Hematology

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	Warm agglutinin AIHA	Cold agglutinin AIHA
Etiology	• Drugs (eg, penicillin) • Viral infections • Autoimmune (eg, SLE) • Immunodeficiency states • Lymphoproliferative (eg, CLL)	• Infections (eg, *Mycoplasma pneumoniae* infection & infectious mononucleosis) • Lymphoproliferative diseases
Clinical presentation	• Asymptomatic to life-threatening anemia • Direct Coombs' positive with anti-**IgG**, anti-C3, or both	• Symptoms of anemia • Livedo reticularis & acral cyanosis with cold exposure that disappear with warming • Direct Coombs' positive with anti-C3 or anti-**IgM**, but usually not IgG
Treatment	• Corticosteroids • Splenectomy for refractory disease	• Avoidance of cold temperatures • Rituximab +/- fludarabine
Complications	• Venous thromboembolism • Lymphoproliferative disorders	• Ischemia & peripheral gangrene • Lymphoproliferative disorders

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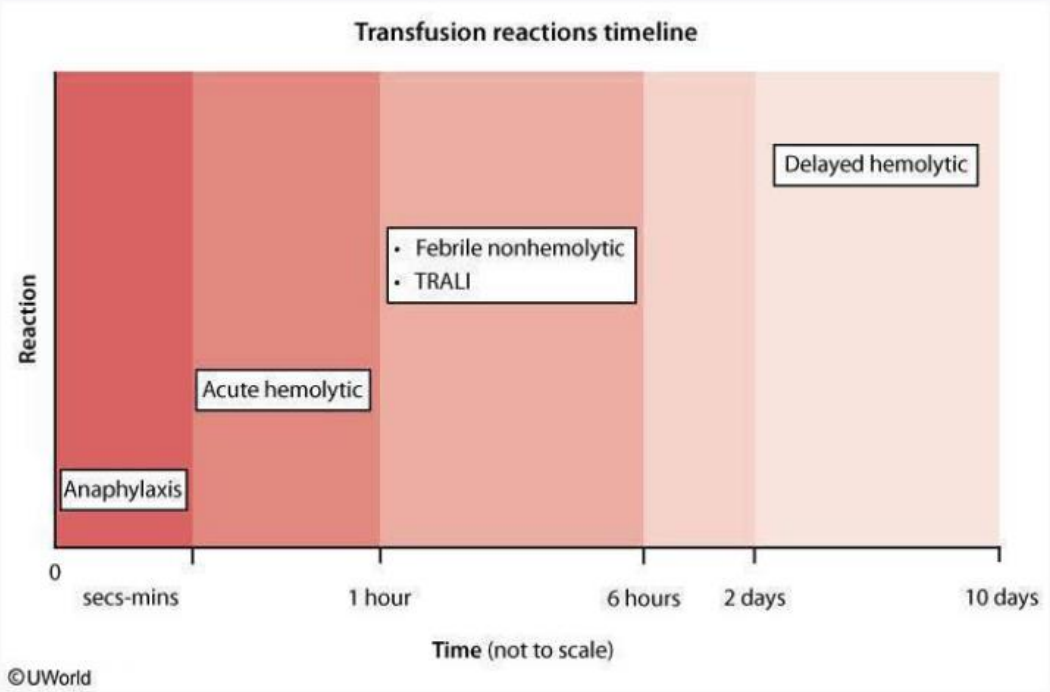


Indications for specialized RBC treatments	
Irradiated	• Bone marrow transplant (BMT) recipients • Acquired or congenital cellular immunodeficiency. • Blood components donated by first or second degree relatives
Leukoreduced	• Chronically transfused patients • CMV seronegative at-risk patients (e.g., AIDS, transplant patients) • Potential transplant recipients • Previous febrile nonhemolytic transfusion reaction
Washed	• IgA deficiency • Complement-dependent autoimmune hemolytic anemia • Continued allergic reactions (e.g., hives) with red cell transfusion despite antihistamine treatment

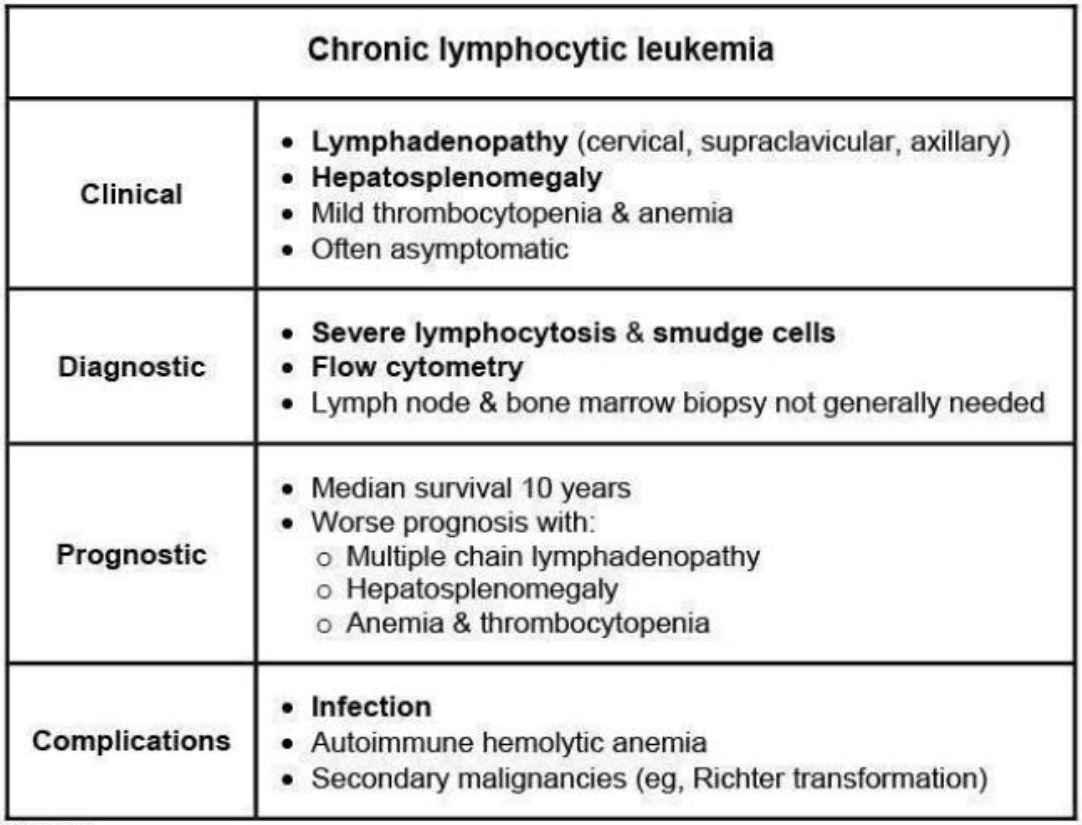
Immunologic blood transfusion reactions	
Transfusion reaction	**Clinical features & etiology**
Febrile nonhemolytic (most common reaction)	• Fever & chills • Within 1-6 hours of transfusion • Caused by cytokine accumulation during blood storage
Acute hemolytic	• Fever, flank pain, hemoglobinuria, renal failure & disseminated intravascular coagulation • Within 1 hour of transfusion • Positive direct Coombs test, pink plasma • Caused by ABO incompatibility
Delayed hemolytic	• Mild fever & hemolytic anemia • Within 2-10 days after transfusion • Positive direct Coombs test, positive new antibody screen • Caused by anamnestic antibody response
Anaphylactic	• Rapid onset of shock, angioedema/urticaria & respiratory distress • Within a few seconds to minutes of transfusion • Caused by recipient anti-IgA antibodies
Urticarial/allergic	• Urticaria, flushing, angioedema & pruritus • Within 2-3 hours of transfusion • Caused by recipient IgE antibodies & mast cell activation
Transfusion-related acute lung injury	• Respiratory distress & signs of noncardiogenic pulmonary edema • Within 6 hours of transfusion • Caused by donor anti-leukocyte antibodies

