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FIRST AID®

CASES FOR THE USMLE STEP 1

Fourth Edition

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Dedication

To Tai Le, who brought us immeasurable love and joy.

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PREFACE

With *First Aid Cases for the USMLE Step 1*, 4th edition, we continue our commitment to providing students with the most useful and up-to-date preparation guides for the USMLE Step 1 exam. This edition represents an outstanding effort by a talented group of authors and includes the following:

- A new full-color design and full-color figures enhance clinical images and illustrations and clarify text presentation.
- A new dedicated Immunology chapter.
- Updated USMLE-style cases with expanded differentials and commonly asked question stems seen on the USMLE Step 1 exam.
- Many new high-yield figures and tables complement the questions and answers.
- Concise yet complete with relevant pathophysiology explanations.
- Organized as a perfect supplement to *First Aid for the USMLE Step 1*.

We invite you to share your thoughts and ideas to help us improve *First Aid Cases for the USMLE Step 1*. See "How to Contribute," on p. xxiii.

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HOW TO CONTRIBUTE

To continue to produce a high-yield review source for the USMLE Step 1 you are invited to submit any suggestions or corrections. We also offer paid internships in medical education and publishing ranging from three months to one year (see below for details). Please send us your suggestions for:

- New facts, mnemonics, diagrams, and clinical images
- High-yield topics that may reappear on future Step 1 exams
- Corrections and other suggestions

For each entry incorporated into the next edition, you will receive up to a $20 Amazon.com gift card as well as personal acknowledgment in the next edition. Significant contributions will be compensated at the discretion of the authors. Also let us know about material in this edition that you feel is low yield and should be deleted.

All submissions including potential errata should ideally be supported with hyperlinks to a dynamically updated Web resource such as UpToDate, AccessMedicine, and ClinicalKey.

We welcome potential errata on grammar and style if the changes improve readability. Please note that *First Aid* style is somewhat unique; for example, we have fully adopted the AMA Manual of Style recommendations on eponyms ("We recommend that the possessive form be omitted in eponymous terms") and on abbreviations (no periods with eg, ie, etc).

The preferred way to submit new entries, clarifications, mnemonics, or potential corrections with a valid, authoritative reference is via our website: **www.firstaidteam.com**.

This website will be continuously updated with validated errata, new high-yield content, and a new online platform to contribute suggestions, mnemonics, diagrams, clinical images, and potential errata.

Alternatively, you can e-mail us at: **firstaid@scholarrx.com**.

NOTE TO CONTRIBUTORS

All entries become property of the authors and are subject to editing and reviewing. Please verify all data and spellings carefully. Contributions should be supported by at least two high-quality references.

Check our website first to avoid duplicate submissions. In the event that similar or duplicate entries are received, only the first complete entry received with valid, authoritative references will be credited. Please follow the style, punctuation, and format of this edition as much as possible.

JOIN THE FIRST AID TEAM

The *First Aid* author team is pleased to offer part-time and full-time paid internships in medical education and publishing to motivated medical students and physicians. Internships range from a few months (eg, a summer) up to a full year. Participants will have an opportunity to author, edit, and earn academic credit on a wide variety of projects, including the popular *First Aid* series.

We are actively seeking passionate medical students and graduates with a specific interest in improving our medical illustrations, expanding our database of medical photographs, and developing the software that supports our crowdsourcing platform. We welcome people with prior experience and talent in these areas. Relevant skills include clinical imaging, digital photography, digital asset management, information design, medical illustration, graphic design, and software development.

Please email us at **firstaid@scholarrx.com** with a CV and summary of your interest or sample work.

1
Biochemistry

CASE 1

A 45-year-old man presents to his physician for chronic arthritis, which is worsening and affecting his lower back, hips, and knees. On physical examination, you notice that the patient's sclerae appear to have a brown discoloration; however, his vision is unchanged from prior examinations. His ear cartilage is similarly discolored. An x-ray of the spine reveals disk degeneration and dense calcification that is most prominent in the lumbar region. His urine appears normal at first but begins to darken with time.

What is the most likely diagnosis?

Alkaptonuria (ochronosis).

What is the biochemical defect in this condition?

Alkaptonuria is characterized by the absence of **homogentisate oxidase**, an enzyme in the tyrosine degradation pathway that catalyzes the conversion of homogentisate to maleylacetoacetate (see Figure 1-1). The accumulation of homogentisate in cartilage leads to arthritis and causes discoloration of sclerae and other body tissues.

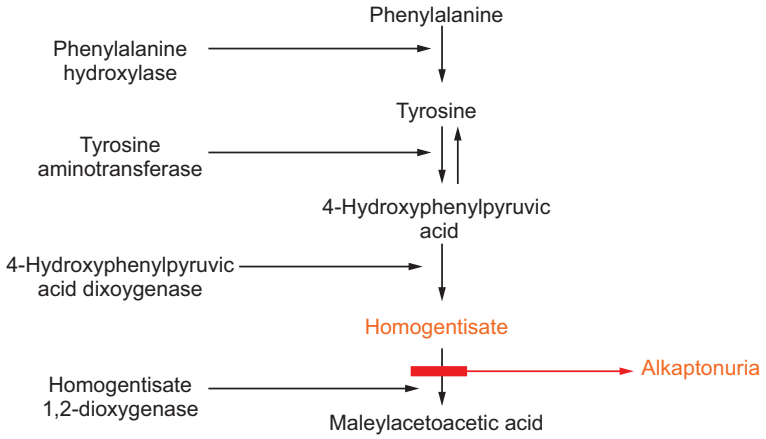

FIGURE 1-1. Metabolic disorder in alkaptonuria. (Reproduced with permission from USMLE-Rx.com.)

The metabolite that accumulates in this condition is derived from which essential amino acid?

Homogentisate is a metabolite of phenylalanine. Homogentisate oxidase is necessary for phenylalanine degradation. Homogentisate is further metabolized to acetoacetate and fumarate (part of the tricarboxylic acid cycle).

Given the extent of joint disease in this patient, how might his mental functioning be affected?

Alkaptonuria has no effect on cognitive functioning. Aside from its effects on joints and discoloration of the sclerae and skin, the disease is benign.

What is the treatment for this condition?

There are no known ways to prevent the build-up of homogentisate. Dietary restriction of tyrosine and phenylalanine reduces the production of homogentisate, but this approach has demonstrated no benefit on the overall condition. Treating the symptoms of the patient's arthritis is the only recommended therapy in this case.

Which amino acids are exclusively ketogenic, and which amino acids are glucogenic?

Leucine and lysine are the only purely ketogenic amino acids. Isoleucine, phenylalanine, threonine, tryptophan, and tyrosine are both ketogenic and glucogenic. The remaining amino acids are purely glucogenic. Glucogenic amino acids are those whose metabolites can be converted into glucose, through gluconeogenesis, whereas ketogenic amino acids are degraded into acetyl-CoA, which can be converted to ketone bodies or acetoacetate.

CASE 2

A 6-year-old girl presents to your office accompanied by her mother, who is concerned about her daughter's recent difficulty walking. She states that her daughter was born full term and there were no complications during the pregnancy, but she has had frequent respiratory infections throughout her life. When you ask the girl to stand, you notice that she wobbles from side to side. The eye exam reveals branching blood vessels patterns (see Figure 1-2).

FIGURE 1-2. (Reproduced with permission from Chen Z, Ye W, Long Z, et al. *PLoS ONE*. 2015;10(10):e0139738.)

What is the most likely diagnosis?

This girl is most likely suffering from ataxia telangiectasia (AT). AT is an autosomal recessive condition caused by a defect in the ATM (AT mutated) gene. AT is characterized by a constellation of symptoms including difficulties with balance or other cerebellar functions, recurrent respiratory infections due to IgA deficiency and a defect in T-cell immunity. Lastly patients have a distinctive spider angioma termed telangiectasia, such as the ocular telangiectasia seen in Figure 1-2.

What type of DNA damage is repaired less efficiently in patients with this condition?

Patients with AT are unable to efficiently repair double-stranded DNA breaks (DSBs) through a process called nonhomologous end joining. Furthermore, checkpoint signaling and apoptosis in response to DSBs are defective. This places individuals with AT at an increased risk for malignancies due to DSBs from sources such as ionizing radiation.

Which phase of the cell cycle is affected by an ATM mutation?

The transition between the G1 and S phase of the cell cycle is most greatly affected by the ATM mutation. During the S phase of the cell cycle, new DNA is synthesized from an intact parent strand template, so that daughter cells will inherit identical copies of DNA. To ensure this, the cell scans the DNA for damage so that it can be repaired prior to S phase DNA synthesis. The ATM protein is essential for activating the checkpoint that halts the cell cycle (see Figure 1-3) from progressing into S phase by phosphorylating p53. p53, when phosphorylated, works with the Rb protein to halt the progression of the cell cycle into S phase while these damaged areas of DNA can be repaired. Without a proper ATM, this process is not halted, and mutations may be passed on to daughter cells. Improper functioning of Rb or p53 is responsible for numerous cancers.

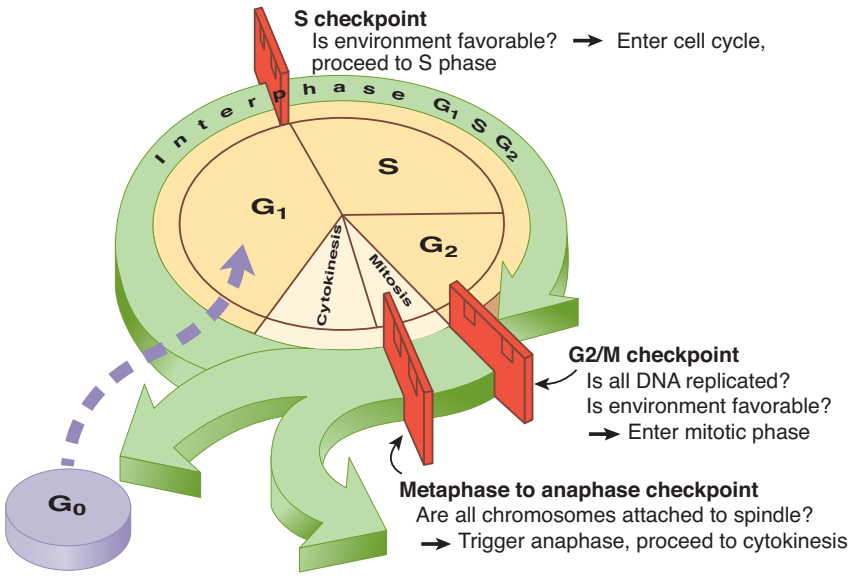

FIGURE 1-3. Cell cycle checkpoints. (Reproduced with permission from USMLE-Rx.com.)

CASE 3

A 36-year-old firefighter races into a burning building trying to extinguish a fire. The building suddenly collapses, and his fellow firefighters rush in to save him. They find him lying on the ground with his mask off. He is rescued and transported to the nearest ED. You are the first medical student to see him (look how far you've come), and on initial assessment you find that the man's skin is bright red and he is breathing rapidly. You also notice that his breath smells like bitter almonds.

What is the most likely diagnosis?

This man has been exposed to cyanide, which may be seen after exposure to burning buildings (the "bitter almond" breath is pathognomonic for cyanide exposure). Carbon monoxide exposure may also present with red skin but will not be associated with bitter almond smelling breath.

What biochemical process is disrupted in this condition?

Cyanide is an inhibitor of cytochrome C oxidase (complex IV) leading to disruption of the electron transport chain (see Figure 1-4).

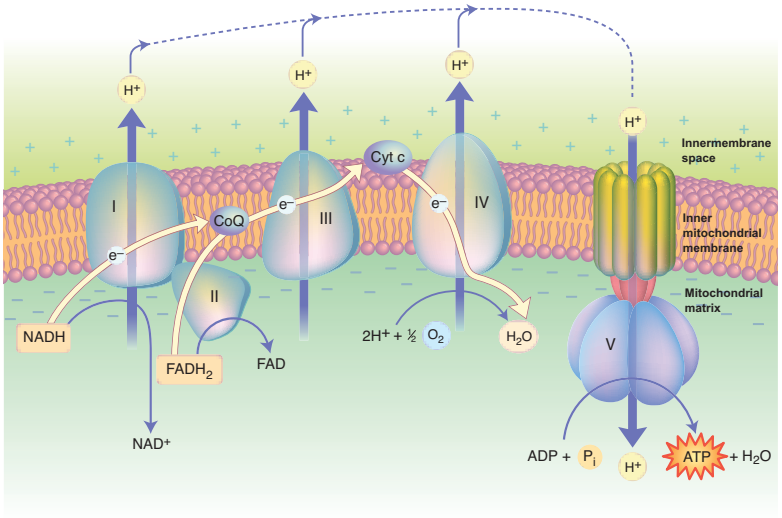

FIGURE 1-4. Overview of electron transport chain and oxidative phosphorylation. (Reproduced with permission from USMLE-Rx.com.)

How does cyanide interfere with ATP production?

The electron transport chain generates a proton gradient across the inner mitochondrial membrane (see Figure 1-4). ATP synthase (complex V) is driven by this proton gradient across the mitochondrial membrane. The ingestion of cyanide inhibits complex IV, decreasing the ability of the electron transport chain to generate the proton gradient. Without this gradient, ATP synthase cannot produce ATP.

What is the treatment for this condition?

Hydroxocobalamin (vitamin B_{12}) and sodium nitrite are used to treat cyanide poisoning. Vitamin B_{12} binds to cyanide, forming cyanocobalamin, which can then be excreted. Sodium nitrite oxidizes hemoglobin to methemoglobin. This is normally undesirable because methemoglobin cannot bind oxygen less avidly. However, methemoglobin strongly binds cyanide, causing it to release complex IV and preventing further disruption of the electron transport chain.

What other substances inhibit the electron transport chain (ETC)?

Rotenone and amytal are inhibitors of complex I (NADH dehydrogenase). Antimycin A inhibits complex III (ubiquinone cytochrome C oxidoreductase). Azide and carbon monoxide inhibit cytochrome C oxidase. Oligomycin is an inhibitor of ATP synthase.

What substances act within the mitochondria and cause decoupling of the ETC?

Compounds such as 2,4 dinitrophenol and aspirin allow protons to leak across the inner mitochondrial membrane, uncoupling ATP synthesis and oxygen consumption. The release of the proton gradient in a way that is not tied to the ATP synthase enzyme leads to decreased ATP production.

CASE 4

A 2-day-old boy is brought to the ED by his mother because of frequent vomiting. The child was born to a 40-year-old mother who reports that she did not undergo any prenatal testing, including amniocentesis or karyotype analysis. The mother reports that since birth, the boy has been vomiting greenish material immediately after eating. He has also become lethargic and progressively less responsive. On physical examination, the boy is found to have several abnormalities, including prominent epicanthal folds, upslanting palpebral fissures, and macroglossia. He also has thick skin at the nape of his neck. X-ray of the abdomen is shown in Figure 1-5.

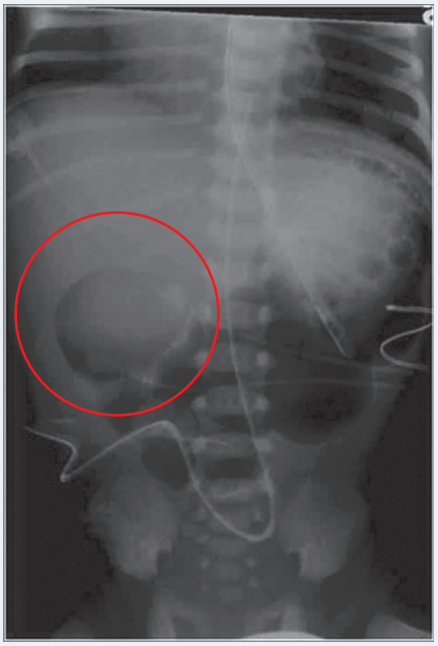

FIGURE 1-5. (Reproduced with permission from USMLE-Rx.com.)

What is the likely diagnosis?

The child most likely has Down syndrome, which can be associated with gastrointestinal disorders such as duodenal atresia (as seen in Figure 1.5) or stenosis, annular pancreas, tracheoesophageal defects, and imperforate anus. Duodenal atresia below the sphincter of Oddi causes bilious vomiting as seen in this patient.

What is the most common cytogenetic abnormality in patients with this condition?

Trisomy 21, resulting from nondisjunction of chromosome 21 during meiotic anaphase 1 or anaphase 2. The risk of nondisjunction increases with maternal age.

What other medical abnormalities are seen in children with this condition?

A single palmar crease; small, folded ears; a short neck; Brushfield spots (pale yellow spots on the iris); and a gap between the first and second toes. They also suffer from heart disease, most often cardiac cushion malformations, and may have ophthalmologic problems, gastrointestinal tract malformations, poor hearing, cognitive disability, and developmental delay. Males with Down syndrome are almost always infertile. Individuals with Down syndrome may also have atlantoaxial instability (increased movement between the C1 and C2 vertebrae), which may lead to spinal cord damage. Fetal alcohol syndrome, in comparison, is characterized by a thin vermillion border, small palpebral fissures, and a smooth philtrum.

What screening is available in utero for this condition?

Markers of Down syndrome in maternal blood include:

- Reduced levels of α-fetoprotein, PAPP-A, and estradiol
- Elevated levels of β-human chorionic gonadotropin (β-hCG) and inhibin

Ultrasound measurements displaying increased nuchal lucency may also been seen. A definitive diagnosis can be made via karyotype analysis of fetal cells obtained via amniocentesis or chorionic villus sampling.

Later in life, what disorders is this baby at risk of developing?

Older individuals with trisomy 21 have a high risk of developing early Alzheimer disease (on average by age 50). This may be because the amyloid-β protein implicated in Alzheimer disease is encoded on chromosome 21. They are also at increased risk of hematologic disorders, particularly acute leukemias, which occur in childhood, most commonly acute lymphoblastic leukemia.

CASE 5

A 7-year-old boy presents to your office accompanied by his mother, who is concerned that her child has developed difficulty walking. On your examination, you notice that the boy walks with a wide-based gait and his calves appear larger than expected (see Figure 1-6). When he gets up from your exam table, he uses his arms to push himself up before standing.

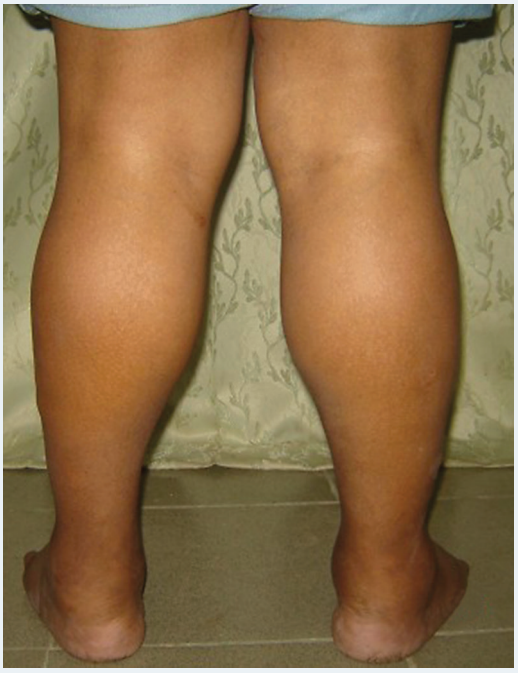

FIGURE 1-6. (Reproduced with permission from Senanayake HM, et al. syndrome: A case report. *Int Arch Med.* 2014;7:2.)

What is the most likely diagnosis?

Duchenne muscular dystrophy (DMD). DMD is an X-linked recessive disorder caused by absence of the dystrophin protein, leading to muscle weakness. A notable characteristic is pseudohypertrophy of the calves caused by fatty replacement of the muscle fibers, as shown in Figure 1-6. Gowers maneuver is a physical exam finding characteristic of DMD in which patients use their upper extremities to help them stand.

What type of mutation causes this patient's condition?

Duchenne muscular dystrophy is caused by a frameshift mutation in the **dystrophin** gene. Frameshift mutations are caused by the addition or deletion of a number of base pairs that is not divisible by 3, which shifts the reading frame of the protein from the point of the mutation onward throughout the rest of the open coding region. Remember that each amino acid is coded for by 3 bases, so any addition or deletion of base pairs that is not divisible by 3 will affect all downstream amino acids. Patients may present with elevated creatine kinase levels, likely secondary to increased muscle breakdown. Patients with DMD often develop dilated cardiomyopathy leading to heart failure.

What other disease has a similar presentation but is typically milder?

Becker muscular dystrophy is caused by a mutation that leads to a partially functional dystrophin protein, as compared to the nonfunctioning version seen in DMD. This leads to a less severe form of muscular dystrophy that typically presents later in life. DMD presents as early as before 5 years of age.

CASE 6

A 5-year-old boy is brought to his pediatrician because of frequent bruising, even after minor trauma. Other than one episode of shoulder dislocation, his medical history is unremarkable. On physical examination the child has many bruises at different stages of healing. He also has hyperextensible joints, flat feet, and dental crowding.

What is the most likely diagnosis?

Ehlers-Danlos syndrome. Although Marfan syndrome can cause joint hypermobility, it is unlikely to cause the easy bruising seen in this patient. Most forms of Ehlers-Danlos syndrome are inherited as autosomal dominant mutations. Zinc deficiency is another possible cause of poor wound healing since this micronutrient is needed for proper collagen synthesis. However, zinc deficiency would be associated with other symptoms such as hair loss, diarrhea, and possible acrodermatitis enteropathica, which is characterized by a perioral and acral rash.

What is the etiology of the easy bruising in this child?

Mutations that affect the formation of type III collagen may prevent proper synthesis or post-translational modification of collagen. The bruising is a direct result of defects in the collagen of vessel walls.

What other abnormalities may be present in individuals with this condition?

Thin, fragile skin; abnormal scar formation; aortic aneurysms; rupture of large arteries; and rupture of the bowel and uterus (pregnancy increases the risk of uterine rupture).

What are the stages of collagen synthesis?

As seen in Figure 1-7:

- Co-translational translocation of α collagen polypeptide by ribosomes docked on the rough endoplasmic reticulum.
- Hydroxylation of proline and lysine residues in the endoplasmic reticulum. This step requires vitamin C.
- Glycosylation of lysine residues on the α chains in the Golgi apparatus, followed by assembly of three α chains to form a triple helix of procollagen.
- The procollagen is secreted by exocytosis.
- The amino and carboxy pro-peptides are removed by specific peptidases to form tropocollagen.
- Many tropocollagen units line up in a staggered arrangement and cross-link to form the mature collagen fibrils.

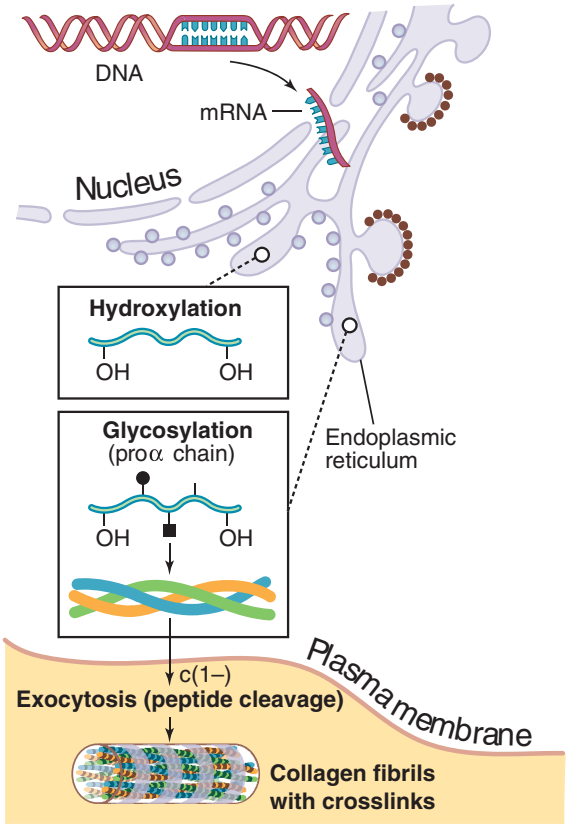

FIGURE 1-7. Collagen synthesis outside the cell. (Reproduced with permission from USMLE-Rx.com.)

Where are the four major types of collagen found in the body?

- Type I: Bone, skin, tendons, fascia, dentin, and the cornea. Most common type of collagen.
- Type II: Cartilage, nucleus pulposus, and the vitreous body.
- Type III: Reticular collagen, found in skin, blood vessels, the uterus, granulation tissue, and fetal tissue.
- Type IV: Basement membranes.

CASE 7

A 27-year-old man with little prior medical care was brought to the ED because of left-sided chest pain followed by sudden collapse. Despite first responders' best efforts, resuscitation attempts were unsuccessful. At autopsy the aorta is opened lengthwise (see Figure 1-8). He was also noted to have had small, raised yellow-brown lesions on the extensor surfaces of his arms.

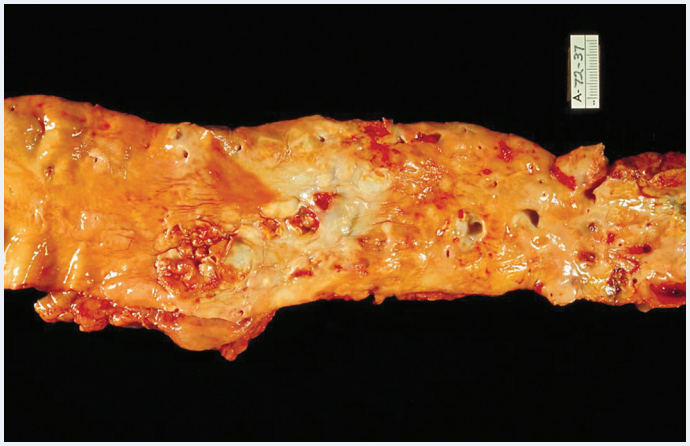

FIGURE 1-8. (Reproduced courtesy of Centers for Disease Control and Prevention/Dr. Edwin P. Ewing, Jr.)

What is the most likely diagnosis?

This patient had familial hypercholesterolemia (FH), an inherited disorder characterized by extremely high serum cholesterol levels that lead to the build-up of plaque, as seen in Figure 1-8. There are many different forms of inherited hyperlipidemias (see Table 1-1).

Table 1-1. Inherited Hyperlipidemias

Hyperlipoproteinemia	Defect	Lipoprotein increased
I	Lipoprotein lipase (LPL)	Chylomicrons
IIa	LDL receptor	LDL
III	Apo E2 synthesis	IDL
IV	VLDL elimination	VLDL

Type I familial hyperlipidemia is caused by a lipoprotein lipase deficiency and results in abdominal pain, xanthomas, and hepatosplenomegaly. Type III is caused by a defect in apolipoprotein E2 synthesis and results in palmar xanthomas and tubo-eruptive xanthomas. Type IV is caused by increased very-low-density lipoprotein (VLDL) production and decreased elimination. Low-density lipoproteins (LDL) transport cholesterol synthesized in the liver to the tissues, whereas high-density lipoproteins (HDL) scavenge cholesterol from the tissues and transport it back to the liver for disposal. Elevated LDL levels increase the risk of cardiac disease due to endothelial damage when they induce an inflammatory cascade and accumulation of cholesterol-laden foam cells in walls of blood vessels. In contrast, elevated HDL levels are mildly protective from such disease, because HDL can scavenge cholesterol from the inflammatory plaques.

What is the genetic pattern of this condition?

FH is inherited in an autosomal dominant manner. Heterozygotes typically have elevated cholesterol, approximately 370 mg/dL, and are at increased risk of myocardial infarctions. Homozygotes frequently have extremely high cholesterol levels, up to 1000 mg/dL, and many die before 30 years of age from cardiovascular disease. Normal total cholesterol is $<$ 200 mg/dL, and levels $>$ 240 mg/dL are considered elevated.

What is the molecular basis of this condition?

In FH there is a mutation in the LDL receptor gene that interferes with LDL uptake by the liver and other tissues. Normally, LDL circulates in the blood and binds to its receptor on hepatocyte membranes and is then taken up into the liver and metabolized. In FH patients, LDL is taken up by the hepatocytes less efficiently. Normally, cellular cholesterol synthesis is down-regulated in response to high levels of serum cholesterol. Without LDL uptake, cells have no way of sensing serum cholesterol levels, resulting in constitutive cholesterol synthesis and elevated LDL levels in the blood.

What would the microscopic examination of the lesions on this patient's arms show?

Cholesterol deposits in the skin, called xanthomas, form when there is a persistently elevated LDL level. They are composed largely of lipid-laden macrophages.

Statin drugs are frequently used to treat this condition. What is their mechanism of action?

Statins (such as atorvastatin and rosuvastatin) inhibit 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG-CoA reductase), a hepatic enzyme that catalyzes the rate-determining step in cholesterol synthesis. They reduce the amount of endogenous cholesterol synthesized by the liver. This leads to the liver increasing the amount of cholesterol it takes up from the bloodstream, which can then be used for processes such as steroid synthesis. This decreases the amount of cholesterol in the bloodstream (see Figure 1-9).

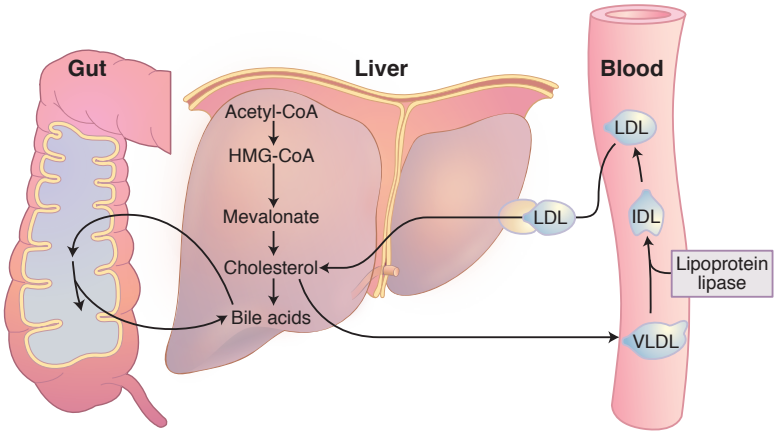

FIGURE 1-9. Cholesterol chemical pathways in gut, liver, and blood. (Reproduced with permission from USMLE-Rx.com.)

CASE 8

A 6-year-old boy is followed by his pediatrician because of delayed language acquisition and behavioral problems at school. On physical exam, he appears to have a long face, large ears, and flat feet. His mother reports a normal pregnancy with standard prenatal care and adds that she did not use drugs or alcohol during the pregnancy.

What is the most likely diagnosis?

This boy has fragile X syndrome. This disease occurs in individuals who have an **expansion of a CGG trinucleotide** repeat sequence on the X chromosome. This expansion results in hypermethylation of DNA in the 5′ region of the **FMR1** gene, which silences the gene by inhibiting its transcription. The FMR1 protein is an RNA-binding protein.

What is the inheritance pattern of this condition?

Fragile X syndrome is an **X-linked genetic disorder**. It is the most common inherited cause of intellectual disability. Down syndrome is the most common chromosomal cause of intellectual disability but is caused by a chromosomal trisomy, most commonly caused by an error during meiosis, rather than a heritable genetic sequence mutation. The hallmark of X-linked disorders is the absence of father-to-son disease transmission, since fathers always pass a Y chromosome to their sons. These disorders are much more common in males than in females. However, mild symptoms of fragile X syndrome appear in a significant minority of female carriers. Fragile X syndrome is not fully penetrant, and many families show a maternal transmission pattern.

What physical abnormalities are associated with this condition?

Individuals with fragile X syndrome frequently have long, narrow faces with a large jaw, large ears, and a prominent forehead. Most postpubertal males also have macro-orchidism.

What are other trinucleotide repeat disorders, and why are they associated with "premutation"?

Other disorders attributable to trinucleotide repeat expansion include:

- Huntington disease—CAG expansion on chromosome 4. Patients with Huntington disease present in their 30s or 40s with dystonia, decreased cognition, aggression or changes in behavior, and chorea.
- Myotonic dystrophy—CTG expansion on chromosome 19. Myotonic dystrophy presents in adulthood and is characterized classically with the muscle wasting and weakness due to the inability to relax muscles.
- Friedreich ataxia—FAA expansion on chromosome 9. Friedreich ataxia usually presents between the ages of 5 and 15 years with posterior cord and lateral corticospinal tract degenerations. Death is commonly due to an enlarged heart.

Typically, higher numbers of trinucleotide repeats result in more severe and earlier onset of the phenotypic expression of disease.

- **Premutation** occurs in patients with an intermediate number of repeats who are clinically normal but whose children are at increased risk of expressing clinical disease.
- **Anticipation** is the worsening of disease through generations because of increasing number of trinucleotide repeats.

CASE 9

A 5-month-old girl is brought to the pediatrician by her parents because she has been very sleepy lately and has been vomiting and sweating profusely at night. The infant's mother says that their daughter was doing fine during the first months of life but began showing these changes shortly after she began weaning from breast milk and started drinking fruit juices. On physical exam, you palpate an enlarged liver. Laboratory testing reveals a serum glucose level of 30 mg/dL. Urinalysis is negative for glucose but does note the presence of a reducing sugar.

What is the most likely diagnosis?

The most likely diagnosis is fructose intolerance given this patient's presentation of symptoms after drinking fruit juices, which have high levels of fructose.

What intermediate is elevated within the liver cells in this condition?

Fructose-1-phosphate is elevated in fructose intolerance.

What enzyme is deficient in this condition?

Aldolase B is deficient in this disorder.

How does this condition cause hypoglycemia?

Aldolase B catalyzes the conversion of fructose-1-phosphate into glyceraldehyde and dihydroxyacetone phosphate (see Figure 1-10). Its absence results in accumulation of fructose-1-phosphate in liver cells and excess serum fructose, which is excreted in the urine. Additionally, the accumulation of fructose-1-phosphate results in depletion of inorganic phosphate and thus decreased ATP synthesis. Aldolase B also plays an essential role in gluconeogenesis, so serum glucose levels are reduced in its absence.

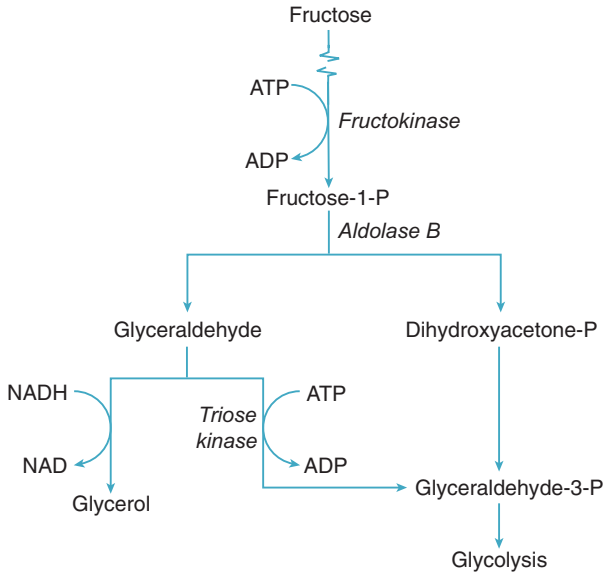

FIGURE 1-10. Fructose Intolerance and role of aldolase B. (Modified with permission from USMLE-Rx.com.)

What is the treatment for this condition?

The condition is treated through the removal of fructose, sucrose (a disaccharide of glucose and fructose), and sorbitol from the diet.

Why did the infant exhibit no symptoms while exclusively fed breast milk?

Carbohydrates in breast milk derive largely from lactose comprised of glucose and galactose rather than fructose, as compared to fruit juices, which have high levels of fructose.

CASE 10

A 12-year-old intellectually disabled boy is brought into a health clinic. His parents have noted that he seems to have difficulty with his vision. Physical examination reveals bilateral dislocated lenses and a tall, thin body habitus with especially long extremities. Laboratory studies show increased levels of serum methionine and serum homocysteine.

What is the most likely diagnosis?

Homocystinuria.

What is the biochemical defect in this condition?

The most common form of inherited homocystinuria results from reduced activity of **cystathionine beta synthase**, an enzyme that converts homocysteine to cystathionine (see Figure 1-11).

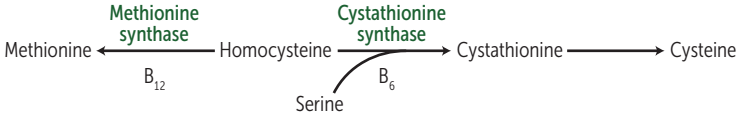

FIGURE 1-11. Homocystinuria. (Reproduced with permission from Le T, et al. *First Aid for the USMLE Step 1: 2019.* New York: McGraw-Hill, 2019.)

What vitamin supplementation is appropriate in this condition?

Vitamin B_6 (pyridoxine) is a necessary cofactor with cystathionine synthase. Vitamin B_6 supplementation has been successful in many patients with this enzyme deficiency.

In addition to vitamin supplementation, what other dietary changes should be made?

The absence of cystathionine beta synthase means that cysteine cannot be formed from methionine. Therefore, cysteine becomes an essential amino acid. This child should be given a diet low in methionine and high in cysteine.

This boy has a marfanoid body habitus and lens subluxation, two characteristics of this condition. For which other conditions is this patient at greatly increased risk?

This child is at increased risk for **cardiovascular disease**. Elevated plasma homocysteine increases risk of coronary artery disease, stroke, and peripheral artery disease because homocysteine is prothrombotic and increases the risk of clot formation. He is also at risk for **osteoporosis**. Homocysteine inhibits collagen cross-linking and over time can cause osteoporosis. Homocystinuria is distinguished from Marfan syndrome by the increased risk of thrombosis, intellectual disability, and the downward displaced lens. Marfan syndrome does not present with intellectual disability or increased risk of thrombosis, and the lenses in Marfan syndrome are displaced upwardly.

What enzyme deficiency is most likely to be found in a patient with increased serum homocysteine but decreased serum methionine?

This could be caused by a deficiency of methionine synthase. This enzyme catalyzes the conversion of homocysteine to methionine. Like patients with cystathionine synthase deficiency, these patients often have central nervous system dysfunction and vascular disease.

CASE 11

A 1-year-old boy is brought to the pediatrician because his parents have recently noted several abnormalities. Although the child was developmentally normal at birth, he does not interact with others the way his older sister did at the same age. His parents also notice that he has coarse facial features. Physical examination reveals skeletal abnormalities and an umbilical hernia. Funduscopic examination shows corneal clouding. Additionally, his liver and spleen are enlarged, and his joints feel stiff.

What is the most likely diagnosis?

Hurler syndrome.

What is the pathophysiology of this condition?

This syndrome results from a defect in α-L-iduronidase, an enzyme essential to the degradation of dermatan sulfate and heparan sulfate. This disease is one of the **mucopolysaccharidoses**, a group of hereditary disorders characterized by defects in glycosaminoglycan (GAG) metabolism. Features that distinguish this disorder from the other lysosomal storage disorders include coarse facial features and corneal clouding. In Hurler syndrome, the GAGs are not appropriately degraded in the lysosomes and are therefore deposited in various tissues. The disease is inherited in an autosomal recessive manner.

What disease has a similar presentation but is typically milder?

Hunter syndrome is another mucopolysaccharidosis. It is due to a deficiency of iduronate sulfatase and has X-linked inheritance. Unlike Hurler syndrome, Hunter syndrome does not present with corneal clouding, but affected patients may exhibit aggressive behavior.

What are the typical findings on electron microscopy?

The lysosomal vesicles appear swollen. This is due to accumulation of partially degraded polysaccharides.

What key modification must be made in the Golgi apparatus for lysosomal enzymes, such as α-L-iduronidase, to be properly targeted to lysosomes?

Lysosomal enzymes must be covalently modified with mannose-6-phosphate (M6P) as they pass through the **cis** Golgi network to be targeted to the lysosomes. These M6P groups are then recognized by M6P receptor proteins in the **trans** Golgi network. Failure of these M6P groups to be added leads to I-cell disease.

CASE 12

A 35-year-old man visits a fertility specialist with his 27-year-old wife. They have been trying to conceive for more than 13 months but have been unsuccessful. The husband has no previous children, but the wife has two children from a prior marriage. Their past medical history is unremarkable except for repeated sinus infections and a chronic cough in the husband. Physical examination reveals a point of maximum impulse located at the right fifth intercostal margin.

What is the most likely diagnosis?

The fact that the wife has had prior children suggests that the cause of infertility lies with the husband. Given the history, Kartagener syndrome (primary ciliary dyskinesia) is most likely. This is a genetic disorder with an autosomal recessive inheritance pattern that affects flagella function in the sperm along with cilia in other areas.

What is the cause of their infertility?

Abnormality in **dynein**, which is an adenosine triphosphatase that acts as a molecular motor and is responsible for retrograde transport of material along microtubules. In addition, it is required for movement of cilia and flagella. If this enzyme is not functional, it results in immotile sperm.

What is the cause of the husband's recurrent sinus infections?

The cilia of the respiratory epithelium require functional dynein for motility. Without it, they are unable to transport bacteria and particles out of the respiratory tract. The retained particles and bacteria can lead to infections as well as a chronic cough with sputum production.

What abnormality is most likely to be observed on x-ray of the chest?

Situs inversus may be seen on an x-ray of the chest displaying the heart predominantly on the right side of the thorax. Situs inversus is a condition that presents with complete reversal of right-left symmetry. It may also show bronchiectasis, with signs of dilated bronchioles.

What immunodeficiency is also caused by a mutation in microtubule polymerization?

Chédiak-Higashi syndrome is an autosomal recessive disorder caused by a defect in microtubule polymerization resulting in impaired migration of immune cells, such as neutrophils, and impaired lysosome fusion, which results in large granules visible within the cytoplasm (see Figure 1-12). These both contribute to immune deficiency. Patients present with recurrent bacterial infections with staphylococci and streptococci. Neutrophils filled with large granules may be seen on microscopy of patients with this condition.

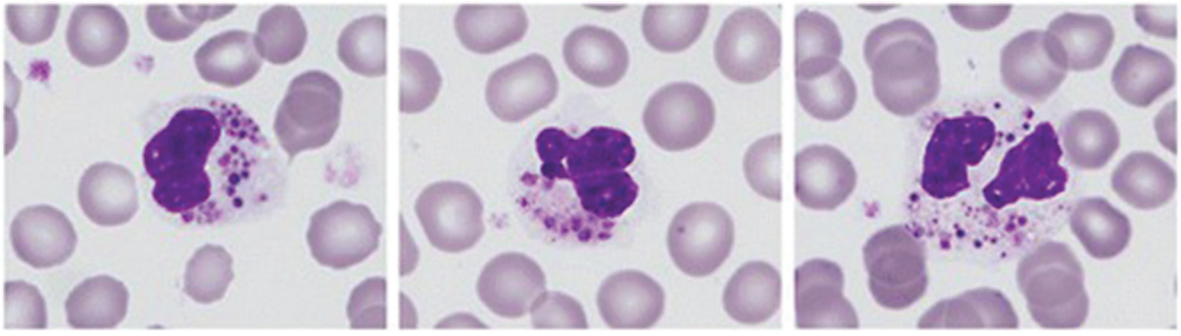

FIGURE 1-12. Peripheral blood smear displaying large granules within cytoplasm of neutrophils in a patient with Chédiak-Higashi syndrome. (Reproduced with permission from Lozano ML, et al. Towards the targeted management of Chédiak-Higashi syndrome. *Orphanet J Rare Dis*. 2014;9:132.)

There are several antimicrobial drugs that inhibit microtubule function. What are some examples?

Mebendazole and related drugs inhibit microtubule activity in helminths. Griseofulvin is an antifungal that acts on microtubules. Several chemotherapeutic agents also interfere with microtubule function, such as vincristine, vinblastine, and taxols such as paclitaxel.

CASE 13

A 2-year-old boy is brought to the pediatrician by his mother, who is visibly upset. The mother reports that her son has recently been biting his fingers and scratching his face incessantly. She says he was developmentally normal for the first months of his life but has become increasingly irritable since about 3 months of age. The mother also mentions that her son often has "orange-colored sand" in his diapers. Laboratory studies reveal a serum uric acid level of 55 mg/dL. Urinalysis reveals crystalluria and microscopic hematuria.

What is the most likely diagnosis?

Lesch-Nyhan syndrome.

What is the biochemical defect in this condition?

Lesch-Nyhan syndrome is characterized by a deficiency in hypoxanthine-guanine phosphoribosyltransferase (HGPRT).

What is the function of the deficient enzyme?

HGPRT plays a key role in the purine salvage pathway (see Figure 1-13), recycling hypoxanthine and guanine to the purine nucleotide pool. In the absence of this enzyme, excess purine bases are degraded into uric acid, thus causing hyperuricemia. Uric acid crystals in the urine give rise to the crystalluria and lead to the "orange-colored sand" seen in the diaper.

