophageal reflux disorder
GI	gastrointestinal
GnRH	gonadotropin-releasing hormone
GU	genitourinary
HBsAg	hepatitis B surface antigen
Hct	hematocrit
HEENT	head, eyes, ears, nose, and throat
HIV	human immunodeficiency virus
HOCM	hypertrophic cardiomyopathy
HP	hypersensitivity pneumonitis
HRT	hormone replacement therapy

(Continued)



HR	heart rate (per minute)
HTN	hypertension
IBD	inflammatory bowel disease
IBS	irritable bowel syndrome
ICU	intensive care unit
IDDM	insulin-dependent diabetes mellitus
IGRA	interferon gamma release assay
IM	intramuscularly
IPF	idiopathic pulmonary fibrosis
IV	intravenously
IVC	inferior vena cava
JVD	jugular venous distension
JVP	jugular venous pressure
LABAs	long-acting beta agonists (LABA)
LAMAs	long-acting muscarinic antagonists
LDH	lactate dehydrogenase
LFTs	liver function tests
LH	luteinizing hormone
LLL	left lower lobe
LLQ	left lower quadrant
LMP	last menstrual period
loc	loss of consciousness
LP	lumbar puncture
LUL	left upper lobe
LUQ	left upper quadrant
MI	myocardial infarction
MIBG scan	metaiodobenzylguanidine scan
MIC	minimum inhibitory concentration

MRI	magnetic resonance imaging
MRSA	methicillin-resistant <i>Staphylococcus aureus</i>
MS	multiple sclerosis
MSSA	methicillin-sensitive <i>Staphylococcus aureus</i>
MVP	mitral valve prolapse (cardiology) or maximum vertical pocket (obstetrics)
NAAT	nucleic acid amplification test
NIDDM	non–insulin-dependent diabetes mellitus
NPH	normal pressure hydrocephalus
NSR	normal sinus rhythm
NST	non-stress test
NRTIs	nucleoside reverse transcriptase inhibitors
NSCLC	non-small-cell lung carcinoma
OCP	oral contraceptive pills
OSA	obstructive sleep apnea
OTC	over-the-counter
p-ANCA	perinuclear anti-neutrophil cytoplasmic antibodies
PA	posteroanterior
PAN	polyarteritis nodosa
PCP	primary care provider
PCP	<i>Pneumocystis carinii</i> pneumonia
PE	physical examination
PE	pulmonary embolus
PEEP	positive end-expiratory pressure
PERRLA	pupils are equal, round, and reactive to light and accommodation
PET	positron emission tomography
PF	pulmonary fibrosis
PFTs	pulmonary function tests

(Continued)



PID	pelvic inflammatory disease
PIs	protease inhibitors
PMI	point of maximum impulse
po	orally
POC	products of conception
pos	positive
PPD	packs per day
PPD	purified protein derivative
PRN	as needed
PSA	prostatic specific antigen
PT	prothrombin time
PTSD	post-traumatic stress disorder
PTT	partial prothrombin time
PUD	peptic ulcer disease
PVD	peripheral vascular disease
RA	rheumatoid arthritis
RBC	red blood cells
RDS	respiratory distress syndrome
RLL	right lower lobe
RLQ	right lower quadrant
RMG	rubs, murmurs, or gallops
ROM	range of motion
RR	respiratory rate
RRR	regular rate and rhythm
RUL	right upper lobe
RUQ	right upper quadrant
SAB	subarachnoid bleed
SABAs	short-acting beta agonists
SBO	small bowel obstruction

SCC	squamous cell carcinoma
SCFE	slipped capital femoral epiphysis
SCLC	small-cell lung carcinoma
SERM	selective estrogen receptor modulator
SH	social history
SHBG	sex hormone binding globulin
SJS	Stevens-Johnson Syndrome
SLE	systemic lupus erythematosus
SLR	straight leg raising
SOB	shortness of breath
SQ	subcutaneous
Staph	<i>Staphylococcus</i>
STD	sexually transmitted disease
Strep	<i>Streptococcus</i>
SV	stroke volume (per heartbeat)
T	temperature
TB	tuberculosis
TBB	transbronchial biopsy
TIA	transient ischemic attack
TMP/SMX	trimethoprim/sulfamethoxazole
TPPA	treponema pallidum particle agglutination
TSH	thyroid stimulating hormone
TURP	transurethral prostatectomy
U/A	urinalysis
UE	upper extremity
UIP	usual interstitial pneumonia
U/S	ultrasound
UTI	urinary tract infection

(Continued)



VATS	video-assisted thoracoscopic surgery
VCUG	voiding cystourethrogram
VDRL	Venereal Disease Research Laboratory
VMA	vanillylmandelic acid
WBC	white blood cells
WNL	within normal limits

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