Blood transfusion reactions associated with hypotension	
Reaction	**Clinical features & etiology**
Anaphylactic	• Rapid onset of shock, angioedema/urticaria & respiratory distress • Within a few seconds to minutes of transfusion • Caused by recipient anti-IgA antibodies
Transfusion-related acute lung injury	• Respiratory distress & signs of noncardiogenic pulmonary edema • Within 6 hours of transfusion • Caused by donor anti-leukocyte antibodies
Primary hypotension reaction	• Transient hypotension often in patients taking angiotensin- converting enzyme inhibitors • Within minutes of transfusion • Caused by bradykinin in blood products (normally degraded by angiotensin-converting enzyme)
Bacterial sepsis	• Fever, chills, septic shock & DIC • Within minutes to hours of transfusion

Popliteal (Baker) cyst	
Etiology	• Extrusion of fluid from knee joint space into semimembranosus/gastrocnemius bursa
Risk factors	• Trauma (eg, meniscal tear) • Underlying joint disease (eg, osteoarthritis, rheumatoid arthritis)
Clinical presentation	• Asymptomatic bulge behind knee that diminishes with flexion • Posterior knee pain, swelling, stiffness
Complications	• Venous compression (leg/ankle swelling) • Dissection into calf (erythema, edema, positive Homan sign) • Cyst **rupture** (acute calf pain, warmth, erythema, ecchymosis)

Cancer-related anorexia/cachexia syndrome (CACS) is a hypercatabolic state associated with weight loss, anorexia, and an excessive reduction in skeletal muscle. Weight loss is multifactorial and thought to be a result of systemic inflammation in addition to caloric reduction. Nutritional counseling and supplementation with enteral or parenteral feeding do little to reverse CACS. Pharmacologic intervention with progesterone analogues (eg, **megestrol acetate**) or corticosteroids is effective at increasing appetite, causing weight gain, and improving well-being. In patients with longer life expectancies, progesterone analogues are preferred over corticosteroids due to their decreased incidence of side effects.

- **Serotonin (5HT) receptor antagonists** (eg, ondansetron) that target the **5HT3 receptor** are considered first-line treatment for **chemotherapy-induced nausea**. They have a low side-effect profile and are highly efficacious. These medications can be used to manage acute emesis but are also useful as prophylaxis, sometimes in combination with corticosteroids.

- 

Chronic lymphocytic leukemia	
Clinical	• **Lymphadenopathy** (cervical, supraclavicular, axillary) • **Hepatosplenomegaly** • Mild thrombocytopenia & anemia • Often asymptomatic
Diagnostic	• **Severe lymphocytosis** & **smudge cells** • **Flow cytometry** • Lymph node & bone marrow biopsy not generally needed

Prognostic	• Median survival 10 years
	• Worse prognosis with:
	  ○ Multiple chain lymphadenopathy
	  ○ Hepatosplenomegaly
	  ○ Anemia & thrombocytopenia

Complications	• **Infection** • Autoimmune hemolytic anemia • Secondary malignancies (eg, Richter transformation)

- **Chronic lymphocytic leukemia (CLL)** is the most common type of leukemia in the United States. It is almost always seen in the **elderly** (median age at diagnosis is 70). Patients are often asymptomatic but can present with **extreme fatigue**, B symptoms (eg, night sweats, fevers), infection, or weight loss. Lymphadenopathy and splenomegaly are often present on physical examination. Dramatic **lymphocytosis** is the classic hallmark of CLL. Peripheral smear reveals **mature lymphocytes** with the presence of **smudge cells** (a pathognomonic characteristic of CLL).
- CLL is diagnosed by flow cytometry (showing a clonality of mature B cells).

	Leukemoid reaction	Chronic myeloid leukemia
Leukocyte count	>50,000/mm^3	Elevated (often >100,000/mm^3)
Cause	Severe infection	*BCR-ABL* fusion
LAP score	High	Low
Neutrophil precursors	More mature (metamyelocytes > myelocytes)	Less mature (metamyelocytes < myelocytes)
Absolute basophilia	Not present	Present

- LAP = leukocyte alkaline phosphatase.

Glucose-6-phosphate dehydrogenase deficiency	
Epidemiology	• Hemolytic anemia following oxidative stress (infection, sulfa drugs, fava beans) • Asian, African, or Middle Eastern descent (X-linked, often men)
Manifestations	• Pallor & fatigue • Dark urine • Jaundice • Abdominal/back pain
Laboratory findings	• Hemolysis (low hemoglobin, increased indirect bilirubin, increased lactate dehydrogenase, decreased haptoglobin) • Bite cells with Heinz bodies (denatured hemoglobin precipitates) on peripheral smear • Negative Coombs test • G6PD activity level (may be normal during attack)
Management	• Remove or treat responsible agent/condition • Supportive care

- The clinical scenario described is typical for acute graft-versus-host disease (GVHD), which is common after bone marrow transplantation. Up to 50% of patients with bone marrow transplantation from matched siblings develop the disease. The target organs for GVHD are the skin (maculopapular rash involving palms, soles, and face that may generalize is typical), intestine (blood-positive diarrhea), and liver (abnormal liver function tests and jaundice). The basic pathophysiologic mechanism involved is recognition of host major and minor HLA-antigens by donor T-cells and consequent cell-mediated immune response.