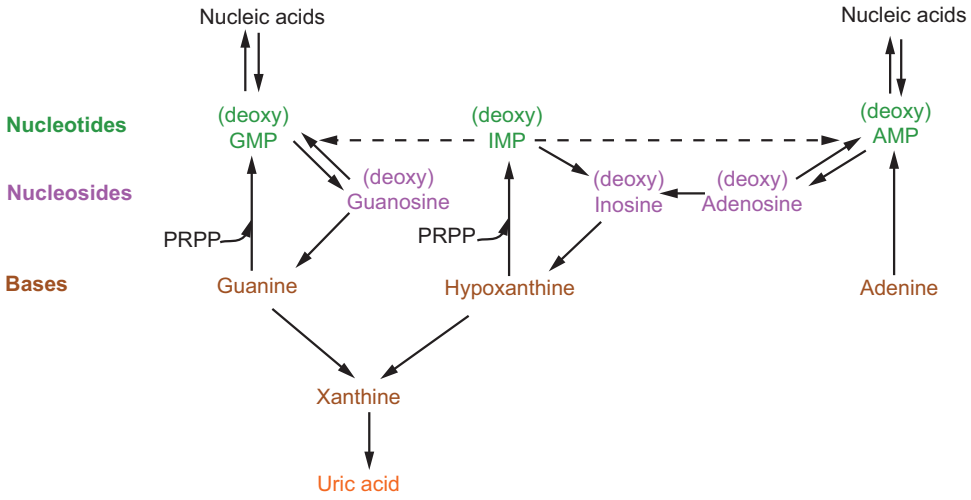

FIGURE 1-13. Purine degradation and salvage pathway. (Reproduced with permission from USMLE-Rx.com.)

What is the treatment for this condition?

Allopurinol is a drug that inhibits xanthine oxidase, thus preventing the formation of uric acid from the more soluble hypoxanthine and xanthine. Hypoxanthine and xanthine can more easily be excreted in the urine. Doses should be titrated to normalize serum uric acid levels. To prevent self-injury, affected children often need lifelong benzodiazepine or barbiturate sedation, restraints, and behavioral therapy. Allopurinol can also be used in the prevention of gout flairs due to the same mechanism of action.

What associated conditions are likely to develop if this condition is not treated?

Kidney stones, renal failure, gouty arthritis, and subcutaneous tophus deposits will result if the disorder is left untreated.

CASE 14

A 19-year-old college student comes to the university health clinic complaining of muscle aches. She recently began an exercise program to lose the 6-8 kg (13-17 lb) that she gained over the past year. After her first day of weightlifting, however, she became extremely sore. Several hours later, her urine was the color of "cherry soda pop." Physical examination is unremarkable. Laboratory tests reveal a serum creatine kinase level of 93970 IU/L. Urinalysis is negative for blood and positive for myoglobin.

What is the most likely diagnosis?

McArdle disease (type V glycogen storage disease). There are several glycogen storage diseases (see Table 1-2).

Table 1-2. Glycogen Storage Diseases

Glycogen storage disease	Defect	Characteristics
I-Von Gierke disease	Glucose-6-phosphatase	Fasting hypoglycemia
II-Pompe disease	Alpha 1,4 glucosidase	Cardiomegaly
III-Cori disease	Glycogen debranching enzyme	Hepatomegaly and normal lactate
IV-Andersen disease	Glycogen branching enzyme	Hepatosplenomegaly
V-McArdle disease	Muscle glycogen phosphorylase	Muscle pain and cramps

Other glycogen storage diseases include Von Gierke disease, which causes severe fasting hypoglycemia; Pompe disease, which is characterized by cardiomegaly and early death; and Cori disease, which is less severe than Von Gierke and has normal lactate levels.

What is the biochemical defect in this condition?

McArdle disease is caused by a deficiency of muscle glycogen phosphorylase. Although glycogen formation is not affected, glycogen cannot be broken back down to glucose-1-phosphate via glycogenolysis.

What are the most likely liver and muscle biopsy findings?

A liver biopsy is normal, as the defective enzyme is present only in muscle. Muscle biopsy shows accumulation of glycogen.

After the patient completes an exercise tolerance test, her lactic acid levels do not increase normally. Why?

Lactic acid is a product of anaerobic glucose metabolism, and during intense exercise, glucose in the muscle comes from muscle glycogen stores. Failure of lactic acid levels to elevate after exercise is an indication of a defect in the metabolism of glycogen or glucose to lactate. This response can be seen in other disorders of glycogenolysis or glycolysis as well.

What accounts for the color of her urine?

During exercise her muscles begin to break down, a process known as rhabdomyolysis, because of the lack of glucose. This causes myoglobinuria as well as elevated creatine kinase. Her urine will be positive for blood due to cross-reactivity with myoglobin and hemoglobin on urine dipstick but will be negative for RBCs.

What is the treatment for this condition?

Oral ingestion of sucrose before exercise has been demonstrated to improve exercise tolerance and reduce the risk of myoglobinuria. The patient should also warm up gently prior to exercise and avoid intense, anaerobic exercise.

CASE 15

A 2-year-old boy is brought to a health clinic in Mexico because of poor development as well as vomiting, irritability, and a skin rash. The boy's mother also notes that his urine has a strange "mousy" odor. Physical examination reveals the child has an eczema-like rash, is hyperreflexive, and has increased muscle tone. He has a surprisingly fair-skinned complexion compared to the rest of his family. Laboratory studies reveal a serum phenylalanine level of 28 mg/dL.

What is the most likely diagnosis?

Phenylketonuria (PKU).

What is the pathophysiology of this condition?

PKU is caused by a defect in the metabolism of **phenylalanine** (see Figure 1-14). This essential amino acid is converted to tyrosine by phenylalanine hydroxylase. However, when phenylalanine hydroxylase activity is reduced or absent, phenylalanine builds up. This leads to excess phenyl ketones in the blood, resulting in the symptoms seen in this patient. PKU is inherited in an autosomal recessive fashion.

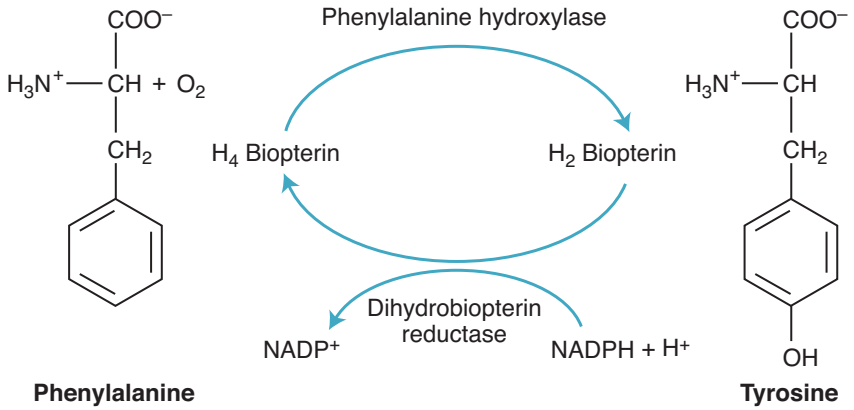

FIGURE 1-14. Phenylalanine hydroxylase reaction. (Modified with permission from USMLE-Rx.com.)

What additional physical characteristics are common at presentation?

Affected children are normal at birth but fail to reach developmental milestones. Other physical findings include failure to thrive and cognitive disability.

What is the cofactor for the defective enzyme in this disease that, when deficient, can also lead to increased levels of phenylalanine in the blood?

A deficiency in tetrahydrobiopterin can also lead to increased blood levels of phenylalanine. Tetrahydrobiopterin is a required cofactor for the synthesis of several neurotransmitters, including norepinephrine, dopamine, serotonin, and the molecule nitric oxide. Deficiency leads to a buildup of phenylalanine, which can be toxic to the brain, as well as an inability to produce those neurotransmitters. Tetrahydrobiopterin deficiency presents with similar symptoms to phenylketonuria, along with progressive neurologic disabilities. It is inherited in an autosomal recessive pattern.

What is the treatment for this condition?

PKU is treated with decreased dietary phenylalanine (which is contained in many foods, including artificial sweeteners). In patients with PKU, tyrosine cannot be derived from phenylalanine, so it becomes an essential amino acid. Therefore, patient should also receive dietary tyrosine supplementation. Currently, screening is mandatory and performed 6 days to 2 weeks after birth, using high-performance liquid chromatography.

CASE 16

A 6-month-old girl is brought to the pediatrician because she has been feeding poorly and has been lethargic for the past several months. The baby has also started breathing more rapidly than normal and recently had a seizure. Laboratory studies reveal a serum pH of 7.20, an anion gap of 19 mEq/L, elevated levels of pyruvate and alanine, and decreased levels of citrate.

What is the most likely diagnosis?

Pyruvate dehydrogenase deficiency.

What is the pathophysiology of this condition?

Glycolysis is the pathway that converts one molecule of glucose into two molecules of pyruvate. Pyruvate dehydrogenase then converts pyruvate to acetyl-CoA, which can enter the tricarboxylic acid (TCA) cycle (see Figure 1-15). Without this enzyme, cells are unable to fully oxidize glucose and must derive adenosine triphosphate (ATP) from glycolysis alone. Pyruvate must be converted to lactate to regenerate oxidized nicotinamide adenine dinucleotide (NAD+), a necessary cofactor in glycolysis. The elevated lactate level is responsible for the acidemia and anion gap observed in this baby.

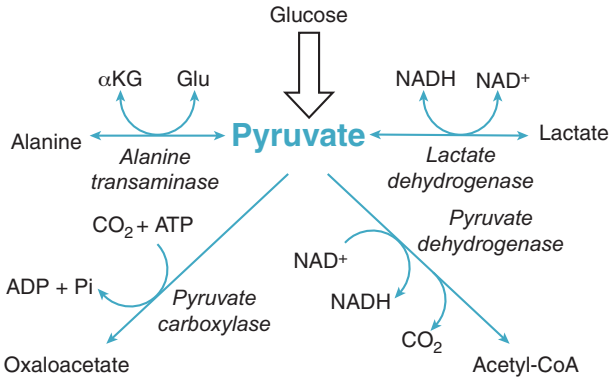

FIGURE 1-15. Pyruvate metabolism pathways. (Modified with permission from USMLE-Rx.com.)

Why are alanine levels high and citrate levels low in this condition?

Alanine levels are high because much of the excess pyruvate in the muscle is converted to alanine in a reversible reaction by alanine aminotransferase. Citrate levels are low because there is little acetyl-CoA to combine with oxaloacetate to form citrate.

What is the treatment for this condition?

Treatment involves increased intake of ketogenic nutrients (foods with high fat content). The breakdown of fatty acids by β-oxidation involves reduction of flavin adenine dinucleotide (FAD) and NAD+ and produces one molecule of acetyl-CoA for every two carbon atoms in the fatty acid chain. The FADH2 (1-5-dihydro-FAD) and NADH (reduced NAD+) can be used by the electron transport chain to produce ATP, whereas the acetyl-CoA can enter the TCA cycle. Oral citrate is also helpful for replenishing the substrates of the citric acid cycle.

Which are the only purely ketogenic amino acids?

Leucine and **lysine** are the only purely ketogenic amino acids.

Why is an anion gap metabolic acidosis seen in this condition?

Anion gap metabolic acidosis is caused by the accumulation of unmeasured anions (such as lactic acid). The anion gap is defined as the difference between sodium in the serum and the sum of bicarbonate plus chloride. The body buffers this excess acid with bicarbonate, decreasing the amount of measured bicarbonate on labs. Because lactic acid is not a directly measured anion, this increases the anion gap leading to an anion gap metabolic acidosis.

CASE 17

A 5-month-old girl of Ashkenazi Jewish descent is brought to her pediatrician because of concerns about developmental regression. Although she was developing normally for the first 4 months, she can no longer roll over by herself. In addition, she often smiled at 3 months of age but no longer does so. Funduscopic examination reveals a cherry-red spot in the macula. The remainder of her physical examination is normal.

What is the most likely diagnosis?

Tay-Sachs disease.

What is the biochemical defect in this condition?

This disease, one of the sphingolipidoses, is caused by a deficiency of **hexosaminidase** A. This enzyme is present within the lysosomes of central nervous system cells and helps degrade a lipid called GM2 ganglioside. GM2 ganglioside accumulation within the neurons leads to progressive neurodegeneration (see Figure 1-16). Children become blind and deaf before paralysis ultimately sets in. Children with Tay-Sachs disease usually die by 3 years of age.

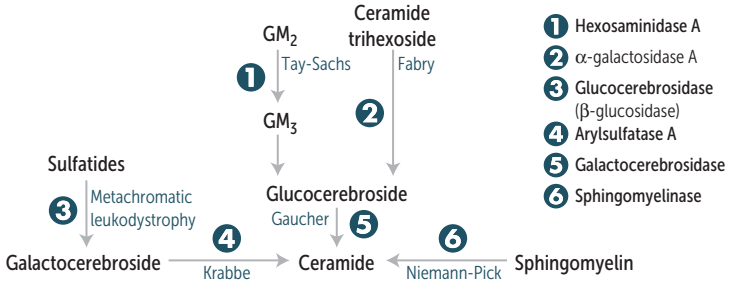

FIGURE 1-16. Biochemistry pathway of sphingolipidoses; lysosomal storage diseases. (Reproduced with permission from USMLE-Rx.com.)

How is the gene responsible for this condition inherited?

Tay-Sachs disease is inherited in an autosomal recessive fashion. Fabry disease is the only one of the sphingolipidoses that is inherited differently; it is X-linked.

What other conditions present with similar physical examination findings?

Niemann-Pick disease, which is caused by a deficiency of sphingomyelinase, also presents with a cherry-red spot in the macula in approximately 50% of cases. These patients often present with anemia, fever, and neurologic deterioration. The prognosis of Niemann-Pick disease is poor as well; most patients die by 3 years of age. Unlike Niemann-Pick, Tay-Sachs does not involve hepatosplenomegaly and demonstrates onion-like lysosomes on microscopy. Foam cells are characteristic of Niemann-Pick.

Which of the other sphingolipidoses also has a higher prevalence among Ashkenazi Jews?

Although Tay-Sachs is considered to have a higher prevalence among Ashkenazi Jews, screening programs have significantly decreased the prevalence of Tay-Sachs in this group. Gaucher disease, which is caused by a deficiency of β-glucocerebrosidase, also has a much higher incidence in this population.

CASE 18

A 36-year-old homeless man presents to a community health clinic complaining of increasing shortness of breath. On questioning, the man admits to an extensive history of alcoholism. A review of systems reveals he has also experienced tingling and burning in his legs for the past several weeks. Physical examination reveals that he is tachycardic (heart rate of 122/min), has rales bilaterally, and has bilateral pitting edema. He also has decreased sensation in his feet and is hyporeflexive in his lower extremities. An x-ray of the chest shows an enlarged cardiac silhouette and bilateral pulmonary congestion.

What is the most likely diagnosis?

Vitamin B_1 (thiamine) deficiency. Although the patient's alcoholism presents a clear etiology, arsenic poisoning also blocks thiamine utilization and can result in a clinical picture resembling thiamine deficiency and should also be considered.

What clinical manifestations are commonly present in this condition?

This patient has the symptoms of both wet and dry beriberi. Patients with wet beriberi present with high-output congestive heart failure and dilated cardiomyopathy. Patients with dry beriberi present with peripheral neuropathy consisting of muscular atrophy and diminished sensation and reflexes. Dry beriberi presents similarly to vitamin B_{12} deficiency; however, vitamin B_{12} deficiency is usually due to a malabsorptive process, does not cause congestive heart failure, and will cause a macrocytic anemia.

The deficient factor in this condition is a cofactor for which enzymes?

Thiamine is part of thiamine pyrophosphate (TPP). TPP acts as a cofactor for transketolase (an enzyme in the hexose monophosphate shunt), pyruvate decarboxylase (a component of the pyruvate dehydrogenase complex) (see Figure 1-17), and α-ketoglutarate decarboxylase (a component of the α-ketoglutarate dehydrogenase complex).

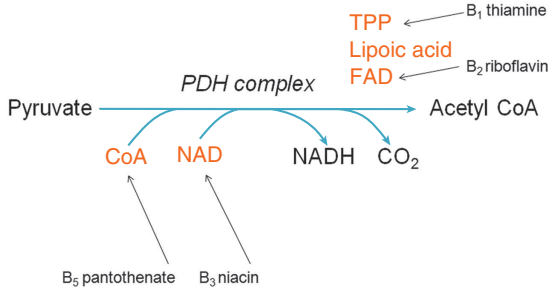

FIGURE 1-17. Conversion of pyruvate to acetyl CoA with necessary cofactors.
(Modified with permission from USMLE-Rx.com.)

What other pathologies are commonly seen with this condition?

Wernicke encephalopathy is the central nervous system manifestation of thiamine deficiency. This disease classically consists of nystagmus, ophthalmoplegia, and cerebellar ataxia. When the additional symptoms of confusion/psychosis and confabulation are seen, the disease is known as **Wernicke-Korsakoff syndrome**. It is standard practice to give thiamine before glucose to any patient with suspected thiamine deficiency to prevent Wernicke-Korsakoff. Administration of glucose prior to thiamine may worsen symptoms of thiamine deficiency due to an inability to complete enzymatic reactions that rely on thiamine and conversion of pyruvate to form lactic acid instead of entering the TCA cycle as acetyl-CoA.

What are the most likely MRI findings?

Although degenerative changes are often seen in the cerebellum, brain stem, and diencephalon, atrophy of the mammillary bodies is most commonly noted.

CASE 19

A 29-year-old man presents to your office along with his wife for preconception genetic counseling. Throughout the patient's life he has had recurrent upper respiratory tract infections. On physical examination, you notice rough, erythematous, and scaly patches of skin over the patient's elbows, as well as petechiae over his abdomen.

What is the most likely diagnosis?

This patient is most likely suffering from Wiskott-Aldrich syndrome. Wiskott-Aldrich syndrome is characterized by a constellation of symptoms, including thrombocytopenia (leading to petechiae), eczema (the scaly patches over his elbows), and recurrent sinopulmonary infections.

If his wife is not a carrier of the gene, what is the chance of them having a son who is affected or a carrier? A daughter?

Wiskott-Aldrich is inherited in an X-linked recessive pattern. In this case, the father is affected. This tells us that he carries a mutated gene on his X chromosome. We are told that his wife is neither affected nor a carrier of the mutated gene. In this scenario, no male progeny of this couple will either be carriers or be affected since the father must pass along his Y chromosome in order to have a son while the mother will pass along one of her unaffected X chromosomes. All daughters will be carriers of the Wiskott-Aldrich gene, since the father must pass along his mutated X chromosome in order to have a daughter, while the mother will pass along one of her unaffected X chromosomes (see Figure 1-18).

		Father	
		X^{WA}	Y
Mother	X	$X^{WA}X$	XY
	X	$X^{WA}X$	XY

FIGURE 1-18. Punnett square cross of X-linked recessive disease with affected father and unaffected mother (WA, Wiskott-Aldrich).

Why is this condition more common in males than females?

Wiskott-Aldrich syndrome is inherited in an X-linked recessive pattern and males only have one X chromosome. Therefore, they only need to inherit one copy of the gene to be affected. Females, in comparison, have two X chromosomes. For an X-linked recessive disease to affect a female, they must inherit two copies of the mutated gene.

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2
Immunology

CASE 1

A 20-year-old woman returns from a day hike in a densely wooded area and develops a rash that evening. The next day she presents to her physician. The patient has never developed a rash like this before and has hiked in this wooded area several times. Physical examination reveals that the rash is mostly on the legs, arms, and hands (see Figure 2-1)—areas the patient says "were not covered by clothing." She is afebrile.

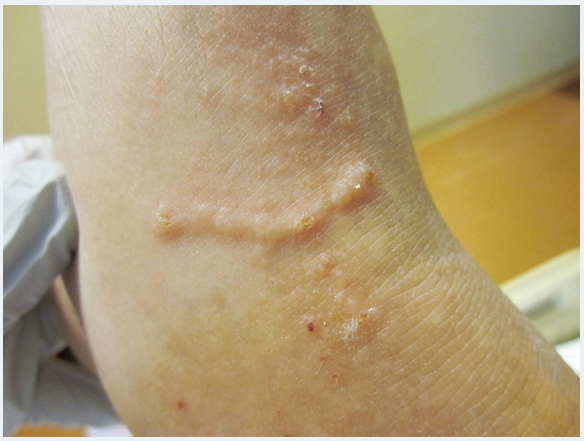


FIGURE 2-1. (Reproduced with permission from USMLE-Rx.com.)

What is the most likely diagnosis?

Contact dermatitis secondary to poison ivy. This rash is characterized by vesicles < 5 mm in diameter, typically in a distribution that reflects the skin's contact with the offending agent (eg, Figure 2-1 shows a linear vesicular rash where the poison ivy brushed against the skin). However, vesicles often coalesce in severe rashes. Causes of contact dermatitis include nickel, shampoos, bleach, and soaps, as well as many others.

Which type of hypersensitivity reaction is occurring in this patient?

Type IV hypersensitivity reactions (delayed or cell-mediated) include contact hypersensitivity from poison ivy, transplant rejection, hypersensitivity pneumonitis, granulomatous hypersensitivity reactions, and the tuberculin skin test (see Table 2-1). Type IV reactions are also important in the control of mycobacterial and fungal infections.

Table 2-1. The Four Types of Hypersensitivity Reactions

	Mechanism	Pathogenesis	Example
Type I	IgE-binding antigen	Massive histamine release	Peanut allergy (anaphylaxis)
Type II	IgG-binding cell surface protein	Tissue damage by immune system	Myasthenia gravis, Hashimoto thyroiditis
Type III	Specific antigen: antibody ratio	Precipitation of immune complexes in vessel walls activates complement	Poststreptococcal glomerulonephritis
Type IV	T cell mediated	Local release of inflammatory cytokines	Poison-ivy rash, tuberculin test

Was this the patient's first exposure to the offending agent?

A key feature of type IV hypersensitivity is that the patient must be sensitized to the antigen before development of hypersensitivity on subsequent exposure. Type IV hypersensitivity reactions typically occur 2-3 days after exposure. The tuberculin skin test relies on the principle of prior sensitization to assess for previous exposure to tuberculosis.

CASE 2

A 6-month-old boy who presents with a history of frequent infections is brought to the ED because of stiff muscles and difficulty feeding. On physical exam he is noted to have a cleft palate and increased distance between his eyes. When you tap on his face in front of his ears, you notice that his facial muscle contracts.

What is the most likely diagnosis?

This child has DiGeorge syndrome (22q11 syndrome), which is characterized by hypoparathyroidism (resulting in hypocalcemia) and T-cell deficiency. Additional severe immunodeficiencies that present in children around this age include severe combined immunodeficiency, hyper-IgM syndrome, IgA deficiency, and Bruton (X-linked) agammaglobulinemia. Severe combined immunodeficiency may cause both B- and T-cell deficiencies or T-cell deficiency exclusively in a given host. Hyper-IgM syndrome, IgA deficiency, and Bruton agammaglobulinemia all primarily affect B cells.

What is the etiology of this condition?

DiGeorge syndrome is due to a deletion on chromosome 22q11. This leads to a developmental defect involving the third and fourth pharyngeal pouches. It results in a hypoplastic thymus and parathyroid glands. Laboratory tests of this patient would show hypocalcemia, inappropriately low parathyroid hormone (parathyroid hormone would normally be elevated in response to low calcium), and low T-cell count. The hypocalcemia causes tetany and carpopedal spasm. Chvostek sign involves tapping on the facial nerve in front of the ear and observing spasm of the facial muscle; it is another indication of hypocalcemia.

This patient is at risk for developing what type of infections?

Because of the aplastic thymus, patients with this disorder have ineffective T cells and are particularly susceptible to viral and fungal infections.

What abnormality is most likely to be observed on an x-ray of the chest in this patient?

An x-ray of the chest in a child with DiGeorge syndrome may show a reduced thymic shadow (see Figure 2-2).

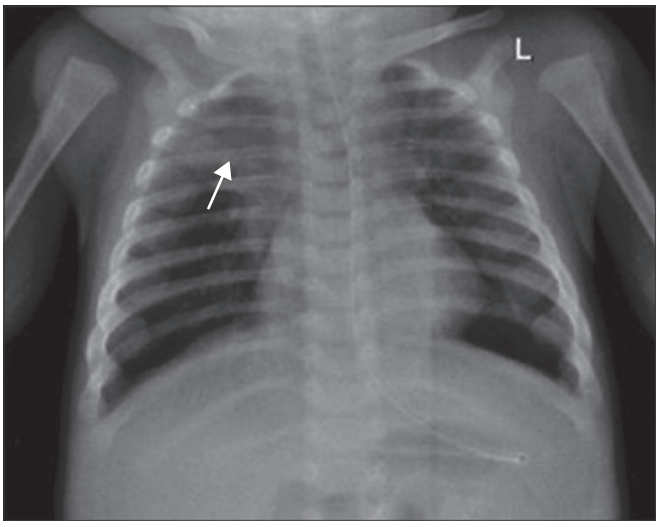


FIGURE 2-2. A Posteroanterior chest x-ray displaying a right upper lobe consolidation, suggestive of possible pneumonia, and a narrowed superior mediastinum suggesting likely thymic agenesis. (Reproduced with permission from Ramachandran R, et al. Role of imaging and cytogenetics in evaluation of DiGeorge syndrome: A rare entity in clinical practice. *J Clin Imaging Sci.* 2015;5:4.)

What other abnormalities are associated with this condition?

CATCH 22 is a mnemonic for the 22q11 syndrome, which involves a deletion in this region of chromosome 22. Clinical manifestations include **C**ardiac abnormalities, **A**bnormal facies, **T**hymic hypoplasia, **C**left palate, and **H**ypocalcemia. Velocardiofacial syndrome also arises from this gene and involves cardiac abnormalities, abnormal facies, and cleft palate.

CASE 3

A 27-year-old man presents to a medical mission in Tanzania with a complaint of paralysis of his lower extremities. He says he had severe diarrhea 2 weeks ago and began to have trouble walking earlier this week. Physical examination demonstrates 0/5 strength and hyporeflexia of the lower extremities. Sensation to pain, temperature, position, and light touch seems to be dulled as well.

What is the most likely diagnosis?

Guillain-Barré syndrome (GBS). GBS is a condition with several forms but may classically present with a progressive, ascending flaccid paralysis most commonly beginning at the distal lower extremities and progressing cranially. It often presents with motor symptoms in excess of sensory symptoms. Transverse myelitis is another diagnosis on the differential and may also present with lower extremity sensory and motor loss but will present with a distinct sensory level and does not typically present in a distal to proximal fashion.

GBS is typically an acute, immunologic reaction, likely an antigenic cross-reactivity, following a preceding infection. *Campylobacter jejuni* infection has the strongest association with GBS, followed by cytomegalovirus, Epstein-Barr virus, HIV, and Zika virus infections also showing some association with GBS. The patient described above presents with paralysis after a bout of diarrhea. *Campylobacter* species (*C jejuni* and *C coli*) are a common cause of acute diarrhea worldwide. Given the association of *C jejuni* with GBS, that is likely the origin of GBS in the patient.

What may be seen on CSF analysis of a patient with this condition?

CSF analysis of patients with Guillain-Barré syndrome characteristically displays elevated protein levels with a normal cell count (albuminocytologic dissociation).

What is the fatal complication of this disease?

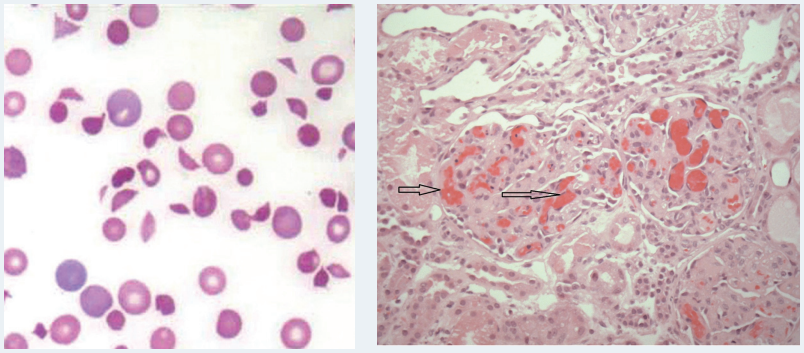
The ascending paralysis may eventually affect the respiratory muscles. Respiratory support is needed until the disease resolves and the patient can adequately breathe on his own.

What disease presents as a progressive descending flaccid paralysis?

Botulism classically presents as a progressive descending flaccid paralysis in comparison to the progressive ascending paralysis seen in Guillain-Barré syndrome. It is caused by toxins produced by *Clostridium botulinum*. The toxin produced cleaves a soluble NSF attachment protein receptor (SNARE), which prevents ACh signaling at the neuromuscular junction (NMJ).

CASE 4

A 9-year-old boy is brought to the ED with a 5-day history of abdominal pain and diarrhea, including blood in the stool. He is admitted to the hospital for intravenous fluid replacement and further workup. His stool is found to be positive for Shiga-like toxin. After 4 days his abdominal pain begins to subside, but he notices that his urine is grossly bloody. Peripheral blood smear (PBS) (see Figure 2-3A) and biopsy of his kidney (see Figure 2-3B) are obtained.



A B

FIGURE 2-3. (Image A reproduced with permission from USMLE-Rx.com. Image B reproduced with permission from McCoy N, Weaver DJ Jr. *BMC Pediatrics*. 2014;14:278.)

What is the most likely causative organism?

Enterohemorrhagic *Escherichia coli* (EHEC) serotype O157:H7 is the most common cause of hemolytic uremic syndrome (HUS). EHEC is also called verocytotoxin-producing *E coli* (VTEC) as well as Shiga-toxin producing *E coli* (STEC).

What is the mechanism of action of Shiga toxin and Shiga-like toxin?

Historically, these toxins have been described separately as shiga toxin from Shigella and shiga-like toxin from *E coli* O157:H7. Recently, they are designated as shiga toxin (Stx), having the same mode of action but immunologically distinct. The toxins produced by either *S dysenteriae* or EHEC are "AB toxins" where the B-chain binds to Gb3 on cells, especially endothelial cells, and the A-chain is enzymatic domain. The A-chain subunit binds to the ribosomes and inhibits its functions. This leads to protein synthesis dysfunction and cell apoptosis.

What is the cause of the blood in the patient's urine?

The patient has developed HUS. This is a complication of infection with *Shigella* and EHEC in which the toxin damages the renal vascular endothelium, compromising vascular integrity. Several schistocytes are apparent on the PBS (see Figure 2-3A), and the kidney biopsy shows a fibrin thrombus (see Figure 2-3B).

What is the classic triad of findings associated with this condition?

In HUS, the triad of findings is renal damage, hemolytic anemia, and thrombocytopenia. Another important distinction is that patients infected with EHEC do not show febrile illness. EHEC infection should be suspected in patients with acute bloody diarrhea, abdominal tenderness, and the absence of fever.

What other conditions feature a similar PBS?

When RBCs are forced past a partial microvascular obstruction, they become damaged and assume the characteristic schistocyte shape. Other conditions in which schistocytosis may be seen are thrombotic thrombocytopenic purpura (TTP) and disseminated intravascular coagulation (DIC). In TTP, an autoantibody destroys ADAMST13, an enzyme responsible for cleaving large multimers of von Willebrand factor (vWF), which is more prone to cause coagulation of blood. By contrast, DIC is caused by an overabundance of tissue factor in the blood, triggering the coagulation cascade. Increased levels of tissue factor may be seen in severe trauma, cancers, or sepsis. DIC has a mortality rate of up to 55%.

What serum markers should be measured to follow disease progression or recovery of this patient?

The platelet count is a useful marker for this syndrome. In addition, the blood urea nitrogen and creatinine levels should be measured to follow renal recovery. The hemoglobin and hematocrit should be followed to assess the need for transfusion.

Why not use antidiarrheal medication to treat?

Antidiarrheal medications would cause a slowing of the intestinal motility and not eradication of the infection. When used, antidiarrheal medication can cause a worsening infection (slowing of intestinal emptying) and would prolong the blood/diarrheal illness. Additionally, due to the inflammation and infection, the risk for intestinal perforation becomes higher if you use antidiarrheal medications with these infections. Antibiotics typically do not add any benefit and, in some cases, may cause HUS.

CASE 5

In January, a 2-year-old girl is brought to her pediatrician by her parents because of a 3-day history of watery, nonbloody diarrhea, nausea, vomiting, and abdominal pain. Per parental history, this has been the child's third GI infection since birth and numerous respiratory infections requiring ED treatments. She has not had any abnormal sick contacts and stays at home with her mother during the day.

What is the most likely diagnosis?

Since most infants do get sick periodically due to day care, multiple care providers, and overall cleanliness, most physicians assume a nonharmful viral infection and treat as such. With a young patient with histories of multiple infections, a more serious cause should be sought out. Of the most common immunodeficiencies is a deficiency in immunoglobulin A, while levels of IgM and IgG are typically normal. Most of the time, patients with IgA deficiency are asymptomatic but can be seen with a history of multiple respiratory and GI infections. Other immunological indicators of an IgA deficiency include a history of atopy and autoimmune diseases.

What is the role of the immunoglobulin that is deficient in this patient?

IgA is the main immunoglobulin that is secreted into mucous membranes. IgA is often secreted as a dimer and is the most abundant form of Ig in the body but the lowest in serum (since it is not secreted into the blood but rather membranes). IgA prevents attachment of bacteria and virus onto mucous membranes in both the GI and respiratory tracts. It is secreted in breast milk (passive immunity for newborns who are breast feeding), tears, saliva, and mucus. IgA is produced by B lymphocytes in the Peyer Patches of the GI system and is the main defense against many GI pathogens causing diarrhea.

What are lab findings in this condition?

Obviously from its name, IgA deficiency results in low numbers of IgA. IgG and IgM are overall normal. Since this is a single immunoglobulin deficiency, there are functional T and B cells (thus many individuals are asymptomatic), except they do not produce adequate numbers of IgA. IgA deficiency has been shown to be due to a variety of possible genetic abnormalities that then results in a lack and/or reduction of cytokine production, including IL-21, IL-4, IL-6, IL-7 and/or IL-10, which plays a role in stimulating an isotype switch to produce IgA.

What is the treatment for this condition?

Treatment is supportive by promptly treating infections, identifying any comorbid conditions (atopy, autoimmune diseases), and preventing infections if able to. IVIG IgA may be used to treat very severe and untreatable infections but overall has no effect on these patients.

In what age group is this condition usually seen?

Infection is not commonly seen before 6 months of age, as children have passive immunity from IgA from the mother's breast milk. This passive immunity is important for these children as IgA is not normally developed.

CASE 6

A 35-year-old man presents to a medical mission near the Benue River in Nigeria complaining of pruritis. Physical examination shows several depigmented nodules on his thorax, hips, legs, and elbows, and thickening of the skin. Visual acuity testing reveals decreased acuity in his right eye.

What is the most likely diagnosis?

Onchocerciasis (river blindness). Onchocerciasis is caused by *Onchocerca volvulus,* a nematode (roundworm) found near rivers. Onchocerciasis is the leading cause of blindness in the developing world. Of the 18 million people infected worldwide, 99% of cases are in Zaire and Nigeria.

How is this condition transmitted?

The bite of a female black fly transmits larvae (microfilariae) into the host's skin (see Figure 2-4). Humans are the only known definitive host of this parasite.

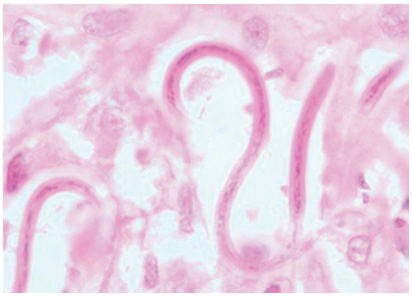


FIGURE 2-4. Microfilariae of *O volvulus* from a skin nodule, stained with H&E. (Reproduced courtesy of the Centers for Disease Control and Prevention, Division of Parasitic Diseases and Malaria.)

What tests can help confirm the diagnosis?

A skin biopsy may show larvae under the microscope, whereas nodules contain the adult filariae. The microfilariae in the eye may be visible on slit-lamp examination. Serologic tests such as enzyme-linked immunosorbent assay, polymerase chain reaction assay, and direct antigen testing are also available but require a laboratory, which is often not available to physicians treating the primary patient population.

What are the treatments for this condition?

Ivermectin is effective against the larvae (microfilariae). It must be given every 6–12 months until the patient is asymptomatic. The subcutaneous nodules containing adult worms can be surgically removed.

On a white blood cell differential, which component may be abnormally elevated in this infection?

Eosinophil levels are commonly elevated in the case of parasitic infection. Eosinophils (see Figure 2-5) are a member of the granulocyte group, along with basophils and neutrophils. Elevated levels of eosinophils may be caused by parasitic infection or as part of an allergic reaction. Interleukin-5, which is produced in part by type-2 T helper cells, is thought to activate eosinophils.

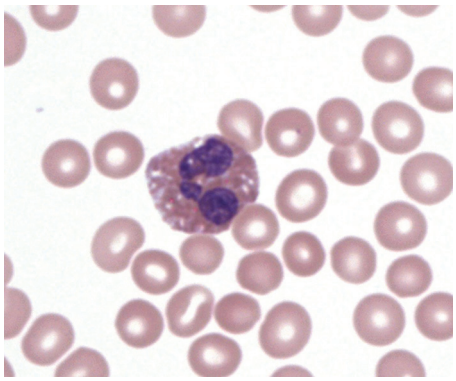


FIGURE 2-5. Eosinophil. Peripheral blood normal eosinophil with prominent red granules, containing histamine, major basic protein, and other substances important in mediation of allergy and fighting of parasites. (Reproduced with permission from USMLE-Rx.com.)

In general, neutrophils are commonly elevated in bacterial infections, whereas lymphocytes are often elevated during viral infections. Neutrophils are effective against numerous bacteria through phagocytosis of the microbes, followed by production of superoxide radical and hydrogen peroxide reactive oxygen species through the respiratory burst. NADPH oxidase is responsible for the formation of superoxide within neutrophils. Lymphocytes, especially activation of Th1 cells, are helpful in fighting intracellular infections, including those caused by viruses. In the case of parasitic worm infections, because parasitic worms are too large to be engulfed by phagocytic cells, parasitic worms can trigger eosinophil recruitment, which are then able to stimulate an inflammatory reaction against the parasitic worm when activated via IgE-mediated antibody-dependent cellular cytotoxicity (ADCC) reaction.

CASE 7

A 30-year-old man presents to the ED complaining of chills, myalgia, and extreme throbbing pain in his right shin. He fractured his tibia 3 weeks ago and required external fixation. His temperature is 40°C (104°F), blood pressure is 130/80 mm Hg, and heart rate is 80/min. Physical examination reveals that his right leg is red, tender, warm, and swollen over the anterior tibia just inferior to the knee. X-ray of the extremity demonstrates periosteal elevation and changes consistent with soft tissue swelling adjacent to the tibia. The patient is admitted, and Gram stain cultures reveal gram-positive coagulase-positive cocci.

What is the most likely diagnosis?

Osteomyelitis. *Staphylococcus aureus*, a gram-positive, coagulase-positive cocci, is responsible for approximately 90% of pyogenic osteomyelitis cases. *S aureus* expresses receptors for the bone matrix, thus allowing it to adhere to bone and produce a focus of infection. Many affected adults have a history of compound fracture or surgery. *Staphylococcus epidermidis* is another cause of osteomyelitis and is frequently associated with the formation of biofilms on surgical equipment. However, *S epidermidis* is coagulase negative and, thus, is not the cause of this patient's presentation.

Toxic shock syndrome is a potential consequence of *S aureus* infection, classically following the use of absorbent tampons. What is the mechanism behind this condition?

Toxic shock syndrome results from the production of a superantigen by *S aureus*. This superantigen causes binding between host T-cells and MHC II receptors. Helper T cells express CD4 molecules, which bind to MHCII on antigen-presenting cells. This interaction leads to the release of cytokines and further immune system activation. This nonspecific binding between host T cells and MHC II receptors by the superantigen leads to massive T cell activation with the release of cytokines leading to fever, hypotension, and a diffuse sunburn-like rash. Toxic shock–like syndrome is a condition that results from *Streptococcus pyogenes* infection and results in a similar disease process and presentation. *S pyogenes*, while a gram-positive cocci, is coagulase negative. Treatment for toxic shock syndrome is with appropriate antibiotic coverage and possible surgery of any infectious source.

What patient populations are susceptible to this patient's condition?

Osteomyelitis can be a sequela of trauma, as is the case in this patient, but it is also often found in intravenous drug abusers (direct injection of bacteria) and patients with diabetes who have poorly controlled blood glucose. Bacteremic patients (typically children) may develop osteomyelitis as a consequence of hematogenous spread, while adults develop osteomyelitis commonly from contiguous spread.

How does a subperiosteal abscess lead to accelerated bone necrosis?

A subperiosteal abscess separates the bone from its blood supply in the periosteum, leading to ischemic injury and necrosis.

A history of sickle cell disease would increase this patient's risk of infection from which pathogen?

Patients with sickle cell disease have an increased risk of developing *Salmonella* osteomyelitis because of the reduced immune clearance of this pathogen. *Salmonella* is a gram-negative rod able to produce hydrogen sulfide but not able to ferment lactose (ie, lactose nonfermenter) and is a member of the enterobacteriaceae.

What are the typical imaging findings?

Periosteal elevation is often found on plain film radiography (see Figure 2-6). This finding, however, can lag up to 2 weeks behind the onset of the infection. MRI is sensitive but not specific as it cannot distinguish osteomyelitis from other causes of marrow edema, such as normal postsurgical changes. Negative MRI findings essentially exclude osteomyelitis.

If this patient's culture had grown MRSA, which cephalosporin would be appropriate for coverage?

Fifth-generation cephalosporins, such as ceftaroline, have activity against MRSA. Cephalosporins are antibiotics that belong to the β-lactam group, which disrupt the bacteria's ability to form their cell wall. Other drugs not belonging to the cephalosporin class, such as vancomycin, would also be appropriate.

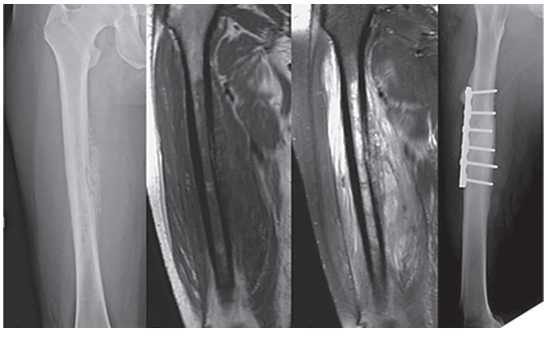


FIGURE 2-6. Osteomyelitis of the femur. (A) Plain film of the femur showing periosteal reaction. (B) T1-weighted MRI. (C) T2-weighted MRI. (D) Plain film 18 months post–open-reduction and internal-fixation surgery. (Reproduced with permission from Huang P-Y, et al. Osteomyelitis of the femur mimicking bone tumors: A review of 10 cases. *World J Surg Oncol*. 2013;11:283.)

CASE 8

A 52-year-old woman with AIDS presents to her physician with difficulty breathing. She has experienced slowly worsening dry cough and dyspnea for approximately the past week. Her most recent CD4+ cell count is 175 cells/mm^3. In the office, her oxygen saturation is 92%. The patient says that she is not currently taking any medications because she is "tired of taking pills."

What is the most likely diagnosis?

Pneumocystis jiroveci pneumonia causes interstitial pneumonia in certain patient populations. Once thought to be a protozoan, *P jiroveci* is now recognized as a fungus (yeast).

What patients are most at risk for developing a clinical infection with this microorganism?

Most individuals are exposed to *P jiroveci* during childhood but develop no symptoms. However, immunocompromised patients (including patients with AIDS who have low CD4+ cell counts) and malnourished infants may develop severe clinical disease. *Pneumocystis* pneumonia in steroid-treated immunocompromised patients is most often seen as steroids are being withdrawn.

What are the likely x-ray findings?

"**Ground-glass**" bilateral infiltrates are commonly seen on x-ray of the chest (see Figure 2-7). In these patients, **hypoxia** is often **out of proportion** to the radiographic findings.

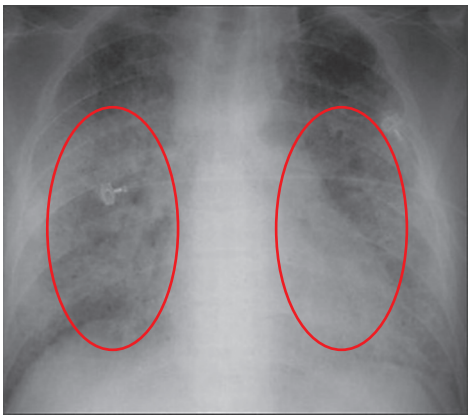


FIGURE 2-7. X-ray of the chest displaying ground glass appearance of *Pneumocystis jirovecii* pneumonia. (Reproduced with permission from Allen CM, et al. Imaging lung manifestations of HIV/AIDS. *Ann Thorac Med*. 2010;5(4):201-216.)

What tests can help confirm the diagnosis?

Sputum samples, bronchoalveolar lavage, or lung biopsy treated with silver stain demonstrate cysts and dark oval bodies contained within the cyst.

What is the treatment for this condition?

Treatment is primarily with trimethoprim-sulfamethoxazole. In immunocompromised patients, trimethoprim-sulfamethoxazole or dapsone (used when patients have a sulfa allergy) may be used as prophylaxis when CD4+ cell counts fall below 200 cells/mm^3. In patients with severe hypoxia, steroids should be given as adjunctive therapy to prevent worsening respiratory status due to the inflammatory response induced by treatment.

What other opportunistic infections are patients with HIV/AIDS at risk for and at what CD4 level should prophylactic medications be given?

Table 2-2. Opportunistic Infections and Antibiotic Prophylaxis in AIDS

Organism	CD4 count (cells/mm^3)	Prophylactic treatment
Pneumocystic jirovecii	200	TMP-SMX
Toxoplasma gondii	100	TMP-SMX
M avium-intracellulare	50	Azithromycin

CASE 9

A 34-year-old Haitian nurse complains to her physician of occasional rust-colored sputum and fever of 6 months' duration. She also notes her clothes fit more loosely than they used to. She does not have a history of smoking or asbestos exposure. Her only medication is an oral contraceptive. X-ray of the chest is performed and a radiology report expresses concern about the structure indicated by the arrow (see Figure 2-8).

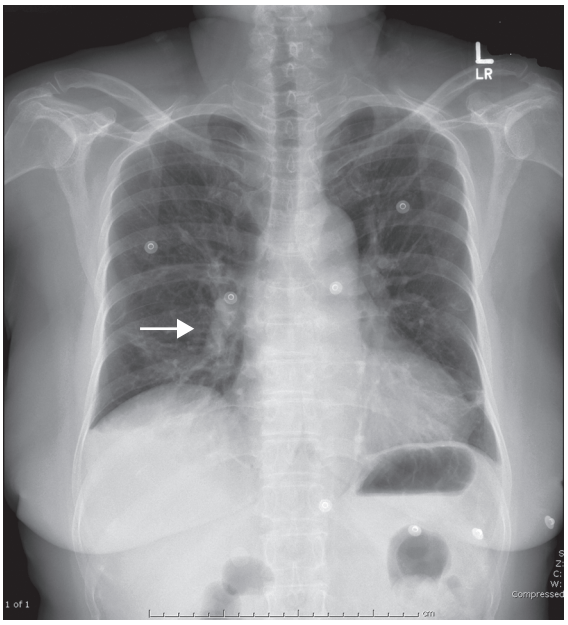


FIGURE 2-8. (Reproduced with permission from USMLE-Rx.com.)

What is the most likely diagnosis?

This patient's symptoms and x-ray of the chest suggest primary tuberculosis (TB). Associated findings include a positive purified protein derivative (PPD) test, positive culture, and/or positive acid-fast staining of bacteria from sputum samples. Primary TB is often seen in the lower lobes of the lung with enlargement of the associated lymph node, whereas reactivation TB tends to cause cavitation in the apices.

What type of lesion does the x-ray show?

Primary lesions are usually found in the lower lobes as Ghon foci (arrow in Figure 2-8). If there is lymph node involvement, the lesions are termed Ghon complexes. Reactivation (secondary) TB lesions are usually seen in the apical and posterior portions of the upper lobes.

How is the microorganism that causes this condition cultured and stained?

Mycobacterium tuberculosis is cultured on **Lowenstein-Jensen agar**. It is an acid-fast bacterium and therefore stains with **Ziehl-Neelsen stain**.

What is the treatment for this condition?

The standard treatment lasts for 6 months. **R**ifampin, **I**soniazid, **P**yrazinamide, and **E**thambutol (**RIPE**) are used for the initial phase of therapy (usually 2 months), followed by rifampin and isoniazid for an additional 4 months. More drugs may need to be used in multidrug-resistant TB. Because emergent drug resistance is often due to medication nonadherence, the United States has installed "observed therapy" programs in which TB patients take their medication in the presence of a health care provider. Prophylactic treatment is with isoniazid.

What are the main adverse effects of treatment with these agents?

Rifampin colors urine, feces, sweat, and tears a reddish-orange color. It also upregulates the cytochrome P-450 isoenzyme system, increasing the metabolism of many drugs, including oral contraceptives. If the patient stays on her current dose of birth control pills and remains sexually active, she is more likely to become pregnant while taking rifampin. Isoniazid causes peripheral neuropathies; vitamin B_6 reduces this adverse event. Rifampin, isoniazid, and pyrazinamide are associated with liver toxicity. Ethambutol can cause retrobulbar optic neuritis, which impairs visual acuity and color vision; patients should receive frequent ophthalmologic examinations during the treatment period.

How does reactivation in this disease occur?

TB is transmitted by aerosol droplets in the air by people who are actively infected. TB can then invade another host's pulmonary alveoli and replicate within the endosomes of the alveoli macrophages. Here TB will create a primary infection area otherwise known as the Ghon focus, which is usually located in the upper or lower part of the infected person's lower lobes. It can lie dormant in these areas until there is immunosuppression or reactivation occurs. Once reactivated, TB then reestablishes an infection in the upper portion of the lungs where there is more oxygen to live. This is why TB reactivation is always found in the upper lobes of the lungs, but an asymptomatic person may not have any findings.

CASE 10

An 18-year-old man with cystic fibrosis (CF) and a history of multiple respiratory infections is brought to the ED after recent onset of dyspnea, chills, and cough productive of purulent sputum. His mother reports he has been lethargic and recorded his temperature at 39°C (102.2°F). Physical examination reveals a poorly responsive man in moderate respiratory distress. Laboratory studies are notable for a WBC of 17,000/mm^3, with a left shift on the differential. Sputum culture yields gram-negative, non-lactose-fermenting bacilli.

What is the most likely diagnosis?

Pseudomonas aeruginosa infection (see Table 2-3). *P aeruginosa* is a **gram-negative**, **aerobic**, **oxidase-positive**, **rod-shaped** bacterium with a single flagellum. As an opportunistic pathogen, it causes infection in patients with impaired defense mechanisms, especially immunocompromised individuals and burn victims. It commonly lives in water or wet environments and can be particularly problematic for patients on ventilators. It is a major cause of respiratory failure in patients with CF over the age of 20 years.

Table 2-3. Most Common Causes of Pneumonia in Patients with Predisposing Disease

Predisposing disease	Most important causes of pneumonia
Cystic fibrosis	*Pseudomonas aeruginosa*
Post-influenza	*Staphylococcus aureus*
COPD	*Haemophilus influenzae*

What other infections does this microorganism cause?

Community-acquired infections include otitis externa ("swimmer's ear"), endocarditis (seen in intravenous drug users), osteomyelitis, and pneumonia. **Nosocomial infections** may present as bacteremia, leading to sepsis in burn victims and neonates. Ventilator-associated pneumonia and infections secondary to Foley catheter placement may also be due to *P aeruginosa*.

What is the pathology of chronic respiratory infection with this microorganism in patients with CF?

Pseudomonas can colonize the lungs of patients with CF. These patients cannot effectively clear the pathogen as the thickened mucus is not easily expectorated. The patient's immune response causes a chronic inflammatory state that eventually results in progressive loss of pulmonary function.

What virulence factors contribute to acute infection with this microorganism?

Pseudomonas has a host of virulence factors that contribute to pathology in acute infection. These include pili and a flagellum for host invasion; lipopolysaccharide (endotoxin); exotoxins A, S, and U; elastase; and various cytotoxins.

What are the treatments for this condition?

Pseudomonas is frequently resistant to multiple-drug regimens, so therapy guided by antimicrobial susceptibility testing is essential. In addition to its intrinsic resistance to many antibiotics, it is able to acquire resistance rapidly during treatment. Potentially useful antibiotics include ceftazidime, cefepime, ciprofloxacin, aztreonam, imipenem, piperacillin-tazobactam, and the aminoglycosides. These drugs are usually employed in combinations of two drugs of different classes. Topical (eg, inhaled) as well as systemic antibiotic therapy are utilized in CF patients. Colistin is a drug of last resort for severe cases of multidrug-resistant *Pseudomonas* infection. A well-used mnemonic for potential *Pseudomonas* drugs is **CAMPFIRE** (**C**arbapenems, **A**minoglycosides, **M**onobactams, **P**olymyxins, **F**luoroquinolones, th**I**rd- and fou**R**th-generation cephalosporins, and **E**xtended-spectrum penicillins).

CASE 11

A 21-year-old college student presents to the clinic with fever, hives, headache, weight loss, and cough. On review of systems, she reports doing field research in Egypt over the summer. She recalls an intense itching sensation while collecting samples in a river. Physical examination reveals lymphadenopathy and hepatosplenomegaly.

What is the most likely diagnosis?

The patient likely acquired schistosomiasis, caused by a type of **trematode** (fluke), from contact with contaminated water. The three main flukes are *Schistosoma japonicum* (in East Asia), *S mansoni* (in South America and Africa), and *S haematobium* (in Africa).

What other species are intermediate hosts of this pathogen?

Snails are the intermediate host for all trematodes. Reservoirs include primates (*S mansoni* and *S haematobium*) and domesticated animals (*S japonicum*).

In which human organs are the organisms found?

S japonicum and *S mansoni* reside in the intestines, where organisms mate in the mesenteric veins and release eggs into the feces as well as the portal circulation. *S haematobium* resides in the bladder, where organisms mate in the vesicular (bladder) veins and release eggs into the urine.

How is this condition diagnosed?

Examination of the urine (*S haematobium*) and stool (all three species) reveals eggs. The terminal spikes of the eggs can help differentiate these types of infections. *S mansoni* has the egg with a lateral spine and *S haematobium* has an egg with a terminal spine. Eosinophilia can be seen in 30%-60% of patients. Hematuria and/or leukocyturia can be seen specifically in a *S haematobium* infection.

What are the chronic manifestations of this condition?

After the initial "**swimmer's itch**," which is a dermatitis that occurs as the organism initially penetrates the skin, there is a lag period of 4–8 weeks. **Katayama fever** occurs as the adult organisms lay eggs. The eggs trigger a granulomatous immune response, fibrosis, and inflammation. For example, eggs that pass into the portal system become foci for granulomatous inflammation of the liver, eventually leading to fibrosis. Complications include portal hypertension (*S japonicum* and *S mansoni*), pulmonary artery hypertension, chronic abdominal pain, and central nervous system injury. Unique to *S haematobium* is the ability to lead to squamous cell **carcinoma of the bladder** (due to chronic inflammation and irritation).

What is the treatment for this condition?

Praziquantel is the treatment of choice. Corticosteroids can reduce acute symptoms of infection.

CASE 12

A 55-year-old man with end-stage renal disease is scheduled to undergo kidney transplantation. While on the operating table, the donor kidney is connected to the patient's blood supply. Within minutes of perfusion, the transplanted organ becomes extremely erythematous. After a short period of time, the kidney becomes ashen gray and urine production ceases. The surgeon immediately removes the organ.

What caused the transplanted organ to fail?

Hyperacute rejection occurs within minutes of the transplantation. Rejection is due to preformed antibodies that recognize graft antigens. The patient's serum must be tested for antibodies that bind to a biopsy of the graft tissue before transplantation. There are three types of graft rejection (see Table 2-4).

Table 2-4. The Three Types of Graft Rejection

Type	Mechanism	Time frame
Hyperacute	Preformed antibodies to graft antigens elicit an immediate immune response	Within minutes of graft perfusion
Acute	Cell-mediated attack elicited by donor MHCs on graft tissue	As soon as 1 week after transplantation but can recur any time, especially if patient is no longer immunosuppressed
Chronic	Fibrosis of graft blood vessels	Years

What would histology show in a kidney that had undergone this complication?

The kidney would show fibrinoid necrosis of the small vessels and thromboses.

What would histology show in a kidney that had undergone acute or chronic forms of this complication?

Acute rejection is primarily cell mediated, although antibodies can also cause damage to graft tissue. A biopsy reveals T-cell and macrophage infiltrates as well as blood vessel and parenchymal damage. Chronic rejection is characterized by vascular damage. Damage to graft blood vessels can be due to antibody binding, complement activation, T-cell activation, and cytokines. The result is intimal proliferation, causing narrowing of the vessel lumen and tissue ischemia. Examination of the graft shows a small, scarred kidney.

Patients who undergo bone marrow or hematopoietic cell transplantation are at risk of another potential complication, graft-versus-host disease (GVHD). What is the mechanism of GVHD?

During bone marrow transplantation, the donor's immune system is essentially introduced into the host's body. As donor-derived T cells have not become immunotolerant toward host antigens, GVHD can occur when grafted T cells bind to host antigen and become activated, damaging host tissue. The most frequent sites of injury are the skin, liver, and gastrointestinal tract. By contrast, GVHD can be exploited in the treatment of certain hematological malignancies. For example, the host's immune system is tolerant toward the malignant plasma cells in multiple myeloma. Allogenic bone marrow transplantation may cause an immune reaction against the cancerous cells.

CASE 13

A 13-year-old girl is brought to the physician's office by her mother. Her mother says the girl had a sudden onset of fever a few days ago, with a temperature of 39.4°C (103°F), lightheadedness, nausea, vomiting, and watery diarrhea. Physical examination reveals a desquamating rash of her palms and soles. She has no sick contacts, and there is no evidence of ingestion of unsafe food. Upon questioning, the patient says she began menstruating a little more than a month ago.

What is the most likely diagnosis?

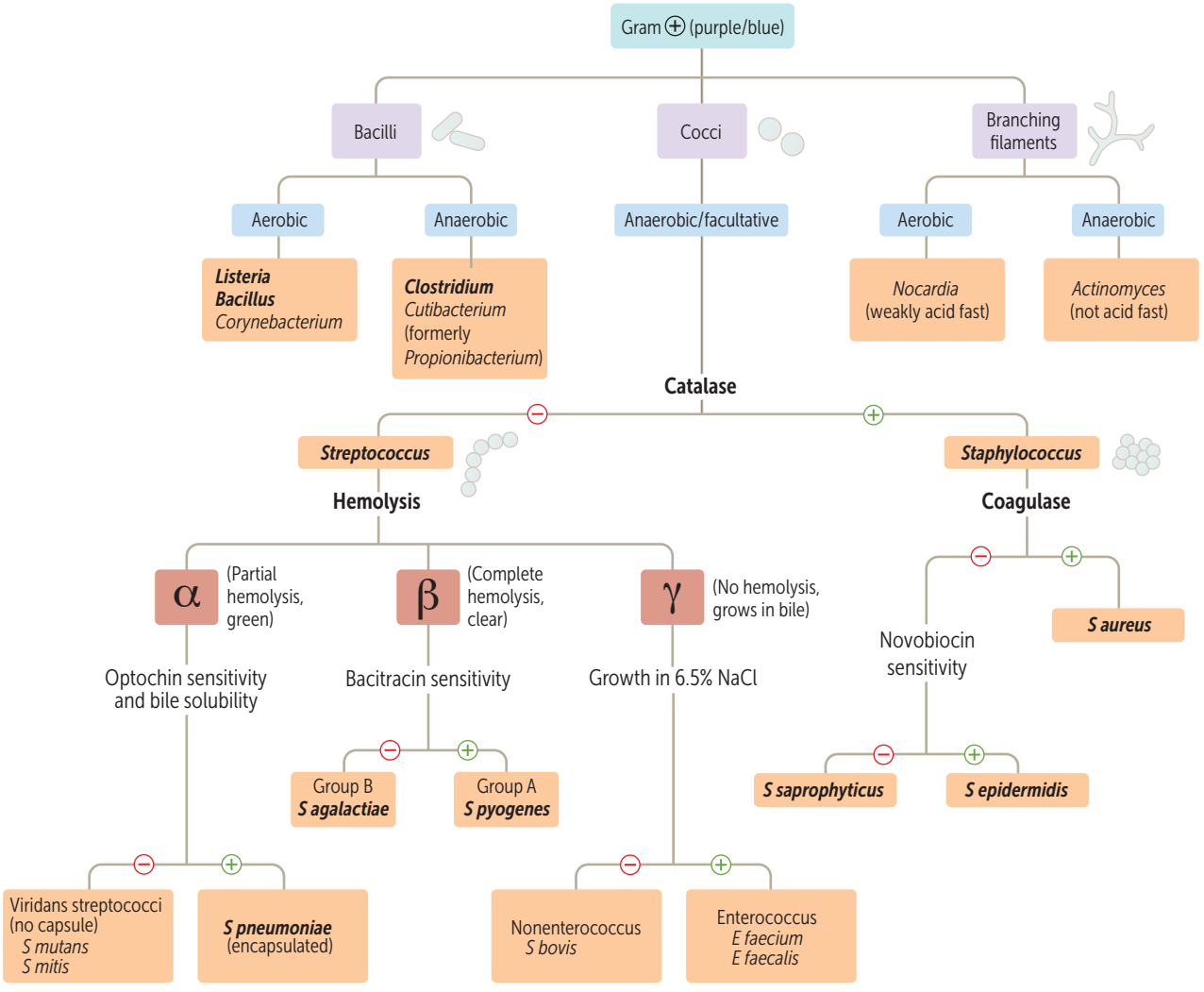
Toxic shock syndrome (TSS).

What microorganism is the most likely cause of this condition?

Staphylococcus aureus is the most common cause, although β-hemolytic group A streptococci can cause a similar presentation. Classically the nidus for infection is from a forgotten tampon in the vagina, but the most common presentation to clinics is from nasal packing after a nosebleed that has been kept in for too long.

What are the distinguishing characteristics of the responsible microorganism?

S aureus is a gram-positive coccus. It is catalase-positive and coagulase-positive and may produce an enterotoxin. Figure 2-9 provides a useful laboratory algorithm for differentiating the gram-positive bacteria.



Important **tests** are in **bold.** Important ***pathogens*** are in ***bold italics.***
Note: Enterococcus is either α- or γ-hemolytic.

FIGURE 2-9. Lab algorithm for differentiating gram-positive bacteria. (Reproduced with permission from USMLE-Rx.com.)

What is the pathophysiology of this condition?

The exotoxin (TSST-1) acts as a "superantigen" and is responsible for this presentation. Superantigens activate large numbers of T cells at once by simultaneously binding directly to T-cell receptors and major histocompatibility complex (MHC) molecules, regardless of the peptide presented by MHC. Activated T cells then release large amounts of inflammatory cytokines, which are responsible for the manifestations of TSS.

What other conditions should be considered in the differential diagnosis?

The differential for desquamating disease is limited. Toxic epidermal necrolysis should be suspected; this is an exacerbation of Stevens-Johnson syndrome that may be a serious adverse reaction to certain medication. Additionally, scalded skin syndrome leads to desquamation of the skin. In this condition, an infection with *S aureus* producing exotoxin A and B causes detachment of the epidermal layer from the dermis. Lastly, pemphigus vulgaris features autoantibodies against desmosomes, leading to flaccid blister formation that may look like desquamation in severe cases. Kawasaki syndrome may also be on the differential but usually will have other characteristics such as strawberry tongue and/or fever for 5 days.

What is the treatment for this condition?

Removal of the infected wound dressing or tampon is the first step, followed by supportive care. Antibiotics that cover both *Staphylococcus* and *Streptococcus* will kill these bacteria and stop the production of additional exotoxin. However, it is the toxin, not the bacteria, that is responsible for the symptoms. In severe cases, intravenous immunoglobulin is also given.

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3
Microbiology

CASE 1

A 19-year-old university student presents with eye pain to the campus nurse. He has been pulling all-nighters for his upcoming exams. While trying to study, he often finds himself falling asleep with his contact lenses still in; he rinses them with tap water occasionally. As finals week ends, he is scratching his eyes often because they feel dry and painful, as if there are foreign bodies in them. He also notices that his eyes are red and that he tears up frequently. These symptoms have occurred gradually during the week. He has no associated upper respiratory symptoms, and no recent sexual activity.

What is the most likely diagnosis?

Keratitis, caused by the free-living ameba *Acanthamoeba,* is the most likely diagnosis. Conditions to consider in the differential diagnosis include herpes simplex virus (HSV), herpes zoster virus, other viruses, and bacterial or fungal infection. However, HSV keratitis would present acutely and progress rapidly to photophobia, decreased visual acuity, and dendritic ulcer formation, which are not seen in this patient. Likewise, a bacterial or other viral keratitis would tend to a more-acute presentation, while a fungal keratitis might present similarly but is comparatively rare. Bacterial orbital cellulitis would be an ophthalmologic emergency.

What are the risk factors for developing this condition?

The number one risk factor for *Acanthamoeba* infection is **extended wearing of contact lenses**. Inadequate disinfection of the lenses with tap water or homemade saline solution and wearing lenses while swimming or showering can also predispose contact lens wearers to this infection. *Acanthamoeba* organisms are common in soil, air, and water and are resistant to chlorine.

What are other symptoms and complications of this condition?

Unlike bacterial keratitis, keratitis from *Acanthamoeba* takes days or weeks to cause symptoms. The initial symptoms are usually redness and a feeling of a foreign body in the eye. Blurring of vision may also be present. Over time, this progresses to pain, lid edema, and conjunctival infection. If untreated, increased intraocular pressure, cataracts, and even loss of vision can develop.

How is this condition diagnosed?

The diagnosis is made by **slit-lamp examination** of the eye, which shows thickened epithelium and rough corneal nerves. A characteristic ring on the cornea may also appear approximately 6 weeks after initial infection. Corneal scraping or biopsy reveals irregular polygonal *Acanthamoeba* cysts.

What is the treatment for this condition?

Initial treatment consists of topical antimicrobials such as miconazole and neomycin for several months. If the infection has been left untreated (ie, at the corneal ring stage), surgery, such as corneal debridement and possibly corneal transplantation, is usually required.

What populations are at risk for systemic infection with this organism?

Patients with significant immunosuppression, such as those with lymphoproliferative disorders, patients on chronic steroids, patients receiving chemotherapy, and patients with AIDS may develop systemic infections with *Acanthamoeba* and other free-living amebae. The central nervous system is frequently involved (termed **granulomatous amebic encephalitis**). These patients may present with changes in mental status, headache, and stiff neck. They can also develop cranial nerve palsies, ataxia, and hemiparesis. Treatment is urgent in such cases, and the mortality rates are high.

CASE 2

A 63-year-old man with no past medical history presents to the physician with jaw pain that began 1 month ago. On examination, the right side of the jaw is asymmetric to the left side of the jaw. Incision and drainage is done under local anesthesia, and a yellow discharge is noticed and collected. A fluid sample of the discharge is collected for Gram stain and culture. The test reveals a gram-positive rod that forms long, branching filaments.

What are the possible bacterial microorganisms found in this sample?

Actinomyces and *Nocardia* both fit this description. Although they somewhat resemble fungi on Gram stain, they are both bacteria, not fungi. They appear as characteristic gram-positive rods with long, branching filaments.

How are these two microorganisms differentiated?

Actinomyces israelii is a non-acid-fast filamentous, anaerobic organism (see Figure 3-1) and has characteristic "sulfur granules." *Nocardia*, on the other hand, is modified-acid-fast positive and an obligately aerobic organism (see Figure 3-2).

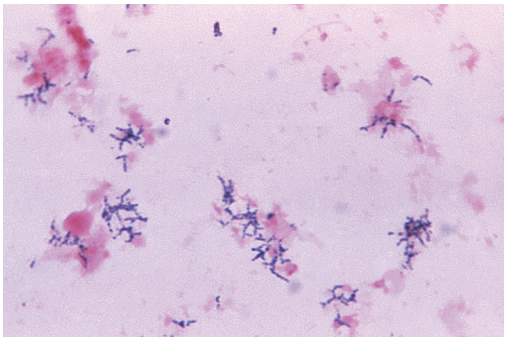


FIGURE 3-1. *Actinomyces* on Gram stain. (Reproduced courtesy of Centers for Disease Control and Prevention/ Dr. Lucille Georg.)

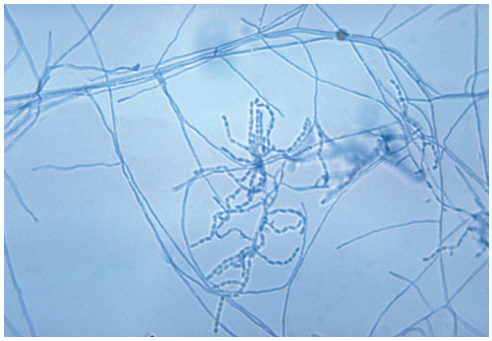


FIGURE 3-2. Gram-positive aerobic *Nocardia* asteroides slide culture revealing chains of bacteria among aerial mycelia. (Reproduced courtesy of Centers for Disease Prevention and Control/Dr. Lucille George.)

What are the other obligate aerobic and anaerobic organisms?

The most common aerobic organisms are ***N****ocardia*, ***P****seudomonas*, ***M****ycobacteria*, and ***B****acillus* species (mnemonic: "**N**agging **P**ests **M**ust **B**reathe").

Some common anaerobic organisms are ***C****lostridium*, ***B****acteroides*, and ***A****ctinomyces* species (mnemonic: "**C**an't **B**reathe **A**ir").

After paging the intern, the pathologist learns the sample was drained from an oral abscess. Now which of these two microorganisms is more likely?

Actinomyces is more likely because it is part of the **normal oral microbiota** and frequently forms abscesses in the mouth or gastrointestinal tract after trauma. *Actinomyces* often forms abscesses that drain though sinus tracts. *Nocardia* is an opportunistic infection seen primarily in compromised hosts, and most often results in pulmonary symptoms due to **lung abscesses** or, rarely, central nervous system symptoms due to brain abscesses.

If this microorganism were found in a sputum sample that stained weakly acid fast, what could be inferred about the patient's immune status?

Nocardia is most often found in **immunocompromised** patients. The diagnosis may be delayed if this organism is not considered; it may grow too slowly to be detected on routine sputum culture. It may be found on fungal or Acid-Fast Bacilli (AFB) cultures, but the medium of choice for detection of *Nocardia* is Buffered Charcoal Yeast Extract (BCYE) agar.

What is the treatment for each of these infections?

Nocardia is most commonly treated with trimethoprim-sulfamethoxazole, though speciation and antimicrobial susceptibility testing is recommended. *Actinomyces* is treated with penicillin G. A mnemonic is **SNAP** (**S**ulfonamides for **N**ocardia, **A**ctinomyces for **P**enicillin).

CASE 3

A 25-year-old man is brought to the ED by ambulance after a motor vehicle collision. He is lucid but has severe bleeding from his leg. His wife is with him and reports that the patient is generally healthy, although he had several bouts of "lung and ear infections" as a child. He suffers from periodic bouts of diarrhea, so he has been trying a gluten-free diet without relief. He was referred to a gastroenterologist last week, but he has not seen her yet. He starts to become pale and less responsive even with the application of a tourniquet, so the decision is made to transfuse him with a unit of whole blood. He is given 1 unit of type-matched RBCs after he is typed and crossed for blood products. Soon afterward he develops a red, itchy rash over most of his body (see Figure 3-3) and begins to develop difficulty breathing and hypotension. On chest radiograph, his lungs are clear, and the bleeding from his leg has stopped. On exam, his abdomen is non-acute, and he has reassuring heart tones.

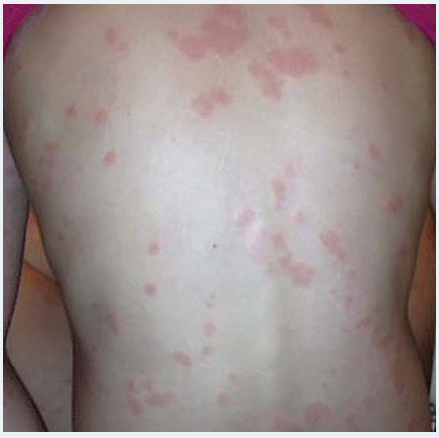


FIGURE 3-3. (Reproduced, with permission, from Sussman G, et al. *Allergy, Asthma, and Clinical Immunology.* 2015;11(1):7.)

What is the likely cause of this patient's repeated infections and reaction to the blood transfusion?

This patient is having an anaphylactic reaction. IgA is a common component in blood products. This patient likely has hereditary IgA deficiency and therefore has developed IgG antibodies against IgA. He is particularly susceptible to gastrointestinal infections, especially giardiasis, for which secretory IgA plays an important protective role. IgA deficiency can occur as an isolated syndrome or may involve concurrent IgG deficiency, which increases the risk of sinopulmonary infections.

What is the next step in management of this condition?

Because of the patient's severe anaphylactic reaction to the transfused blood products, it is imperative to discontinue transfusion and administer an epinephrine injection. Epinephrine counteracts the bronchospasm and vasodilation that is causing his respiratory difficulty and decreasing blood pressure.

What is the cause of the patient's milk allergy?

In the absence of intestinal IgA, large proteins are more likely to enter the bloodstream whole. An IgG antibody reaction to these proteins can then cause an allergic reaction. (This is different from lactose intolerance, which is not a true allergy and involves a deficiency of lactase.) For the same reasons, patients with IgA deficiency are at increased risk of developing antibodies against wheat proteins and thus celiac disease. IgA is found on the mucosa of the gastrointestinal tract.

What are the stages in B-cell development that lead up to IgA secretion?

Pluripotent stem cells first differentiate into lymphoid stem cells, then to pro-B cells, then to pre-B cells. Pre-B cells contain the IgM (mu) heavy chains intracellularly but no surface IgM. The next step is formation of immature or naive B cells that express surface IgM. After stimulation by antigen, the immature cells can mature into IgM-secreting cells or, with CD4+ T-cell stimulation (CD40 ligand-CD40 receptor activation), can class switch to express IgG, IgA, or IgE antibodies. After class switching, the cells can undergo affinity maturation to select for antibodies with higher binding affinities for the antigen and subsequently form plasma cells that secrete the specialized antibodies. IgA exists in pairs, IgG and IgE exist as single units, and IgM can exist in pentamers.

CASE 4

A 43-year-old local craftsman who makes garments from the hides of goats visits his physician because over the past few days he has developed disturbing black lesions on his hands and arms (see Figure 3-4). This lesion is not painful, but he is alarmed by its appearance. He is afebrile and his physical examination is unremarkable.

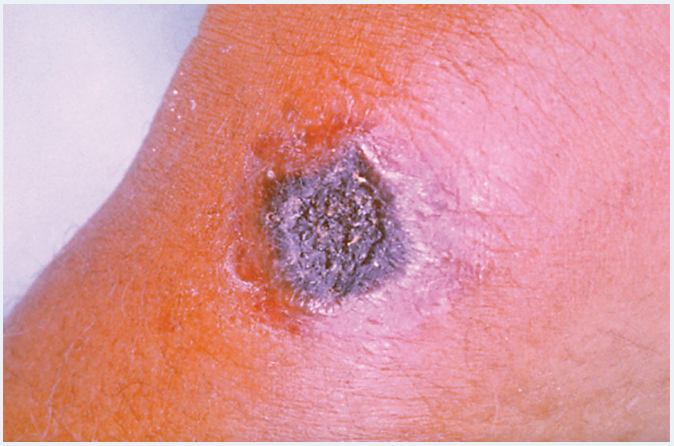


FIGURE 3-4. (Reproduced with permission from USMLE-Rx.com.)

What is the most likely diagnosis?

Cutaneous anthrax, caused by *Bacillus anthracis*. The skin lesions are painless and dark or charred ulcerations known as black eschar (as shown in Figure 3-4). Cutaneous anthrax lesions frequently exhibit edema out of proportion to the size of the lesion, which can make lesions on the face or neck particularly dangerous. Cutaneous anthrax is classically transmitted by contact with the hide of a goat or other animal at the site of a minor open wound.

How will the causative microorganism appear on Gram staining?

B anthracis is a **gram-positive spore-forming rod**. The spores are resistant to many chemical disinfectants, heat, ultraviolet light, and drying and are therefore a feared agent of biological warfare. Unlike other bacteria, *B anthracis* has a poly-peptide capsule containing D-glutamate, which can sometimes be seen on Gram or India ink staining from tissue (but not from culture).

What is the other common spore-forming microorganism?

Clostridium species are the other gram-positive spore-forming bacteria. *Bacillus* and *Clostridium* species can be differentiated by their ability to neutralize oxygen free radicals. *Bacillus* species (like the other aerobic bacteria) have catalase and superoxide dismutase, enzymes that can neutralize oxygen free radicals and therefore survive in aerobic environments. *Clostridium* species do not have these enzymes and are therefore obligate anaerobic microorganisms.

What other medically important species are included in this genera?

While there are numerous *Bacillus* (and related genera) species, the most important medically is *Bacillus cereus*. This organism is far less virulent compared to *Bacillus anthracis*. *B cereus* causes food poisoning when the spores survive the cooking process and enter the gastrointestinal system. The most common associated food is warm rice. Nausea and vomiting is seen within the first 1-5 hours and caused by a preformed toxin. Diarrhea is seen 8 to 20 hours later. *B cereus* can also rarely cause systemic infections.

What is the other primary manifestation of this infection?

B anthracis also causes pulmonary anthrax, or wool-sorters' disease. In this condition, inhaled anthrax spores reach the alveoli, where they are taken up by macrophages and carried to mediastinal lymph nodes. This can result in mediastinal hemorrhage and a bloody pleural effusion. X-ray of the chest reveals a **widened mediastinum**. The organism makes its way quickly to the bloodstream to cause a frequently fatal systemic illness.

How is this infection treated?

The treatment of anthrax generally involves a fluoroquinolone, such as ciprofloxacin.

CASE 5

A 49-year-old woman from Indonesia presents with diffuse, crampy abdominal pain that has persisted for the previous 4 days. She has had no bowel movements since the pain started and has noticed a weight loss of about 4.5 kg (10 lb) over the past month. She had a screening colonoscopy 3 months before presentation, which was negative. CT of the abdomen reveals an inflamed gallbladder and an irregular mass in the second portion of the duodenum. Stool sample reveals rough-surfaced eggs. Complete blood count and liver function test results are as follows:

White blood cell (WBC) count: 14,000/mm^3
Platelet count: 250,000/mm^3
Albumin: 3.2 g/dL
Aspartate transaminase (AST): 29 IU/L
Alanine transaminase (ALT): 27 IU/L
Alkaline phosphatase: 210 IU/L
Bilirubin, total: 4.0 mg/dL
Bilirubin, direct: 3.7 mg/dL

What is the most likely diagnosis?

Ascariasis, caused by *Ascaris lumbricoides,* a nematode (roundworm) found in the southern United States and tropical climates. Ascariasis is the most common helminthic infection worldwide. Eosinophilia is a classic finding in helminth infections and is due to the increased need for eosinophilic release of major basic protein, a key antiparasitic factor.

What tests can be used to confirm the diagnosis?

Analysis of a stool sample shows eggs with a knobby, rough surface (see Figure 3-5).

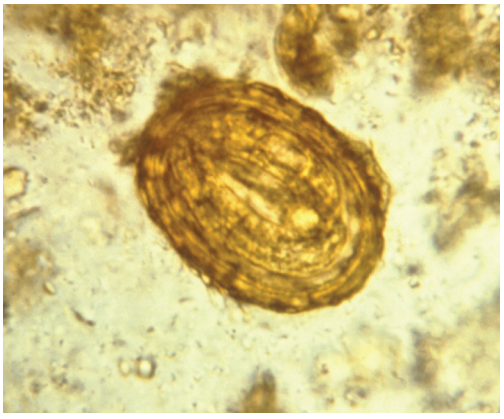


FIGURE 3-5. Ascariasis egg on stool ova and parasite test. (Reproduced courtesy of the Centers for Disease Control and Prevention.)

What are the treatments for this condition?

As with many nematode infections, mebendazole or albendazole is the drug of choice. The benzimidazoles work by disrupting helminthic microtubule synthesis, which weakens cell structure.

What are some other Nematodes (roundworms)?

Enterobius vermicularis (pinworm) is a roundworm that is transmitted by fecal-oral route. This roundworm infects the intestines and causes anal pruritus. Classically, this organism is seen in pediatric patients with itching of the bottom. This is diagnosed by visualizing the ova with a "tape test." Mebendazole is often used to treat the disease and should be given to the whole family.

Trichinella spiralis is another nematode that is transmitted by fecal-oral route but can also be transmitted by eating undercooked pork. This nematode can infect the intestine, and then the larval forms infect the body through the bloodstream. From the bloodstream, the worm travels to the muscle, where it causes inflammation of the muscle. The disease is called "trichinosis" and is characterized by fever, nausea, vomiting, and myalgia. Treatment is with mebendazole or albendazole plus prednisone.

CASE 6

A 54-year-old man with a history of tobacco use and chronic obstructive pulmonary disease (COPD) presents to the ED because of severe shortness of breath. The patient has been steroid-dependent for his COPD for approximately a year but developed hemoptysis 1 week ago. He was started on empiric antibiotics and underwent bronchoalveolar lavage, which revealed the presence of fungal elements with 45-degree branching septate hyphae (see Figure 3-6).

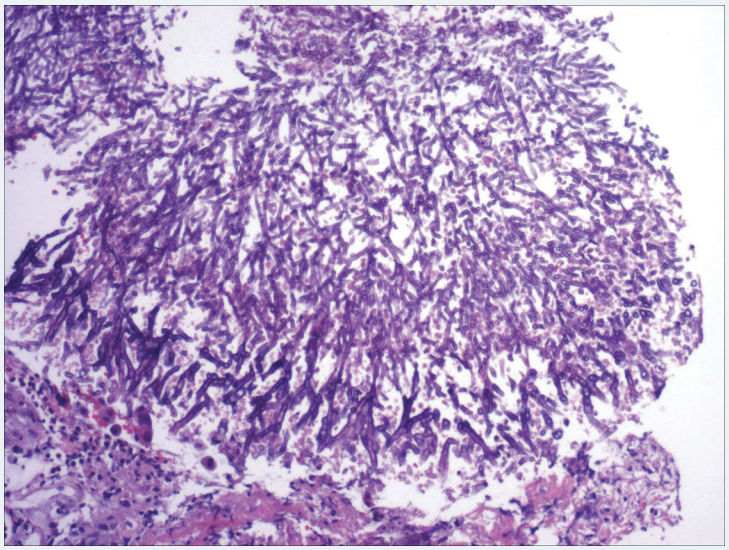


FIGURE 3-6. (Reproduced with permission from USMLE-Rx.com.)

What is the most likely diagnosis?

The hemoptysis and pulmonary symptoms, along with the acute-angle branching septate hyphae found on lavage (and visible in Figure 3-6), indicate *Aspergillus* infection. *Aspergillus* is an opportunistic infection, secondary to the patient's chronic immunosuppression from corticosteroid use. Mucormycosis most commonly presents with sinusitis, black nasal discharge, and craniofacial invasion, but may also cause pulmonary disease, but lavage findings would indicate 90-degree branching nonseptate hyphae.

What patient population is at risk for this condition?

This infection is most common in patients with neutropenia, and those with type 1 diabetes mellitus ketoacidosis and other forms of acidosis. Neutropenia may be secondary to hematologic malignancy, chemotherapy, immunosuppressive therapy, solid organ transplant, or HIV infection.

What is x-ray of the chest likely to show?

Aspergillus can appear as a "fungus ball" or a circular mobile lung mass within preexisting cavitary lesions in the lungs. This form of *Aspergillus* infection is called an **aspergilloma** and tends to be seen in patients with pre-existing pulmonary disease. In neutropenic patients, an x-ray of the chest is likely to show dense infiltrates, often with wedge-shape infarcts.

The patient is treated with voriconazole. What is the drug's mechanism of action?

Voriconazole is one of the azole antifungal agents. Azoles primarily work by inhibiting the lanosterol 14-alpha-demethylase enzyme. This enzyme converts lanosterol to ergosterol, which is an important component in the synthesis of fungi's cellular membrane. The lack of ergosterol increases the permeability of the cell membrane, causing lysis of fungi.

If, instead of COPD, this patient had a history of severe asthma, to what type of fungal infection would he be most susceptible?

Allergic bronchopulmonary aspergillosis is an IgE-mediated hypersensitivity reaction to *Aspergillus* spores. The hyperactive inflammatory response in the airways of asthmatics predisposes them to bronchospasm and pneumonitis in response to an otherwise benign inoculation of *Aspergillus* spores.

CASE 7

A 41-year-old man presents to the ED complaining of the sudden onset of weakness, nausea, vomiting, and blurred vision. On physical examination, he has fixed, dilated pupils and a decreased gag reflex. When asked, he admits that he often eats food that he has canned himself. The patient is admitted to the hospital for further monitoring.

What is the most likely diagnosis?

Botulism, resulting from ingestion of the botulinum toxin made by the gram-positive, spore-forming bacteria *Clostridium botulinum*.

How does the toxin work?

Acetylcholine is normally released by motor neurons into the neuromuscular junction, where it binds to muscarinic receptors on the motor endplate of the muscle fiber. This binding depolarizes the membrane and subsequently contracts the muscle. Botulinum toxin acts on the **presynaptic neuron** by cleaving the SNARE proteins within the neuron. As a result, acetylcholine cannot be released from inside the neuron and into the **neuromuscular junction**. The result is a flaccid paralysis, or inability to contract. The binding is irreversible, and it takes approximately 6 months for new synapses to form.

What is the typical course in adult patients with this condition?

Ingestion of the botulinum toxin in food usually causes symptoms within 12–36 hours. The first symptoms are gastrointestinal distress (eg, cramps and nausea), due to enteric nervous system dysfunction, followed by neurologic symptoms. The first nerves affected are the cranial nerves, causing blurred vision, decreased eye movements, and a decreased gag reflex. The paralysis is symmetric and **descending**. Autonomic nerves can also be affected, resulting in ileus, urinary retention, and orthostatic hypotension. Respiratory muscles can also be affected, necessitating ventilator support.

What is the differential diagnosis for this presentation?

The major differential includes Guillain-Barré syndrome, myasthenia gravis, and Lambert-Eaton syndrome. Unlike botulism, the paralysis seen in **Guillain-Barré syndrome** is due to a postinfectious demyelination of alpha motor neurons and is ascending. The most common infection leading to Guillain-Barré syndrome is *Campylobacter jejuni*. **Myasthenia gravis** is an autoimmune condition caused by antibodies created against the muscarinic acetylcholine receptor. Patients with this condition have muscle weakness after prolonged muscle use, classically at the end of the day, and typically have more gradual onset of illness. **Lambert-Eaton syndrome** is a paraneoplastic anti–calcium channel antibody syndrome that causes muscle weakness that improves with prolonged muscle use.

How can this toxicity be acquired?

In adults, it is acquired most commonly from ingestion of **preformed toxin** in contaminated canned foods (usually home canned). In infants, ingestion of **bacterial spores** found in honey can result in toxicity referred to as "floppy baby syndrome" due to intestinal overgrowth with *C botulism*.

What other organism in this genus causes paralysis?

Clostridia tetani is a gram-positive organism that creates an exotoxin that can cause paralysis. However, this paralysis is opposite to *Clostridia botulinum*. The paralysis is spastic and classically presents with trismus and risus sardonicus. The toxin cleaves the SNARE protein for neurotransmitter just like botulism toxin does. This toxin blocks GABA and glycine instead of acetylcholine. The TdaP vaccine is given to prevent this disease. Treatment includes diazepam, which is a muscle relaxer, and with antitoxin.

CASE 8

A 57-year-old patient with diabetes presents to her physician with a white, flaky, adherent substance on the skin under her breasts. Her last Hgb A1c was 10.2, which was done 3 months ago. Patient was prescribed home insulin. Upon questioning, the patient admits to not being compliant with her daily injections of insulin. She has had worsening symptoms of urinary frequency and thirst. Her complaints with the skin began 2 weeks ago.

What is the most likely diagnosis?

The fungus *Candida albicans* can result in systemic or superficial fungal infection (candidiasis). Skinfold infection, vaginitis (yeast infection), and oral thrush are common manifestations of local candidiasis and present as a white, flaky, cheesy exudate on the affected surface.

Where is the microorganism that causes this condition normally found?

C albicans is part of the normal microbiota of mucous membranes of the gastrointestinal tract, respiratory tract, and women's genital tract. Overgrowth, due to alteration of normal microbiota in women taking **antibiotic** therapy or patients who are **immunocompromised**, causes candidiasis.

What laboratory tests can help confirm the diagnosis?

A potassium hydroxide preparation (**KOH mount**) is used for skin or tissue scrapings. **Pseudohyphae** and **budding yeast** (see Figure 3-7) are observed in the tissues. Pseudohyphae are seen in culture at 20°C (68°F). Germ tube formation in the laboratory distinguishes *C albicans* and other *Candida* species. For (rare) systemic disease (eg, invasive candidiasis found primarily in neutropenic patients), blood cultures are positive for the fungus.

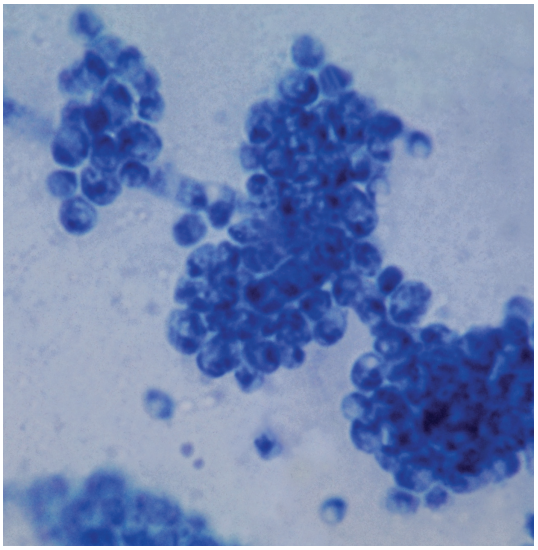


FIGURE 3-7. *Candida albicans.* (Reproduced courtesy of the Centers for Disease Control and Prevention/Dr. Gordon Roberstad.)

What populations other than immunocompromised patients are at risk for serious forms of this condition?

Intravenous drug users are at higher risk for candidal endocarditis. The fungi enter the skin by the needle and affect the heart. Hospitalized patients with medical devices (intravascular and urinary catheters) who receive broad-spectrum antibiotic therapy are at risk for bloodstream and urinary tract *Candida* infections. Patients that have had recent antibiotic treatment may have vaginal discharge that is due to *candida*. This is because the normal microbiota of the vaginal tract is disrupted due to the antibiotics.

What are the treatments for this condition?