Hairy cell leukemia	
Features	• **Clonal B-cell neoplasm** • Middle age/older adults • *BRAF* mutation

Manifestations	• **Pancytopenia** due to bone marrow fibrosis
	  ○ Granulocytopenia (infections)
	  ○ Anemia (fatigue, weakness)
	  ○ Thrombocytopenia (bleeding, bruising)
	• **Splenomegaly** (early satiety)
	• Hepatomegaly/lymphadenopathy rare

Diagnosis	• Peripheral smear – **"hairy" leukocyte cells** • **Bone marrow biopsy** with flow cytometry
Treatment	• Chemotherapy (for moderate/severe) • Life expectancy is often near-normal

Clinical manifestations of hereditary hemochromatosis	
Skin	Hyperpigmentation (bronze diabetes)
Musculoskeletal	Arthralgia, arthropathy & chondrocalcinosis
Gastrointestinal	Elevated hepatic enzymes with hepatomegaly (early), cirrhosis (later) & increased risk of hepatocellular carcinoma
Endocrine	Diabetes mellitus, secondary hypogonadism & hypothyroidism
Cardiac	Restrictive or dilated cardiomyopathy & conduction abnormalities
Infections	Increased susceptibility to *Listeria*, *Vibrio vulnificus* & *Yersinia enterocolitica*

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Hemophilia A & B	
Inheritance	• X-linked recessive
Clinical features	• Delayed/prolonged bleeding after mild trauma or procedure o Hemarthrosis, hemophilic arthropathy o Intramuscular hematomas o Gastrointestinal or genitourinary tract bleeding
Laboratory findings	• Prolonged activated partial thromboplastin time • Normal platelet count, bleeding time, prothrombin time • Decreased or absent factor VIII (hemophilia A) or factor IX (hemophilia B) activity
Treatment	• Administration of factor VIII or factor IX • Desmopressin for mild hemophilia A

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- The most frequent sites of bleeding are the joints (80%), especially the knee. Hemarthrosis can occur with minimal or no trauma with episodes beginning during toddlerhood when the child is active and ambulatory

Clinical features of type 2 heparin-induced thrombocytopenia	
Clinical signs	Suspected with heparin exposure >5 days **&** any of the following: • Platelet count reduction >50% from baseline • Arterial or venous thrombosis • Necrotic skin lesions at heparin injection sites • Acute systemic (anaphylactoid) reactions after heparin
Diagnostic evaluation	• **Serotonin release assay**: Gold standard confirmatory test • Start treatment in suspected cases prior to confirmatory tests
Therapy	• Stop **ALL** heparin products • Start a direct thrombin inhibitor (eg, argatroban) or fondaparinux (synthetic pentasaccharide)

- Initial treatment with warfarin is contraindicated in patients with HIT as it rapidly lowers protein C levels, which may transiently increase the risk of thrombus
- The risk of thrombus is as high as 50% in untreated HIT.
- In patients receiving heparin subcutaneously (eg, enoxaparin), a classic thrombotic complication of HIT is skin necrosis at the abdominal injection site

This patient most likely has hereditary telangiectasia (Osler-Weber-Rendu syndrome), an autosomal dominant disorder characterized by diffuse telangiectasias, recurrent epistaxis, and widespread AV malformations (AVMs). In hereditary telangiectasia, AVMs tend to occur in the mucous membranes, skin, and gastrointestinal tract, but may also be present in the liver, brain, and lung. AVMs in the lungs can shunt blood from the right to the left side of the heart, causing chronic hypoxemia and a reactive polycythemia. Pulmonary AVMs can also present as massive, sometimes fatal, hemoptysis.

Hereditary spherocytosis	
Epidemiology	• Autosomal dominant inheritance (~75%) • Northern European descent
Clinical presentation	• Hemolytic anemia • Jaundice • Splenomegaly
Laboratory findings	• ↑ **Mean corpuscular hemoglobin concentration** • **Spherocytes** on peripheral smear • Negative Coombs test • ↑ Osmotic fragility on **acidified glycerol lysis test** • Abnormal **eosin-5-maleimide binding test**
Treatment	• Folic acid supplementation • Blood transfusions • Splenectomy
Complications	• Pigment gallstones • Aplastic crises from parvovirus B19 infection

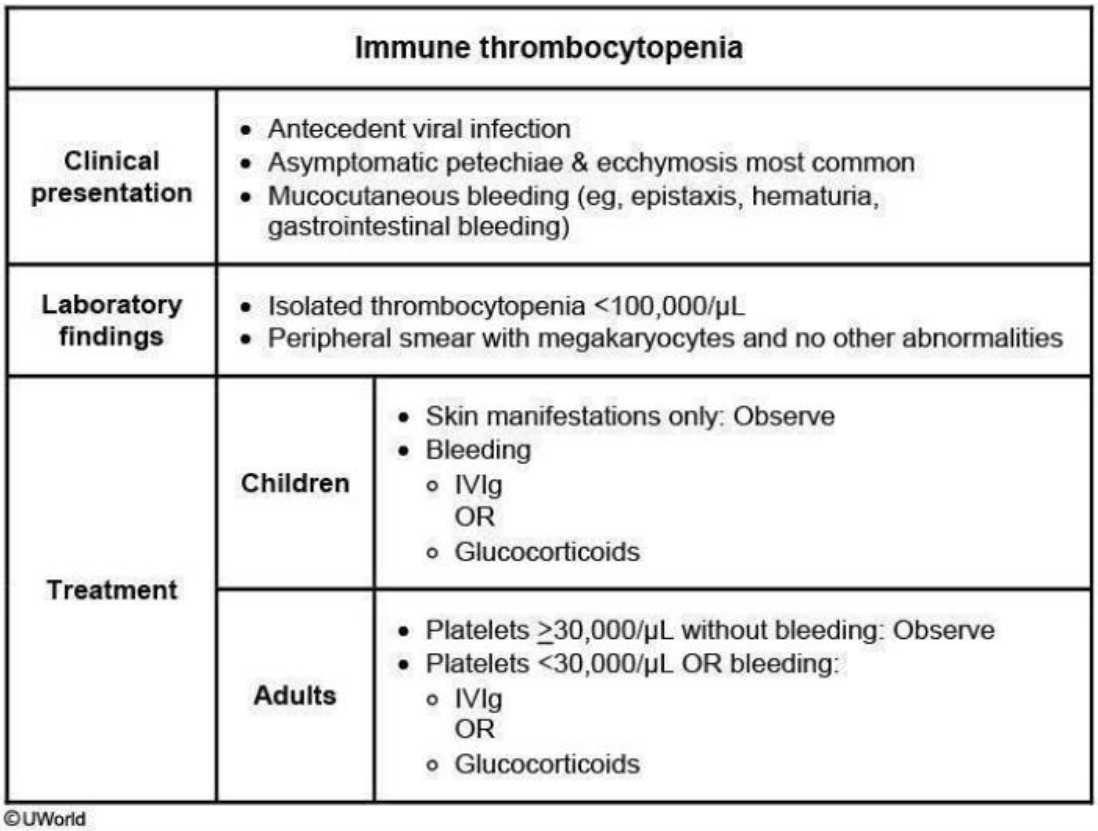
- Splenectomy can improve anemia and reduce gallstone risk, but it does not change the increased MCHC in the RBCs.