Oral fluconazole or nystatin is used for superficial infections. Fluconazole, an echinocandin, or amphotericin B can be used for systemic infections.

CASE 9

A 49-year-old woman who recently immigrated to the United States from Nicaragua presents to the clinic with difficulty swallowing, constipation, and abdominal pain. She says her last bowel movement was more than a week ago. Physical examination reveals tachycardia and a distended abdomen. An electrocardiogram (ECG) shows Mobitz type I heart block.

What is the most likely diagnosis?

Chagas disease, or American trypanosomiasis, caused by the protozoan *Trypanosoma cruzi*.

What is the vector of the responsible protozoan?

The vector is the reduviid bug, also known as the "kissing bug" because the bite is painless (see Figure 3-8). It can also be acquired orally via food or juice contaminated with the vector.

What is the classic sign associated with the acute form of this condition?

The Romaña sign is painless, unilateral periorbital edema and conjunctivitis that results from acute Chagas disease. This sign is typical but not sensitive for acute *T cruzi* infection.

Where in the world is this condition commonly found?

Chagas disease is commonly found in the southern United States, Mexico, and Central and South America (ie, only in the Western hemisphere). Rarely, it is transmitted in the southern United States.

FIGURE 3-8. ***Triatoma infestans*** **(Reduviidae family, the "kissing bug," "assassin bug," or "cone-nose bug"), a vector for Chagas disease.** (Reproduced courtesy of the Centers for Disease Control and Prevention/ Donated by the World Health Organization, Geneva, Switzerland.)

What is the pathophysiology of this condition?

This woman is experiencing chronic Chagas disease, which is most often characterized by heart block, ventricular tachycardia, and dilated cardiomyopathy. Dilatation of the esophagus and colon (megaesophagus and megacolon) can cause difficulty swallowing and constipation. The acute phase of the disease can be characterized by a swollen red area called a chagoma at the parasite's site of entry into the host, rarely accompanied by fever and acute systemic symptoms, myocarditis, or meningoencephalitis. In endemic areas, the acute phase is seen more frequently in children.

What is the treatment for this condition?

Nifurtimox and benznidazole are used to treat acute cases. In chronic illness, the data suggest that treatment of patients with cardiac disease may slow progression prior to development of congestive heart failure. Antiparasitic therapy does not alter established pathology in the cardiovascular or GI systems. For chronic heart disease, supportive measures for congestive heart failure, antiarrhythmics to prevent recurrent ventricular tachycardia, and pacemaker implantation for heart block are used. For gastrointestinal disease, dilation of the esophageal sphincter, changes in diet, the use of laxatives and/or enemas, and in some cases eventual resection of the megacolon are used.

What other disease is caused by the protozoan genus that causes this condition?

The protozoa *Trypanosoma gambiense* and *Trypanosoma rhodesiense* cause African sleeping sickness. This illness is characterized by lymphadenopathy, recurrent fevers due to antigenic variation, somnolence, and eventually coma. It is transmitted by the tsetse fly, whose bite is painful.

CASE 10

A 24-year-old American man is traveling in rural India during the monsoon season. Over the course of a few hours, he develops severe watery diarrhea. In the next 30 hours, he has approximately one episode per hour of liquid stools that appear clear with small white flecks of mucus. He also has occasional episodes of vomiting. He quickly becomes lethargic and generally ill with crampy abdominal pain but is afebrile. He rehydrates himself aggressively during the illness, and the symptoms resolve within approximately 48 hours.

What is the most likely diagnosis?

This patient has cholera, a potentially fatal dehydrating illness caused by *Vibrio cholerae*. This microorganism is a gram-negative, curved, motile, polar flagellated rod (see Figure 3-9). Symptomatic cholera usually manifests in epidemics, and it is endemic to developing regions in Africa, Asia, South and Latin America, and recently the Middle East.

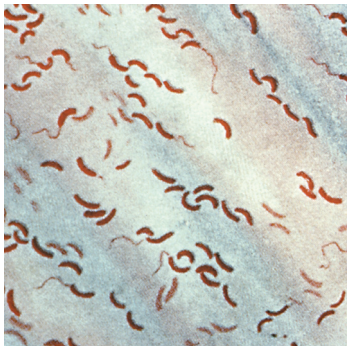


FIGURE 3-9. Gram-stained specimen of *Vibrio cholerae*, revealing the presence of single polar flagellum. (Reproduced courtesy of Centers for Disease Control and Prevention.)

What is the primary differential diagnosis?

Watery diarrhea induced during travel within a foreign country makes the noninvasive enterotoxigenic *Escherichia coli* (ETEC) infection the primary differential diagnosis ("traveler's diarrhea"). However, ETEC diarrhea generally is not as voluminous as the diarrhea induced by cholera and is not associated with white mucus flecks.

How does the microorganism involved in this condition exert its effect on the gastrointestinal tract?

V cholerae is ingested through fecally contaminated water. It secretes an exotoxin (cholera toxin) that binds to the surface of intestinal epithelium. This toxin ADP-ribosylates adenylyl cyclase, thus increasing levels of cyclic adenosine monophosphate (cAMP) within the intestinal mucosa (see Figure 3-10). *E coli* produces a toxin that has a similar effect on the enterocyte. This causes increased chloride secretion and decreased sodium absorption, leading to a massive secretory loss of fluids and electrolytes.

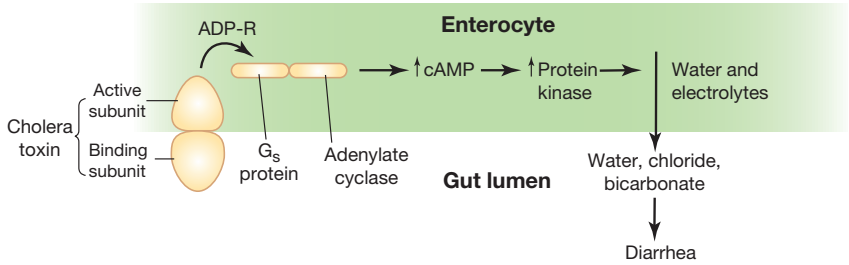


FIGURE 3-10. cAMP induction by exotoxins of *Vibrio cholerae* and *Escherichia coli*. (Reproduced with permission from USMLE-Rx.com.)

What are the clinical manifestations of this condition?

The hallmark of cholera is **rice-water stools**, so described because the small white flecks of mucus resemble grains of rice in the voluminous, watery fluid. The onset of this diarrhea typically occurs 1–3 days after infection. Vomiting and abdominal cramping is common, but fever is rare because *V cholerae* itself is noninvasive and thus remains in the gastrointestinal tract. Many infections are asymptomatic, but severe cholera can lead to extreme dehydration that can cause death within hours due to the excretion of electrolytes leading to renal failure, arrhythmias from hypokalemia, metabolic acidosis from bicarbonate loss, and hypovolemic shock.

What is the treatment for this condition?

Oral rehydration solution (ORS), which has reduced mortality rates from 50% to < 1%. A typical preparation of ORS contains glucose, potassium chloride, sodium chloride, and sodium bicarbonate. Glucose facilitates sodium absorption from the gut, which allows for the concurrent absorption of water. Antibiotics are of limited use in stopping the diarrhea, although early use of doxycycline can reduce the volume of diarrhea and decrease the duration of bacteria excretion by 1 day.

CASE 11

A 3-year-old boy is brought to his pediatrician with a fever, tachypnea, and a cough productive of rusty sputum. He has a history of recurrent lung and skin infections. He has had several fungal infections of his skin, as well as a staphylococcal abscess that formed where he scraped his arm. An x-ray of the chest shows a normal thymic shadow but some hilar lymphadenopathy. Further questioning of the parents reveals a maternal male cousin who died at 5 years of age from severe pneumonia and a maternal uncle who has severe pulmonary disease and two surgeries for intracranial fungal infections.

What is the most likely diagnosis?

The most likely diagnosis is chronic granulomatous disease (CGD), an X-linked inherited immunodeficiency syndrome. This patient is predisposed to bacterial and fungal infections. The normal thymic shadow suggests normal T-cell maturation, which effectively rules out a diagnosis of severe combined immunodeficiency or DiGeorge syndrome. The strong family history of male involvement on the maternal side indicates an X-linked hereditary condition and suggests CGD as the likely diagnosis in this patient.

Infections with which organisms could be particularly severe and problematic in this patient?

Patients with CGD are at risk for serious infections with catalase-positive bacteria, including *Staphylococcus aureus*, *Aspergillus species*, and *Burkholderia cepacia*.

Why are patients with this condition especially susceptible to catalase-positive organisms?

Reduced nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, which is required for production of reactive oxygen species, is deficient in patients with CGD. The radicals are used by neutrophils during the oxidative burst to kill engulfed organisms. In the absence of the killing ability of the deficient neutrophils, the primary method of host immunity is containment of the offending organism, leading to numerous granulomas.

What laboratory test can confirm this diagnosis?

The nitroblue tetrazolium test can detect the presence of a respiratory burst in neutrophils. In normal individuals the test is positive, but in patients with CGD the test is negative because the superoxide free radical is not produced.

A more modern test for CGD is the dihydrorhodamine 123 test, where dihydrorodamine (DHR) is ingested by the neutrophil. DHR is then oxidized by the cell and produces a product that can be seen when run through the flow cytometry.

What medical treatments are available for this condition?

Infections must be treated aggressively with appropriate antimicrobials. Trimethoprim-sulfamethoxazole can be used as long-term prophylaxis. In addition, interferon-α, an immunomodulator, is used in patients with CGD.

What therapy or procedure provides a definitive cure for this patient?

Bone marrow transplantation provides a source of functional neutrophils with the ability to create oxygen free radicals to effectively kill organisms engulfed by phagocytosis.

What are some other immunodeficiencies?

Severe combined immunodeficiency (SCID) is a type of X-linked disease if there is a defective IL-2R γ chain. SCID can be autosomal recessive where there is an adenosine deaminase deficiency. This condition presents with opportune infections, fungal infections, and protozoal infections. Thrush and chronic diarrhea can also be seen. A thymic shadow is absent, unlike in the patient in this case. Treatment is a bone marrow transplant.

Wiskott-Aldrich syndrome is an X-linked disease; there is a mutation in the WAS gene where T cells are unable to reorganize actin cytoskeleton.

CASE 12

An 85-year-old man is hospitalized for community-acquired pneumonia. He is treated with moxifloxacin and over the next week he feels that he is slowly recovering. On hospital day 10, he develops a low-grade fever, watery diarrhea, and lower abdominal pain.

What is the most likely diagnosis?

Antibiotic-associated colitis or pseudomembranous colitis caused by *Clostridium difficile* superinfection (or overgrowth). *C difficile* is a gram-positive, spore-forming anaerobe. It should be noted that most antibiotic-associated diarrhea (without fever) is osmotic, resulting from decreased carbohydrate digestion secondary to a loss of gut microbiota. However, *C difficile* infection will present with fever and leukocytosis, and can be a very serious complication of prolonged antibiotic use.

What are the manifestations of this condition?

Approximately 20% of hospitalized patients are asymptomatically colonized with *Clostridium difficile*. Patients with disease usually present with a low-grade fever, watery diarrhea, lower abdominal pain, leukocytosis, and a recent history (within 10 weeks) of antibiotic use. In severe cases, peritonitis (inflammation of the peritoneum) can result from microperforation of the diseased colon. These patients present with signs of peritonitis such as rebound tenderness and involuntary guarding. On colonoscopy, they likely have **pseudomembranes** on the colon, which are raised yellow-white plaques created by the *C difficile* toxins (see Figure 3-11). Risks include ileus and toxic megacolon, which can grossly perforate and cause death. Emergent colectomy is indicated and can be a lifesaving procedure if performed in a timely manner.

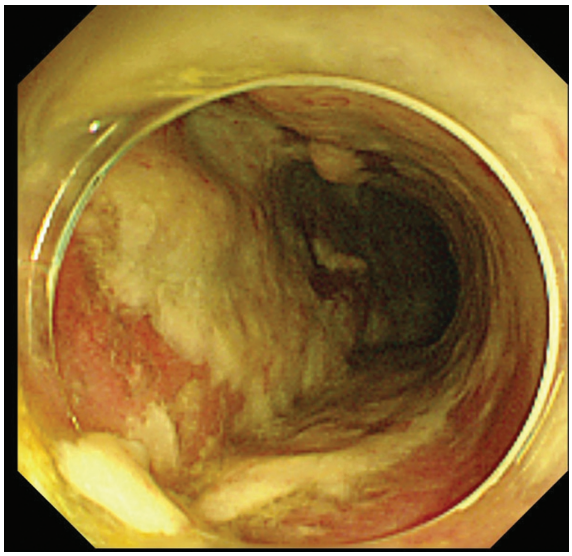


FIGURE 3-11. Pseudomembrane in *C difficile* infection. (Reproduced with permission from Abe I, et al. Acute fulminant pseudomembranous colitis which developed after ileostomy closure and required emergent total colectomy: A case report. *J Med Case Rep.* 2012;6:130.)

What population of patients is susceptible to this condition?

Infection is most often seen in elderly hospitalized patients. *C difficile* produces resistant spores, which are commonly found on hospital objects and on the hands of health care workers. Common alcohol-based hand sanitizers are ineffective at eliminating *C difficile* spores. *C difficile* colonizes the gastrointestinal (GI) tract (usually the colon) after the normal gut microbiota is killed or altered by antibiotics. The antibiotics most commonly associated with this disease are the penicillins, cephalosporins, quinolones, and clindamycin.

What is the pathophysiology of this disease?

Once it has colonized the GI tract, *C difficile* releases toxins (toxins A and B) that destroy intestinal epithelial cells. A new, more virulent strain of this bacterium that produces a binary toxin in addition to toxins A and B is often associated with the use of fluoroquinolones.

How is this condition diagnosed and treated?

Definitive diagnosis can be made with a cytotoxicity assay, an enzyme-linked immunosorbent assay for *C difficile* toxin A, or polymerase chain reaction. First-line treatment is with oral metronidazole or vancomycin. Fecal transplantation is an emerging therapy that aims to replenish the missing gut microbiota in patients with *C difficile* overgrowth by introducing normal fecal bacteria from a healthy patient. Several well-controlled studies reveal a high success rate of this procedure, and it is emerging as standard of care for recurrent or refractory *C difficile* infections.

CASE 13

A 5-year-old girl is brought to the clinic with a 3-month history of worsening vision and behavioral difficulty in school. She immigrated to the United States from Guatemala 2 years ago with her mother and a younger sibling. Her mother received no prenatal care and, through a translator, reports that the patient was delivered without complication at home. As an infant, the girl had a "wart-like" perioral maculopapular rash and three or four recurrent right-sided ear infections. Physical examination reveals that the girl is in the 30th percentile for weight and the 35th percentile for height. Additional observations include fundi that are notable for nummular keratitis, prominent notching of her upper two incisors and molars, and outward bowing of the tibia bilaterally.

What is the most likely diagnosis?

Congenital syphilis. This infection is one of the so-called **TORCHeS** infections (**T**oxoplasmosis, **O**ther infections, **R**ubella, **C**ytomegalovirus, **He**rpes simplex virus, **S**yphilis), the most common causes of congenital infection.

What is the causative microorganism in this condition?

Treponema pallidum.

What symptoms are commonly found in patients with this condition?

Congenital syphilis is a cause of hydrops fetalis, or stillbirth due to fluid accumulation in the fetus. If the newborn survives, it can develop various abnormalities, including the classic facial anomalies (tooth abnormalities known as Hutchinson incisors and mulberry molars, saddle nose, frontal bossing, and short maxilla), as well as recurrent ear infections and interstitial keratitis, leading to vision problems.

In the newborn, what tests can help confirm the diagnosis?

Serum rapid plasma reagin (RPR) test: Umbilical cord blood may show false-positive results because of maternal titers but remains the best screening tool for detecting syphilis infection. Serum and CSF (cerebrospinal fluid) can be tested by the **Venereal Disease Research Laboratory (VDRL) testing**. VDRL, like RPR, detects anticardiolipin antibodies that are produced by patients with syphilis. The serum VDRL is used for screening purposes. VDRL testing from CSF samples is used to detect central nervous system involvement of the disease, known as neurosyphilis. Other CSF findings such as pleocytosis (increased number of cells) and elevated protein levels also suggest infection. The presence of anticardiolipin antibodies is not specific to syphilis and can return false-positive results in patients with Epstein-Barr virus, systemic lupus erythematosus, rheumatoid arthritis, and other autoimmune or inflammatory conditions. For that reason, confirmatory serological testing using a treponemal test (TP-PA; various EIA/CIA methods) is recommended to confirm RPR or VDRL positive cases.

How does infection with this organism present in an adult?

Syphilis in adults is a sexually transmitted infection. Primary syphilis presents as a macule or papule that becomes an ulceration that usually occurs on the genitals but may be in the oral cavity. Secondary syphilis occurs 4–11 weeks afterwards and involves mucous membranes and skin. A non-itchy maculopapular rash presents on the extremities or trunk. Tertiary syphilis occurs years after initial infection. Without treatment, an infected person still has syphilis even though there are no signs or symptoms. It remains in the body, and it may begin to damage the internal organs, including the brain, nerves, eyes, heart, blood vessels, liver, bones, and joints. Gummas occur anywhere on the body and are inflammatory lesions (see Figure 3-12). Symptoms may involve the central nervous system, including general paralysis, tabes dorsalis, dementia, or Argyll Robertson pupils. Syphilis has the potential to inflame the vasa vasorum of the aorta, which results in aortic aneurysm.

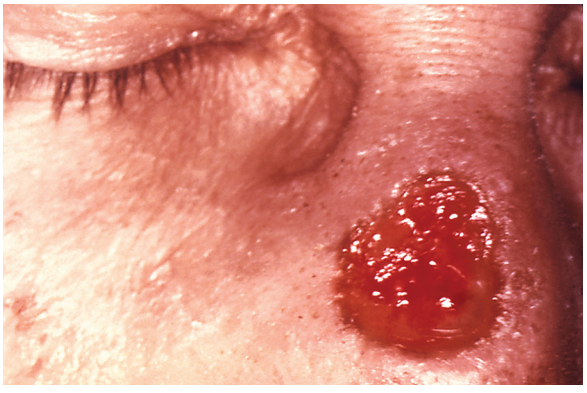


FIGURE 3-12. Tertiary syphilis. Gumma of the nose due to a long-standing tertiary syphilitic *Treponema pallidum* infection. (Reproduced courtesy of Centers for Disease Control and Prevention/J. Pledger.)

CASE 14

A pathologist is performing an autopsy on a 56-year-old university professor who suffered a rapid demise from an undiagnosed neurologic disease. Approximately 1 year previously, the patient presented to a psychiatrist with symptoms of psychosis. Shortly thereafter, his symptoms advanced to include unsteadiness and involuntary movements, and the patient ultimately became immobile and unable to speak. A sample of brain tissue is shown in Figure 3-13.

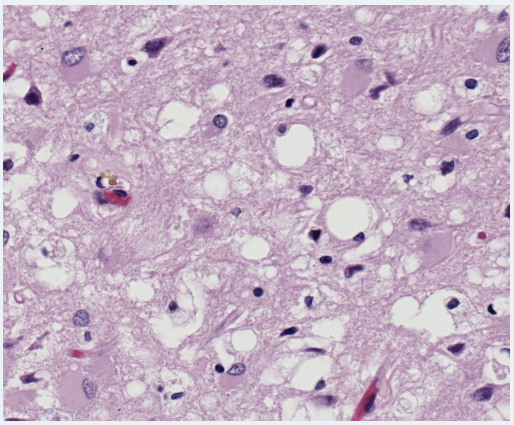


FIGURE 3-13. (Reproduced courtesy of the Centers for Disease Control and Prevention/Teresa Hammett.)

What is the most likely diagnosis?

Creutzfeldt-Jakob disease (CJD) is a prion disease characterized by rapidly progressive dementia with ataxia, myoclonus, and death within 1 year.

What are the classic brain histology findings in this condition?

On histology, prion disease presents with dramatic neuronal loss with numerous vacuoles in the gray matter resembling a porous sponge (see Figure 3-13). This is therefore known as spongiform encephalopathy.

How does the causative agent in this condition differ from other pathogens?

Prions do not contain RNA or DNA; they are composed only of abnormally folded proteins.

How is this condition transmitted?

Disease can be transmitted by central nervous system (CNS) tissue containing prions (transmission has been seen secondary to corneal transplants, ingestion, and implantable electrodes or other intracranial surgery with contaminated instruments as prions are not destroyed by routine autoclaving). Prion disease can also be inherited, but most cases are sporadic.

What other condition is associated with this type of pathogen?

Prions cause two acquired degenerative CNS diseases in humans: **CJD** and **kuru**, a slowly progressive, fatal disease formerly found among tribes in Papua, New Guinea, who practice cannibalism, as well as several extremely rare heritable prion diseases.

How does the structure of normal prions differ from that of pathologic prions?

Normal prions have α-helix conformations, whereas pathologic prions are composed of an abnormal isoform of β-pleated sheets. The new structure renders them undegradable, and buildup leads to neuronal toxicity. Further, the abnormal prions cause normal prions to change conformation into β-pleated sheets, leading to the contagiousness of the disease.

CASE 15

A 32-year-old man with a medical history of HIV presents to the ED with complaints of worsening headache, fever, and a stiff neck. Lumbar puncture is performed, and analysis reveals an elevated opening pressure, increased protein, and decreased glucose level. Gram staining of the spinal fluid reveals budding yeast; an antigen test is positive.

What is the most likely diagnosis?

Cryptococcal meningitis is the most common fungal cause of meningitis and is prevalent among patients with AIDS.

What microorganism causes this disease?

Cryptococcus neoformans is a heavily encapsulated yeast. It is found only as a yeast; it is not a dimorphic microorganism.

How does this microorganism cause illness?

C neoformans is found in pigeon droppings and in soil. When inhaled, the yeast causes a local infection in the lung; this infection is commonly asymptomatic but can result in pneumonia. Hematogenous spread to the central nervous system (CNS) results in meningitis. As in other common causes of meningitis, the capsule is thought to be an important virulence factor for gaining access into the CNS.

What laboratory tests can help confirm the diagnosis?

Tests for the polysaccharide capsular antigen are the diagnostic procedures of choice; a lateral-flow immunoassay is now the test of choice. The microorganism can also be cultured on Sabouraud agar. India ink stains the heavy polysaccharide capsule and reveals budding yeast (see Figure 3-14) but is insensitive and no longer standard of care.

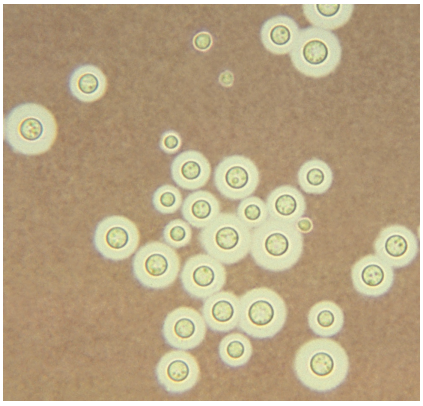


FIGURE 3-14. India ink stain of *Cryptococcus neoformans*. (Reproduced courtesy of the Centers for Disease Control and Prevention/ Dr. Leanor Haley.)

CD4+ cell counts are typically at or below what level when infection with this microorganism occurs?

C neoformans usually infects severely lymphopenic patients with CD4+ cell counts $<$ 100 cells/mm^3.

What is the treatment for this condition?

Patients who are not immunocompromised can be treated sufficiently with amphotericin B and flucytosine for the meningitis. Patients with AIDS require long-term suppression with fluconazole after induction with amphotericin B and flucytosine. In these patients, long-term suppression may be stopped if the patient responds to highly active antiretroviral therapy (HAART) and has repeated measurements demonstrating high CD4+ counts.

What cerebrospinal fluid findings are expected in this condition?

Like viral meningitis, fungal meningitis has an elevated WBC count with a lymphocytic predominance. However, all other laboratory results mimic those of bacterial meningitis: increased opening pressure, increased protein, and decreased glucose in cerebrospinal fluid.

CASE 16

A 42-year-old man who immigrated from Mexico 5 years ago presented to the ED with new-onset seizures. CT of the head (see Figure 3-15) reveals several calcified regions and cystic masses but no solid mass lesion or evidence of bleeding. A complete blood count reveals mild anemia and a WBC count of 78,000/mm^3 with 12% eosinophils.

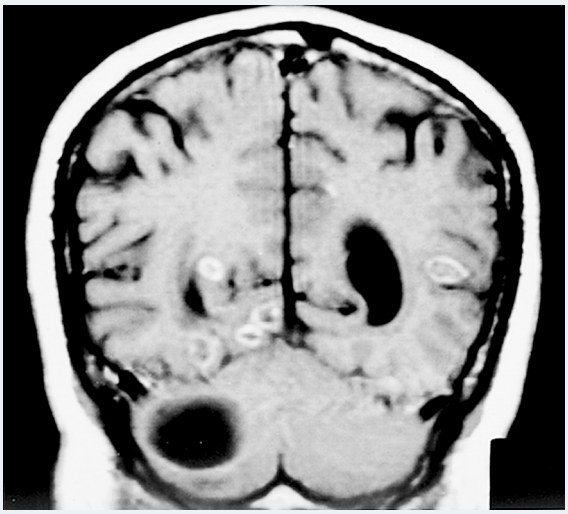


FIGURE 3-15. (Reproduced with permission from Rooper AH, et al. *Adams & Victor's Principles of Neurology,* 9th ed. New York: McGraw-Hill, 2009: Figure 32-8.)

What is the most likely diagnosis?

Cysticercosis, caused by *Taenia solium* (pork tapeworm), is a cestode (tapeworm) infection. When the tapeworm invades the brain, it forms small nonpurulent abscesses. The disease is known as neurocysticercosis and is responsible for the majority of adult-onset seizures in developing nations.

How does the organism involved in this condition cause illness?

Ingestion of undercooked pork introduces larvae from pig muscle into the human gastrointestinal (GI) system. These larvae mature in the small intestine into adult tapeworms. Eggs from the adult worms are released into the feces. Ingestion of these eggs via the fecal-oral route from a tape worm–infected human host allows eggs to enter the GI tract, where they develop into larvae. The larvae then penetrate the intestinal wall and migrate into the blood and tissues, encysting in various organs, including the brain, as seen in Figure 3-15.

What signs and symptoms are associated with this condition?

Infection with the tapeworm is usually asymptomatic or can cause mild abdominal discomfort. Cysticercosis can be found anywhere in the body, unfortunately, including the brain and eye, leading to seizures, focal neurological symptoms, and blindness.

What tests can help confirm the diagnosis?

Intestinal infection is revealed by eggs in stool. Cysticerci can be observed on imaging of the head when cysticercosis occurs in the brain. X-ray may reveal calcified cysticerci in other parts of the body, such as muscle. Serological testing for T solium antibody can complement imaging in diagnosis.

What are the treatments for this condition?

Praziquantel is used for cysticercosis, and albendazole with steroids is used for neurocysticercosis. In addition, steroids and anticonvulsants may be given for decreasing complications of neurocysticercosis. Asymptomatic patients with only calcified cysts are rarely treated.

What are the other cestodes?

Diphyllobothrium latum is a cestode transmitted by ingestion from freshwater fish that rarely causes vitamin B_{12}-deficient macrocytic anemia. *Echinococcus granulosus* eggs are ingested from dog feces and can cause liver cysts.

CASE 17

A 48-year-old woman who recently underwent a lung transplant presents to the ED with a fever and slight cough. She states that she had some difficulty breathing; however, she has not had chest pain. She is currently on immunosuppressive therapy for the transplant. An x-ray of the chest is taken and shows bilateral interstitial infiltrates. The patient undergoes a bronchoscopic biopsy (see Figure 3-16).

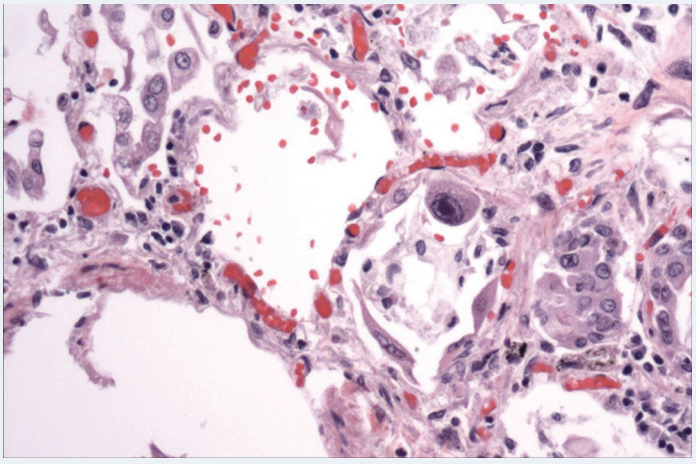


FIGURE 3-16. (Reproduced with permission from USMLE-Rx.com.)

What is the most likely diagnosis?

Pneumonia due to cytomegalovirus (CMV) infection. CMV is a double-stranded linear virus in the family *Herpesviridae*. Infected cells have intranuclear inclusions, and on histology have an "**owl's-eye**" appearance, as seen in the center of Figure 3-16.

What is the presentation of this condition?

In most people, CMV infection is asymptomatic. In those with symptoms, it usually presents with a mononucleosis-like syndrome, which includes pharyngitis, cervical lymphadenopathy, fever, lethargy, and, less often, splenomegaly. Unlike the mononucleosis syndrome seen with Epstein-Barr virus, the monospot test is negative. CMV can be transmitted by direct contact, blood transfusions, organ transplantation, breast milk, sexual contact, and vertically (ie, mother to fetus). It is one of the **TORCHeS** infections (**T**oxoplasmosis, **O**ther infections, **R**ubella, **C**ytomegalovirus, **He**rpes simplex virus, **S**yphilis).

What populations are at risk for complications of this condition?

The populations most at risk are those with decreased cellular immunity, such as patients with AIDS and organ transplants (especially bone marrow and lung transplants). The main complication in the transplantation population is CMV pneumonia. The main complication in the AIDS population is CMV retinitis, which usually presents when the CD4+ cell count is < 50 cells/mm^3. In both populations, prophylactic ganciclovir can be given.

How does this condition present in patients infected congenitally?

In patients congenitally infected with CMV, the complications include petechiae, jaundice, microcephaly, microsomia, retinitis, neurologic abnormalities, and deafness. At-risk fetuses are those whose mothers have a primary infection, which is seen with positive IgM levels (the IgG levels could be low or high). Mothers with negative IgM and positive IgG likely have a prior infection and are unlikely to transmit from mother to fetus.

What is the treatment for this condition?

Although most immunocompetent patients do not need treatment, the treatment is ganciclovir, a nucleoside analog. This drug requires activation by viral kinase, which phosphorylates the drug and allows it to inhibit CMV DNA polymerase. Acyclovir is not effective against CMV.

What are the most common adverse effects of the treatment for this condition?

Ganciclovir is more toxic than acyclovir. Adverse effects include leukopenia, neutropenia, thrombocytopenia, and renal toxicity.

CASE 18

A 36-year-old woman who has recently returned from Southeast Asia presents to her physician with sudden-onset fever, severe muscle pain in her back and extremities, and recent joint pain in her knees. Examination reveals an erythematous macular rash that covers her face and body.

What is the most likely diagnosis?

This woman is likely experiencing dengue fever, also known as "breakbone fever" because of the severe joint and muscle pain associated with it.

What is the vector for this condition?

The vector is the *Aedes aegypti* mosquito. These mosquitoes are diurnal and live near cities. They are most commonly found in pools of stagnant water. This distinguishes them from malaria-carrying *Anopheles* mosquitoes, which are nocturnal and are typically less populous near urban areas. Once a rare disease in the Western hemisphere, dengue fever began to reappear in the 1970s, when bans on pesticides such as DDT allowed these mosquitoes to thrive. The same vector can also carry yellow fever and chikungunya.

Which microorganism causes this condition?

Dengue fever is a disease caused by a positive, single-stranded RNA virus of the *Flaviviridae* family. This family also includes St. Louis encephalitis virus, Japanese encephalitis virus, hepatitis C virus, and West Nile virus.

How does this condition differ from yellow fever?

Yellow fever virus is also a member of the *Flaviviridae* family and has a similar endemic region and transmission as dengue fever virus. However, yellow fever presents with high fever, black vomit, jaundice, and acute hepatic necrosis and is not associated with severe joint and muscle pain.

After recovering from this condition, will the patient be immune to it in the future?

The dengue fever virus has four serotypes. The patient will develop lasting immunity to the serotype of the virus with which she was infected but not to the remaining three serotypes. This means that she could contract dengue fever four times in all.

Infection with a different serotype of this virus poses what potential complications?

The most serious complications of dengue fever are dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS), both of which can be fatal. These conditions are characterized by bleeding (often from the gastrointestinal tract or from mucosa); petechiae, ecchymoses, or purpura; thrombocytopenia; fluid leakage (manifested as pleural effusions, ascites, or hemoconcentration); and shock. Such complications most frequently occur in patients who have already been infected with another serotype of the virus. One theory underlying this phenomenon, termed antibody-dependent enhancement, proposes that antibodies from previous infections permit increased viral replication upon reinfection with a different serotype. This has also hindered the development of a vaccine since the vaccine must provide adequate protection against all four serotypes or it could put the patient at risk for DHF/DSS.

CASE 19

A 7-year-old girl who recently immigrated to the United States from Africa is brought to her primary care physician because of a sore throat and fever of 38.3°C (101°F). Physical examination reveals a grayish membrane covering her pharynx (see Figure 3-17) as well as cervical lymphadenopathy.

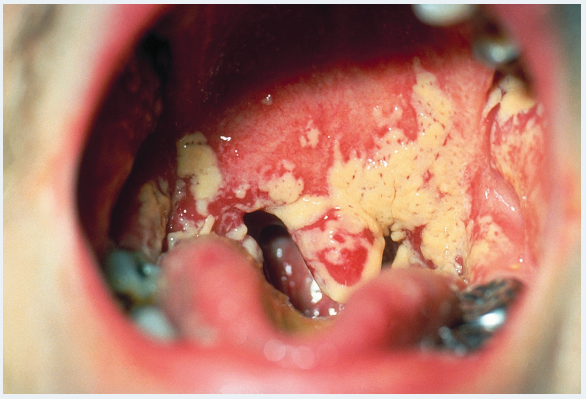


FIGURE 3-17. (Reproduced courtesy of the Centers for Disease Control and Prevention.)

What is the most likely diagnosis?

Diphtheria caused by the toxin-producing, gram-positive *Corynebacterium diphtheriae*. The pathognomonic findings are the gray pharyngeal pseudomembranes on physical exam, as seen in Figure 3-17.

How does the microorganism involved in this condition cause this presentation?

Exotoxin A is an enzyme that blocks protein synthesis by inactivating elongation factor EF-2 by ribosylating adenosine phosphate. This results in decreased mRNA translation and protein synthesis. (*Pseudomonas* toxin has a similar mechanism.)

What growth media are used to identify the microorganism involved in this condition?

Potassium tellurite agar and Loeffler coagulated blood serum media are used to isolate this microorganism. *C diphtheriae* is a gram-positive rod (see Figure 3-18). In culture, it often appears in clumps described as "**Chinese characters**."

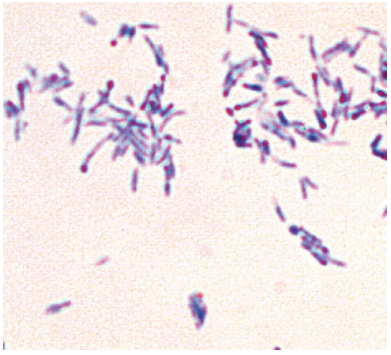


FIGURE 3-18. ***Corynebacterium diphtheriae.*** (Reproduced courtesy of the Centers for Disease Control and Prevention.)

Which vaccine would have prevented this child's condition?

The inactivated form, or toxoid, is a component of the **D**iphtheria, **T**etanus, and **a**cellular **P**ertussis (**DTaP**) vaccine. Children in the United States are required to have the DTaP vaccine by the age of 15–18 months, with a booster shot given between 4 and 6 years of age. Recent immigrants, especially children, frequently do not have up-to-date vaccinations.

What is the treatment for this condition?

Careful airway management to prevent respiratory compromise is essential. Antitoxin can inactivate circulating toxin that has not yet reached its target tissue. Penicillin or erythromycin can be given to prevent further bacterial growth and exotoxin release, thus making the patient noncontagious. The patient should receive cardiac monitoring with ECG and telemetry to monitor for myocarditis. The patient likewise needs treatment for heart failure or arrhythmia, and monitoring of neurologic function for motor deficits.

CASE 20

A 32-year-old man who recently immigrated from Cambodia presents to his physician with extreme swelling of his legs (see Figure 3-19) and scrotum. The skin associated with the swollen areas is thick and scaly. The patient admits to an episode of fever associated with enlarged inguinal lymph nodes some time ago, but he did not think much of it.

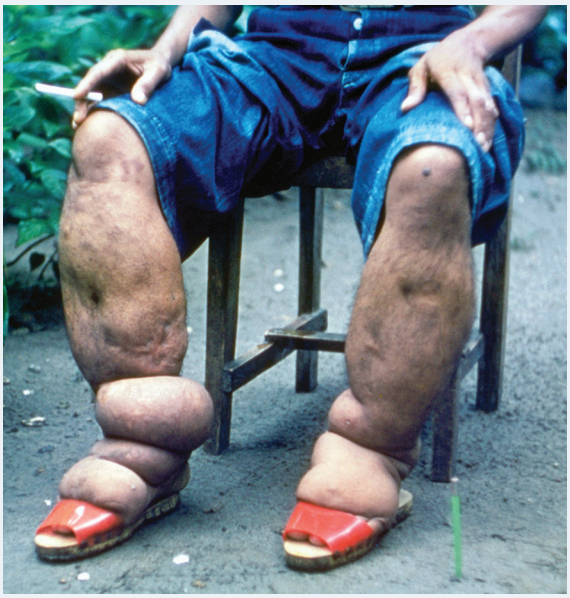


FIGURE 3-19. (Reproduced courtesy of Centers for Disease Control and Prevention.)

What is the most likely diagnosis?

Elephantiasis is caused by the nematode (roundworm) *Wuchereria bancrofti* and (in Asia) *Brugi malayi* and *timori*.

How does the organism involved in this condition cause illness?

The organism is transmitted by the bite of a female mosquito. Larvae are released into the bloodstream and travel to the lymphatics of the lower extremities and genitals, where they mature. Approximately 1 year later, adult worms, which reside in lymph nodes, trigger an inflammatory response.

What signs and symptoms are associated with this condition?

Inflammation resulting from the presence of adult worms causes **fever** and **swelling of lymph nodes**. Repeated infections cause repeated bouts of inflammation, resulting in **fibrosis** around the dead adult worms in the lymph nodes. This fibrosis can **obstruct lymphatic drainage** and lead to scaly skin and edema (as seen in Figure 3-19).

What test can help confirm the diagnosis?

Blood smears reveal larvae (**microfilariae**). Because larvae usually emerge at night, drawing blood in the evening is preferred. Consult the CDC Yellow Book for details on filarial species present in different countries and the best time to collect specimens.

What is the treatment for this condition?

Diethylcarbamazine is effective in killing the larvae but is not as effective against the adult worms. Adding doxycycline improves activity against the adults and may decrease clinical pathology.

CASE 21

A previously healthy 24-year-old man visits his physician complaining of significant weight loss, flatulence, and foul-smelling stools. He reports feeling fatigued since his return from Peru 3 months previously and has suffered abdominal cramping and intermittent loose, nonbloody stools since then. The patient's stool ova and parasite studies demonstrated characteristic trophozoites on two occasions (see Figure 3-20). He was prescribed a course of drug therapy and warned that consumption of alcohol during treatment could lead to nausea and vomiting.

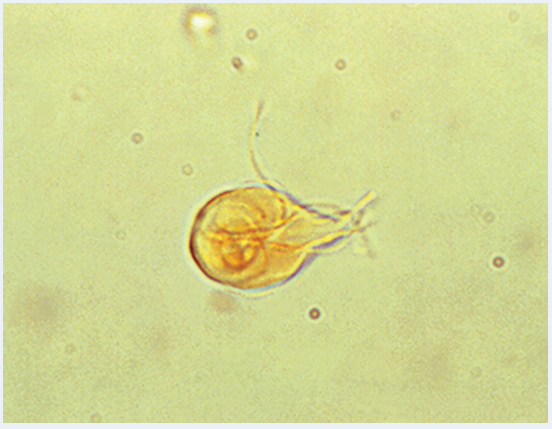


FIGURE 3-20. (Reproduced courtesy of the Centers for Disease Control and Prevention/Dr. Mae Melvin.)

What is the most likely diagnosis?

Giardiasis due to *Giardia lamblia* infection. *Giardia* appears as both a flagellated, motile, binucleated trophozoite (as seen in Figure 3-20) and as a round Tetranucleate cyst. Flatulence, foul-smelling stools, and chronic watery diarrhea in a patient with a recent travel history or exposure to well water is characteristic of *Giardia* infection. The ova and parasite test that reveals "smiley face" trophozoites is diagnostic.

What is the differential diagnosis for this condition?

Entamoeba histolytica can cause a similar spectrum of symptoms but might present with bloody diarrhea instead of watery diarrhea. Both *Cryptosporidium* and *Cyclospora* infections can produce similar symptoms. Infections with enterotoxigenic *Escherichia coli*, *Vibrio cholerae*, and *Campylobacter jejuni* can also cause watery diarrhea, but the onset in these cases is generally acute and tends to resolve within a few days. Inflammatory bowel disease and gluten enteropathy can also be associated with chronic diarrheal illnesses, though the travel history suggests an infectious etiology.

What is the treatment for this condition?

Metronidazole is the agent used to treat giardiasis. Concurrent alcohol use with metronidazole produces a disulfiram-like effect (disulfiram is occasionally prescribed to discourage alcohol consumption in situations of alcohol addiction). Metronidazole interferes with the action of aldehyde dehydrogenase in ethanol metabolism, which increases serum acetaldehyde levels and thus leads to nausea, vomiting, flushing, thirst, palpitations, vertigo, and chest pain.

What is the mechanism of action of the medication used to treat this condition?

Metronidazole is effective specifically against anaerobic microorganisms. It diffuses across the cell membrane of microorganisms and is reduced in the mitochondria of obligate anaerobes to cytotoxic intermediates. These intermediates cause DNA strand breakage and generate free radicals that consequently damage the cell. Furthermore, the reduction of metronidazole creates a concentration gradient that leads to further uptake of the drug.

What are other uses of this medication?

Metronidazole is used to treat *Clostridium difficile* (anaerobe) infection in pseudomembranous colitis, amebic dysentery, bacterial vaginitis, and *Trichomonas* vaginitis and as a component of triple therapy for *Helicobacter pylori* eradication. Broadly, it is effective against most anaerobic bacteria and various protozoa.

CASE 22

A 22-year-old woman presents to the ED in labor. She states that she has not received any prenatal care, and this is her first pregnancy. While in triage for the ED, she has a normal spontaneous vaginal delivery of a boy. The baby appears normal at birth, but after 12 hours, he seems lethargic. He starts to become tachypneic, his blood pressure drops, and his hands and feet begin to feel cold and clammy.

What infectious agents are most frequently responsible for neonatal sepsis?

Group B streptococci (GBS), *Escherichia coli*, and *Listeria monocytogenes* are common causes of sepsis, pneumonia, and meningitis in newborns. GBS often colonizes the vaginal flora of women and can be transmitted vertically during vaginal delivery. Most women are tested by a vaginal swab at 37-38 weeks. If they are not tested during this period, they are tested immediately prior to delivery. This patient's lack of prenatal care, vaginal delivery, and onset soon after birth make GBS sepsis a likely diagnosis.

What is the next step in identifying the causative agent?

In **Gram staining** of a blood sample, GBS appear as gram-positive cocci, *L monocytogenes* appears as motile gram-positive rods, and *E coli* appears as gram-negative rods.

How did the infant become infected?

These bacteria can spread through the placenta or be acquired from the birth canal during delivery. The mother may be infected or colonized but asymptomatic. However, pregnant and postpartum women are also at risk for GBS urinary tract infection or chorioamnionitis.

What prenatal testing is routinely performed to reduce the infant's risk of this infection in the birth canal?

If the patient receives good prenatal care, cultures of the mother's vagina and rectum are performed between 35 and 37 weeks of gestation to determine whether she is colonized with GBS.

What treatment is initiated if prenatal testing is positive?

Treatment of GBS in infected mothers or newborns involves the use of intrapartum antibiotics such as penicillin. In mothers who are colonized vaginally or rectally, but who are not actively infected, intrapartum penicillin is recommended. If the status of the mother is unknown, the mother is prophylactically given penicillin while she is in labor. If the patient is allergic to penicillin, the patient should be desensitized to penicillin, then given penicillin.

If the baby develops meningitis from this organism, what cerebrospinal fluid findings are expected?

In bacterial meningitis, the cerebrospinal fluid may show bacteria on Gram stain. In addition, the WBC count is elevated, primarily with neutrophils; the protein level is elevated; and the glucose level is reduced.

CASE 23

A 3-year-old boy is brought to the pediatrician by his mother because she is worried her son is not eating and drinking. He began to refuse solid foods 2 days ago, and he has only been drinking small sips. Today, the mother noticed a rash on the child's hands, feet, and face (see Figure 3-21). His temperature is 100°F. She noticed other children at the day care seem to have the same thing. She is starting to notice symptoms in her other young children at home. She is worried he has picked up herpes from a relative that has a history of cold sores.