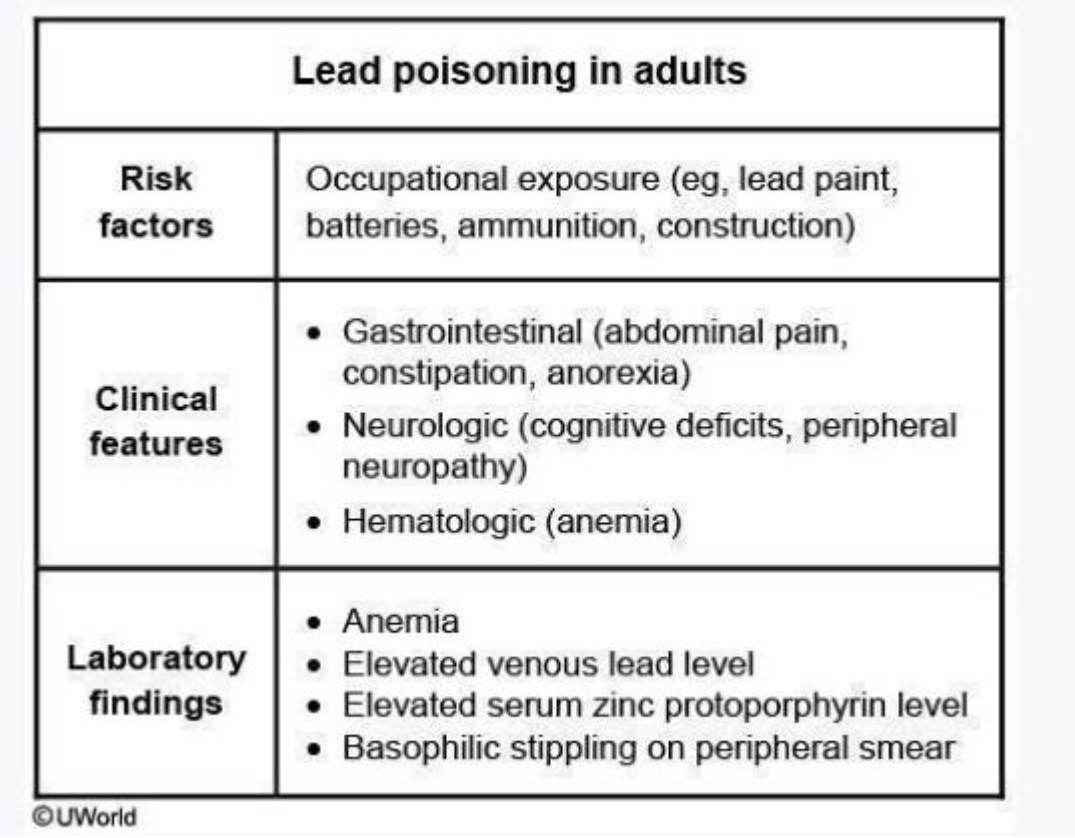
- Homocysteine can be metabolized to cysteine or methylated to form methionine. If either of these pathways is disrupted by an enzyme or cofactor deficiency, elevated homocysteine levels result. The homocysteine to cysteine pathway is catalyzed by cystathionine β-synthase (CBS) using the cofactor pyridoxine (B6). The homocysteine to methionine pathway is catalyzed by methylenetetrahydrofolate reductase (MTHFR) and methionine synthase (MS), with folate and cobalamin (B12) as essential cofactors (see figure).

  Independent of the underlying cause, homocysteine levels can usually be normalized by administration of pyridoxine (B6) and folate. Vitamin B12 should be added if a B12 deficiency is documented. Although this treatment does correct homocysteine levels, it is still unclear whether it reverses hypercoagulability.

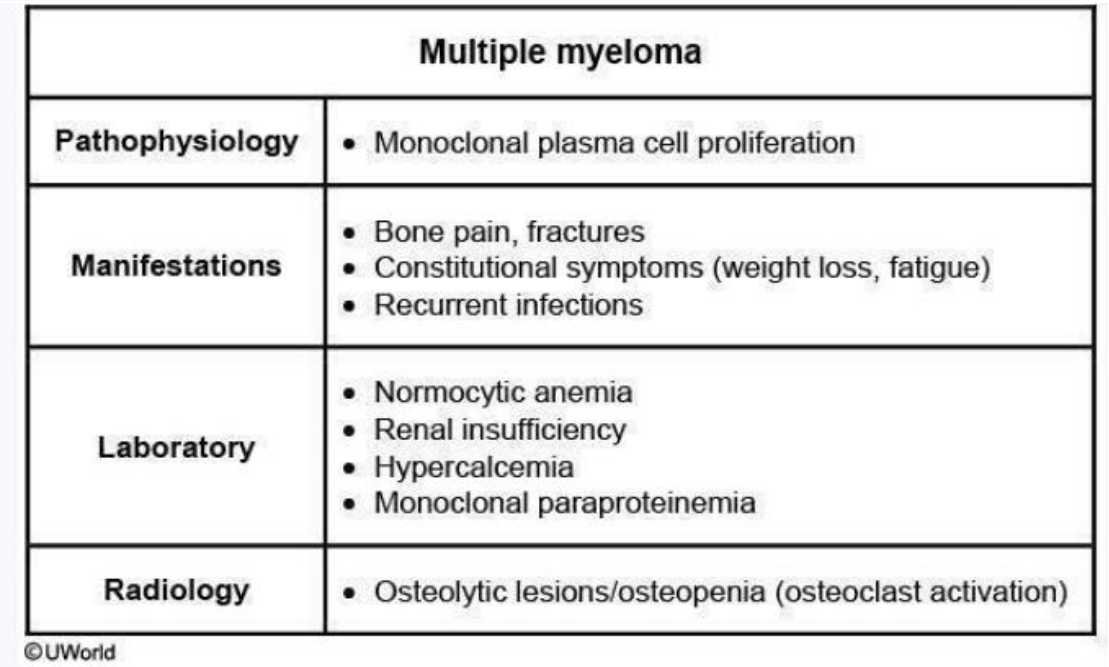
- This is a classic presentation of infectious mononucleosis (IM). IM is an acute, benign and self-limiting lymphoproliferative condition caused by Epstein-Bar Virus (EBV). EBV is transmitted primarily by close contact with infectious oropharyngeal secretions. Clinical manifestations include extreme fatigue, malaise, sore throat, fever, and a generalized maculopapular rash. Posterior cervical lymphadenopathy and palatal petechiae can be present. Splenomegaly is also common. Contact sports should be avoided to prevent the chances of splenic rupture. When rupture occurs, the mortality is significant. Hematological studies reveal leukocytosis with variant lymphocytes (atypical lymphocytes). Heterophile antibodies are very sensitive and specific, but may be negative early in the illness. Repeating the test may be helpful. For this reason, a negative antibody test does not exclude the diagnosis of IM.

- Pagophagia is pica for ice and is quite specific for iron deficiency.

- 

- 

Lead poisoning in adults	
Risk factors	Occupational exposure (eg, lead paint, batteries, ammunition, construction)
Clinical features	• Gastrointestinal (abdominal pain, constipation, anorexia) • Neurologic (cognitive deficits, peripheral neuropathy) • Hematologic (anemia)
Laboratory findings	• Anemia • Elevated venous lead level • Elevated serum zinc protoporphyrin level • Basophilic stippling on peripheral smear

- 

Multiple myeloma	
Pathophysiology	• Monoclonal plasma cell proliferation
Manifestations	• Bone pain, fractures • Constitutional symptoms (weight loss, fatigue) • Recurrent infections
Laboratory	• Normocytic anemia • Renal insufficiency • Hypercalcemia • Monoclonal paraproteinemia
Radiology	• Osteolytic lesions/osteopenia (osteoclast activation)

- Patients with suspected MM should have serum/urine protein electrophoresis (M-spike), a peripheral blood smear (rouleaux), and a serum free light chain analysis. If these screening tests suggest MM, diagnosis can be confirmed by bone marrow biopsy
- Patients with MM are prone to **infection**. Neoplastic infiltration of the bone marrow alters and impairs the normal lymphocyte population, resulting in ineffective antibody production and **hypogammaglobulinemia**. Respiratory (eg, streptococcal pneumonia) and urinary tract infections are the most common infections seen in MM.

Clinical features of paroxysmal nocturnal hemoglobinuria	
Clinical manifestations	• Hemolysis → fatigue • Cytopenias (impaired hematopoiesis) • Venous thrombosis (intraabdominal, cerebral veins)
Workup	• Complete blood count (**hypoplastic/aplastic anemia,** thrombocytopenia, leukopenia) • Elevated lactate dehydrogenase & low haptoglobin (hemolysis) • Indirect hyperbilirubinemia • Urinalysis (**hemoglobinuria**) • Flow cytometry (**absence of CD55 & CD59**)
Treatment	• Iron & folate supplementation • **Eculizumab** (monoclonal antibody that inhibits complement activation)

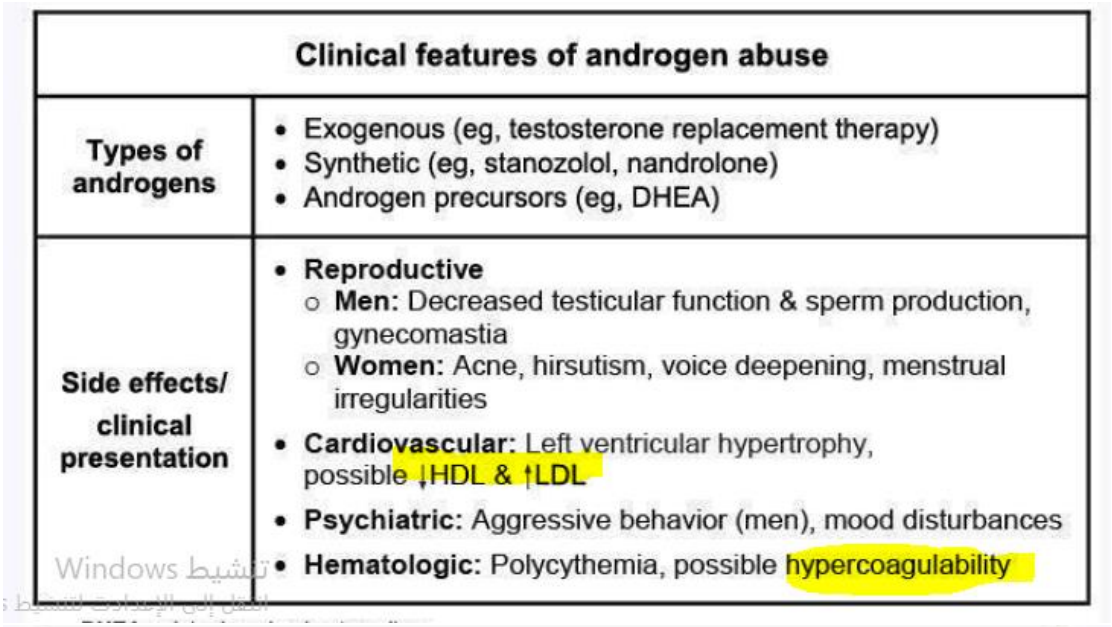
- Pernicious anemia is the most common cause of vitamin B12 deficiency in whites of northern European background.
- This atrophic gastritis increases the risk of intestinal-type gastric cancer and gastric carcinoid tumors by 2-3 times over the general population. Thus, patients with pernicious anemia need to be monitored for the development of gastric cancer (periodic stool testing for the presence of blood).