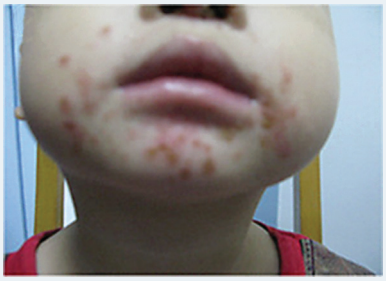


FIGURE 3-21. (Reproduced with permission from Di B, et al. *Virol J* 2014;11:157.

What is the most likely diagnosis?

This is a case of hand, foot, and mouth disease, caused by **coxsackie A virus**. This syndrome presents with a tender rash (see Figure 3-21) on the palms, soles, and often the buttocks and painful vesicles on the oral mucosa. This patient's avoidance of solid food strongly suggests involvement of the oral mucosa.

What other microorganisms are included in this family that caused this condition?

The *Picornaviridae* are a family of **single-stranded positive-sense RNA viruses**. The members of this family cause a wide array of illness, possibly because of the high virulence of positive-sense single-stranded RNA, which can be directly translated into protein products by host ribosomes. These can cause a wide variety of encephalitis, meningitis, and cardiomyopathy, as more of the extreme infections from these. Members of the *Picornaviridae* family include:

- Poliovirus
- Echovirus
- Hepatitis A virus
- Coxsackie viruses
- Rhinovirus

What other conditions can this microorganism cause?

Herpangina, which presents with sore throat, red vesicles on the back of the throat, pain with swallowing, and fever. Herpangina is a mild, self-limited disease that presents in children and usually results in complete recovery. Less commonly, coxsackie A virus can cause petechial and purpuric rashes, which may also have a hemorrhagic component.

What illnesses may be caused by the group B coxsackie viruses?

The coxsackie B virus may cause aseptic meningitis, myocarditis, pericarditis, dilated cardiomyopathy, orchitis, and epidemic pleurodynia (fever, headache, spasms of the chest wall muscles, and pleuritic pain). Nephritic syndrome may also occur after a coxsackie B virus infection.

What is the differential diagnosis for a rash of the palms and soles?

Other than **C**oxsackie **A** virus, **R**ocky mountain spotted fever caused by *Rickettsia rickettsii*, secondary **S**yphilis, and Kawasaki disease (vasculitis) commonly present with a rash on the palms and soles (mnemonic: **Kawasaki CARS**).

CASE 24

An 18-year-old woman presents to the clinic with itching and dysuria. She also has a fever and headache. When asked, she says that she recently became sexually active with a new partner. She states that she was recently tested for "some sexually transmitted diseases" at her annual exam with her gynecologist, 3 weeks ago. She was positive for chlamydia at the time and was treated before she had the encounter with a new partner. She does not take birth control and does not use any protection from STDs. The patient's sexual partner denied any STDs. She never received an HPV vaccination as a child. She has recently started using a new douche, and she thinks this could be causing these lesions. Physical examination reveals tender inguinal lymphadenopathy and red, pustular, painful vesicles on her labia majora (see Figure 3-22).

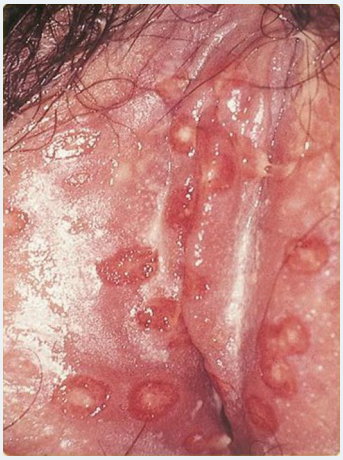


FIGURE 3-22. (Reproduced courtesy of SOA-AIDS Amsterdam.)

What is the most likely diagnosis?

Herpes simplex virus type 2 (HSV-2). The pathognomonic findings for herpes infections are painful vesicles. Both HSV-1 and HSV-2 can cause genital herpes (as shown in Figure 3-22), but more than 80% of genital lesions are due to HSV-2.

What are the characteristics of this pathogen?

HSV-2 is a member of the Herpesviridae family, which are double-stranded DNA viruses and include: HSV-1, varicella-zoster virus (VZV), Epstein-Barr virus (EBV), cytomegalovirus, human herpesvirus-6, and human herpesvirus-8. They can be recognized by multinucleated giant cells on Tzanck smear and by eosinophilic intranuclear inclusions.

What is the differential diagnosis of painful genital lesions?

Chancroid caused by *Haemophilus ducreyi* infection. Lymphogranuloma venereum caused by *Chlamydia trachomatis* and granuloma inguinale caused by *Klebsiella granulomatis* also cause painful genital lesions.

What is the typical course of this infection?

HSV-2 is transmitted by direct contact of the virus with mucosal surfaces or open skin surfaces. It can also be transmitted from mother to newborn during delivery. Approximately 80% of infected patients are asymptomatic. The primary infection often presents with constitutional symptoms such as fever, headache, malaise, and myalgia. Later, genital vesicles may appear that can rupture and leave behind painful ulcers. Other genital symptoms include itching and tender inguinal lymphadenopathy. Like other viruses in the family, HSV-2 becomes latent and can be reactivated. Triggers for reactivation include fever, trauma, emotional stress, sunlight, and menstruation. Upon reactivation, there is often a viral prodrome that involves tenderness, pain, and burning at the future site of vesicle eruption. The lesions last 4–15 days before crusting over and re-epithelializing. It is important to remember herpes encephalitis for test questions involving a patient with personality changes and a meningitis-like presentation. Lesions typically originate in the temporal lobe.

Where does this species remain latent?

In the peripheral nervous system ganglia. HSV-1 tends to remain latent in the trigeminal ganglion, reactivating and causing oral herpes or "cold sores." HSV-2 and VZV tend to remain latent in the dorsal root ganglia of the sensory afferents. This gives rise to the pathognomonic dermatomal distribution of reactivated zoster infections.

What is the treatment for this condition?

The treatment for HSV-2 is acyclovir, a nucleoside analog that acts by inhibiting viral DNA polymerase when it is phosphorylated by viral thymidine kinase. However, because efficacy requires viral thymidine kinase activity, any herpesvirus lacking a functional thymidine kinase will be resistant. Although there is suppressive treatment with acyclovir, there is no cure for herpes. Herpes is a chronic life-long infection. It can be important during pregnancy because if the mother has an active infection at time of delivery, she should have a C-section instead of a vaginal delivery.

CASE 25

A 9-year-old girl is brought to a university pediatric clinic for a well-child exam. During the history, you find that the family recently immigrated from Guatemala. Per her growth chart, the girl is small for her age, and she is not very active. She is not caught up on her vaccinations currently, and her mother would like her to be caught up. She has not received any vaccinations previously. For the last year, she has had some trouble breathing and gastrointestinal issues such as chronic constipation. Physical examination reveals a small girl with a thin, scaphoid abdomen. In laboratory studies, she is found to be anemic and protein deficient. The mother relays that the child has been eating a varied diet, so she is surprised that she is protein deficient. The mother has hepatitis B, and she is worried she may have passed it to the child. Relevant laboratory findings are as follows:

Hematocrit: 36%
Mean corpuscular volume: 73 fL
WBC count: 11,000/mm^3
Differential: 35% segmented cells, 1% bands,
33% lymphocytes, 21% eosinophils

Figure 3-23 shows stool testing using wet mount.

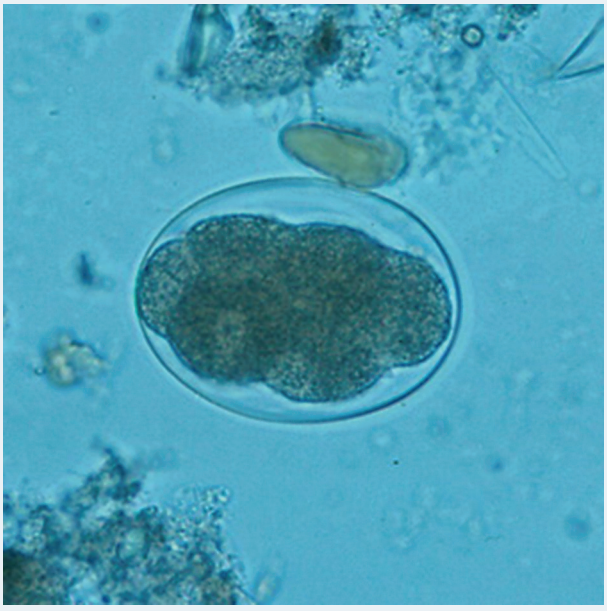


FIGURE 3-23. (Reproduced with permission from USMLE-Rx.com.)

What is the most likely diagnosis?

Hookworm, or nematode, infection. The findings of eosinophilia and microcytic anemia with recent immigration from an endemic area are highly suggestive of this condition.

What is the next step in confirming the diagnosis?

Stool ova and parasite tests can confirm the presence of characteristic small, round eggs (as seen in Figure 3-23) and occasional worms approximately 1 cm in size. Stool ova and parasite tests can also be used to delineate the species of helminth.

What are the other species in this genus?

Ancylostoma duodenale, *Necator americanus*, and *Ancylostoma braziliense* are the most common hookworms. Of the three, *N americanus* is the most commonly tested, and it causes the classic gastrointestinal symptoms and microcytic anemia seen in this patient. *A braziliense* can manifest as a condition known as cutaneous larva migrans, in which the larva migrate to the subcutaneous tissue and create pruritic, serpiginous tracts underneath the skin.

What other helminth is known to cause anemia?

Diphyllobothrium latum, a tapeworm, causes vitamin B_{12} deficiency leading to a macrocytic anemia.

How does this infection cause disease in humans?

Percutaneous infection occurs generally through the soles of the feet and is acquired commonly from sandboxes. The larvae pass into the lungs, and 8–21 days later they cross the pulmonary vasculature and enter the airways. They ascend to the pharynx and are swallowed. This swallowing of the worms often leads to a chronic cough. By the time they reach the small intestine, the larvae have become adult worms. The adults "hook" onto the mucosa and feed on the host's blood with the help of an orally secreted factor X inhibitor. This results in the microcytic anemia. The females produce eggs that are passed through the stool and deposited in the soil.

What are the treatments for this condition?

Since hookworm is a helminthic infection, mebendazole and albendazole are the first-line agents. These agents disrupt helminthic microtubule synthesis, leading to structural weakening and death of helminthic cells. Pyrantel pamoate can be used as a second-line agent.

CASE 26

A 46-year-old woman visits her physician in January complaining of "feeling poorly." She has had fever, chills, muscle aches, dry cough, and sore throat with no improvement from taking over-the-counter medication for the past few days. She works as a secretary at a primary care office and says many patients have been coming to the office with these symptoms. She has been having some diarrhea as well. She is worried that it is "something serious" because she received an influenza vaccine this year. Physical examination reveals small, tender cervical lymphadenopathy, swollen nasal mucosa, and an erythematous pharynx.

What is the most likely diagnosis?

She is most likely infected with the influenza virus, an orthomyxovirus.

What are the defining structural features of this class of microorganisms?

Orthomyxoviruses are helical, enveloped, negative, single-stranded RNA viruses with eight segments. Their primary virulence factors are hemagglutinin and neuraminidase. Hemagglutinin aids in the viral entry into host cells whereas neuraminidase aids in progeny release from infected host cells. The isotypes of these two proteins determine the virulence of each particular strain of virus and are the targets of the influenza vaccine. Figure 3-24 shows the general structure of the influenza virus and the location of the neuraminidase and hemagglutinin.

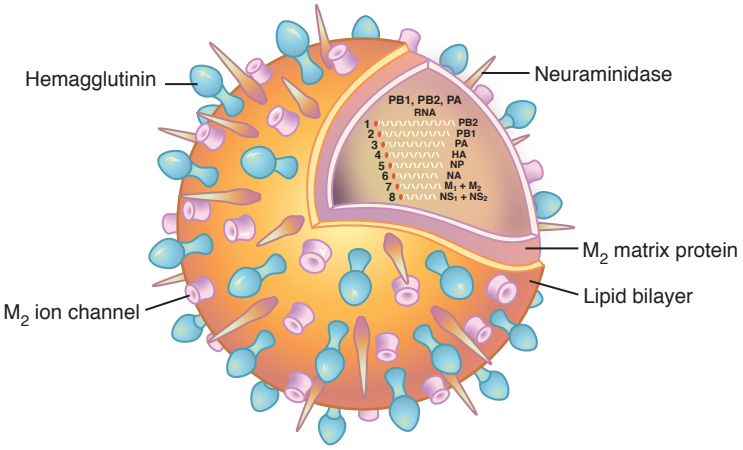


FIGURE 3-24. The general structure of the influenza virus and the location of neuraminidase and hemagglutinin. (Reproduced with permission from USMLE-Rx.com.)

The patient has had a similar infection in the past. Why is her immune system not protecting her from this illness?

The isotype of hemagglutinin and neuraminidase is constantly changing because of a phenomenon known as antigenic drift. This is the result of random small mutations that cause changes in the antigenic structure of the virus. These mutations result in antigen structures that are only partially recognized by the host immune system.

What characteristic of this microorganism's genome makes deadly epidemics possible?

Influenza A virus infects diverse species including birds, horses, and swine; by contrast, influenza B and influenza C infect only humans. With its segmented genome, influenza A can swap segments of RNA between animal and human strains (a process known as reassortment), leading to new human strains with novel surface antigens not recognized by the immune system. This type of change is termed **antigenic shift** and was responsible for the "swine flu" or hemagglutinin isotype 1 and neuraminidase isotype 1 (H1N1) influenza A virus outbreak in 2009.

What pharmacologic agents can be used as prophylaxis and treatment against this infection?

Amantadine and rimantadine block viral penetration by inhibiting the M2 protein responsible for uncoating and can be used to treat influenza A infection. However, these drugs are rarely used anymore because of the high levels of resistance that have developed against them. Instead, zanamivir and oseltamivir (neuraminidase inhibitors) are used to treat both influenza A and influenza B infections. These agents are most effective if started within 48 hours of symptom onset. The influenza vaccine should be given in October or November before the start of flu season. It takes approximately 2 weeks for the body to make antibodies to the viruses. The vaccine generally has four strains chosen by the Centers for Disease Control and Prevention.

CASE 27

A 43-year-old man with HIV infection presents to the HIV clinic with multiple purple-red plaques and papules distributed across his skin (see Figure 3-25). He has a history of medication noncompliance. He reports that he has stopped taking his HARRT therapy because he had been feeling better. He has noticed some increased diarrhea and blood on the toilet paper when he wiped. He has had hemorrhoids before, but he does not feel the typical itching that he usually feels with them. The patient says he feels fine and denies fever, chills, malaise, or headache. He has not been using any illicit drugs, and he has been practicing safe sex. He has had "some type of fungus" in his lungs before, and he was hospitalized 2 years ago for it. A complete blood count reveals his CD4+ cell count is 180 cells/mm^3.

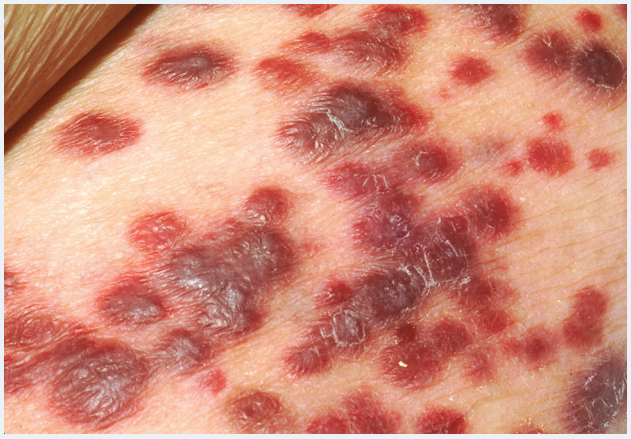


FIGURE 3-25. (Reproduced courtesy of the National Cancer Institute.)

What is the most likely diagnosis?

This is Kaposi sarcoma, an angiogenic neoplasm prevalent in HIV-positive patients. Kaposi sarcoma is caused by **human herpesvirus-8** (HHV-8), a member of the *Herpesviridae* family. Members of this family are DNA viruses with a double-stranded, linear genome in an enveloped, icosahedral capsid.

What important alternative diagnosis must be ruled out?

An important alternative diagnosis for such skin lesions in HIV patients is bacillary angiomatosis (BA), which typically presents with systemic symptoms such as fever, chills, and malaise. However, because BA is caused by *Bartonella henselae*, cat-scratch fever, it is non-neoplastic and can readily be treated with antibiotics.

How does the microorganism cause the characteristic discolored skin lesions?

HHV-8 has a tropism for endothelium cells and is thought to induce vascular endothelial growth factor, which causes irregular vascular channels to develop in the skin. RBCs extravasate into these spaces, causing the characteristic purple-red skin lesions as seen in Figure 3-25.

What other diseases are associated with this microorganism?

Kaposi sarcoma is not limited to the skin; it can affect other mucosal surfaces such as the gastrointestinal tract, oral mucosa, lungs, lymph nodes, and other visceral organs. This can lead to gastrointestinal bleeding. HHV-8 also infects B lymphocytes and has been linked to body-cavity **B-cell lymphoma** (a non-Hodgkin lymphoma subtype) and to **Castleman disease** (a lymphoproliferative disorder that may progress to lymphoma).

What other patient population is at increased risk for developing this infection?

Transplantation patients, who, like patients with HIV, are chronically immunosuppressed, have a higher incidence of infection than the general public. Middle-aged men of Mediterranean descent can also be affected by Kaposi sarcoma, and it is not related to immunosuppression.

What are the treatments for this condition?

Daunorubicin or doxorubicin is the treatment of choice. Both cause DNA breaks by two mechanisms: (1) intercalating into the DNA double helix and (2) creating oxygen free radicals that damage DNA. A major adverse effect of their use, however, is cardiotoxicity. In HIV-positive patients, the first goal is to boost immunity by starting highly active antiretroviral therapy (HAART), which often leads to improvement of the disease.

At a CD4+ cell count of < 200 cells/mm^3, what preventative measures should be taken?

The patient should be started on trimethoprim-sulfamethoxazole therapy for *Pneumocystis jiroveci* pneumonia and toxoplasmosis prophylaxis.

CASE 28

A 64-year-old man with a history of smoking and well-controlled diabetes mellitus presents to the ED with a 3-day history of low-grade fevers, mild diarrhea, and nonproductive cough. He works as a maintenance worker in a local apartment complex, and he states that many of the tenants have been in the hospital with a "lung infection." Workup includes a Gram stain of sputum, which shows prominent polymorphonuclear leukocytes but no microorganisms. X-ray of the chest reveals diffuse, patchy bilateral infiltrates. Silver stain of the specimen is shown in Figure 3-26. Relevant laboratory findings are as follows:

Hemoglobin: 14 g/mL
Sodium: 128 mEq/L
Hematocrit: 40%
Chloride: 100 mEq/L
Platelets: 200,000/mm^3
Potassium: 4.2 mEq/L
WBC count: 15,000/mm^3

Bicarbonate: 17 mEq/L
Blood urea nitrogen: 16 mg/dL
Glucose: 110 mg/dL
Creatinine: 1.2 mg/dL
Urinalysis: 2+ proteinuria; no glucose, ketones, or blood

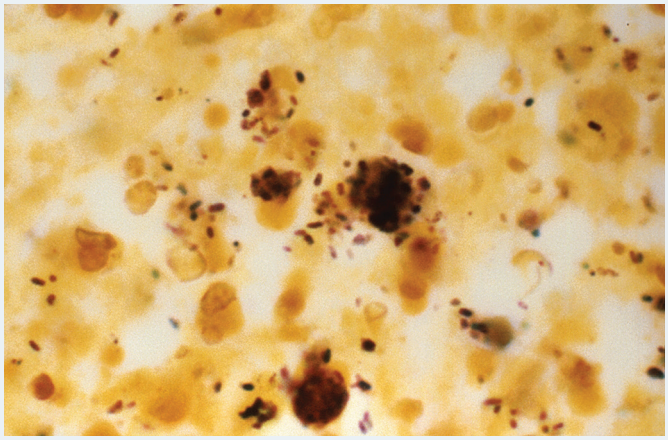


FIGURE 3-26. (Reproduced courtesy of the Centers for Disease Control and Prevention/Dr. William Cherry.)

What is the most likely diagnosis?

Legionnaires disease, an infection caused by the gram-negative rod *Legionella pneumophila*. Any patient presenting with diarrhea and pneumonia-like symptoms has *Legionella* until proven otherwise. The patient will also have low sodium with suspected pneumonia, which raises suspicion for *Legionella*. This patient has evidence of interstitial pneumonia, which makes the diagnosis even more likely. Legionella does not Gram stain well, but it stains well with silver stain (see Figure 3-26). It grows only on charcoal yeast extract medium with iron and cysteine added.

What is the differential diagnosis for atypical pneumonia?

The common differential diagnosis for atypical pneumonia is first and foremost viral infection, followed by *Chlamydia*, *Mycoplasma*, or *Legionella* infection.

What test can help confirm the diagnosis?

Urinary *Legionella* antigen test can establish the diagnosis. *Legionella* is unique in that it is the only form of community-acquired pneumonia that can be diagnosed with a urine test.

What risk factors does the patient have for developing this condition?

The patient's history of diabetes and smoking predisposes him to *Legionella* infection. Given his occupation as a maintenance man, he likely works with air conditioning systems. As this microorganism grows in infected water sources, the patient's occupation places him at risk.

What are the treatments for this condition?

Legionella responds best to antibiotics that can achieve a high intracellular concentration, such as macrolides (eg, erythromycin, clarithromycin, and azithromycin) and tetracyclines. *Legionella* produces β-lactamase, so cephalosporins and penicillins are ineffective.

CASE 29

A 41-year-old woman who is a recent immigrant from Mexico presents to a local clinic complaining of "white spots" on her body. She says she first noticed the lesions about 1 month ago and thought they were from the sun, but they have gradually increased in number and have not improved despite her new job indoors. Physical examination reveals multiple, asymmetrically distributed, hypopigmented lesions on the patient's arms, abdomen, back, and feet (see Figure 3-27). The lesions are sharply demarcated, with raised, erythematous borders and atrophic, scaly centers. The lesions are anesthetic, and there is no hair growth within any of the hypopigmented areas. Biopsy of the lesions demonstrates granuloma formation within the dermal nerves of the forearm.

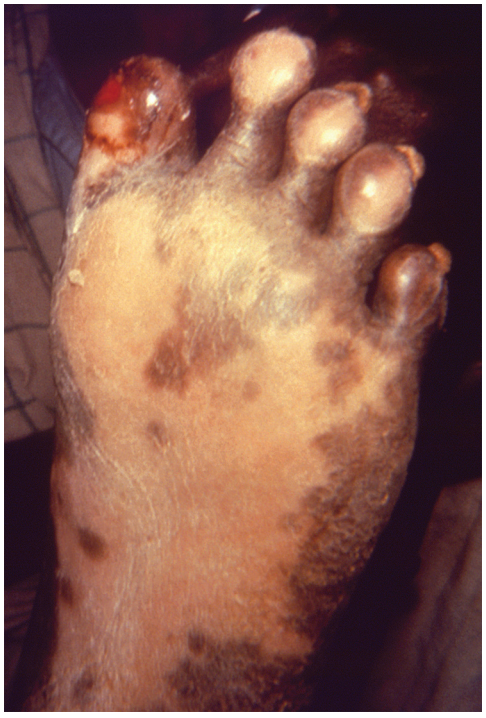


FIGURE 3-27. (Reproduced courtesy of Centers for Disease Control and Prevention/Dr. Andre J. Lebrun.)

Under what conditions does the causative microorganism grow?

Both lepromatous and tuberculoid leprosy are caused by *Mycobacterium leprae*, an acid-fast bacillus that cannot be grown in vitro. *M leprae* is an obligate intracellular bacillus that, like other mycobacteria, contains mycolic acid in its cell wall. *M leprae* grows best in cooler temperatures (eg, skin, peripheral nerves, testes, upper respiratory tract).

How does this patient's condition differ from a more severe form?

This patient has tuberculoid leprosy, which is largely confined to the skin (hypopigmented macules as seen in Figure 3-27) and peripheral nerves. Cell-mediated immunity is intact, and patients' T cells recognize *M leprae* (positive lepromin skin test). Lepromatous leprosy holds a much worse prognosis because patients have ineffective cell-mediated immunity (negative lepromin skin test). Skin lesions and nerve involvement are much more extensive than in the tuberculoid form, and there may be involvement of the testes, upper respiratory tract, and anterior chamber of the eye.

What is the treatment for this condition?

Both tuberculoid and lepromatous leprosy can be treated with a course of oral dapsone. The tuberculoid form is reliably cured by a short course of this medication. Patients with lepromatous leprosy have an exceptionally high bacterial load and may require an extended or even lifelong course of chemotherapy. Alternate therapies for leprosy include rifampin or a combination of clofazimine and dapsone.

What are the adverse effects of treatment?

Dapsone can cause agranulocytosis, so patients should be monitored initially with weekly or biweekly complete blood counts. Rifampin can turn body fluids such as sweat, tears, and urine a red-orange color. This can startle patients and clinicians into thinking that the urine is bloody if they are not counseled before commencing therapy.

CASE 30

The mother of a 1-week-old girl calls her pediatrician because the infant has been fussy all morning. The infant's temperature is 103°F, and the mother is asked to bring the infant to the hospital. The workup includes cerebrospinal fluid (CSF) analysis, hematology studies, and cultures. Empiric antibiotic therapy is initiated. Later, upon microscopic examination of the CSF, microorganisms with tumbling end-over-end motility are visualized.

What is the most likely diagnosis?

Meningitis due to *Listeria monocytogenes* infection. This microorganism, identifiable by its classical tumbling motility, is a gram-positive rod and a common cause of meningitis in newborns and the elderly (see Table 3-1).

Table 3-1. What Are Some Examples of Live-Attenuated Vaccines vs Killed?

Organism	Newborn	Infant/Child	Teen/Adult	Elderly
Streptococcus pneumoniae		X	X	X
Neisseria menigitidis		X	X	
Enterovirus		X	X	
Escherichia coli (gram-negative rod)	X			X
Listeria	X		X	
Group B Streptococcus	X			

How is the pathogen in this condition transmitted?

L monocytogenes is transmitted through ingestion of unpasteurized dairy products such as milk, cheese, ice cream, deli meat, and most recently, hummus.

What microorganisms should empiric antibiotic therapy target?

Group B streptococcus, *Escherichia coli*, and *L monocytogenes* are the most common causes of sepsis and bacterial meningitis in infants younger than 1 month of age. Therefore, empiric therapy should be aminopenicillin or vancomycin for gram-positive infection and aminoglycosides, antipseudomonal penicillins, or third- or fourth-generation cephalosporins for gram-negative infection.

How does this microorganism evade the host immune response?

L monocytogenes is a facultative intracellular bacterium able to survive in the macrophages of neonates and immunosuppressed patients. In an immunocompetent host, activation of macrophages destroys phagocytosed *Listeria*.

What other population is at particular risk for developing the same infection?

Pregnant patients are at increased risk of developing a serious illness from *Listeria* known as granulomatosis infantiseptica. It can cause various complications to the mother and baby from premature rupture of membranes and intrauterine fetal demise. The elderly and immunocompromised are also at increased risk for this infection.

CASE 31

A 30-year-old woman presents to the clinic with abdominal pain, a low-grade fever, and a sensation of abdominal fullness. She says the symptoms have been going on for some time and have been gradually worsening. On physical examination she appears jaundiced with notable scleral icterus. She says she is originally from South America. She mentions that she breeds and trains sheep dogs for a living. Based on radiographic findings, surgery is performed and a biopsy specimen is shown in Figure 3-28.

What is the most likely diagnosis?

The patient most likely has a hydatid cyst, which is a liver cyst due to *Echinococcus* infection.

How is this infection transmitted?

Echinococcus is a tapeworm that is transmitted by food or water contaminated with feces containing eggs from the tapeworm. Infection is not endemic to the United States and so is most commonly seen in immigrants or those with a travel history to endemic areas. The sheep dog is an intermediate host, while humans serve as dead-end hosts for these organisms.

What is the typical presentation of this infection?

Echinococcus causes slow-growing cysts in the liver, as seen in Figure 3-28. As a result, symptoms are often gradual in onset and include abdominal pain, cough, low-grade fever, a sense of abdominal fullness, hepatomegaly, and obstructive jaundice. Leakage of cysts can cause flushing and urticaria, whereas rupture can cause anaphylaxis and death. Other organs that can be involved include the lungs and the brain. In the lungs, the presentation includes chronic cough, dyspnea, hemoptysis, and pleuritic chest pain. In the brain, presentation includes headache, dizziness, increased intracranial pressure, and hydrocephalus.

How is this condition diagnosed?

On x-ray of the abdomen, a rim of calcification around the cyst is able to distinguish hydatid cyst from amebic and pyogenic cysts. However, the diagnosis usually cannot be made with radiology alone and requires an enzyme-linked immunosorbent assay (ELISA). In addition, 25% of patients have eosinophilia.

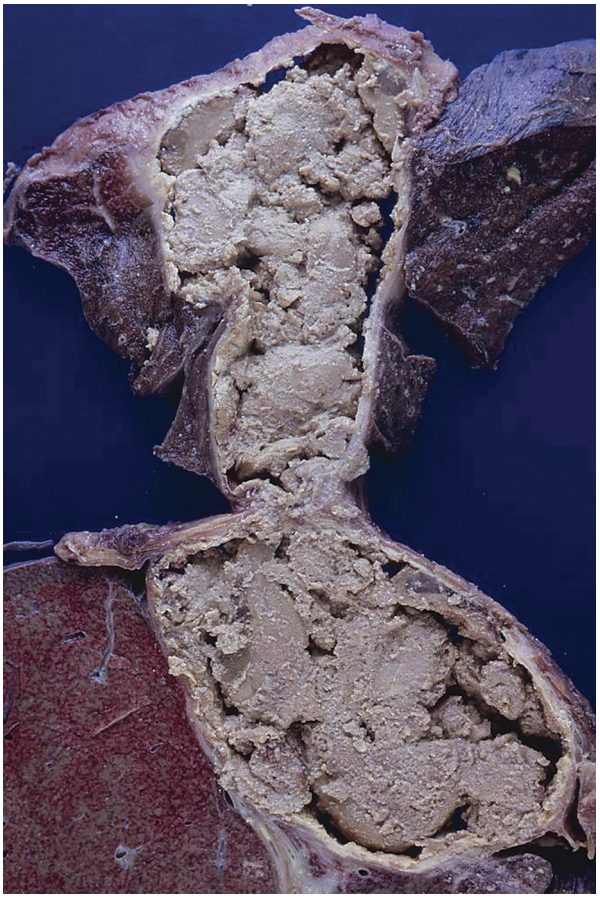


FIGURE 3-28. (Reproduced courtesy of Dr. Yale Rosen.)

What is the treatment for this condition?

The treatment for *Echinococcus* infection is usually surgical and involves aspiration of cyst contents followed by excision. However, during drainage, the interventional radiologist or surgeon must be careful not to rupture the cyst as this can lead to anaphylaxis. Therefore, many physicians prefer to inject formalin or ethanol into the cyst to kill the organism before aspirating. In some cases, therapy with a combination of albendazole and mebendazole is sufficient.

What other organisms are classified as cestodes?

Diphyllobothrium latum is a cestode transmitted by ingestion from freshwater fish that causes vitamin B_{12}-deficient macrocytic anemia. *D latum* is treated with praziquantel. *Taenia solium* larvae are ingested from undercooked pork and can cause calcified cysts in various organs, including the brain (cysticercosis or neurocysticercosis). Cysticercosis is treated with praziquantel, whereas neurocysticercosis is treated with albendazole.

CASE 32

A 49-year-old man presents to the ED after a syncopal episode. He said he had just stood up from urinating, and he felt dizzy and fell down. He thought he might have hit his head, so his boss made him go to the ED. He denies any chronic health problems and states that he stays fit by walking several miles through the local park every day. He recently returned from a camping trip to Vermont. Physical examination shows bradycardia and a 12-lead ECG is ordered (see Figure 3-29). On review of systems, the patient states that he has had low-grade fevers over the past few days. Upon physical exam, the resident notices an area of induration in his left groin surrounded by an erythematous ring.

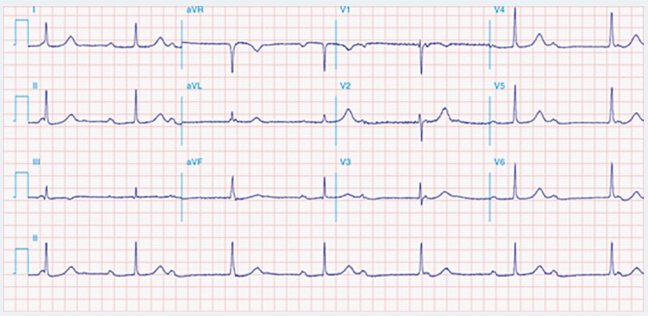


FIGURE 3-29. (Reproduced, with permission, from Kasper D, et al. eds. *Harrison's Principles of Internal Medicine*, 19th ed. New York, NY: McGraw-Hill; 2014.)

What is the most likely diagnosis?

Third-degree atrioventricular (AV) block secondary to Lyme disease. This condition is caused by *Borrelia burgdorferi*, a gram-negative spirochete that is poorly grown in culture and too small to be seen under regular light microscopy. Fluorescence may be used to visualize the corkscrew-shaped bacterium. However, the diagnosis is usually made clinically, supported by serology. Early local infection may present with a bull's-eye rash (**erythema chronicum migrans**) after several days. The early-disseminated stage may develop as early as a few days later and presents with cardiac conduction abnormalities (Lyme carditis), cranial nerve palsies (especially cranial nerve VII), and meningitis. Up to 43% of patients with Lyme carditis develop complete heart block. The diagnosis of Lyme disease is usually clinical, and PCR tests can be inaccurate. If there is suspected infection, even in children, the treatment of choice is doxycycline. If a tick is found soon after a hike through the woods, there does not need to be prophylaxis. The tick needs 36 hours of latching to spread the disease.

What other conditions can cause this condition?

Damage to the heart's conduction system by fibrosis, ischemia, cardiomyopathy, myocarditis, or iatrogenic damage (eg, after valve replacement) may cause complete heart block. Digitalis, calcium channel blockers, and β-blockers may produce a temporary conduction abnormality.

What is the route of infection?

Lyme disease is an arthropod-borne infection. The ***Ixodes* tick** transmits *B burgdorferi*. Mice and deer are reservoirs for the disease. These ticks are most often found in wooded areas in the Northeastern United States.

What is the prognosis for this patient?

The prognosis is good. The conduction abnormalities secondary to Lyme carditis are self-limited and short-lived and often resolve within days to weeks. It is uncommon for residual conduction abnormalities to persist after the infection has been cleared.

What is the immediate treatment for this patient?

The patient's ECG demonstrates bradycardia at a rate of 40/min. The episode of syncope indicates that cerebral perfusion is inadequate at this heart rate. Consequently, transvenous pacing may be initiated, but a permanent pacemaker is not needed. Antibiotic treatment for Lyme carditis consists of intravenous ceftriaxone until the PR interval is $<$ 300 ms, at which point oral antibiotics may be initiated. The same regimen applies to Lyme disease with neurological features. Doxycycline or amoxicillin is used for primary infection and Lyme arthritis only.

CASE 33

While doing a rotation in Ghana, a medical student encounters a patient who has been having nearly continuous high-grade fevers with occasional chills and sweats. The fevers seem to be cycling between incredibly high then back to normal over the day. Physical examination reveals a palpable spleen. The medical student remembers a lecture from parasitology and wants to do a test he heard about before, so he places a drop of the patient's blood in a copper sulfate solution, which reveals anemia. Over the next few days, while waiting for medication to arrive, the patient's level of consciousness waxes and wanes, and he is somnolent at times.

What is the most likely diagnosis?

Malaria due to *Plasmodium falciparum*. The symptoms give clues as to the species. The patient's altered mental status is consistent with a diagnosis of *P falciparum* malaria, since this is the only strain that commonly has cerebral involvement. This patient's continuous fever and irregular chills and sweats are also characteristic of *P falciparum* malaria. Early in infection, irregular fevers are common in all types of malaria, but the fever can become periodic in well-established cases of non-*falciparum* disease. For example, *P vivax* and *P ovale* cause episodes of fever, chills, and sweats every 48 hours. With *P malariae*, these episodes occur every 72 hours. Splenomegaly is a common finding in malaria due to work hypertrophy from increased RBC breakdown. This is differentiated from *Trypanosoma brucei*, which would not have the splenic involvement, but it would have fever, headache, fatigue, muscle aches, and swollen lymph nodes. The *tsetse* fly spreads *Trypanosoma brucei* (African Sleeping Sickness), which is endemic to Africa as well. Do not be tricked into thinking malaria is always the answer.

What phase of the microorganism's life cycle results in the development of anemia?

RBC lysis occurs during the erythrocytic cycle, when the products of asexual replication inside the RBCs (the merozoite form) are released. The immune response to the merozoites and resulting cytokine release is responsible for the fever, chills, and sweats. If left untreated, malaria can migrate to the brain, and there it blocks the capillaries and blood vessels in the brain, leading to coma and death. It can also cause severe anemia and hypoglycemia.

What are the likely peripheral blood smear (PBS) findings?

A PBS is likely to show ring-shaped trophozoites inside the RBCs (see Figure 3-30), and there may be several trophozoites per RBC. **Schizonts**, the large, multinucleated cells formed from the trophozoite by multiple cycles of nuclear division, may be visible in the erythrocytes in non-*falciparum* malaria but are very rarely seen in *falciparum* disease. Outside the RBCs, oblong **gametocytes**, diagnostic for *P falciparum*, may also be visible.

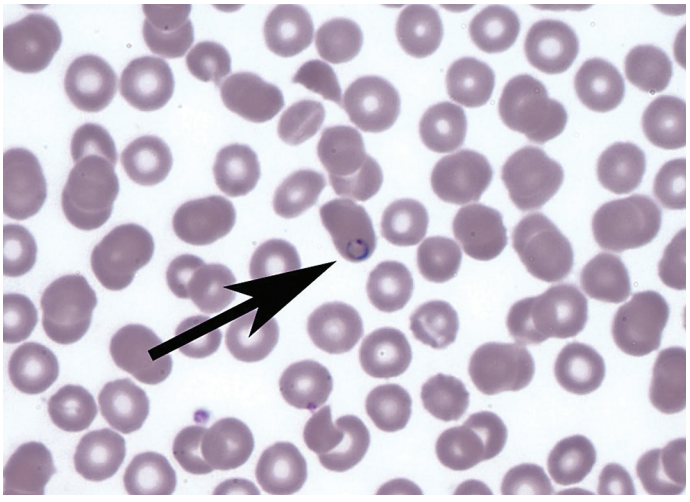


FIGURE 3-30. Malaria shown in the peripheral smear shows ring formation within the erythrocyte. (Reproduced with permission from USMLE-Rx.com.)

What is the treatment of choice for this condition?

Chloroquine is the drug of choice in the few areas where there is no resistance. Its major mode of action against *Plasmodium* is inhibition of the enzyme responsible for polymerizing heme. This results in the accumulation of free heme, which is toxic to the protozoan. Quinidine in combination with doxycycline or pyrimethamine/sulfadoxine is commonly used as first-line treatment for chloroquine-resistant *P falciparum*. Other effective drugs include mefloquine and atovaquone-proguanil.

What conditions provide protection again this condition?

Sickle cell trait and glucose-6-phosphate dehydrogenase (G6PD) deficiency both protect against malaria. The hypothesis is that increased fragility of the erythrocytes in these diseases does not allow for *Plasmodium* species to effectively replicate.

CASE 34

A mother brings her 14-year-old son to the pediatrician because the child has been experiencing flu-like symptoms and conjunctivitis for the past 3 days. The child is pale and febrile at 39.9°C (102.7°F), and his respiratory rate is 25/min. His buccal mucosa has multiple blue-gray spots (see Figure 3-31), and he has a maculopapular rash (see Figure 3-32). His mother states that the rash started on his face but has spread to his torso. The physician notes that the skin lesions blanch with pressure. The mother states that she usually uses naturopathic home remedies for her family's illnesses, and she has never vaccinated her family.

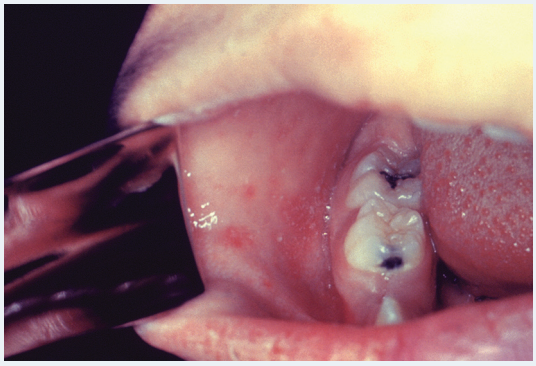


FIGURE 3-31. (Reproduced courtesy of the Centers for Disease Control and Prevention.)

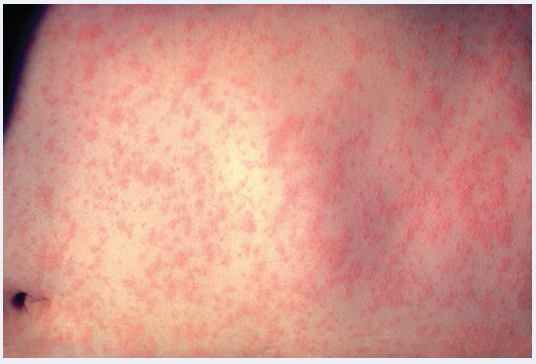


FIGURE 3-32. (Reproduced courtesy of the Centers for Disease Control and Prevention/Heinz F. Eichenwald, MD.)

What is the most likely diagnosis?

This child has measles, one of the most transmissible viral infections. Measles is caused by an RNA virus that is a member of the family Paramyxoviridae. Transmission occurs by respiratory droplets, and the incubation period is approximately 10 days. Two of this patient's symptoms are pathognomonic of measles: **Koplik spots** on the buccal mucosa (see Figure 3-31) and **blanching rash** (see Figure 3-32) with **cephalocaudal spread**.

What should be considered in the differential diagnosis?

Flu-like symptoms may also be caused by infection with rhinoviruses, parainfluenza, influenza, adenovirus, or respiratory syncytial virus. Common causes of rash include *Mycoplasma pneumoniae*, human herpesvirus-6, rubella, Rocky Mountain spotted fever, scarlet fever, or a drug reaction. However, none of these rashes have cephalocaudal spread and none feature Koplik spots.

What are potential neurologic sequelae of this condition?

Approximately 1:1000 patients with measles develop encephalitis, which is rapidly fatal in 15% of cases and leads to permanent neurological damage in 25% of patients. Infection with *Morbillivirus* can trigger acute disseminating encephalomyelitis, an autoimmune attack on the central nervous system, which is lethal in up to 20% of cases. Survivors often suffer intellectual disability and epilepsy. Approximately 7–10 years after a measles infection, subacute sclerosing panencephalitis may develop; this infection, although rare, is almost always fatal. This often presents as sudden encephalitis of an unvaccinated teenager.

What tests can confirm the diagnosis?

Anti-measles IgM is seen in patient serum approximately 48 hours after the onset of the rash. A mucosal biopsy may demonstrate **Warthin-Finkeldey** cells (multinucleated giant cells with inclusion bodies in the nucleus and cytoplasm).

What is the treatment for this condition?

There is no treatment for active infection; care is limited to supportive measures. Measles is a reportable disease, and the patient must be placed in isolation. If other children in the family have not received the measles-mumps-rubella vaccine, it is likely that they will develop measles because this virus is **highly** transmissible.

CASE 35

A 19-year-old college sophomore presents to the university health center with a 7-day history of sore throat, headache, and fatigue. He has a temperature of 37.7°C (99.9°F). Physical examination reveals enlarged, tender cervical lymph nodes in both the anterior and posterior cervical chain. The spleen is found to protrude 5 cm under the costal margin with inspiration. Upon examination of his oropharynx, gray-green tonsillar exudate is noted. He was originally given amoxicillin by an urgent care provider, but he stated this caused him to break out in a rash.

What is the most likely diagnosis?

Infectious mononucleosis is most frequently caused by Epstein-Barr virus (EBV), a member of the Herpesviridae family, but it can be also caused by the cytomegalovirus.

What should be considered in the differential diagnosis?

Several diseases present with symptoms similar to mononucleosis. However, streptococcal infection of the oropharynx is usually not associated with splenomegaly, and cytomegalovirus pharyngitis tends to be mild if clinically apparent at all. Low-grade fever, lymphadenopathy, and splenomegaly may also be seen in lymphoma. Lymphoproliferative disorders generally do not present with tonsillar exudate.

What are the PBS findings?

Infectious mononucleosis leads to lymphocytosis. The WBC count is often elevated (12,000–18,000/mm^3) with more than 50% lymphocytes. Up to 10% "atypical" lymphocytes containing large amounts of cytoplasm may be seen. However, these findings may also be seen in other infections (eg, cytomegalovirus, rubella, and toxoplasmosis), in some malignancies, and as a result of drug reactions.

Which malignancies are associated with this infection?

Burkitt lymphoma is endemic to Africa and primarily affects children. The disease is a B-cell lymphoma and often presents with a tumor of the jaw. This tumor often has a "starry sky" appearance under light microscope. **Nasopharyngeal carcinoma** is one of the most common cancers in southern China, and evidence supports EBV as its primary causative agent.