Polycythemia vera	

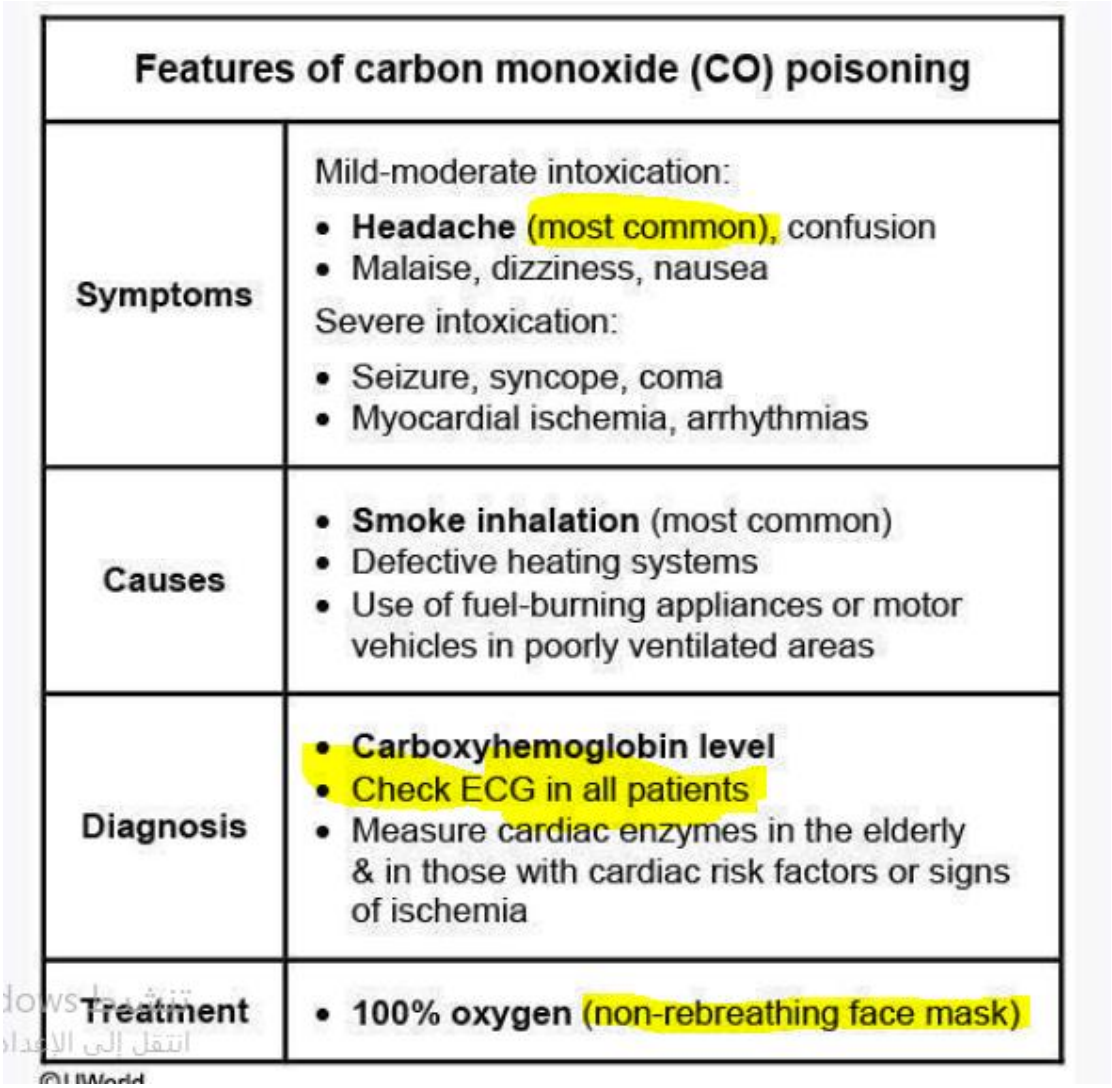
Manifestations	• ↑ Blood viscosity
	  ○ **Hypertension**
	  ○ **Erythromelalgia** (burning cyanosis in hands/feet)
	  ○ Transient visual disturbances
	• ↑ RBC turnover (gouty arthritis)
	• **Aquagenic pruritus**
	• Bleeding

Examination	• Facial plethora (ruddy cyanosis) • Splenomegaly
Laboratory findings	• **Elevated hemoglobin** • Leukocytosis & thrombocytosis • **Low erythropoietin** level • **JAK2 mutation** positive Low ESR
Complications	• **Thrombosis** • Myelofibrosis & acute leukemia
Treatment	• **Phlebotomy** • Hydroxyurea (if ↑ risk of thrombus)

- In PV there is a higher relative concentration of erythrocytes to fibrinogen, which causes a low ESR .
- Serum Iron is low in most pts w/ PV due to increased consumption.

- 

Clinical features of androgen abuse	
Types of androgens	• Exogenous (eg, testosterone replacement therapy) • Synthetic (eg, stanozolol, nandrolone) • Androgen precursors (eg, DHEA)
Side effects/ clinical presentation	• **Reproductive** o **Men:** Decreased testicular function & sperm production, gynecomastia o **Women:** Acne, hirsutism, voice deepening, menstrual irregularities • **Cardiovascular:** Left ventricular hypertrophy, possible ↓HDL & ↑LDL • **Psychiatric:** Aggressive behavior (men), mood disturbances • **Hematologic:** Polycythemia, possible hypercoagulability

- 

Features of carbon monoxide (CO) poisoning	
Symptoms	Mild-moderate intoxication: • **Headache** (most common), confusion • Malaise, dizziness, nausea Severe intoxication: • Seizure, syncope, coma • Myocardial ischemia, arrhythmias
Causes	• **Smoke inhalation** (most common) • Defective heating systems • Use of fuel-burning appliances or motor vehicles in poorly ventilated areas
Diagnosis	• **Carboxyhemoglobin level** • Check ECG in all patients • Measure cardiac enzymes in the elderly & in those with cardiac risk factors or signs of ischemia
Treatment	• **100% oxygen** (non-rebreathing face mask)

- Pulse oximetry **does not differentiate** between carboxyhemoglobin and oxyhemoglobin; it cannot be used in the diagnosis of CO poisoning. Diagnosis is made by arterial blood gas with cooximetry

Hereditary thrombophilias*	
Factor V Leiden	• Most common in those of white ethnicity • Activated protein C resistance
Prothrombin mutation	• 2nd most common in those of white ethnicity • ↑Prothrombin levels
Antithrombin deficiency	• Inherited form is rare • Acquired: DIC, cirrhosis, nephrotic syndrome
Protein C or S deficiency	• ↓Inactivation of factors Va & VIIIa • Warfarin-induced skin necrosis (protein C only)

*Typically autosomal dominant with variable penetrance;
DIC = disseminated intravascular coagulation.

- This patient's nocturia is most likely secondary to an impairment in his kidney's ability to concentrate urine, a condition called hyposthenuria. Hyposthenuria is found in patients with sickle cell disease, but is also common, though usually less severe, in patients with sickle cell trait. Because this is an African American patient with a family history of a fatal blood disorder, he is likely to be a carrier of the sickle cell trait. Hyposthenuria is thought to result from red blood cell sickling in the vasa rectae of the inner medulla, which impairs countercurrent exchange and free water reabsorption.
- SVC : Malignancy is the most common cause of obstruction (i.e. lung cancer, non-Hodgkin lymphoma), accounting for >60% of cases. CXR identify the cause in 80%.

Diagnostic criteria for antiphospholipid antibody syndrome (1 clinical & 1 laboratory criterion must be met)	
Clinical	**Vascular thrombosis** • Arterial/venous thrombosis **Pregnancy morbidity** • ≥3 consecutive unexplained fetal losses before 10th week • ≥1 unexplained fetal loss after 10th week • ≥1 premature birth of normal neonate before 34th week due to preeclampsia, eclampsia, placental insufficiency
Laboratory	• Lupus anticoagulant • Anticardiolipin antibody (IgG/IgM – medium or high titer) • Anti-b2GP1 antibody (IgG/IgM – high titer)

APS is characterized by:

1. **Venous thromboembolism** or **recurrent early miscarriages**
2. Presence of an antiphospholipid antibody such as the lupus anticoagulant (LA), anticardiolipin antibody, or beta 2 glycoprotein 1 antibody

The LA occurs in 10%-30% of patients with SLE. The exact mechanism by which LA promotes coagulation in vivo is unclear. In vitro, it prolongs the partial thromboplastin time (PTT) as it binds the phospholipids used in most assays. This is a laboratory artifact and does not correlate with bleeding in vivo. The prothrombin time may also be prolonged. The PTT will not correct if mixed in a 1:1 dilution with normal plasma. Prolonged PTT is an indirect indicator for the presence of LA and highly suggestive in the correct clinical setting. Specific tests include the diluted Russell viper venom test and the kaolin clotting time.

- About 20%-40% of patients with APS may have thrombocytopenia. However, it is usually mild, does not prolong bleeding time, and does not require treatment.

Hematologic manifestations of systemic lupus erythematosus

	Common mechanisms	Uncommon mechanisms
Anemia	• Anemia of chronic disease • Renal insufficiency from SLE nephritis • Iron deficiency anemia (gastrointestinal loss) • Autoimmune hemolytic anemia	• Medications • Hypersplenism • Microangiopathic hemolytic anemia • Aplastic anemia
Leukopenia	Autoimmune-mediated destruction	• Medications • Hypersplenism • Bone marrow dysfunction
Thrombocytopenia	Immune-mediated destruction	• Medications • Increased consumption due to thrombotic microangiopathy (thrombotic thrombocytopenic purpura)

Parameter	Iron deficiency anemia	α-thalassemia minor	β-thalassemia minor
MCV	↓	↓	↓
RDW	↑	Normal	Normal
RBCs	↓	Normal	Normal
Peripheral smear	Microcytosis, hypochromia	Target cells	Target cells
Serum iron studies	↓ Iron & ferritin ↑ TIBC	Normal/ ↑ iron & ferritin (RBC turnover)	Normal/ ↑ iron & ferritin (RBC turnover)
Response to iron supplementation	↑ Hemoglobin	No improvement	No improvement
Hemoglobin electrophoresis	Normal	Normal	↑ Hemoglobin A2

MCV = mean corpuscular volume; **RBC** = red blood cell; **RDW** = red cell distribution width; **TIBC** = total iron-binding capacity.

Thalassemias			
	Disorder (genotype)	**Hb electrophoresis**	**Anemia severity**
Alpha thalassemia	Silent carrier (α α / α -)	Normal	Asymptomatic
	Trait (α α / - - **OR** α - / α -)	Normal	Mild symptoms
	Hb H disease (α - / - -)	5%-30% Hb H (adults)	Chronic hemolysis
	Major (fetal hydrops) (- - / - -)	• Hb Barts, Hb Portland & Hb H present • Absent Hb A, Hb F & Hb A2	Fatal in utero
Beta thalassemia	Trait (β / β°)	Increased Hb A2	Mild
	Intermediate (β^{+} / β^{+}, others)	Increased Hb F	Moderate
	Major ($\beta^{\circ} / \beta^{\circ}$)	Absent Hb A, only Hb A2 & Hb F present	Severe

- all patients with presumed ITP should be tested for HIV and hepatitis C virus as platelet counts can be affected by treating the underlying disease

Clinical findings in chronic HIV infection
• Oral candidiasis or hairy leukoplakia • Aggressive seborrheic dermatitis • Peripheral neuropathy • Unexplained weight loss • Generalized lymphadenopathy • Fever of unknown origin • Disseminated herpes zoster • Opportunistic infections • Kaposi's sarcoma • B cell lymphoma • Unexplained cytopenias

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Thrombotic thrombocytopenic purpura	
Pathophysiology	• ↓ **ADAMTS13** activity leading to **large vWF multimers** & resulting in diffuse **microvascular platelet-rich thrombi** • Acquired (autoantibody) or hereditary
Clinical features	• Hemolytic **anemia** (↑ LDH, ↓ haptoglobin) with **schistocytes** • **Thrombocytopenia** (↑ bleeding time, normal PT/PTT) Sometimes with • Renal failure • Neurologic manifestations • Fever
Management	• Plasma exchange

LDH = lactate dehydrogenase; **PT** = prothrombin time; **PTT** = partial thromboplastin time; **vWF** = von Willebrand factor.

- TTP is usually due to an acquired **autoantibody** to ADAMTS13, a plasma protease that cleaves von Willebrand factor (vWF) off the endothelial surface. As ADAMTS13 levels fall (due to the antibody), vWF multimers accumulate on the endothelial wall, trapping platelets at areas of high shearing force (eg, small arterioles, capillaries) and leading to the formation of thrombi.