What treatments are available for this condition?

Symptomatic treatment, usually with nonsteroidal anti-inflammatory drugs, is usually used. Although EBV might be expected to be susceptible to acyclovir since it is a herpesvirus, studies have shown that acyclovir produces reduction of oral shedding of the virus but no other significant clinical benefit. Ampicillin should be avoided, not just because it is ineffective against viruses but because it can precipitate a rash.

CASE 36

A 55-year-old woman presents to the ED with confusion and lethargy. On physical examination she is found to be tachypneic and tachycardic, and her breath smells sweet and fruity. A review of her electronic medical record reveals that she was diagnosed with type 1 diabetes mellitus at 12 years of age. She has never been very compliant with her diabetes and insulin regimen. She has been admitted three times in the past year with diabetic ketoacidosis. She is admitted to the hospital and treated for diabetic ketoacidosis, and her symptoms begin to improve. However, 4 days after admission she develops fever, mucoid nasal discharge, and periorbital swelling (see Figure 3-33). While cultures are pending, she is treated with empiric antibiotics but fails to improve.

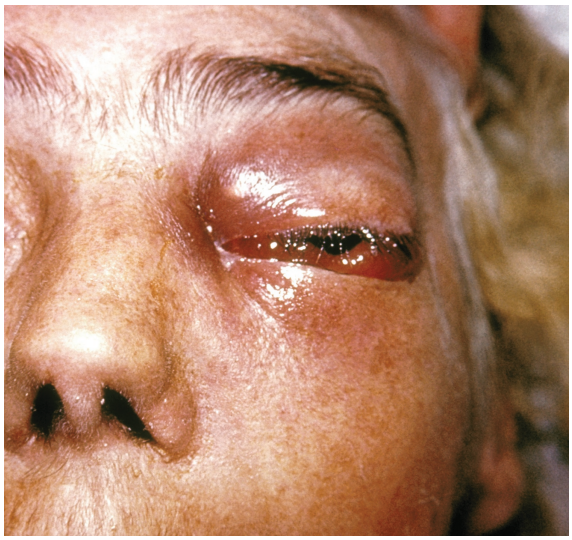


FIGURE 3-33. (Courtesy of the Centers for Disease Control and Prevention/Dr. Thomas F. Sellers/Emory University.)

What is the most likely diagnosis?

Mucormycosis.

What is the microscopic appearance of the fungus involved in this condition?

The zygomycetes are nonseptate, branching fungi, with wide (> 90-degree) branch angles and large hyphae. By contrast, *Aspergillus* tends to have narrow, septated hyphae and branches in acute angles. Figure 3-34 shows the large irregular nonseptations.

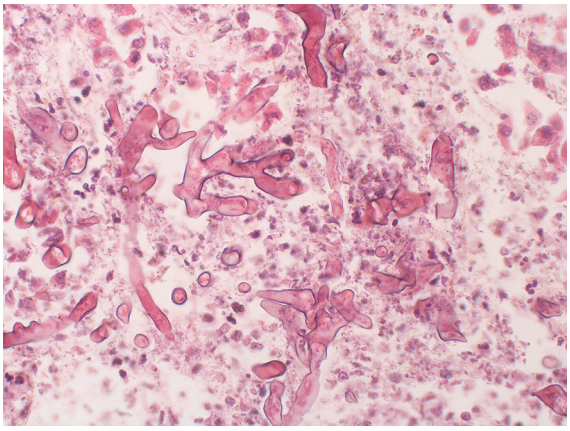


FIGURE 3-34. Zygomycetes of *Mucor*. (Reproduced courtesy of Dr. Yale Rosen.)

What patient populations are at increased risk for this condition?

The fungus is ubiquitous in nature and spores can be transmitted in air. Most patients are exposed to these spores several times per year, but an intact immune system is usually sufficient protection. Therefore, mucormycosis is typically seen in diabetic patients with poor glucose control or those with ketoacidosis. Neutropenic patients, burn victims, and patients treated with iron-chelating drugs are also at risk.

What is the pathogenesis of this condition?

The fungi grow along blood vessels and invade their walls. Protruding hyphae are highly thrombogenic, resulting in ischemia and necrosis of distal tissues, which, in turn, provide nutrients for continued fungal growth. Necrosis compromises the integrity of the bony walls of the sinuses and the cribriform plate, allowing fungal growth into paranasal sinuses, the bony orbit around the eye (as seen in Figure 3-33), or the brain. This rhinocephalic form of infection is rapidly progressive and carries a high mortality rate. Other forms include pulmonary, gastrointestinal, cutaneous, and disseminated infection.

What is the management for this condition?

Surgical debridement of infected and necrotic tissue is paramount. Reversal of the permissive condition (in this case ketoacidosis) should be initiated in conjunction with potent antifungal therapy with amphotericin B. However, despite optimal management, this condition still carries a high mortality rate.

CASE 37

A 21-year-old man from Honduras presents to his physician with a 2-day history of painful unilateral testicular swelling. The patient complains of minimal fever and myalgia about a week earlier. Physical examination reveals swollen and painful parotid glands. He immigrated to the United States when he was younger, and he does not remember much of his medical history.

What is the most likely diagnosis?

Orchitis secondary to mumps. In rare instances, orchitis can affect both testes and lead to sterility. It can also cause sterility if it affects the ovaries.

How is this condition transmitted?

The mumps virus is a member of the Paramyxoviridae family of single-stranded RNA viruses. It is not stable enough to be aerosolized but can be transmitted by droplets (eg, sneeze). The virus has a 2- to 3-week incubation period, after which the infection results in painful inflammation and edema of glandular tissues, including the parotid gland, testes, and ovaries. This question would typically state the person had not been vaccinated or had immigrated to the United States, which could point to a lack of immunization.

What other clinical syndrome can result from infection with this microorganism?

If the viral infection spreads to the meninges, **aseptic meningitis** may develop. Pancreatitis can also develop from this as well. This can be differentiated from bacterial meningitis by analysis of the cerebrospinal fluid (CSF):

Viral meningitis:
CSF protein ~ 150 mg/dL
Normal CSF glucose
CSF lymphocytes

Bacterial meningitis:
CSF protein > 300 mg/dL
Low CSF glucose
CSF neutrophils

Most viral meningitides are self limited and require only symptomatic treatment. Other common pathogens are coxsackievirus and echovirus. Mumps meningitis is rare in the United States because of vaccination.

How is the underlying condition diagnosed?

For the most part, the diagnosis of mumps can be made clinically. Supportive laboratory values include elevated amylase due to infection in the parotid glands. In uncertain cases, viral polymerase chain reaction assay may also be used.

What is the treatment for this condition?

The treatment is supportive and directed at reducing pain. Analgesics, compression, and icing of the parotid gland can be useful. In children, aspirin should be avoided as it has been linked to Reye syndrome. Vaccination with live attenuated mumps virus as part of the measles-mumps-rubella vaccine is used to prevent disease.

CASE 38

A 23-year-old sexually active woman presents 2 weeks after having sex with a new partner. She has been having worsening pain in her left knee and pain with urination. Physical exam reveals a swollen, tender, painful knee with decreased range of motion. Examination of her skin reveals small papules with an erythematous base on her arms. Pelvic examination is notable for purulent endocervical discharge (see Figure 3-35). Synovial fluid was sampled from the joint space, and it was purulent with 50,000 polymorphonuclear lymphocytes.

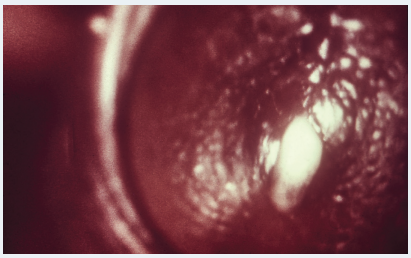


FIGURE 3-35. (Reproduced courtesy of the Centers for Disease Control and Prevention/Susan Lindsley.)

What is the likely causative organism of this condition?

Neisseria gonorrhoeae is contracted through sexual contact with an infected partner, and males are usually asymptomatic. The vaginal infection can cause discharge (see Figure 3-35) and dysuria. If the bacteria disseminate, skin lesions, tenosynovitis, or septic arthritis can develop. Septic arthritis is a serious condition that must be treated aggressively to prevent permanent damage to the joint. Septic arthritis is treated with intravenous antibiotics, analgesia, and joint washout.

How are septic arthritis, reactive arthritis, rheumatoid arthritis, and osteoarthritis differentiated and what is the gold standard of diagnosis?

Synovial fluid WBC count is the gold standard for diagnosis and differentiation between the various types of arthritis.

- **Osteoarthritis** is the most benign and is considered a non-inflammatory arthritis. The synovial fluid WBC count in osteoarthritis is < 2000 cells/mm^3. Gram stain will be negative.
- **Reactive arthritis** (most commonly associated with *Chlamydia* infection leading to the classic triad of uveitis, urethritis, and arthritis) and **rheumatoid arthritis** are both types of inflammatory arthritis. The synovial fluid WBC count in these conditions is 2000–75,000 cells/mm^3. Gram stain will be negative.
- **Septic arthritis**, which this patient has, presents with a synovial fluid WBC count of $> 100{,}000$ cells/mm^3, and Gram stain/culture of the fluid yields the causative organism.

In this patient, what is Gram stain of a cervical swab likely to show?

Gram-negative kidney-shaped cocci in pairs. However, the endocervical Gram stain is insensitive and nonspecific and is best diagnosed by nucleic acid testing (see Figure 3-36).

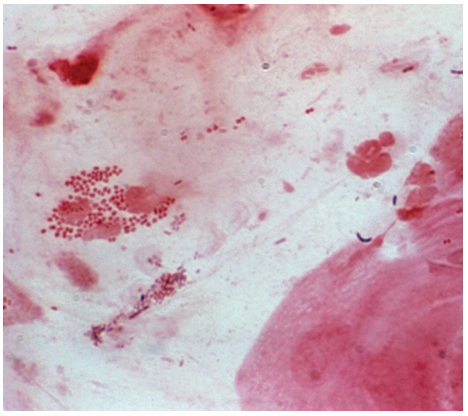


FIGURE 3-36. *Neisseria gonorrhoeae* in a cervical smear using the Gram-stain technique. (Reproduced courtesy of the Centers for Disease Control and Prevention/Joe Miller.)

What antibiotic is recommended for treatment of this condition?

Ceftriaxone is a first-line treatment for gonococcal infections, particularly if disseminated. Patients with gonorrhea have a high risk of co-infection with *Chlamydia trachomatis*. Therefore, patients are also empirically treated for *Chlamydia* with doxycycline or azithromycin because chlamydia is the most prevalent STD. If just gonorrhea is positive, the CDC recommends dual coverage ceftriaxone and azithromycin. If only the chlamydia is positive, then azithromycin or doxycycline only is used. Azithromycin can be added not only for the coverage of chlamydia, but it can be used because of the growing resistance of gonorrhea to cephalosporins.

If not treated early, what is a serious potential gynecologic complication of this condition?

If the infection persists, it can develop into pelvic inflammatory disease. The bacteria can ascend to the uterus, fallopian tubes, and ovaries, which can cause endometritis, salpingitis, oophoritis, and tubo-ovarian abscesses. The infection and subsequent scarring can reduce the patient's fertility, as oocytes are unable to travel through the scarred uterine tubes. In addition, untreated infection increases the risk of ectopic tubular pregnancy. In advanced stages, fibrotic adhesions between the fallopian tubes, uterus, and liver can occur in a condition known as Fitz-Hugh–Curtis syndrome. Empirical treatment for both gonorrhea and chlamydia is important because they both can cause infertility, so both are covered in treatment modalities, even if testing is negative for one.

CASE 39

An 18-year-old college freshman is brought to the university health center by his dormitory roommate because he was delirious and becoming less responsive. The patient's roommate says that he has had 2 days of fever, several episodes of vomiting, and joint and muscle pain. The patient's temperature is 38.9°C (102°F). Physical examination reveals a petechial rash on the lower extremities and photophobia; both Kernig and Brudzinski signs are positive.

What is the most likely diagnosis, and what other organ can be affected?

This patient likely has *Neisseria meningitidis* meningitis, a gram-negative, kidney-shaped diplococci infection. The adrenal glands can be affected, which is called Waterhouse-Friderichsen. There is hemorrhage into the adrenal glands. Figure 3-37 is a Gram stain showing the diplococcal bacteria of the *Neisseria meningitidis*.

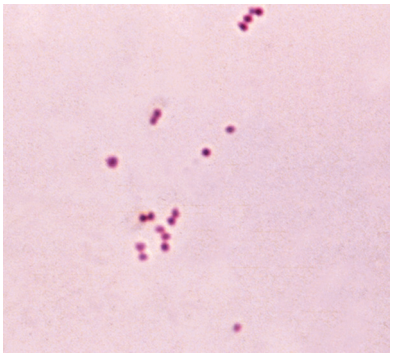


FIGURE 3-37. Gram stain shows *Neisseria meningitidis*. (Reproduced courtesy of the Centers for Disease Control and Prevention/ Dr. Brodsky.)

What test can confirm the diagnosis?

Culture of meningococcus from cerebrospinal fluid (CSF) or blood. Lumbar puncture shows an elevated WBC count (with mainly polymorphonuclear cells), decreased glucose levels, and normal to high protein levels. Bacteria are visible on Gram stain. This pathogen can also be cultured on Thayer-Martin media (chocolate agar with antibiotics to kill competing bacteria). *N meningitidis* is oxidase positive and ferments both maltose and glucose.

What are Kernig and Brudzinski signs?

Kernig sign is considered positive when the patient resists straightening of the knee joint while the hip is flexed. Brudzinski sign is considered positive when the patient, while supine, lifts the legs when the examiner flexes the neck. Neither test is very sensitive, but a positive result is suggestive of meningeal irritation either by blood or inflammation.

What are the most important virulence factors and toxins of this microorganism?

N meningitidis has thin protrusions called pili that help it attach to nasopharyngeal epithelial cells. Once attached to the nasopharynx, the pathogen secretes IgA protease to neutralize the predominant antibody idiotype found on mucous membranes. *N meningitidis* also features a capsule that protects it from other host defenses such as complement and phagocytosis. As with all gram-negative bacteria, *N meningitidis* has lipopolysaccharide, a potent endotoxin, in its cell wall.

What is the treatment for this condition?

Intravenous penicillin G or ceftriaxone must be administered immediately. Bacterial meningitis can be fatal within hours, so empiric antimicrobial treatment must be started before culture results or other confirmatory tests become available. Rifampin is recommended as prophylactic treatment for contacts of the patient, especially if they are immunocompromised or have not been vaccinated. Contacts can include those sitting on a plane nearby and those intubating the patient.

CASE 40

A 4-year-old boy is brought to the pediatrician because of perianal itching, which is worse at night. He attends preschool during the day, where he shares toys and play areas with other children. The patient's mother recalls her son playing with another child who had been "scratching his backside" and wonders if there is a connection. The doctor performs a Scotch tape test which reveals the findings below (see Figure 3-38).

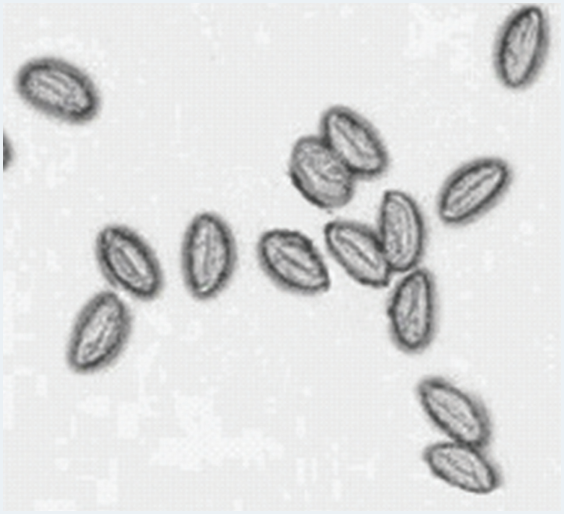


FIGURE 3-38. (Reproduced with permission from Zahariou A, et al. *J Med Case Rep.* 2007;1:137.)

What is the most likely diagnosis?

Pinworm infection caused by *Enterobius vermicularis*, a nematode (roundworm).

What is the life cycle of this organism?

After **fecal-oral transmission**, the eggs hatch in the small intestine. Adults mature in the ileum and large intestine and mate in the colon. Females exit the rectum at night to lay eggs in the perianal area. This irritates the perianal area, inducing the host to scratch. Scratching transfers eggs onto hands, greatly increasing the likelihood of transmission to another host and reinfection of the original host.

What sequelae may this infection have?

Intense scratching may compromise the integrity of the perianal skin, predisposing the patient to dermatitis or folliculitis due to dermal invasion of fecal bacteria.

What test can help confirm the diagnosis?

The adhesive or **"Scotch" tape test** (result shown in FIgure 3-38). The physician places adhesive tape over the perianal area and then removes and examines the tape. The presence of eggs under light microscopy indicates pinworm infection.

What are the treatments for this condition?

Mebendazole or albendazole is first-line therapy. Pyrantel pamoate can also be helpful. Individual cases are easily treated, but institutional outbreaks (such as in preschool) are more difficult to treat because undertreated patients quickly reinfect others who had already been cured.

CASE 41

A 10-year-old boy is camping with his family in the Adirondack Mountains when he is bitten on the leg by a raccoon. The animal was not provoked by the boy but attacked him unexpectedly. His family brings the boy to the nearest ED.

What condition is this boy at risk of contracting?

Rabies. If left untreated, rabies results in a nearly 100% mortality rate. Rabies causes only a few deaths per year in the United States but is significantly more dangerous in countries with unvaccinated domestic animals. For example, rabies-infected dog bites cause tens of thousands of deaths each year in India.

What is the morphology of the pathogen that causes this condition?

Rabies is caused by a rhabdovirus, a single-stranded RNA virus enveloped by a bullet-shaped capsid, covered by glycoprotein "spikes" (see Figure 3-39). The spikes bind to acetylcholine receptors, a property that may contribute to its virulence.

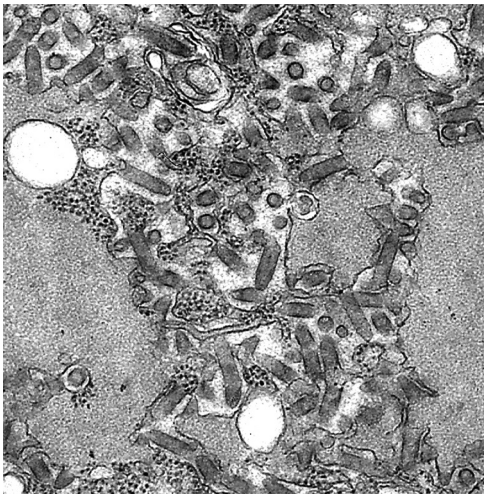


FIGURE 3-39. Electron micrograph of rabies virus. (Reproduced with permission from USMLE-Rx.com.)

What is the pathogenesis of this condition?

Animals transfer the virus to humans through bites that inoculate the host. The virus remains local for a period of days to months, then binds to acetylcholine receptors on neurons and travels to the central nervous system (CNS), utilizing axonal retrograde transport mechanisms. In the CNS, the virus infects neurons, including Ammon horn cells of the hippocampus. Rabies carries a significant person-to-person transmission risk through bites or mucous membrane exposure.

What signs and symptoms are associated with this condition?

Spasms of the pharyngeal muscles cause dysphagia, which leads to painful swallowing and accidental aspiration. This often leads to hydrophobia, a fear of water. Excess autonomic stimulation can cause hypersalivation. The buildup of saliva accounts for the apparent "foaming at the mouth." As rabies multiplies in the CNS, nonfocal neurological symptoms result, including confusion, agitation, hallucinations, and photophobia. Focal neurological deficits include cranial nerve palsies. Encephalitis can give rise to seizures, and inflammatory edema eventually leads to coma, then death.

How is the condition diagnosed and treated?

Identifying cytoplasmic inclusions called **Negri bodies** in tissues obtained from brain biopsy, polymerase chain reaction for viral RNA, and serology are diagnostic. In the event of a bite by an infected animal, the **human diploid cell vaccine** (a live attenuated virus) is administered. Additionally, **human rabies immune globulin (IgG)** is used to confer passive immunity to the patient. Both treatments are effective only in the lag period between the bite and onset of symptoms. Once symptoms appear, there is no effective treatment.

CASE 42

A 30-year-old man who recently joined a gym complains of itching between his toes. Physical examination reveals pustules on the fingers of both hands and white macerated tissue between the toes (see Figure 3-40). The patient says the pustules have been itchy and appeared about a week after the itching between the toes began.

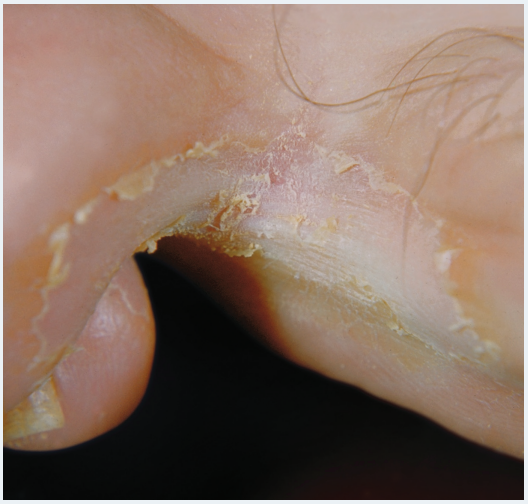


FIGURE 3-40. (Reproduced courtesy of the Centers for Disease Control and Prevention/Dr. Lucille K. Georg.)

What is the most likely diagnosis?

Ringworm (tinea pedis) infection. Although caused by the same group of fungi, each dermatophytosis is named after the region of the body that it infects: tinea cruris (perineum and creases of inner thigh; "jock itch"), tinea pedis ("athlete's foot," see Figure 3-40), tinea capitis (scalp), tinea unguium (nails), and tinea corporis (body).

What three microorganisms are often responsible for this presentation?

Microsporum, *Trichophyton*, and *Epidermophyton* are three filamentous fungi that cause **dermatophytosis**.

How is the microorganism transmitted?

After contact with an infected host, the keratinized epithelium of warm, moist skin is colonized. The infection expands radially and is characterized by curvy (wormlike) circular borders. Thus, it is termed "ringworm," despite the fact that the causative microorganism is actually a fungus.

What tests can help confirm the diagnosis?

Branched hyphae are observed on potassium hydroxide preparation (**KOH mount**). This fungus is not dimorphic. A sample from the lesions on the patient's feet will likely demonstrate the organism.

What is the treatment for this condition?

Topical azoles (eg, fluconazole), butenafine, terbinafine, or griseofulvin is used for treatment of tinea pedis.

CASE 43

A 13-year-old boy, who had been camping in the Appalachian Mountains with his family, was brought to the ED because of a headache, rash, and the abrupt onset of a high fever. The rash began on his palms and soles but spread up his ankles and arms (see Figure 3-41). On physical examination he was found to have palpable purpura on his wrists and lower legs.

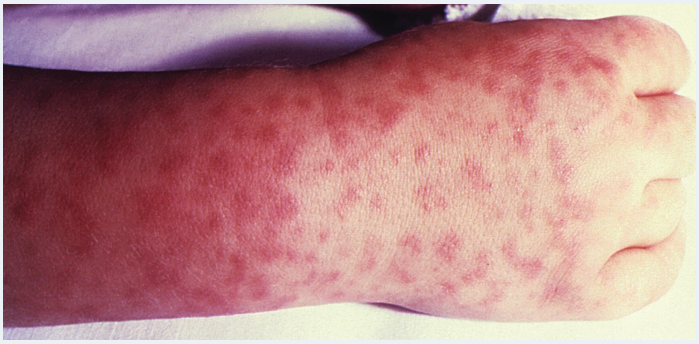


FIGURE 3-41. (Reproduced courtesy of the Centers for Disease Control and Prevention.)

What infections frequently cause a rash on the palms and soles?

Infections with *Rickettsia rickettsii*, *Treponema pallidum*, and coxsackievirus A can all cause a rash in this distribution.

What is the most likely infectious agent in this case?

This patient is most likely infected with *R rickettsii*. The clinical course is typical for Rocky Mountain spotted fever (RMSF), which is characterized by fever with abrupt onset and a rash that spreads from the extremities toward the trunk (as shown in Figure 3-41). RMSF can occur throughout the United States, Canada, and Mexico and is the most common rickettsial infection in the United States. Palpable purpura is a poor prognostic sign, as it indicates active vasculitis and leakage of blood into the skin. The rash in syphilis and coxsackievirus is typically more gradual in onset. However, syphilis should never be excluded because of the patient's age, as it is occasionally seen in sexually abused children.

How is this pathogen transmitted to humans?

R rickettsii is acquired from *Dermacentor* tick bites.

What other diseases are caused by these organisms?

Endemic typhus (also known as murine typhus) is caused by *R typhi*. This illness presents with vasculitis leading to headache, fever, chills, and myalgia. Epidemic typhus is caused by *R prowazekii* and often presents with high fevers, hypotension, and delirium. It often occurs in conditions of crowding and after disasters (eg, refugee camps). Both diseases are caused by arthropod-borne agents: endemic typhus is transmitted by fleas, whereas epidemic typhus is transmitted by the human body louse.

What is the pathogenesis of this disease?

R rickettsia is an obligate intracellular microbe that infects vascular endothelial cells, resulting in damage to the endothelium and vascular injury. The prostaglandins produced by the endothelial cells play an important role in the increased vascular permeability and inflammation. The infection also results in activation of the clotting cascade. The host response to the infection also contributes to the disease but is secondary to the vascular damage.

What laboratory technique can be used to identify the cause of this patient's illness?

Diagnosis is made clinically. Direct fluorescent antibody or polymerase chain reaction testing of a skin biopsy of one of the petechial lesions will confirm the diagnosis but not early enough to guide therapy. Rocky Mountain spotted fever antibody testing can also be used to confirm the diagnosis after recovery.

What is the treatment of choice for organisms of this class?

Tetracyclines (such as doxycycline) are most frequently used in rickettsial infections. The rickettsiae are obligate intracellular organisms, as they require coenzyme A and nicotinamide adenine dinucleotide from the host cell; they also lack the peptidoglycan cell wall targeted by many antibiotic classes. Tetracyclines can enter cells and act on ribosomal targets. Tetracyclines are typically not used in children but are in the case of Rocky Mountain Spotted Fever due to the harm of not treating the infection in comparison to the potential adverse effects, which are not as risky or likely to occur (tooth staining).

CASE 44

A 59-year-old woman presents to her physician with prominent scattered erythematous papules (see Figure 3-42) on the right side of her forehead. She says she has had a "burning" pain and general hypersensitivity in that area for the past 2 days. On review of systems, she denies headaches, mental status changes, or recent infections. Neurological examination indicates that her pain is localized to the right supraorbital area.

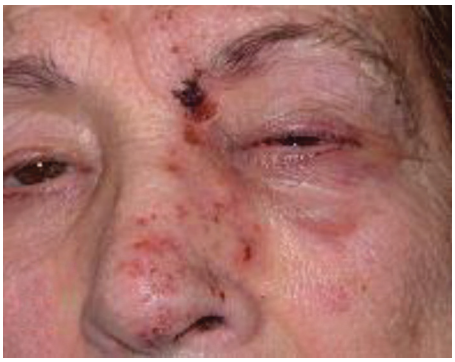


FIGURE 3-42. (Reproduced with permission from Kalogeropoulos CD, et al. *Med Hypothesis Discov Innov Ophthalmol.* 2015;4(4):142-156.)

Which nerve relays the painful sensation in this patient?

Sensory information from the face is relayed by the trigeminal nerve to the ventral posterolateral nucleus of the thalamus. The trigeminal nerve, as the name suggests, has three main branches: V1, V2, and V3. The V1 sensory branch covers most the forehead, supraorbital, and nasal bridge areas. V2 is termed the maxillary branch and covers the area of the maxillary bone as well as the alar areas of the nose (V2 comes out at the infraorbital foramen to the skull, high yield). V3 covers the mandibular portion of the face and so it is named. Specifically, the area described by the patient is the left V1 dermatome.

What infectious agent may be responsible for this woman's pain?

This woman is suffering from herpes zoster, or "shingles," a late complication of prior infection with varicella zoster virus, one of the herpes viruses.

What are the characteristic distribution patterns of this condition?

The virus remains latent in the ganglia of sensory nerves after the primary infection. When reactivation occurs (usually under conditions such as high stress or immunosuppression), virions are transported to the dermatome innervated by this sensory nerve using axonal transport mechanisms. Therefore, the characteristic shingles rash is always confined to a dermatome and does not cross the midline. In Figure 3-42, note that the rash occurs along the distribution of V1 on the left side of the face.

What are the likely findings on histologic examination of these vesicles?

A **Tzanck smear** is a historical assay that may demonstrate multinucleate giant cells, which are typical for infection with varicella and herpes simplex viruses. This test is rarely used for diagnosis, having been superseded by more specific molecular tests such as polymerase chain reaction or a direct antibody immunoassay. Further, shingles is more of a clinical diagnosis as the classic rash and symptoms of hypersensitivity and pain is enough to provide a diagnosis and treatment.

What are the treatments for this condition?

Acyclovir is activated by viral thymidine kinase to inhibit viral DNA polymerase. Valacyclovir and famciclovir have a similar mechanism and longer half-lives. These drugs target herpesviruses and may provide relief, speed recovery, and prevent postherpetic neuralgia. The drug doses for varicella are substantially higher than for herpes simplex virus. Primary infection with varicella and zoster can be prevented by vaccination. A zoster vaccine is available for the elderly population.

What are the advantages of a live attenuated vaccine?

Three general types of vaccinations are available: live attenuated, killed, or passive. Passive vaccination is the transfer of antibodies and is limited by antibody half-life in the bloodstream. A killed vaccine can stimulate only a humoral response as the virus cannot replicate within cells; therefore, no viral proteins can be displayed on major histocompatibility complex receptors. Live attenuated virus vaccine stimulates both arms of the immune system (humoral and cell mediated) as it leads to limited viral replication. Live attenuated vaccines should be avoided in pregnancy as only the humoral arm of the mother's immune system can protect the fetus across the placental barrier. Table 3-2 provides examples of types of vaccines.

Table 3-2. Live vs Killed Vaccines

Live attenuated vaccines	Killed vaccines
Smallpox	Rabies
Yellow Fever	Influenza
Varicella Zoster	Polio (Salk)
Sabin's Polio	Hepatitis A
MMR	

Helpful mnemonic for killed vaccines:
RIP Always: **R**abies, **I**nfluenza, **P**olio (Salk), Hep **A**.

CASE 45

A 36-year-old woman from Alabama presents with diffuse abdominal pain and diarrhea of 3 days' duration. She denies nausea, vomiting, or fever. She has no sick contacts or significant travel history. A complete blood count shows eosinophilia. A stool sample reveals larvae. On further questioning, she describes that she frequently gardens in her backyard while barefoot.

What is the most likely diagnosis?

Strongyloidiasis, caused by *Strongyloides stercoralis*, a nematode (roundworm).

What is the life cycle of this parasite?

Larvae in the soil penetrate the skin, usually the sole of the foot (fecal-cutaneous transmission). Local itching at the entry site promotes scratching, which aids larval entry into the bloodstream. Once in the blood, the larvae settle in the respiratory tree and travel up the trachea into the pharynx to be swallowed. They enter the small intestine, where the larvae mature into adults. Female adults invade the intestinal wall and lay eggs. During passage through the gastrointestinal tract, the eggs hatch into larvae. Most of these larvae pass with the stool and can continue the life cycle in the soil; some, however, directly penetrate the colonic wall or perianal skin and, uniquely, continue the life cycle within the original host. These continually migrating parasites are responsible for the eosinophilia commonly seen in chronic *Strongyloides* infections.

What other two organisms demonstrate the same route of transmission in humans?

Necator americanus (New World hookworm), and *Ancylostoma duodenale* (Old World hookworm).

What is the pathogenesis of hyperinfection syndrome?

Hyperinfection syndrome, caused by an uncontrolled autoinfection, can increase parasitic burden and widely disseminated disease. This is more common in individuals with defective eosinophil function, such as patients treated with steroids or cytotoxic chemotherapeutic agents that cause granulocytopenia.

What tests can help confirm the diagnosis?

Stool sample reveals larvae (not eggs as in hookworm infection). Blood samples reveal eosinophilia. *Strongyloides* antibody testing can also be valuable in patients with unexplained eosinophilia, as larvae are not always detectable in the stool.

What are the treatments for this condition?

Ivermectin or thiabendazole. Due to the intestinal nature of this organism, it can interfere with the normal absorption role of the small intestine. Specifically, *Strongyloides* can cause a B_{12} deficiency, which will manifest as a macrocytic anemia. Replenishment of B_{12} will be helpful in these circumstances.

CASE 46

A 52-year-old man from Michigan presents with worsening cough, fever, chills, and pleuritic chest pain. He was diagnosed with community-acquired pneumonia at a hospital but seeks a second opinion. He recently developed multiple ulcerated sores on his skin, which began as pimple-like lesions. X-ray of the chest reveals segmental consolidation. Biopsy of a skin lesion reveals big, broad-based, budding yeasts (see Figure 3-43).

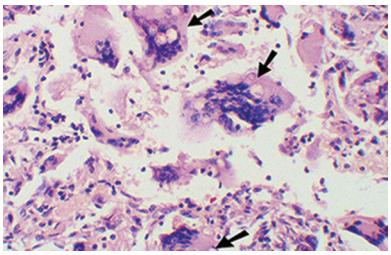


FIGURE 3-43. (Reproduced courtesy of Dr. Yale Rosen.)

What is the most likely diagnosis?

Blastomycosis, one of the systemic mycoses.

Which diagnostic tests can differentiate between the systemic mycoses?

Systemic mycoses are caused by dimorphic fungi, which grow as molds in the cold (eg, in the soil) and as yeast at higher temperatures (eg, in tissues at 37°C [98.6°F]), as shown in Figure 3-43. The exception is coccidioidomycosis, which is a spherule in tissue. Therefore, growing cultures on Sabouraud agar at multiple temperatures aids in the diagnosis. In addition, a tissue biopsy revealing broad-based budding yeast is diagnostic for blastomycosis. Tissue biopsy demonstrating yeast cells within macrophages is diagnostic of histoplasmosis. A biopsy showing "captain's wheel" morphology of budding yeast is diagnostic of paracoccidioidomycosis. Serologic testing for antifungal antibodies is also useful in some patients, and a histoplasma antigen test is the diagnostic test of choice for systemic (but not localized) *Histoplasma* infections.

What are the typical x-ray findings?

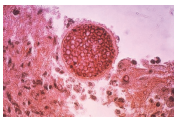
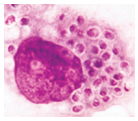
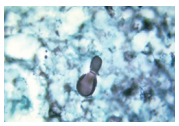
These diseases can mimic tuberculosis, forming **granulomas**, which appear as small calcium deposits on x-ray.

What is the treatment for this condition?

Systemic infection is treated with itraconazole or amphotericin B.

What are the other types of systemic mycoses? Where do they infect? (See Table 3-3.)

Table 3-3. Types of Systemic Mycoses

Name of fungus	Location	Important characteristics
Coccidiomycosis  **A**	Southwestern United States	Can cause pneumonia and meningitis with dissemination to bone (arthralgia) and skin (erythema nodosum) Increased rate of infection after earthquakes Spherule (much larger than RBC) is filled with endospores
Histoplasmosis  **B**	Mississippi and Ohio River Valleys (United States)	Causes mainly pneumonia in infected individuals Infects macrophages (invasive) and is smaller than RBCs Caused by bird or bat droppings
Blastomycosis  **C**	East of the Mississippi River (United States)	Causes inflammatory lung disease and can disseminate to skin and bone Typically forms granulomatous nodules Has broad base budding (same size as RBCs)
Paracoccidioidomycosis  **D**	Latin America	Characteristically looks like a "captain's wheel" Look for travel to Latin America

(Images reproduced courtesy of the US Department of Health and Human Services and authors Dr. D.T. McClenan [histoplasmosis], Dr. Libero Ajello [blastomycosis], and Dr. Lucille K. Georg [paracoccidioidomycosis].)

CASE 47

A 54-year-old man with HIV infection presents to the ED after suffering a grand mal seizure. He has no known personal or family history of seizures. He is afebrile, and his vital signs are stable. Funduscopic examination reveals yellow cotton-like lesions on his retina. Findings on physical examination are otherwise unremarkable. CT scan of the head demonstrates multiple ring-enhancing lesions in the cerebral cortex. Laboratory findings reveal a CD4+ cell count of 53 cells/mm^3.

What is the most likely cause of this patient's seizure?

Toxoplasma gondii infection.

How did this patient likely become infected with this microorganism?

It is likely that this man (like most individuals) has been latently infected with this protozoan for many years. However, his immunocompromised status has resulted in disease reactivation. Humans are most often infected by ingestion of cysts in undercooked meat or by fecal-oral transmission of cat feces. Cats may shed the protozoan, and pregnant women are discouraged from cleaning the litter box as inhaled aerosolized particles are sufficient to cause infection.

Why is this condition dangerous in pregnancy?

Primary infection with *T gondii* in a pregnant woman can allow parasites to cross the placenta. This leads to congenital problems in the newborn, including intellectual disability, microcephaly, chorioretinitis, intracerebral calcifications, and blindness. It is one of the **TORCHeS** infections (**T**oxoplasmosis, **O**ther infections, **R**ubella, **C**ytomegalovirus, **He**rpes simplex virus, **S**yphilis).

Given this patient's ring-enhancing lesions on CT scan, what other conditions should be included in the differential diagnosis?

This patient is also at an increased risk of lymphoma, cryptococcosis, and tuberculosis, all of which appear as ring-enhancing lesions on CT scan (although less likely to cause multiple lesions) and can also cause seizures.

What is the treatment for this condition?

First-line treatment is a regimen of pyrimethamine and sulfadiazine.

What other opportunistic infections occur with HIV, and at what viral load are they likely to occur?
(See Table 3-4.)

Table 3-4. Common HIV Infections and Viral Loads

Viral load (cells/μL)	Infections
< 200	*Pneumocystitis jiroveci* TB Coccidiodomycosis Candidiasis
< 100	Toxoplasmosis *Cryptococcus*
< 50	CMV MAC PML

CASE 48

A 17-year-old boy who recently immigrated to the United States from India presents to the ED with complaints of spiking fevers, weight loss, lethargy, and a large skin ulcer. He has not previously received any vaccinations. He reports that he has been generally healthy until he immigrated and has been having these symptoms. He is afraid that he has hepatitis or malaria because he had siblings die from each. On examination he is cachectic with a gray skin tone, and he is found to have pronounced splenomegaly and mild hepatomegaly. Laboratory tests reveal pancytopenia. Microscopic examination of a bone marrow aspirate reveals parasites in the histiocytes (see Figure 3-44).

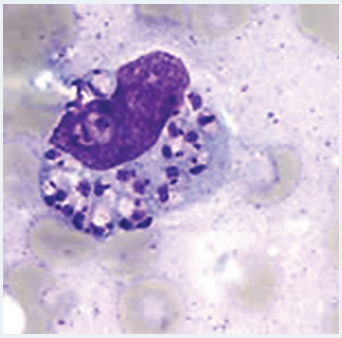


FIGURE 3-44. (Reproduced with permission from the Centers for Disease Control and Prevention.)

What is the most likely diagnosis?

This patient is suffering from kala azar, or visceral leishmaniasis. Visceral leishmaniasis is caused by the protozoan *Leishmania donovani* and is characterized by spiking fevers, hepatosplenomegaly, and pancytopenia.

Is the organism found in the amastigote or promastigote form in the infected human?

The form found in the **human host** is the **amastigote**, which is small and round and has a flagellum that is difficult to visualize. The prominently flagellated form of the parasite is found in the **insect vector** and is known as the **promastigote**.

What is the vector of this pathogen?

Humans are infected with *Leishmania donovani* through the bite of a sandfly. It can also be transmitted by intravenous drug use or blood transfusion. There is especially high prevalence in India and Africa.

On the blood smear, some macrophages contain basophilic inclusions. What are these inclusions?

These inclusions are called Donovan bodies and consist of the amastigote form of the parasite (see Figure 3-44).

What is the treatment for this condition?

Treatment is sodium stibogluconate or pentamidine.

What diseases are caused by other blood-borne flagellates?

Trypanosomes are another flagellated parasite that can be found in the blood. *Trypanosoma cruzi* is transmitted by the reduviid bug found in South America and causes Chagas disease. *T gambiense* and *T rhodesiense* are transmitted by the tsetse fly and are the cause of African sleeping sickness.

CASE 49

A 45-year-old man visiting rural Brazil develops fever, headache, pain in his knees and back, and nausea and vomiting. After 3 days these symptoms resolve, and he decides not to seek medical help. However, 2 days later the symptoms return, and he develops epigastric pain and yellowing of his skin. His vomitus is now dark in color.

What is the most likely diagnosis?

Yellow fever is endemic in South America and parts of Africa. It is characterized by an initial febrile illness, during which time serum aspartate aminotransferase and alanine aminotransferase levels begin to rise, followed by a remission of symptoms. Approximately 15% of infected patients experience a return of symptoms 2–3 days later, developing further liver dysfunction (resulting in jaundice and coagulopathy), renal damage, and myocardial damage.

What type of organism is responsible for this patient's condition?

The yellow fever virus is a **flavivirus**. These viruses have **positive, single-stranded RNA** genomes and icosahedral, enveloped capsids.

What are the most likely liver biopsy findings?

The characteristic finding on liver biopsy is midzone hepatocellular death, with sparing of cells bordering the central vein and portal tracts. **Councilman bodies** are found in the affected hepatocytes. These are eosinophilic inclusions that represent condensed chromatin. Typically, there is no inflammatory response. Liver biopsies are usually not done because of their concomitant coagulopathy. Specifically, yellow fever can infect Zone 2 of the liver.

Enzyme-linked immunosorbent assay (ELISA) may be useful in confirming the diagnosis by detecting antibody to the virus. How does ELISA work?

ELISA is a technique often used for serologic testing. It involves coating the surface with the desired antigen (in this case, yellow fever viral particles) and then placing the patient's serum on the surface, followed by a secondary antibody (antihuman antibody) that is linked to an enzyme. If the patient's serum has antibody to the antigen, the secondary antibody will bind. The linked enzyme can be detected by a reaction that produces an alteration in color with a colorimetric agent (eg, horseradish peroxidise). The color change can be quantified by spectroscopy. Detection of antibody to yellow fever virus in a patient with exposure can support a clinical diagnosis of the disease.

What are some other infections commonly found in Africa?

Dengue fever is a flavivirus (RNA, enveloped, single stranded, with icosahedral capsid) that uses an arthropod as a vector. It classically causes high fever, headache, vomiting, arthralgias, malaise, and a skin rash. The rash is described as a morbilliform rash with macular lesions. At its worst, dengue fever can cause a thrombocytopenia and anemia by infecting the bone marrow, which can then develop into shock.

Another infection that may show up is West Nile virus. It is also a flavivirus and uses the mosquito as its vector (like Dengue). It is characterized by headache, nausea, vomiting, and may progress to encephalitis and viral meningitis. The prominent finding of West Nile virus, if left untreated, can cause muscle weakness and flaccid paralysis. Its reservoir is known to be birds of the region.

4
Pharmacology

CASE 1

A 22-year-old woman is brought to the ED by her roommate, who found the woman lethargic and covered in vomit. The roommate explains that the woman has seemed "down" lately and that she has a history of epilepsy that is controlled with medications. On examination, the patient is sweaty, jaundiced, and lethargic, with marked right upper quadrant tenderness. Transaminase values are markedly elevated (aspartate aminotransferase: 12,450 U/L). A serum toxicology screen is sent.

This woman most likely overdosed on what medication?

Acetaminophen toxicity is the leading cause of acute liver failure. Anticonvulsant medications can increase the toxicity of acetaminophen (phenytoin and carbamazepine both induce the isoenzyme CYP2E1, which metabolizes acetaminophen into hepatotoxic metabolites).

What is the pathogenesis for this condition?

At therapeutic doses, a small quantity of acetaminophen is metabolized by hepatic cytochrome P-450 into a hepatotoxic intermediate, *N*-acetyl-p-benzoquinone imine (NAPQI). Glutathione is one of the main molecules involved in enzymatic detoxification of free radicals. Glutathione rapidly conjugates with NAPQI to form nontoxic compounds. At toxic doses of acetaminophen, glutathione storage is depleted, and hepatic damage ensues (see Figure 4-1).

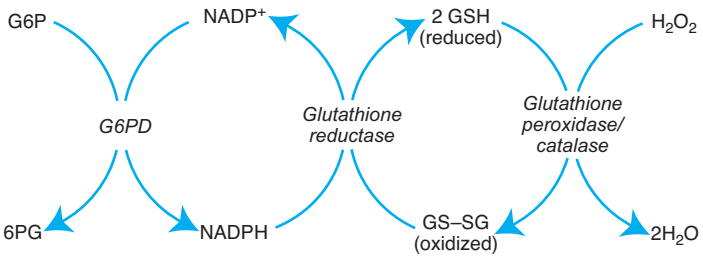


FIGURE 4-1. Glutathione metabolism. (Modified with permission from USMLE-Rx.com.)

What is the mechanism of action of the antidote?

N-acetylcysteine (NAC), the antidote, works via several pathways. NAC enhances the conjugation of NAPQI into a nontoxic compound, in part by increasing glutathione. Due to the pharmacokinetics of acetaminophen, the administration of NAC typically requires admission to the hospital.

Given the patient's presentation, approximately how long ago was the overdose?

There are four stages in an acetaminophen overdose:

- Stage 1 (< 24 hours after ingestion): Nonspecific complaints such as nausea and vomiting; sometimes asymptomatic and normal lab values.
- Stage 2 (1–3 days): Subclinical elevations in liver and/or renal function tests; resolution of stage 1 symptoms.
- Stage 3 (3–4 days): Peak of abnormal liver function tests and a return of stage 1 symptoms; clinical evidence of hepatic dysfunction; sometimes fatal. The patient in this case was most likely in this stage.
- Stage 4 (> 4 days): Recovery stage, if other stages are survived; complete by approximately day 7 if there is no underlying disease.

Note that the Rumack-Matthew nomogram plots the serum concentration of acetaminophen in relation to time after ingestion, starting at 4 hours after intake. It is used to determine risk of hepatotoxicity and can help guide treatment.

Additionally, a high anion gap metabolic acidosis has been associated with early and late acetaminophen toxicity. Compensation would then occur via hyperventilation causing respiratory alkalosis. This can be especially prominent in patients who are already clinically ill. Unlike salicylates, however, acetaminophen does not have set time frames for when this occurs.

What histologic regions of the liver would be most affected in this case?

The centrilobular zone (zone III—the area surrounding the central hepatic venule of a lobule, furthest from the branch of the hepatic vein; see Figure 4-2) is most involved because it has the highest concentration of CYP4502E1. Histologic recovery takes approximately 3 months.

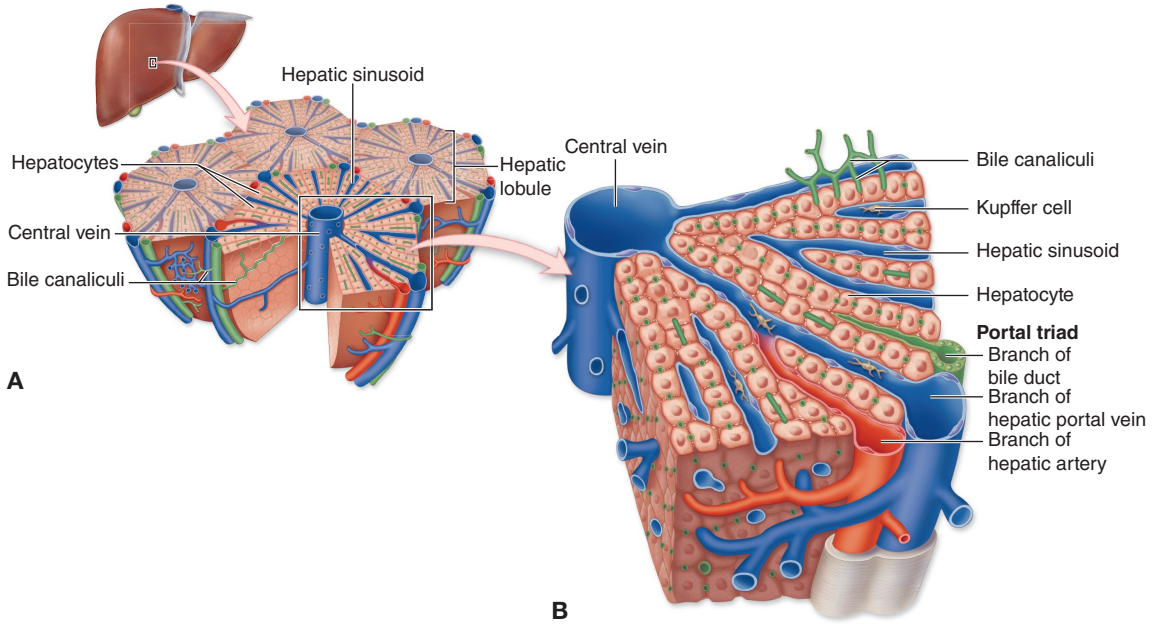


FIGURE 4-2. A. Hepatic lobules; B. Hepatocytes and sinusoids. (Modified with permission from McKinley M, et al. *Human Anatomy*. 3rd ed. New York, NY: McGraw-Hill; 2012.)

CASE 2

A 45-year-old woman is brought to the ED by the police for unusual and disruptive behavior. She is muttering to herself and does not make eye contact or answer any of the physician's questions but is otherwise cooperative. The patient's temperature is 38°C (100.4°F). A mouth examination yields the findings shown in Figure 4-3. Her urine and serum drug screens are negative for acetaminophen, salicylates, and drugs of abuse. She is HIV negative. Her CBC shows:

WBC count: 2000/mm^3
Neutrophils: 1%
Monocytes: 15%
Eosinophils: 8%
Basophils: 2%
Hemoglobin: 12 g/dL
Lymphocytes: 74%
Platelet count: 270,000/mm^3

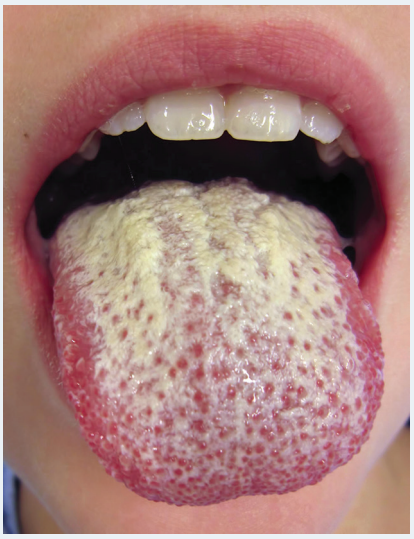


FIGURE 4-3. (Reproduced courtesy of Dr. James Heilman.)

Given her presentation, what medication is the patient likely to be taking?

This patient is acutely psychotic and suffering from agranulocytosis (lack of granulocytes [neutrophils, eosinophils, and basophils]), which can lead to oral candidiasis (thrush), as seen in Figure 4-3. **Clozapine**, an antipsychotic, causes agranulocytosis in 1%–2% of patients and will usually do so in the initial months of treatment. Although agranulocytosis is the most dangerous adverse effect, the most common adverse effect of clozapine is metabolic syndrome. It is used in treatment of refractory psychosis, and the decision to use it should be evaluated carefully because patients will need to cooperate with frequent blood tests to monitor ANC levels. Additionally, clozapine, as well as lithium (Li) and electroconvulsive therapy (ECT), can be used to treat acute suicidality.

What is the management for this patient?

First, the medication causing neutropenia should be discontinued immediately, which should cause neutropenia to resolve within 1–3 weeks. Treatment may include granulocyte colony–stimulating factor, which has been shown to restore immune function in some neutropenic patients with serious infections. Other drugs that can cause agranulocytosis include carbamazepine, propylthiouracil, methimazole, colchicine, and ganciclovir.

What are the pharmacokinetics of the medication this patient is taking?

Note that **pharmacokinetics** refers to the body's effect on the drug, whereas **pharmacodynamics** refers to the drug's effect on the body. Pharmacokinetics can be remembered by the mnemonic **ADME**, which stands for **A**bsorption, **D**istribution, **M**etabolism, **E**xcretion. Clozapine is rapidly absorbed orally; however, only about 27%–50% reaches systemic circulation because it has an extensive first-pass metabolism. It is rapidly distributed and can cross the blood-brain barrier and placenta. At steady state, its elimination half-life is about 12 hours. About 50% of the administered dose is excreted in urine and 30% in feces.

If a patient took bromocriptine and clozapine simultaneously, how would the receptor binding graph look?

Bromocriptine, used in hyperprolactinemia and parkinsonism, is a dopamine receptor agonist, whereas clozapine is a dopamine receptor antagonist. Concomitant administration of these drugs would result in competitive inhibition (see Figure 4-4).

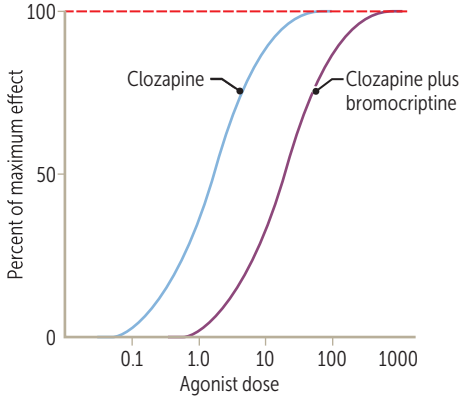


FIGURE 4-4. Competitive antagonist receptor binding. (Reproduced with permission from USMLE-Rx.com.)

CASE 3

A 37-year-old lawyer is brought to the ED by the police. He was seen yelling and stumbling and says that he feels bugs crawling all over him. Physical examination reveals tachycardia, diaphoresis, tachypnea, tremor of the hands, and normal-sized pupils.

What is the most likely diagnosis?

The first step in reaching a diagnosis is determining whether the patient's presentation is due to substance abuse/withdrawal or to a psychiatric condition such as schizophrenia. The constellation of physical symptoms here suggests a sympathomimetic toxidrome. The specific sensation of feeling bugs crawling over him, called formication, is highly suggestive of alcohol withdrawal. Cocaine intoxication could also be considered, but alcohol withdrawal is more likely due to normal pupillary size and stumbling gait. Cocaine is more often considered if there is a young male with chest pain.

What is the treatment for this condition?

Alcohol withdrawal is treated with benzodiazepines, usually chlordiazepoxide, diazepam, or lorazepam. If the person has liver disease, prescribe LOT therapy, either lorazepam, oxazepam, or temazepam. Additionally, note that short-acting benzos can be remembered by the mnemonic **ATOM**, **A**lprazolam, **T**riazolam, **O**xazepam, **M**idazolam.

What are other indications of the treatment?

Benzodiazepines have many indications, including acute anxiety, status epilepticus, night terrors, and somnambulism. Benzodiazepines act by increasing the **frequency** of the g-aminobutyric acid $(GABA)_A$ chloride channel opening. $GABA_A$ is a ligand-gated chloride channel; $GABA_B$ is linked via G-proteins to potassium channels.

How do benzodiazepines differ from barbiturates?

Barbiturates increase $GABA_A$ signaling (see Figure 4-5) by increasing the **duration** of chloride channel opening, which causes hyperpolarization. Barbiturates are contraindicated in porphyria and are used primarily for their sedative effects. Importantly, barbiturates have a greater risk of coma and respiratory depression than benzodiazepines. In clinical practice, benzodiazepines have largely replaced barbiturates.

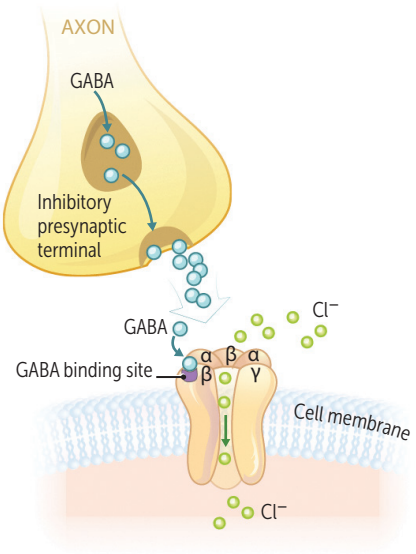


FIGURE 4-5. GABA receptors at work. (Reproduced with permission from USMLE-Rx.com.)

Is there an antidote for benzodiazepine overdose or for barbiturate overdose?

Benzodiazepine overdose can be reversed with flumazenil, a competitive antagonist at the GABA receptor. However, flumazenil is used only in a controlled setting due to the risk of unmasking seizures in benzodiazepine-naïve patients. **Barbiturate overdose is more dangerous** because there is no reversal agent. Therefore, symptomatic management and ventilator support are the only treatments for barbiturate overdose.

What is the time course of events that can occur in this condition?

Symptoms of alcohol withdrawal often start 4–10 hours after alcohol cessation (when the blood alcohol concentration drops below 100 mg/dL) (see Table 4-1). Severity of symptoms usually peaks at day 2–3. The most concerning event of alcohol withdrawal is delirium tremens (DT).

Table 4-1. Time for Alcohol Withdrawal Symptoms

Time	Alcohol withdrawal symptoms
4–10 hours	Autonomic hyperactivity (increased respiratory rate, temperature, pulse, sweating), headache, tremors, agitation
1–3 days	Hallucinations (typically visual) and seizures
2–4 days	Delirium tremens (DT): disorientation, hypertension, tachycardia, fever, hallucinations, seizures

CASE 4

A 32-year-old woman with a history of asthma begins to have difficulty breathing. She has forgotten her inhaler and is brought to the ED, where she is noted to be in moderate respiratory distress. She is using her accessory muscles, and her oxygen saturation is 89%. She is becoming anxious because it is increasingly difficult for her to breathe. She is immediately given an inhalant treatment.

What type of drug was likely given?

Short-acting β_2-adrenergic receptor agonists (β_2-agonists) such as albuterol are a mainstay in treating acute asthma. β_2-agonists such as albuterol cause bronchodilation. Other β_2-agonists include terbutaline, metaproterenol, and ritodrine.

In what other locations can this subset of receptors be found?

β_2-adrenergic receptors are found

- on the smooth muscle of blood vessels, where they induce vasodilation.
- on bronchioles, where they facilitate bronchodilation.
- in pancreatic α cells, where they stimulate glucagon release.
- in the eyes, where they increase aqueous humor production and cause ciliary muscle relaxation.
- on parietal cells of the gastric mucosa, where they stimulate acid secretion.
- in the uterine myometrium, where they cause uterine relaxation.

Stimulation of these receptors activates what second-messenger system?

All adrenergic receptors, including α- and β-adrenergic receptors (see Table 4-2), are G protein–linked receptors, and β_2-receptors are linked to the S class of G proteins.

Table 4-2. G Protein-Linked Second Messengers

	G_I Receptor	**G_S Receptor**	**G_Q Receptor**
Action	Adenyl cyclase $\rightarrow \downarrow$ cAMP $\rightarrow \downarrow$ PKA	Adenyl cyclase $\rightarrow \uparrow$ cAMP $\rightarrow \uparrow$ PKA	PLC $\rightarrow PIP_2 \rightarrow IP_3 \rightarrow \uparrow Ca^{2+}$
Types of receptors	α_2 M_2 D_2	$\beta_1, \beta_2, \beta_3$ H_2 D_1 V_2	α_1 M_1, M_3 H_1 V_1

What is the mechanism of action of this subclass of G receptors?

The G_s protein activates adenyl cyclase, which converts adenosine triphosphate to cyclic adenosine monophosphate, which in turn activates protein kinase A (PKA). In uterine myometrial cells, the activated PKA phosphorylates other proteins; this reduces intracellular calcium concentration, decreases activity of myosin light-chain kinase, and diminishes contractility of the uterine muscle cells.

What other classes of receptors are linked to this subclass of G receptors?

Other receptors linked to G_s include β_1, D_1, H_2, and V_2 receptors. Activation of any of these receptors leads to activation of G_s and adenyl cyclase.

CASE 5

A 53-year-old African-American woman presents to her primary care physician for a follow-up visit after being hospitalized for congestive heart failure. She was discharged on carvedilol, furosemide, and hydralazine and has continued to take these medications daily. The woman takes no additional prescription or over-the-counter medications. Recently she has been experiencing muscle aches, joint pain, and rash. Physical exam reveals a temperature of 37.7°C (100.0°F) and a scaling erythematous rash on her face. The physician orders an autoantibody panel that yields the following results:

Antinuclear antibodies (ANA): Positive
Anti–ribonucleic protein (RNP) antibodies: Negative
Anti-Smith (Sm) antibodies: Negative
Anti-DNA antibodies: Negative
Anti-histone antibodies: Positive
Rheumatoid factor: Negative

What is the most likely diagnosis?

Rash, arthralgias, and anti-histone antibodies suggest drug-induced systemic lupus erythematosus (SLE). Hydralazine is the causative drug in this case. Anti-histone antibodies are a very sensitive lab value for drug-induced SLE. Positive ANA is nonspecific, as there are many conditions, mostly infectious and autoimmune, that show positive ANA. However, the sensitivity of ANA for drug-induced SLE is 100%, so if ANA is negative, drug-induced SLE can be ruled out.

What other medications can cause a similar presentation?

Drugs known to induce SLE include etanercept, diltiazem, phenytoin, procainamide, chlorpromazine, isoniazid, methyldopa, minocycline, penicillamine.

How do spontaneous forms of this disorder differ from drug-induced forms?

Drug-induced SLE typically manifests with arthralgias and myalgias. Cutaneous features of DISLE are usually more widespread and can include a vasculitis-like presentation. It is difficult to diagnose DISLE vs. SLE based on timing, because DISLE can occur within weeks to years of drug initiation. DISLE, however, typically lacks visceral and hematologic abnormalities such as CNS effects, nephritis, and thrombocytopenia.

CASE 6

A small biotechnology company has developed a new drug that holds promise for the treatment of osteoarthritis. Currently, it is being tested on a group of 100 patients with osteoarthritis, some of whom are receiving placebo.

In which phase of testing is this drug?

The drug is in **phase II** of clinical testing, which entails the enrollment of a small group of patients, usually 100–300, into a trial. The trial, usually single-blinded, compares the new product to placebo as well as to an older drug that has already been proven effective.

What characterizes the phase of testing that the drug has already been through?

The first step of clinical testing, **phase I**, involves non-blinded testing on a small group (20–30) of healthy volunteers (see Figure 4-6). The goals in this phase are to determine whether the response of humans to the drug is significantly different from the response of animals (before reaching clinical trials, a drug is extensively tested on animals for toxicity, carcinogenicity, etc.) and whether the effects of the drug are a function of dose

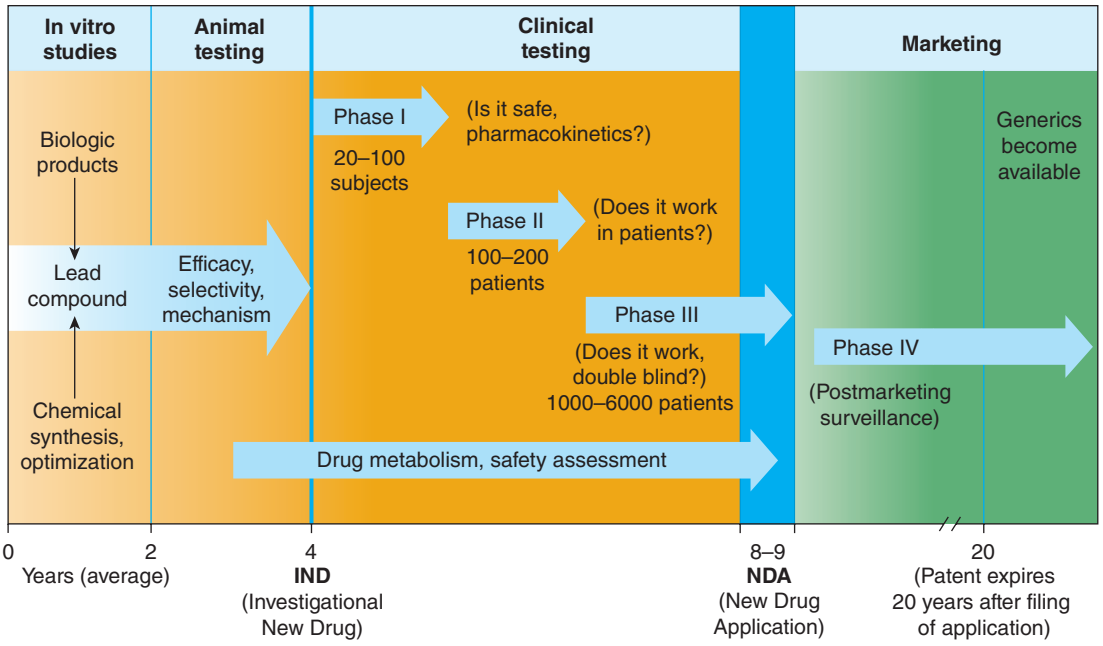


FIGURE 4-6. Phases of the FDA review process. (Reproduced with permission from Katzung BG, ed.: *Basic & Clinical Pharmacology*, 14th ed. McGraw-Hill, 2018)

What happens in the next phases of testing?

Phase III testing involves evaluating the drug in a trial of a large group of patients (hundreds to thousands). The trial is usually double-blinded and evaluates the overall benefit-risk relationship to provide an adequate basis for physician labeling. If phase III testing is successful, the company will submit a New Drug Application to the Food and Drug Administration (FDA), which will include preclinical and clinical data. The FDA will then review this material and if the drug is approved for market, phase IV testing starts. **Phase IV** entails post-marketing surveillance, or in other words, monitoring the drug as it is used in real conditions with large numbers of patients. **This phase is important for discovering low-incidence toxicities that would not be uncovered in clinical trials**. Phase IV is the last phase of testing and continues indefinitely.

What is a double-blinded study and why is it the most powerful type of research study?

In a **double-blinded study**, neither the subjects nor researchers know who is receiving the experimental drug and who is receiving placebo. Masking this information eliminates both observer and subject bias, which is why it is considered to be the best format for obtaining objective data.

If this drug passes all phases of testing, when will a generic form become available?

A drug patent is typically issued for 20 years, after which time generic forms become available. However, the evaluation of the application by the FDA may take several years. Up to 5 years of the review time may be added back to the patent.

CASE 7

A man calls the police because he hears someone moving around in the garage of his house. When the police arrive, they find an intoxicated homeless man with slurred speech collapsed by a closet full of automotive supplies. The homeless man is immediately rushed to the ED. Blood tests show a large anion gap acidosis and markedly elevated creatinine. Eye exam is normal.

What is the most likely diagnosis?

This could be either methanol or ethylene glycol poisoning, as both are found in antifreeze. Both methanol and ethylene glycol cause a high anion gap metabolic acidosis. The osmolar gap is elevated in ethylene glycol and early methanol poisoning; however, it tends to normalize for methanol later in toxicity progression. This can be used to potentially differentiate between the two substances. However, the most likely diagnosis is ethylene glycol poisoning because methanol poisoning leads to ophthalmologic abnormalities such as afferent papillary defect and mydriasis. Ethylene glycol has a mildly sweet taste, which allows unintentional consumption by both children and adults, often in large quantities. Although ethylene glycol and methanol themselves are mostly nontoxic, accumulation of the metabolites is toxic (see Figure 4-7).

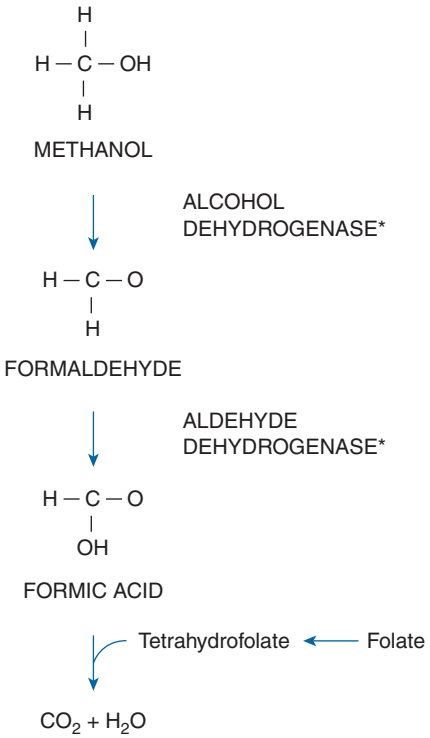


FIGURE 4-7. Methanol metabolism. *Blocked by ethanol and fomepizole.

Without treatment, what symptoms would likely occur?

Ethylene glycol poisoning typically follows three stages. Stage 1 is pure intoxication with dizziness and slurred speech. Stage 2 (12–24 hours after ingestion) comprises metabolic acidosis, tachycardia, and hypertension due to the toxic metabolite oxalic acid that is formed by metabolism of ethylene glycol by alcohol dehydrogenase. Stage 3 (24–48 hours after ingestion) is often kidney failure.

Why might kidney failure occur if this patient is not treated?

Alcohol dehydrogenase is an endogenous enzyme that can metabolize ethanol, methanol, and ethylene glycol to eventually produce acetate, formaldehyde, and oxalate, respectively. Calcium in renal tubules can combine with the oxalate to produce calcium oxalate stones causing decreased tubular reabsorption and dilation, which can then progress to kidney failure.

What is the treatment for this patient's condition?

There are three possible treatments:

1. **Fomepizole** is a competitive inhibitor of alcohol dehydrogenase. It blocks metabolism of ethylene glycol (or methanol), allowing it to be excreted in a harmless premetabolic stage.
2. An intravenous infusion of alcohol can be administered if fomepizole is not available, which also works by competitive inhibition.
3. Hemodialysis may be needed in patients that present with ethylene glycol toxicity late enough that their kidneys are severely affected.

Of note, gastric lavage and emesis are no longer recommended methods of decontamination for any ingestion.

CASE 8

A 3-year-old boy is brought to the ED by his mother, who states that for the past several days she has noticed that his appetite has decreased, and he has intermittently indicated that his tummy hurts. She and her husband have experienced similar but milder symptoms. They live in rural New Mexico and make jewelry on a small scale at home.

What is the most likely diagnosis?

Subacute lead poisoning. In terms of presentation, abdominal colic is one of the hallmark symptoms of lead poisoning and can be followed by bloody diarrhea. This family has been exposed to lead because of their occupation as jewelers. Of note, a common case-vignette to be aware of for subacute lead toxicity will include the patient living in an "old house" (typically built before 1975), from which it can be assumed that the paint is lead-based.

If a smear of this patient's blood were examined microscopically, what signs would help confirm the diagnosis?

Basophilic stippling of erythrocytes (see Figure 4-8) is commonly seen with lead poisoning. In addition, lead poisoning may present in the form of sideroblastic anemia. Sideroblastic anemias impair heme synthesis in developing RBCs, leading to impaired hemoglobin production and the formation of hypochromic and microcytic cells. In addition to lead poisoning, sideroblastic anemia can also be seen in alcohol use disorder, prescription drug use (isoniazid, chloramphenicol), copper deficiency, refractory anemia, and some rare congenital diseases.

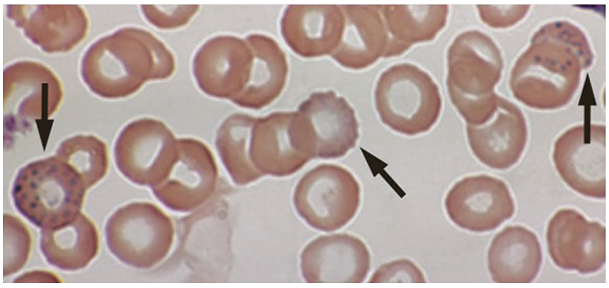


FIGURE 4-8. Basophilic stippling. (Reproduced courtesy of Herbert L. Fred, MD, et al. *Images of Memorable Cases: Case 81*. OpenStax CNX. Dec 3, 2008.)

What neurologic complications can occur in this condition?

Lead poisoning may present with a range of neurological symptoms, including hearing loss, developmental delay, and neuropathies. Two neuropathies often seen are wrist and foot drop, reflecting radial and common peroneal neuropathies, respectively. Lead poisoning may also cause encephalopathy.

What radiographic findings might be present in chronic forms of this condition?

In chronic pediatric lead poisoning, lead deposits can form in the epiphyses of long bones.

How does treatment differ between children and adults with this condition?

In both children and adults, further prevention of lead exposure is the most important treatment. The use of chelation agents, such as dimercaprol, D-penicillamine, dimercaptosuccinic acid (DMSA), and Edetate calcium disodium ($CaNa_2$ EDTA), depend on lead levels. For children, 5–44 μg/dL does not require chelation; however, repeat lead level testing must be done in one month; $>$ 45 μg/dL is typically treated with DMSA; $>$ 70 μg/dL is a medical emergency treated with combination dimercaprol and $CaNa_2$ EDTA in the setting of encephalopathy. For adults, chelation is considered with lead levels $>$ 70 μg/dL or if symptomatic. First-line treatment is $CaNa_2$ EDTA or dimercaprol.

CASE 9

A 36-year-old man is brought to the ED by his wife, who explains that he has felt lightheaded, dizzy, and weak. When asked about his medical history, she states that he recently switched to a new medication to treat his depression. When asked about symptoms of his depression, she states that he had been overeating, oversleeping, and had a strange sensation of heaviness in his arms and legs. Physical exam reveals a blood pressure of 80/45 mm Hg.

What class of drug has the patient recently started?

The signs described by the wife indicate atypical depression. Monoamine oxidase inhibitors (MAOIs) (eg, selegiline, tranylcypromine) are frequently used to treat patients with atypical depression (but not those with typical depression), especially after other medications have failed. Atypical depression is characterized by mood reactivity and leaden paralysis, noted by the "heaviness" in the arms and legs.

What precautions should a patient take when starting this class of drugs?

Orthostatic hypotension is a common adverse effect of MAOIs, although the mechanism is not completely understood. Paradoxically, various factors can cause a hypertensive crisis in patients taking MAOIs, including co-administration of a sympathomimetic (including over-the-counter medications and nutritional supplements such as St. John's wort, dextromethorphan, pseudoephedrine) and ingestion of foods rich in tyramine, such as strong or aged cheeses and cured meats such as pepperoni and salami. In the latter case, when MAO is inhibited, excess tyramine is taken up by adrenergic neurons, which must then release norepinephrine, leading to acute hypertension. Hypertensive crisis is treated with the α_1-blocker, phentolamine.

The drugs that could be used to increase this patient's blood pressure act on what receptors?

For a hypotensive patient, activity should be increased on the α_1-receptor. The α_1-receptor is a G(G_q) protein–coupled receptor that vasoconstricts the arteries. Conversely, activity on the α_2-receptor (also a G protein–coupled receptor, but G_i) leads to vasodilation. For this reason, midodrine is preferred to phenylephrine or epinephrine, as it is most selective for α_1. In practice, the most commonly used first-line medication for chronic hypotension is fludrocortisone, which acts by increasing sensitivity of blood vessels to catecholamines and increasing norepinephrine release.

Assuming a target plasma concentration of 100 ng/mL and first-order elimination, calculate the daily maintenance dose of tranylcypromine for this 70 kg patient. F = 0.7, V_d = 1.2 L/kg, $t_{1/2}$ = 2 hr

To calculate the maintenance dose, first calculate clearance using the formula:

$$t_{1/2} = (0.693 \times V_d)/CL$$
$$CL = 29.1 \text{ L/hr}$$

Then use the formula:

$$\text{Maintenance dose} = (C_p \times CL \times \tau)/F$$

where τ is the dosage interval, C_p is the target plasma concentration, and F is bioavailability. Note that the dosage interval is 24 hours.

$$\text{Maintenance dose} = 100 \text{ mg}$$

Note that if this patient were hepatically or renally impaired, the maintenance dose would have to be decreased.

Calculate the loading dose based on the above calculations.

$$\text{Loading dose} = (C_p \times V_d)/F$$
$$\text{Loading dose} = 12 \text{ mg}$$

CASE 10

A 17-year-old high school student is brought to the ED after feeling a tearing sensation in his knee when he was tackled playing football. After the initial consult, it is determined that the boy will need surgery to reattach a torn ligament. During anesthesia, a neuromuscular blocking drug (NMBD) is given.

In what clinical settings are NMBDs used?

The NMBDs are used for muscle paralysis during surgery or mechanical ventilation.

What are some examples of NMBDs?

Examples of these agents include succinylcholine, tubocurarine, and most drugs that end in "–curium" (eg, atracurium) or "–curonium" (eg, rocuronium).

For what type of receptors is this class of drug selective?

Neuromuscular agents are specific for the motor nicotinic acetylcholine receptors present at the neuromuscular junction (see Figure 4-9).

What are the two types of neuromuscular blocking drugs?

Depolarizing and non-depolarizing agents. The majority of agents in clinical use are non-depolarizing. The only commonly used depolarizing agent is succinylcholine.

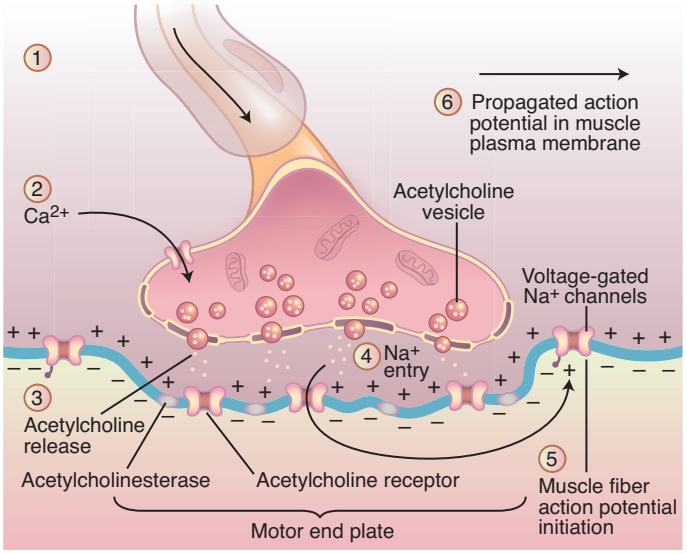


FIGURE 4-9. Acetylcholine mechanism on neuromuscular junction. (Reproduced with permission from USMLE-Rx.com.)

What is the mechanism of action of depolarizing blocking agents?

Depolarizing agents such as succinylcholine act in two phases. Phase I causes sustained depolarization of Na channels leading to muscle fasciculations; however, these Na channels eventually become inactivated to where action potentials can no longer be generated, so Ca influx cannot occur. This leads to flaccid paralysis. Acetylcholinesterase inhibitors potentiate paralysis during phase I. Desensitization occurs in phase II, for which succinylcholine causes a conformational change in the Ach-receptor with continued blockage; however, the receptor is now able to repolarize, and action potentials can regenerate. Phase II can be **reversed** with acetylcholinesterase inhibitors.

What is the mechanism of action of non-depolarizing blocking agents?

These drugs are mostly close relatives of tubocurarine. They act by competing with acetylcholine for nicotinic motor receptors. These drugs can be reversed using cholinesterase inhibitors.

What is an important potential risk of using succinylcholine?

Succinylcholine may result in malignant hyperthermia (sympathetic hyperactivity, hyperreflexia, acidosis) due to a defect in the ryanodine receptor, which increases release of calcium from the sarcoplasmic reticulum. This condition can be treated with dantrolene. The risk of malignant hyperthermia is greatly increased by the concurrent administration of inhalational anesthetics. Succinylcholine can also cause hyperkalemia, especially in burn and crush injuries; therefore, cardiac monitoring is vital. There is a black box warning for succinylcholine use in pediatric populations because of possible undiagnosed myopathies, which could then lead to cardiac arrest.

CASE 11

A 30-year-old migrant farmer is brought to the ED with severe diarrhea, shortness of breath, sweating, abdominal pain, and urinary incontinence. The patient appears confused, and his speech is slurred. His brother said he saw the farmer drink liquid from an unlabeled bottle approximately 1 hour earlier.

What is the most likely diagnosis?

Organophosphate ingestion. Organophosphates such as parathion, malathion, and echothiopate are cholinesterase inhibitors, which cause an excess of acetylcholine (ACh) in the synapse. They are commonly found in insecticides and can be ingested, inhaled, or cutaneously absorbed. Always suspect it in patients exposed to grass/cut lawns. Organophosphorus nerve agents are a known deadly chemical weapon and have been used to this end in the past—most notably in the 1995 attack on the Tokyo subway system by a religious cult using sarin.

What symptoms can be expected in this patient's condition?

Symptoms resulting from parasympathetic excess are due to stimulation of M_1, M_2, and M_3 receptors and can be summarized by the mnemonic **DUMBBELSS: D**iarrhea, **U**rinary incontinence, **M**iosis, **B**ronchospasm, **B**radycardia, **E**xcitation of skeletal muscle and central nervous system, **L**acrimation, **S**weating, and **S**alivation. Central nervous system effects, such as confusion or slurred speech, are common.

What are two treatments and their mechanisms of action?

Atropine and pralidoxime (2-PAM) can reverse organophosphate poisoning. Atropine works by competitively inhibiting muscarinic receptors, thereby decreasing the effect of acetylcholine. 2-PAM works best if given early on by regenerating acetylcholinesterase and inhibiting its binding to organophosphates. A schematic of neuromuscular blockade is shown in Figure 4-10.

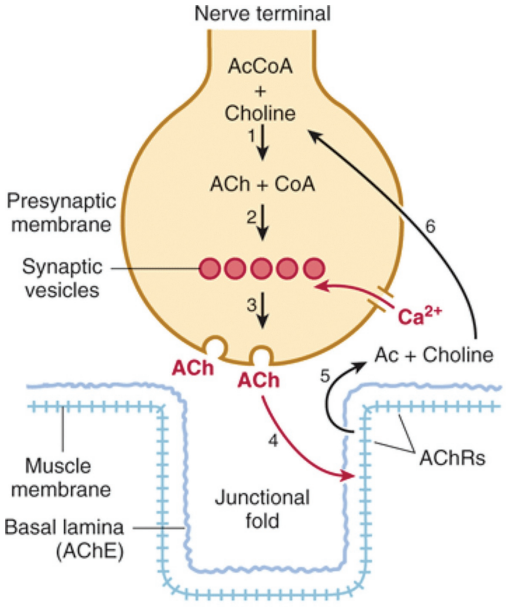


FIGURE 4-10. Representation of some of the events involved in neurotransmitter synthesis, release, and action at a prototypic synapse, the neuromuscular junction. Acetylcholine (ACh) is the transmitter at this synapse. Synthesis of ACh occurs in the presynaptic terminal from acetyl-coenzyme A (CoA) and choline (1). ACh is then incorporated into membrane-bound synaptic vessels (2). Exocytosis of ACh then occurs via the fusion of the vesicles with the presynaptic membrane, which is also mediated by an influx of Ca^{2+}, which is triggered by the action potential (3). Approximately 200 synaptic vesicles are released into the synaptic cleft in response to a single action potential. The released ACh diffuses rapidly across the synaptic cleft (4) and binds to postsynaptic ACh receptors (5), where a conformational change in the channel triggers the influx of Na^+ ions into the muscle, which depolarizes the membrane. Once the channel closes, the ACh dissociates and is hydrolyzed by acetylcholinesterase (6). (Reproduced with permission from Waxman SG. *Clinical Neuroanatomy,* 26th ed. New York: McGraw-Hill, 2010: Figure 3-9. Originally from Murray RK, et al. *Harper's Biochemistry*, 24th ed. Appleton & Lange, 1996.)

What adverse events are associated with this treatment?

Atropine poisoning can lead to sympathomimetic adverse effects, including pupillary dilation, dry mouth, dry skin, constipation, increased body temperature, rapid heart rate, and disorientation. Consider the mnemonic: **"blind as a bat, dry as a bone, red as a beet, hot as Hades, and mad as a hatter."**

CASE 12

Several new drugs are being tested for their effects on β_2-adrenergic receptors. The investigator plots an S-shaped curve of the activity of adenylate cyclase vs. drug dose in response to drug A. When the response of drug D is similarly plotted, D is found to have a lower median effective dose (ED_{50}) and a lower maximal response than A. In the presence of drug A plus drug B, the curve has the same shape but is now shifted to the right. In the presence of drug A plus drug C, the curve is not shifted, but the maximal response is lower.

Which drug, A or D, has a higher efficacy?

Efficacy refers to the maximal response a drug elicits. Thus, drug A has a higher efficacy since it produces a higher maximal response (see Figure 4-11).

Which drug is more potent?

Drug D is more potent (see Figure 4-11). **Potency** is the amount of drug required for a specified response. Typically, potency is measured by the ED_{50}, or the dose that gives 50% of the maximal response. The **lower** the ED_{50}, the more potent the drug.

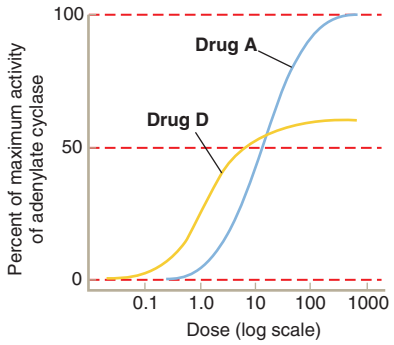


FIGURE 4-11. **Dose-response curves comparing drug A and drug D.**

What type of antagonist is drug B?

Drug B is a competitive antagonist—that is, it binds to the same site on the receptor as does drug A (see Figure 4-12A). It does not affect the maximal response the agonist can elicit, but it does increase the ED_{50}, requiring more agonist to achieve the same response, thus decreasing potency.

What type of antagonist is drug C?

Drug C is a **noncompetitive antagonist** (see Figure 4-12B). These drugs act by binding irreversibly to a site on the receptor distinct from the site of agonist binding. Noncompetitive antagonists do not affect the ED_{50} but do affect the maximal response (decrease efficacy) that the agonist can elicit.

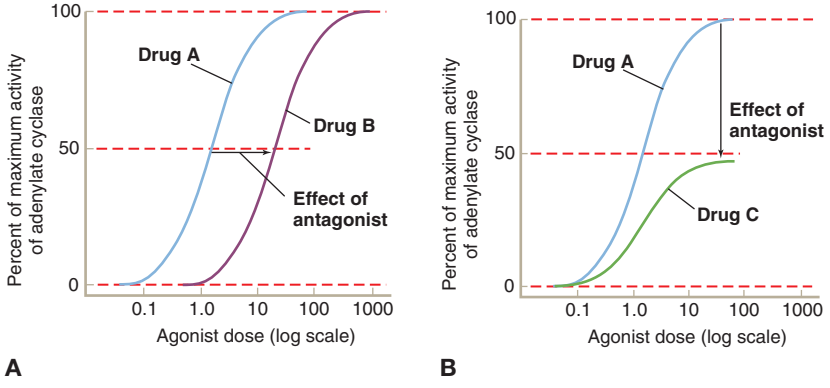


FIGURE 4-12. A and B: **Dose-response curves showing drug A, drug B, and drug C.**

How can the effect of drug B be overcome?

Since **competitive antagonists** bind at the same site as the agonist, their action can be overcome by increasing agonist dose. If enough agonist is present, the same efficacy can be reached that the agonist had in the absence of an antagonist.

What is therapeutic index?

The therapeutic index (TI) is a safety profile measure of a drug based on its toxicity. It can be calculated using TD_{50}/ED_{50}, for which TD is toxic dose and ED is effective dose. It is a measure of the distance between the toxic dose and effective dose concentrations with a 50% response rate on the dose response curve. The higher the TI, the safer the drug, because the chance of causing toxicity is not as high with an increased dosage.

CASE 13

The kinetics of a new pharmaceutical agent are being tested in an animal model. A dose of 50 mg of the substance is injected intravenously into a rat. The concentration of the substance in the animal's blood is measured every 30 minutes thereafter for the next 10 hours. The concentration of the drug plotted against time produces the graph shown in Figure 4-13.

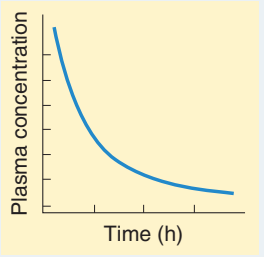


FIGURE 4-13.

Is this substance being metabolized by first-order or zero-order kinetics?

The shape of the graph shows that the drug is being eliminated by **first-order kinetics** (see Figure 4-14A), meaning that a constant **fraction** of the substance is eliminated per unit of time. As a result, the rate of elimination is proportional to the concentration of the drug. By contrast, **zero-order kinetics** (see Figure 4-14B) results in a constant **amount** of the substance being cleared per unit of time; the elimination rate is constant regardless of the **plasma concentration** (C_p), and the plot of C_p vs. time is a straight line.

Which drugs follow zero-order kinetics?

Nearly all medications follow first-order kinetics. Three notable exceptions are aspirin, phenytoin, and alcohol.

Why does the volume of distribution affect the half-life of a drug?

Volume of distribution (V_d) is the theoretical volume in which the total amount of drug would need to be uniformly distributed to produce the desired blood concentration of a drug. This can be written as

V_d = amount of drug in the body/plasma drug concentration. A useful equation is:

$$V_d = \text{Clearance} \sim t_{1/2}/0.7$$

As indicated by the equation above, $t_{1/2}$ is directly proportional to V_d. This is because the larger the V_d, the smaller the amount of drug present in the plasma compartment and therefore the smaller the amount of drug circulated through the kidneys and liver for metabolism and excretion.

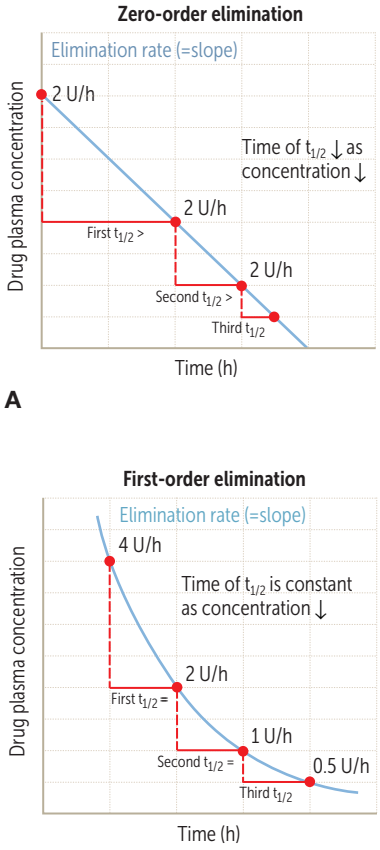


FIGURE 4-14. First-order drug elimination (A) and zero-order drug elimination (B). (Reproduced with permission from USMLE-Rx.com.)