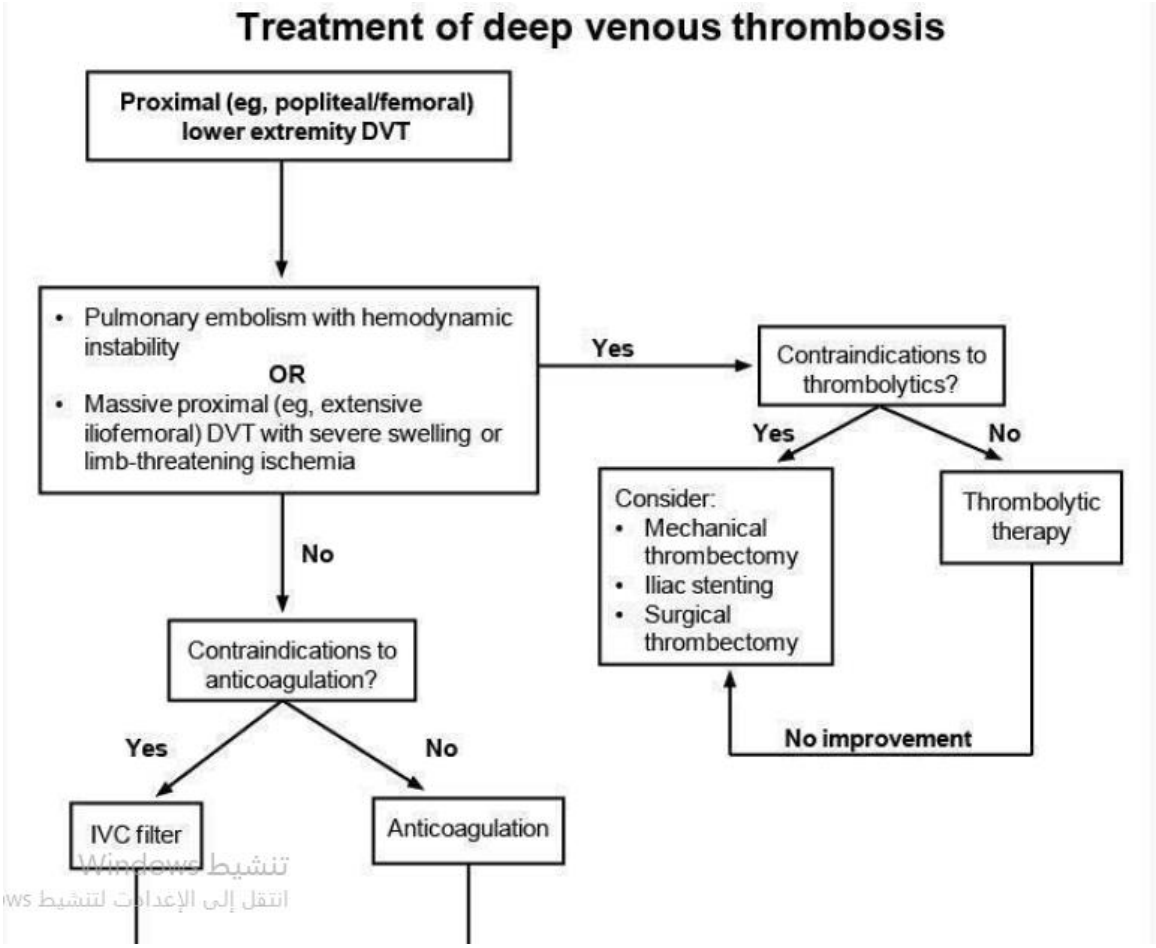
  TTP is typically a disease of young adults (unlike hemolytic uremic syndrome, which primarily affects children) and is often idiopathic but may be triggered by infections (eg, HIV), malignancy, or medications. Diagnosis is based primarily on clinical and laboratory data. Evidence of thrombocytopenia and MAHA (eg, increased levels of indirect bilirubin, aspartate aminotransferase [AST], alanine aminotransferase [ALT], and lactate dehydrogenase) should always raise suspicion for TTP. A manual **peripheral blood smear** is a crucial test in the diagnostic workup and would show signs of intravascular hemolysis (eg, **schistocytes**, helmet cells, triangle cells).

  TTP must be **treated emergently** with **plasma exchange**. Glucocorticoids are often added. Without treatment, the mortality rate is as high as 90%.
- In TTP , Laboratory markers of coagulation (eg, prothrombin time [PT]) are normal in TTP (unlike in disseminated intravascular coagulation [DIC]).
- In the absence of any clear provoking factors (eg, recent procedure, immobilization), patients with a first episode of VTE (such as this patient) should be referred for **age-appropriate cancer screening** (eg, **colonoscopy**). In addition:

  - If there is concern for occult malignancy (eg, due to suggestive symptoms such as weight loss or pain), extensive cancer screening (eg, CT scan of the chest, abdomen, pelvis) can be considered **(Choice B)**. Although this patient is a smoker, he has a normal chest x-ray, has no symptoms concerning for lung cancer (eg, hemoptysis, cough), and does not meet **lung cancer screening criteria** (age <55). Therefore, he does not require any additional workup for lung cancer. In addition, positron emission tomography, which can identify foci of malignancy, is more commonly used for cancer staging than for diagnosing **(Choice C)**.
  - Extensive testing for an underlying inherited cause (eg, deficiency of protein C, protein S, or antithrombin III) is generally only performed when the patient's history is suggestive (eg, age <45, recurrent DVT, multiple or unusual sites of thrombosis, family history of VTE). Protein C, protein S, and antithrombin III levels are also affected by anticoagulant therapy **(Choice D)**.

Recommendations for lung cancer screening	
Recommended test	• Low-dose chest CT
Recommended interval	• Yearly
Age for screening	• 55-80
Eligibility for screening based on smoking history	• Patient has ≥30-pack-year smoking history **AND** • Patient is a current smoker or quit smoking within the last 15 years
Termination of screening	• Age >80 **OR** • Patient successfully quit smoking for ≥15 years **OR** • Patient has other medical problems that significantly limit life expectancy or ability/willingness to undergo lung cancer surgery

Modified Wells criteria for pretest probability of DVT	
Score +1 points	• Previously documented DVT • Active cancer • Recent immobilization of the legs • Recently bedridden >3 days • Localized tenderness along vein distribution • Swollen leg • Calf swelling >3 cm compared to other leg • Pitting edema • Collateral superficial nonvaricose veins • Alternate diagnosis more likely (−2 points)
Total score for clinical probability	≤1: DVT unlikely ≥2: DVT likely



- Alcohol abuse is the most common cause of nutritional folic acid deficiency in the United States, leading to a megaloblastic anemia.
- The liver can normally store a 30-day supply of vitamin K, but an acutely ill person with underlying liver disease can become vitamin K deficient in as little as 7-10 days.

	Waldenström macroglobulinemia	Multiple myeloma
Major manifestations	• **Hyperviscosity syndrome** • Neuropathy • Bleeding • **Hepatosplenomegaly** • Lymphadenopathy	• **Osteolytic lesions/fractures** • Anemia • **Hypercalcemia** • Renal insufficiency
Monoclonal antibody	**IgM**	IgG, IgA, light chains
Peripheral smear	Rouleaux	Rouleaux
Bone marrow biopsy	>10% clonal B cells	>10% clonal plasma cells

Aplastic anemia	
Pathogenesis	Bone marrow failure due to **hematopoietic stem cell deficiency** ($CD34^+$)
Causes	• **Autoimmune** • **Infections** (eg, parvovirus B19, Epstein-Barr virus) • **Drugs** (eg, carbamazepine, chloramphenicol, sulfonamides) • Exposure to radiation or toxins (eg, benzene, solvents)
Clinical findings	Symptoms result from **pancytopenia**: • Anemia (fatigue, weakness, pallor) • Thrombocytopenia (mucosal bleeding, easy bruising, petechiae) • Leukopenia (recurrent infections)
Diagnosis	Biopsy showing **hypocellular** bone marrow composed mainly of fat & stromal cells