What is the half-life of this substance, and how does the half-life change if a dosage of 100 mg is administered?

Half-life ($t_{1/2}$) is the time necessary to decrease the C_p of the drug by 50%. As shown in Figure 4-14, at 5 hours the C_p of the drug is half of the initial concentration, and thus $t_{1/2}$ is 5 hours. Half-life does not depend on the size of the dose being eliminated. As a side note, the time it takes to reach steady state for most drugs (first-order kinetics) is about 4 to 5 times the half life.

How would the therapeutic index of this drug be determined, and why is this important?

Therapeutic index is the ratio of a drug's toxic dose to the therapeutic dose. Safe drugs will have a high therapeutic index, indicating a large difference between the dose used to treat patients and the dose resulting in toxicity. Drugs with a low index, such as digoxin, have to be carefully monitored by checking serum levels of the drug.

$$\text{Therapeutic ratio} = LD_{50}/ED_{50}$$

LD_{50} = lethal dose of drug for 50% of population.

ED_{50} = effective dose of drug for 50% of population.

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5
Public Health Sciences

CASE 1

A 44-year-old man is brought to the ED by paramedics after he was found stumbling and confused at home. On physical examination, the patient appears slightly sedated and admits to recent heavy drinking but says his last drink was 34 hours ago. He also says he vomited three times earlier that morning. He denies chest and abdominal pain. He has a 15-year history of heavy alcohol abuse and usually drinks six to seven beers a day. CT scan of the head is negative for mass lesions or bleeding. Relevant laboratory findings are as follows:

Aspartate aminotransferase (AST): 57 U/L
Alanine aminotransferase (ALT): 18 U/L
Lactate dehydrogenase: 398 U/L

What is the most likely diagnosis?

Alcohol withdrawal. An AST: ALT ratio greater than 2:1 suggests alcoholic liver disease; his is 57:18.

What is the pathophysiology of this condition?

Alcohol acts as a central nervous system depressant by stimulating the γ-aminobutyric acid $(GABA)_A$ receptor. (GABA is an inhibitory neurotransmitter.) Repeated consumption of alcohol desensitizes $GABA_A$ receptors, resulting in tolerance and physical dependence. When a person suddenly stops consuming alcohol, the nervous system is hyperaroused and synapses fire uncontrollably; the result is the symptoms seen in alcohol withdrawal (see Figure 5-1). Increased serum norepinephrine and altered serotonin levels have also been implicated in both alcohol craving and tolerance.

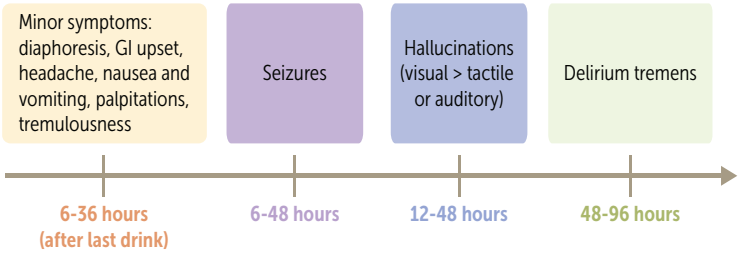


FIGURE 5-1. Symptoms of alcohol withdrawal. (Reproduced with permission of USMLE-Rx.com.)

What are the symptoms of this condition?

Minor symptoms, which occur 6–36 hours after the last drink, include diaphoresis, GI upset, headache, nausea and vomiting, palpitations, and tremulousness. Seizures can occur within 6–48 hours of the last drink. Visual (or, less commonly, tactile or auditory) hallucinations can occur within 12–48 hours of the last drink, and delirium tremens may occur within 48–96 hours.

What is delirium tremens?

Delirium tremens is a collection of severe alcohol withdrawal symptoms that includes delirium, agitations, and autonomic instability such as tachycardia, hypertension, low-grade fever, and diaphoresis. Approximately 5% of patients with alcohol withdrawal symptoms develop delirium tremens.

What is the treatment for this condition?

Benzodiazepines, particularly lorazepam or diazepam, are the treatment of choice for all types of alcohol withdrawal symptoms.

Chronic alcoholics are often deficient in thiamine because of malnutrition. If they are, they may present acutely with ataxia (cerebellar dysfunction), ophthalmoplegia, and confusion—the triad of Wernicke encephalopathy. First and foremost, fluids should be given. The next step is to give thiamine **followed by** glucose. Thiamine is given first because it is a necessary cofactor for ATP synthesis; glucose given without thiamine will be converted to lactic acid.

The neurologic symptoms of Wernicke encephalopathy may persist, in what is known as Wernicke-Korsakoff syndrome.

CASE 2

A 24-year-old woman is brought to the ED with confusion, blurred vision, dizziness, and somnolence. Her friend states that the woman is generally healthy but is taking medication for occasional episodes of intense fear, sweating, nausea, and abdominal and chest pain. Physical examination reveals a respiratory rate of 8/min.

What class of drugs is most likely responsible for this patient's presenting symptoms?

Her friend's description of her episodes of intense fear is consistent with a diagnosis of panic disorder. Benzodiazepines (such as clonazepam, lorazepam, and alprazolam) are commonly used in the short-term treatment of panic disorder.

Benzodiazepine toxicity is characterized by respiratory depression, confusion, and other symptoms of central nervous system depression (dizziness, somnolence/drowsiness, blurred vision, unresponsiveness). These are the patient's presenting symptoms.

What treatment was likely administered to this patient in the ED?

Flumazenil, a competitive antagonist at the γ-aminobutyric acid (GABA) receptor, is effective in reversing symptoms of benzodiazepine overdose.

How does the mechanism of action of benzodiazepines differ from that of barbiturates?

Normally, $GABA_A$ receptors respond to GABA binding by opening chloride channels, which raises the membrane potential of the neuron and inhibits neuronal firing. Benzodiazepines and barbiturates enhance the affinity of GABA for $GABA_A$ receptors. **Benzodiazepines** increase the **frequency** of chloride channel openings. **Barbiturates** increase the **duration** of chloride channel openings.

What are the advantages of treatment with benzodiazepines over barbiturates?

Benzodiazepines have a lower risk of dependence, cytochrome P-450 system involvement, respiratory depression, coma, and loss of REM sleep. They are considered to be much safer than barbiturates in cases of overdose (specifically, barbiturates have a lower therapeutic index).

What drugs, when taken with benzodiazepines, increase the risk of toxicity?

- Acetaminophen
- Alcohol
- Cimetidine
- Disulfiram
- Isoniazid
- Valproic acid

CASE 3

A 65-year-old man with diabetes is admitted to the hospital for repair of a hip fracture. On postoperative day 4, his wife reports that he is confused and cannot remember her name. Evaluation confirms that the patient is inattentive and confused. However, his nurse notes that he was fine both the day before and 3 hours earlier. The patient is taking morphine as well as previously prescribed β-blockers and angiotensin-converting enzyme inhibitors for hypertension. He is afebrile, and his blood pressure is 105/51 mm Hg. Relevant laboratory findings are as follows:

Sodium: 133 mEq/L
Calcium: 8.9 mg/dL
Potassium: 3.9 mEq/L
Chloride: 99 mEq/L
Magnesium: 1.9 mg/dL
Bicarbonate: 25.1 mEq/L
Phosphate: 3.0 mg/dL
Blood urea nitrogen: 18 mg/dL
Creatinine: 1.5 mg/dL
Glucose: 58 mg/dL
Urinalysis: unremarkable

What is the most likely diagnosis?

Delirium. The patient is hospitalized in pain after surgery, and he is taking morphine, which itself can cause delirium. Key features of delirium include acute onset, reduced attention, waxing and waning course, disorganized thinking, and altered level of consciousness.

How is this condition distinguished from dementia?

Acute presentation and a waxing and waning course are found in delirium but not dementia whereas dementia is a chronic presentation. The ability to stay focused is significantly impaired in delirium, whereas patients with dementia generally remain alert.

What risk factors are associated with this condition?

Prolonged hospitalization, pain, dehydration, metabolic and electrolyte disturbances, medication-induced, infections, and postoperative state.

What drugs most commonly cause this condition?

Major classes of drugs that commonly cause delirium are opioids, anticholinergic agents, sedative-hypnotics, antihistamine agents, benzodiazepines, and corticosteroids.

What are the treatments for this condition?

The key is to treat the underlying etiology. The first step of the evaluation is a thorough review of the medication list and lab abnormalities that can contribute to delirium and to examine the patient for evidence of infection and pain control. The next step is to reorient the patient.

CASE 4

A 19-year-old college student is brought to the ED by his female roommate, who found him wandering outside and behaving in a hostile manner. The patient is difficult to understand. He is violently thrashing about. Physical examination is unremarkable. The roommate admits they were both at a party earlier in the evening, but she lost track of the patient and is not sure what else he could have ingested.

What drugs of abuse could be involved in this case, and which is the most likely culprit?

- Alcohol
- Amphetamines
- Benzodiazepines or barbiturates
- Cocaine
- Heroin (opioids)
- Lysergic acid diethylamide (LSD)
- Phencyclidine (PCP)

PCP is most likely the culprit due to the patient's violent behavior.

What signs and symptoms are associated with alcohol intoxication and withdrawal?

- Intoxication: Slurred speech, incoordination, unsteady gait, nystagmus, impaired attention, stupor/coma.
- Withdrawal: Autonomic hyperactivity, tremor, insomnia, nausea, hallucinations, agitation, anxiety, seizures.

What signs and symptoms are associated with opioid intoxication and withdrawal?

- Intoxication: Intense euphoria, drowsiness, slurred speech, decreased memory, pupil constriction, decreased respirations.
- Withdrawal: Nausea, vomiting, pupil dilation, insomnia.

What signs and symptoms are associated with cocaine intoxication and withdrawal?

- Intoxication: Tachycardia, hallucinations, paranoid delusions, dilated pupils.
- Withdrawal: Increased appetite, irritability, depressed mood.

What signs and symptoms are associated with benzodiazepine or barbiturate intoxication and withdrawal?

- Intoxication: Respiratory and cardiac depression, disinhibition, unsteady gait.
- Withdrawal: Agitation, anxiety, depression, tremor, seizures, delirium.

What signs and symptoms are associated with PCP and LSD intoxication and withdrawal?

- PCP intoxication: Intense psychosis, violence, rhabdomyolysis, hyperthermia.
  - Treatment: Activated charcoal if the patient recently took PCP by mouth, benzodiazepines for anxiety and/or seizures. Barbiturates and/or propofol can be used for seizures after benzodiazepines have been given.
- PCP withdrawal: Anxiety, depression, irritable and angry mood.
- LSD intoxication: Increased sensation (colors richer, tastes heightened), visual hallucinations, dilated pupils.
  - Treatment: Supportive care (if the patient only consumed LSD); address symptoms.
- LSD withdrawal: There are no physical withdrawal symptoms from LSD.

CASE 5

A 16-year-old girl is brought to the physician by her mother who is worried about her daughter's rapid weight loss and erratic behavior. The girl states she has been exercising frequently and has not had menses for several months. Upon further questioning, she reluctantly states that she is afraid of gaining weight and eats only cereal and vegetables. Her weight is 44.1 kg (97 lb), and her body mass index is 17 kg/m^2. She complains of right foot pain, and an x-ray of her foot is taken (see Figure 5-2). Relevant laboratory findings are as follows:

Hemoglobin: 10.8 g/dL (reference 12.0–16.0 g/dL)
Hematocrit: 33.5% (reference 36%–46%)
Mean corpuscular volume (MCV): 78.5 fL (reference 80–100 fL)

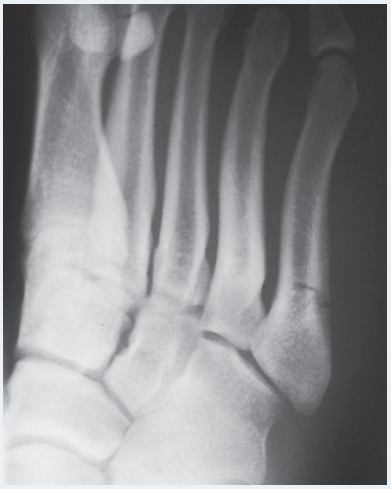


FIGURE 5-2. (Reproduced courtesy of Alan B. Storrow, MD, as published in Knoop KJ, et al. *Atlas of Emergency Medicine*, 2nd ed. New York: McGraw-Hill, 2002.)

What is the most likely diagnosis?

Anorexia nervosa.

What other symptoms of this condition are common at presentation?

Patients typically present with severe weight loss (with body weight $<$ 85% of ideal body weight and BMI certainly $<$ 18.5 and generally $<$ 17.5) and clinical manifestations of multiple nutritional deficiencies. Despite being underweight, anorexic patients are obsessed with calories, preoccupied with dieting, and intensely fearful of gaining weight. Dental caries and erosions (see Figure 5-3) may be present if patients are also inducing vomiting. Additional purging via laxative abuse may cause palpitations, lightheadedness, or chest pain due to electrolyte abnormalities.

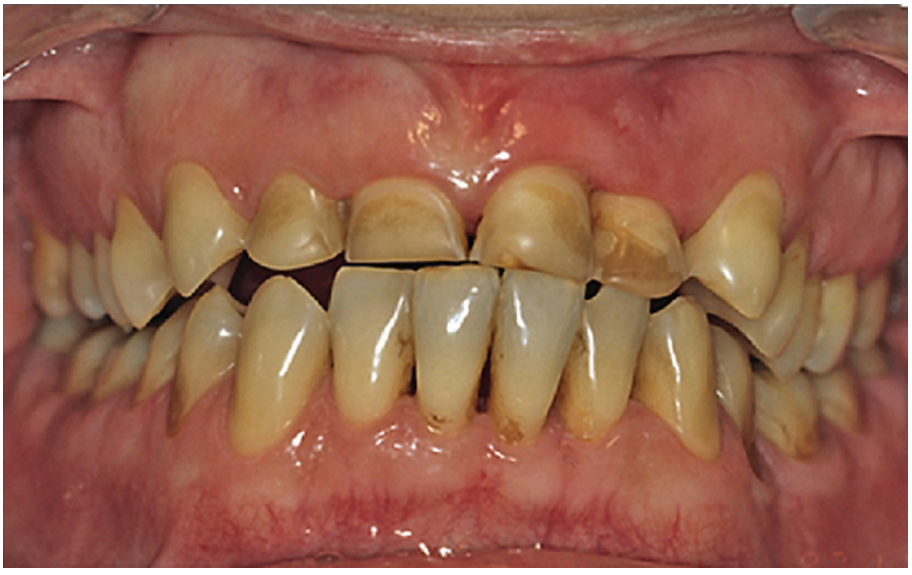


FIGURE 5-3. Dental erosions. (Reproduced with permission from Johansson A-K, et al. Dental erosion and its growing importance in clinical practice: From past to present. *Int J Dent*. 2012;2012:632907.)

What is Russell's sign?

Russell's sign is calluses on the knuckles or on the back of the hand due to repeated self-induced vomiting purges.

What nutritional deficiency may contribute to the radiographic findings in Figure 5-2?

Fractures of the fifth metatarsal bone in anorexic patients are often related in part to osteopenia or osteoporosis secondary to vitamin D and calcium deficiency.

What region of the brain regulates appetite and is thought to play a role in eating disorders?

The feeding center is located in the lateral nucleus of the hypothalamus. When stimulated, it promotes eating/appetite. The satiety center is located in the ventromedial nucleus. When stimulated, it signals the body to stop eating. Lesions to this area cause hyperphagia and obesity.

What kind of anemia does this patient likely have?

Low hematocrit and low MCV suggest microcytic anemia, most likely due to iron deficiency, a common feature in patients with anorexia. Inadequate vitamin B_{12} and folate intake cause macrocytic anemia. Some patients may have overall normocytic anemia due to the combined microcytic and macrocytic anemias.

What is the treatment and prognosis of this condition?

A multidisciplinary treatment approach focuses on restoring the patient to a healthy weight and uses psychotherapy to correct the thoughts and behaviors that initially caused the disordered eating. (Suicide is a leading cause of death in anorexia nervosa.) Prognosis is variable, as one-fifth of patients remain severely ill, one-fifth recover fully, and three-fifths have a fluctuating, chronic course. Fluids and electrolytes must be monitored closely; the refeeding syndrome is a feared complication of anorexia treatment.

Total parenteral nutrition solutions used in refeeding should include phosphate. Refeeding causes increased levels of insulin secretion and decreased levels of glucagon secretion. Insulin stimulates synthesis of glycogen, fat, and protein; these processes require phosphate and magnesium. Moreover, as glucose is taken into cells, thanks to insulin, so is potassium. The result is that refeeding can cause already depleted levels of phosphate, magnesium, and potassium to decrease even further, with complications as serious as organ failure.

How is this condition differentiated from bulimia?

Bulimia nervosa can present with findings similar to anorexia. Its hallmark is uncontrollable binge eating followed by purging. Inappropriate behavior to compensate for the binging differentiates bulimia from binge eating disorder. Patients with bulimia usually have normal weight (BMI of 18.5 to 24.9) and irregular menses. Nutritional deficiencies, however, are uncommon.

What are the DSM-5 criteria to diagnose bulimia?

All of the following criteria must be satisfied:

- Binge eating: consuming **excessive amounts of food** (this is the key element) totaling two or more meals or about 2000+ kcal.
- Preventing subsequent weight gain by compensating for the binges through inappropriate behaviors, classically by purging. (Purging is **not** unique to bulimia and can be seen in anorexia as well.)
- Binge eating and inappropriate compensatory behaviors must occur an average of at least once weekly for three months.
- Patient's sense of self must be overly influenced by body shape and weight.
- These issues must not occur exclusively during episodes of anorexia nervosa.

CASE 6

A 67-year-old man presents with crushing, substernal chest pain that he claims used to occur only on exertion but now occurs randomly throughout the day. His wife is concerned and asks the attending physician what can be done. The attending physician meets with the patient and his wife and discusses the diagnosis of unstable angina and its association with myocardial infarction. The physician then explains the option of bypass surgery and asks the patient if he would like to have this surgery.

What is the difference between capacity and competency?

Capacity is the ability to make rational decisions. A physician (often a psychiatrist) can determine capacity, but only a court can determine **competency**/competence, which is the ability to execute a legally recognized act in a rational manner.

If the patient decides, with full mental capacity, that he does not want to have this surgery, what should the physician do?

Under the core ethical principle of **autonomy**, the physician has an obligation to respect and honor the medical care choices of the patient.

If the physician believes that not proceeding with this surgery is against the patient's best interest, what should the physician do?

The physician has a fiduciary duty to act in the patient's best interest under the ethical principle of **beneficence**; however, if the patient can make an informed decision (ie, is aware of the risks, benefits, and alternatives to surgery/treatment), he has the right to decide what type of treatment he will receive, and the physician must respect that decision.

What ethical principle is violated in all surgeries?

Because the benefits of a surgical intervention often outweigh the risks, the principle of nonmaleficence, or "to do no harm," is often broken as a means to a better end.

What is the last ethical principle that we haven't discussed yet?

Justice, which is to treat all people fairly without any exceptions.

If the patient decides he wants to proceed with the surgery, what should the physician do?

The physician must obtain **informed consent** from the patient. This is a process in which the physician discloses the risks and benefits of the procedure, the available alternatives, and the risks and benefits of refusing the procedure. As a result, the patient is able to make an informed decision about whether he will have the procedure.

What is the difference between durable power of attorney for health care and a living will?

Power of attorney allows an individual to designate another person to make health care decisions. **Durable** power of attorney remains effective even if said individual becomes incapacitated or incompetent. Power of attorney can be made effective immediately or can take effect when the individual becomes incapacitated or incompetent. In contrast, a living will is a type of advanced directive that allows an individual to delineate exact wishes for end-of-life care and is used if he or she becomes unable to communicate. It is different from a last will and testament, which is used to distribute assets after death.

CASE 7

Scientists in Japan have devised a new HIV screening test and have administered it to 400 persons. Although 57 of the 400 persons are infected, this new test is positive in only 30 cases. Among uninfected persons, the test is negative in 300 cases (see Table 5-1).

TABLE 5-1. Determining Diagnostic Test Data

	Persons with infection	Persons without infection	Number of persons tested
Test positive	30	43	73
Test negative	27	300	327
Total	57	343	400

What is the sensitivity of this test?

Sensitivity is defined as the percentage of test subjects who have the infection and test positive for it. In other words, sensitivity = true positives/(true positives + false negatives). Therefore, the sensitivity of this test is 30/57, or 52.6%.

What is the specificity of this test?

Specificity is defined as the percentage of test subjects who do not have the infection and test negative for it. In other words, specificity = true negatives/(true negatives + false positives). Therefore, the specificity of this test is 300/343, or 87.5%.

Higher specificity makes for higher positive predictive value (PPV). Here's why:

Higher specificity means more true negatives relative to false positives (or relatively fewer false positives). Because PPV = true positives/(true positives + false positives), fewer false positives means a smaller denominator and a higher PPV.

When is it best to use a highly sensitive test, and when is it best to use a highly specific test?

A highly **sensitive** test is ideal for preliminary screening (eg, ELISA [enzyme-linked immunosorbent assay], the first test for HIV).

A highly **specific** test is ideal for **confirming** a preliminary diagnosis (eg, Western blot to confirm an ELISA positive for HIV).

What is the PPV of this test?

PPV is defined as the probability that a person with a positive test result is actually infected:

$$PPV = TP/(TP+FP)$$

Therefore, the PPV of this test is 30/73, or 41.1%. The PPV is directly proportional to the prevalence of the disease being tested; therefore, if the disease is prevalent, the PPV of the test will be high.

What is the negative predictive value (NPV) of this test?

NPV is defined as the probability that a person with a negative test result is truly uninfected:

$$NPV = TN/(TN+FN)$$

Therefore, the NPV of this test is 300/327, or 91.7%.

What is the prevalence of HIV in the population tested?

Prevalence is defined as the proportion of people in the population who are infected at any given point. Therefore, the prevalence of HIV in this population is 57/400, or 14.3%.

Higher prevalence means higher PPV (more true positives) and lower NPV.

Lower prevalence means higher NPV (more true negatives) and lower PPV.

What is the difference between accuracy and reliability?

Accuracy is the degree to which a test/study measures the true value of something, whereas **reliability** is simply the consistency with which a test/study produces results. A test can be reliably inaccurate!

CASE 8

While on a medical mission to a developing country, a 30-year-old urology resident develops a terrible case of Fournier gangrene with many complications. He is ultimately returned to the United States, where he is now on a ventilator in an intensive care unit. He is completely unresponsive and not expected to survive. He has no advanced directives of any kind. His mother and his wife both wish to manage his end-of-life care.

If his mother wants to withdraw care but his wife wants to continue with the ventilator, whose decision takes precedence?

Who has the final say varies by state. Generally speaking, the spouse does. Next would be any adult children and then either parent.

How could the resident have ensured his wishes would be followed?

He could have completed a living will, a type of advanced directive that would have allowed him to delineate his wishes for end-of-life care. A living will would have come into force as soon as he could no longer communicate.

Without a living will, what could he have done to ensure that all health care decisions at the end of his life would be made by the person of his choice?

Durable power of attorney for health care allows an individual to designate another person to make health care decisions and takes effect if said individual becomes incapacitated or incompetent. The resident could have had durable power of attorney designated to take effect upon his incapacitation.

CASE 9

A married couple has just retired in Florida. The 66-year-old husband takes metformin for diabetes mellitus, while the 70-year-old wife has to attend physical therapy after having a stroke. They are both worried about paying for health care and confused about what Medicare will cover. They have asked their primary care physician to explain.

What is Medicare? Who is eligible?

Medicare is the U.S. federal government's health insurance plan for senior citizens ages 65 and older and selected younger individuals with disabilities. Americans under age 65 can qualify if they have end-stage renal disease, are blind, or are receiving Social Security Disability Insurance (SSDI) from Social Security. Medicare comes in four forms, known as parts and named with the letters A through D. It is funded through dedicated taxes withheld from working Americans' wages.

Which part of Medicare pays for hospitalization as an inpatient?

Part A. Most hospital services are covered, including meals and medications, as part of inpatient treatment. Medicare will not pay for private rooms unless medically necessary, and it will not pay for private nursing.

What does Part B of Medicare cover?

Part B covers outpatient care and medically necessary laboratory diagnostic services. Outpatient care isn't limited to doctor's visits. It also includes physical therapy, occupational therapy, and speech-language pathology services.

Which part of Medicare covers prescription drugs?

Part D.

How can patients augment their Medicare coverage?

Patients can purchase Medicare Advantage (Part C) plans, such as HMOs (health maintenance organizations) and PPOs (preferred provider organizations), which are insurance options offered by private companies. Medicare Advantage plans often encompass Parts A, B, and D.

How does Medicaid differ from Medicare?

Medicaid is a form of public assistance without age restrictions. It provides more generous coverage for nursing homes than Medicare does. Many Medicaid recipients also receive Supplemental Security Income (SSI). Unlike SSDI, SSI does not require a history of employment.

CASE 10

The mother of 15-month-old fraternal twin boys consults her pediatrician because she is concerned about the development of one twin. The older twin began to walk at approximately 12 months of age, but the younger twin is still unable to walk by himself. Physical examination reveals no significant issues.

Is it normal that the younger twin has not begun to walk?

Yes. The approximate age that children reach the motor milestone of walking is 15 months. Between 6 and 9 months of age, children should be able to sit without help.

By what age should the infant reflexes have disappeared?

Infant reflexes normally disappear within the first year. They include the Moro reflex (extension of limbs when startled), the rooting reflex (nipple seeking when cheek brushed), the palmar reflex (grasping of objects in palm), and the Babinski reflex (large toe dorsiflexion with plantar stimulation).

What cognitive/social milestones should these infants have reached?

Cognitive/social milestones reached by this age include social smile (3 months), recognition of people (4–5 months), stranger anxiety (7–9 months), voice orientation (7–9 months), and separation anxiety (15 months).

What language milestones should these infants have reached?

Language milestones reached by this age include cooing (3 months), babbling (6 months), saying a couple of words like "mama" or "dada" (12 months), and speaking a few words (15 months).

What motor milestones should these infants have reached?

Motor milestones reached by this age include sitting without support (6–8 months), cruising (12 months), and walking independently (12–14 months).

What is an APGAR score?

APGAR scores help physicians assess whether newborns require resuscitation. APGAR stands for **A**ppearance, **P**ulse, **G**rimace, **A**ctivity, and **R**espiration (see Table 5-2). Each category is scored from 0–2 (see Table 5-2); a total of 10 is a perfect score. Scoring is done at 1 and 5 minutes after birth. APGAR score is not a prognostic tool for future childhood developmental milestones.

TABLE 5-2. APGAR Scoring System

Category	Score 0	Score 1	Score 2
Appearance (color)	Blue/pale	Trunk pink	All pink
Pulse	None	< 100/min	> 100/min
Grimace (reflex irritability)	None	Grimace	Grimace + cough
Activity (muscle tone)	Limp	Some	Active
Respiration (effort)	None	Irregular	Regular

What upcoming motor milestones should the mother expect to see? (see Table 5-3.)

TABLE 5-3. Developmental Motor Milestones

Motor milestone	Age
Climbing stairs	12–24 months
Stacking six blocks	18–24 months
Riding a tricycle	3 years
Hopping on one foot	4 years

CASE 11

A 21-year-old man and his mother visit the clinic because his daytime sleepiness is interfering with his studies. The man is slightly obese and has a history of pulmonary hypertension. His mother says that he has a medication "for sleep" but that he does not use it. On questioning, the man says he has a prescription for amphetamines and is taking sertraline. His mother also mentions that while they were in the waiting room, the man heard "bells ringing," which no one else heard. Shortly thereafter, the young man fell asleep during their conversation.

What is the most likely diagnosis?

The hallucinations, sudden onset of sleep, and amphetamine treatment are consistent with a diagnosis of narcolepsy. Narcolepsy is caused by a lack of orexin (hypocretin) neuropeptides in the lateral hypothalamus and has a strong genetic component.

What kind of hallucinations is the patient having?

Hallucinations that occur before falling asleep are termed **hypnagogic hallucinations** ("gogic"—"go" to sleep). **Hypnopompic hallucinations**, which occur during waking, are less commonly associated with narcolepsy.

What are the four classic signs and symptoms of this diagnosis?

The four classic signs and symptoms of narcolepsy are:

- Cataplexy: A sudden, transient loss of muscle tone ranging from mild weakness to full body collapse; a common example is feeling weak or losing muscle tone when laughing or otherwise responding to a strong emotion.
- Sleep paralysis: The inability to talk or move upon waking or falling asleep.
- Hypnagogic hallucinations.
- Excessive daytime sleepiness.

What sleep stage is the patient likely to enter immediately after falling asleep?

Narcolepsy is associated with **REM** sleep within 10 minutes of falling asleep.

What behavioral and pharmacologic therapies can be used to treat this condition?

Central nervous system stimulants (eg, methylphenidate and amphetamine) are used to treat excessive daytime sleepiness, and tricyclic antidepressants (eg, clomipramine and imipramine) are used to treat cataplexy. Lifestyle changes, including reducing stress, increasing exercise, and taking frequent daytime naps, can also be therapeutic.

What other electroencephalographic (EEG) abnormalities might be expected in this patient?

His use of sertraline, a selective serotonin reuptake inhibitor (SSRI), suggests he is depressed. **Depression** is associated with decreased REM latency and decreased stage 4, slow-wave sleep, but effective treatment with antidepressants usually reverses these EEG abnormalities.

What other common sleep abnormality might account for poor quality of sleep?

Obesity and pulmonary hypertension are associated with **sleep apnea**, which can be disruptive and can lead to significant daytime fatigue. Arrhythmias and loud snoring are also associated with sleep apnea.

CASE 12

A couple is eating dinner at home with their quiet 6-year-old son. The couple gets into an argument. The father, still angry at his wife, starts to yell at his son, who begins to cry. The mother gives the child candy, which temporarily relieves the crying. Throughout the meal, she continues to give him candy every time he cries. Eventually, she runs out of candy, but the boy keeps crying. While she runs to the store to buy more candy, the father ignores the child's cries. The family is using defense mechanisms.

What are Common Defense Mechanisms?

Table 5-4. A Sampling of Common Defense Mechanisms

Defense mechanism	Description
Acting out	Impulsively performing an action to express a thought or feeling
Denial	Unconsciously avoiding unpleasant realities
Displacement	Transferring unacceptable feelings from one object or person to another that is similar
Humor	Finding comic relief in an unpleasant situation
Reaction formation	Converting an unpleasant thought impulse to its polar opposite
Splitting	Categorizing people, places, and things into extremes; not appreciating nuances and thereby avoiding internal conflicts
Suppression	Consciously deciding not to think about something

What defense mechanism is the father using?

The father is using displacement, transferring unacceptable feelings from one object or person to another that is similar. In this case, the father's anger at the mother is displaced onto their child.

What defense mechanism is the child using?

The child is **acting out**, performing an action, often extreme, to express a thought or feeling rather than managing his impulse to do so. In this case, the child is so overcome with anger that he cannot simply state, "I'm angry with you"; instead, he acts out by throwing food across the table.

What type of reinforcement is the child using on the mother?

This is an example of **positive reinforcement**, in which the consequences of a response increase the likelihood that the response will recur. Specifically, the child cries because crying makes it more likely the mother will continue to give him candy.

How does negative reinforcement differ from punishment?

In **negative reinforcement**, a behavior is **encouraged** or reinforced by the removal of an aversive stimulus (eg, if a mother constantly yells at her child to pick up his toys, he will learn to pick up his toys to avoid mom's yelling). In **punishment**, behavior is **discouraged**/reduced by administration of an aversive stimulus (eg, a boy pulls his dog's hair and his mother responds by taking away one of the boy's toys, discouraging the boy from pulling the dog's hair again).

Which method of conditioning is the father using by ignoring the child's cries?

The father is employing **extinction**, which is the elimination of a behavior by nonreinforcement. The child likely will stop crying after discovering that there is no reward for the behavior.

CASE 13

A newborn boy who was delivered at home is brought to the ED by his grandmother 30 minutes after birth. The grandmother says the baby "isn't acting right." The baby, born at 35 weeks' gestation, weighs 2700 g (approximately 6 lb). He is limp and unresponsive and breathing infrequently, with bluish skin and pupils 2 mm in diameter. The infant is immediately resuscitated and stabilized for transfer to the neonatal intensive care unit. On day 3 of life, his nurse says he is vomiting, has diarrhea, and cries excessively. Physical examination reveals tachycardia, tachypnea, dilated pupils, diaphoresis, tremors, increased muscle tone, and piloerection.

What is the most likely diagnosis?

The diagnosis is most likely opioid intoxication, heralded by the triad of respiratory depression, central nervous system depression, and pinpoint pupils (miosis). Importantly, **pinpoint pupils** due to opioid intoxication will be present despite opioid tolerance. Other common findings in infants exposed to opioids include low birth weight, premature birth, and intrauterine growth retardation syndrome.

What pharmacologic agent should this patient receive in the ED?

Naloxone. This opioid antagonist reverses the effects of opioid agonists by selectively binding to opioid receptors.

What is the most likely diagnosis on day 3 of life?

On day 3, the infant demonstrates symptoms of opiate withdrawal, also known as neonatal abstinence syndrome. Tachycardia, dilated pupils, diaphoresis, and other opiate withdrawal symptoms are related to sympathetic hyperactivity.

What is the long-term treatment for this patient?

An opioid agonist, such as methadone, relieves symptoms of acute opiate withdrawal. Methadone administration can be tapered as the baby is weaned.

Once the newborn is stabilized, what other issues need to be addressed?

The mother may need substance abuse treatment and counseling. Drug abuse during pregnancy is associated with medical and psychological problems that require evaluation and treatment. If she admits to IV drug use, she should be screened for infectious diseases, including HIV, hepatitis B, and hepatitis C. Also, it is important to arrange follow-up care within the first few weeks of discharge.

CASE 14

A 57-year-old woman comes to the ED with burns and bruises in unusual locations. The burns appear to have been caused by cigarettes. X-ray of the chest shows three broken ribs. Upon questioning, the woman tells the physician that her boyfriend got upset with her because she overcooked his steak. She claims that she provoked the incident by not preparing his food correctly and asks the doctor not to tell the police or anyone else. The electronic medical record reveals that she has a history of presenting to the ED with similar bruises and that her father abused her mother when she was a child. She also has a history of working as a prostitute and abusing intravenous drugs.

Suppose 70% of victims of domestic violence present with cigarette burns, but only 1% of the general public not exposed to domestic violence has this finding. What statistic compares these probabilities in such a way that allows for the finding of cigarette burns to be used as a measure of diagnostic accuracy?

The likelihood ratio (LR) is the probability of seeing a **finding** in affected patients divided by the probability of seeing that same finding in unaffected patients. In this case, the LR is 70%/1% or 70. (Note that these statistics are hypothetical.)

What is the odds ratio? What is the difference between the likelihood ratio and the odds ratio?

The odds ratio measures the association between an **exposure** (eg, history of domestic violence) and an **outcome** (eg, subsequent domestic violence). It is the ratio of the proportion of (number of exposed, affected patients/number of unexposed yet affected patients) to the proportion of (number of exposed but unaffected patients/number of unexposed, unaffected patients). Classically, a 2 × 2 matrix is used to teach the odds ratio (see Figure 5-4):

The odds ratio is (a/c)/(b/d) = ad/bc.

		Outcome status: Affected +	Outcome status: Unaffected –
Exposure status	+	a	b
	–	c	d

FIGURE 5-4. Sample Punnett square for determining odds ratio. (Reproduced with permission from USMLE-Rx.com.)

What is the difference between primary and secondary prevention?

Primary prevention is an attempt to reduce the incidence of disease to prevent new cases before there is any sign of disease. If we continue to treat domestic violence as our disease, primary prevention might include educating middle schoolers about domestic violence and healthy relationships.

Secondary prevention is an attempt at early diagnosis before symptoms appear so that the disease can be slowed, stopped, or reversed. In our domestic violence example, secondary prevention may include teaching college dormitory staff how to recognize domestic violence in its early stages (eg, verbal abuse, before it escalates to physical abuse).

Suppose ED physicians miss 75% of domestic violence cases when they don't administer a domestic violence questionnaire to each patient but only 25% when they do. In this hypothetical scenario, what is the number needed to treat?

The number needed to treat is the inverse of the absolute risk reduction, which is 75% − 25% = 50% or ½. The inverse of ½ is 1/(½) = 2, meaning that the domestic violence questionnaire has to be administered only twice for the physicians to catch one more case.

What is the difference between type I and type II error?

Type I error is wrongly rejecting a true null hypothesis, whereas type II error is wrongly failing to reject a false null hypothesis. In other words, type I error is a false positive, while type II error is a false negative. If a domestic violence questionnaire does nothing to increase the number of cases we catch, but we conduct a study and conclude that it does, we have made a type I error. The likelihood of type I error is equal to the level of statistical significance (α) we select, often 0.05. In contrast, if the questionnaire **does** help us identify domestic violence, but we fail to reject the null hypothesis, we have made a type II error. Statistical tables or calculators are required to determine the probability of type II error.

What is the *Tarasoff* decision?

The **Tarasoff** decision is a law requiring a physician to **directly** inform and protect potential victims from harm. In this case, for example, if the woman told the physician that she had a gun and was going to go back home and kill her boyfriend for abusing her, the physician would have a duty to inform the boyfriend and report the patient to the police.

What is the physician's duty if a patient has a serious infectious disease and is putting others at risk?

Physicians have a duty to warn public officials and other identifiable persons at risk if a patient has certain infectious diseases. These diseases include hepatitis A and B, salmonella, shigella, syphilis, measles, mumps, rubella, AIDS, tuberculosis, chickenpox, and gonorrhea.

CASE 15

An overseer of clinical trials is given an application for the study of a new drug that is intended to independently reduce anxiety. The company seeking to test this drug wants to distribute it to volunteer members of local meditation groups for 3 weeks and then follow up with participants 3 months later.

In terms of study design, what is bias?

Bias refers to any source of error in the determination of association between the exposure (drug use, in this case) and outcome (reduction in anxiety, in this case).

What types of bias can be found in this study?

There are three types of bias in this drug company's proposal:

- **Sampling bias**: All the subjects are members of a meditation group and are therefore likely to have less anxiety than members of the general population. For this reason, the results of the trial cannot be generalized to the targeted population as a whole.
- **Selection bias**: All the subjects are able to choose whether they want to try the new drug. Because of this nonrandom assignment, there is no way to eliminate the placebo effects of the drug.
- **Recall bias**: The drug company plans to contact participants 3 months after the study is completed. Because the subjects know what is expected of them, the subjects may be more likely to claim that they have less anxiety.

What are other important types of bias found in some studies?

Late-look bias pertains to gathering information at an inappropriate time, eg, using a survey to study a fatal disease at a late stage when most patients have already died. Lead-time bias is when early detection/diagnosis makes it appear as if patients are surviving longer when in fact they are merely living **with the knowledge of** their diagnosis for a longer time; the natural history of the disease remains unchanged.

What are some ways that bias can be reduced?

Bias can be reduced by using placebos, randomizing the subjects who are using the drug, designing a double-blind study, and employing a crossover study in which the subject acts as his or her own control.

What is blinding and what types of blinding are there?

Blinding is an aspect of study design that conceals information that could bias the results of the study from some or all of the people involved in the study. In other words, blinding reduces experimenter/research bias; those leading the trial are less able to influence its results. Trials may be single-blind or double-blind. In single-blind trials, subjects do not know whether they have been assigned to the experimental or the control group. In double-blind trials, neither the subjects nor the researchers know who has been assigned to the experimental group and who has been assigned to the control group.

6
Cardiovascular

CASE 1

A 75-year-old man visits his physician complaining of lower back pain. He has a history of hyperlipidemia and hypertension, and he has smoked a pack a day for 45 years. On physical examination, he is obese and has moderately limited range of motion of the back. There is a palpable, pulsatile mass just left and somewhat superior to the umbilicus (see Figure 6-1).

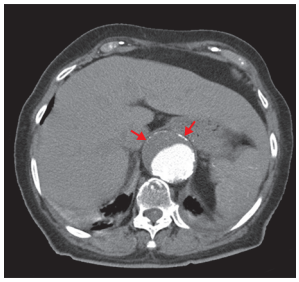


FIGURE 6-1. (Reproduced with permission from USMLE-Rx.com.)

What is the most likely diagnosis?

Abdominal aortic aneurysm (AAA), as indicated by the arrows in Figure 6.1.

What are the major branches of the aorta below the diaphragm?

Blood flow to the major organs is of special concern with an AAA. The inferior phrenic arteries, celiac trunk, middle suprarenal arteries, renal arteries, superior mesenteric artery, testicular arteries, inferior mesenteric artery, lumbar arteries, and the common iliac arteries are located below the diaphragm.

What is the three-layer composition of muscular arteries?

- The **tunica intima** is adjacent to the lumen and includes the endothelial layer and the internal elastic lamina.
- The **tunica media** includes smooth muscle, collagen, and reticular and elastic fibers.
- The **tunica adventitia** contains blood and lymph vessels and nerves supplying the artery.

See Figure 6-2A for the layers of an artery. Figure 6-2B shows the histologic image of an artery.

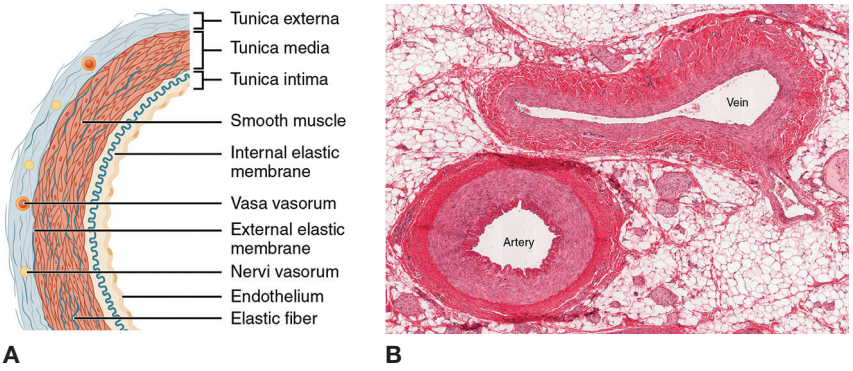


FIGURE 6-2. (A) Layers of an artery. (B) Histologic image of an artery. (A and B reproduced with permission from OpenStax College, The Cardiovascular System: Blood Vessels and Circulation In Anatomy & Physiology, Connexions Web site.)

An increased risk of this patient's condition is associated with defects in the genes coding for which proteins?

Fibrillin and **collagen**. Marfan syndrome is linked to a mutation in the *fibrillin-1* gene and typically presents as a tall, slender male with long limbs. Ehlers-Danlos syndrome results from various defects in collagen synthesis or structure and can be distinguished from Marfan syndrome by hyperelastic skin, meaning that these patients can easily retract their skin away from their body. Both syndromes are associated with an increased incidence of AAA.

Once the aortic wall is disrupted, how does coagulation proceed?

Exposure of tissue factor in the vessel wall initiates the extrinsic pathway of coagulation. Circulating factor VII comes into contact with tissue factor, activating factor X. Activated factor X helps convert prothrombin to thrombin. Thrombin then cleaves fibrinogen to fibrin, allowing fibrin deposition and cross-linking to form a clot. The functionality of the extrinsic pathway is measured by the prothrombin time (PT) and international normalized ratio (INR).

What are the risk factors for this condition?

AAA occurs most frequently in males. Advanced age and smoking are the most common risk factors. A one-time screening abdominal ultrasound is recommended in men ages 65–75 years with any history of smoking. Atherosclerotic lesions in the abdominal aorta are thought to increase the risk of AAA; by contrast, hypertension is thought to increase the risk of aortic dissection. Other risk factors for aneurysmal disease of the aorta include aortic infection, trauma, vasculitis, and connective tissue disorders such as cystic medial necrosis as seen in Ehlers-Danlos syndrome and Marfan syndrome.

What are the treatment options for this condition?

A small, asymptomatic AAA can be treated conservatively with frequent ultrasound surveillance and smoking cessation. Rapidly expanding aneurysms of $>$ 0.5 cm per year or those $\geq$ 5.5 cm in diameter require surgical repair.

CASE 2

A 65-year-old man presents to his cardiologist for evaluation of recurrent episodes of lightheadedness, chest pain, and shortness of breath with exertion. One week earlier, he experienced an episode of syncope while walking up the stairs in his house. Doppler echocardiography demonstrates a heavily calcified aortic valve with a calculated valve area that is 40% its normal size. Echocardiogram is shown in Figure 6-3.

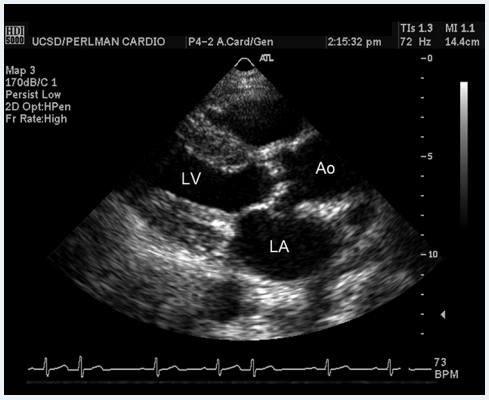


FIGURE 6-3. (Reproduced with permission from Fuster V, et al. *Hurst's The Heart,* 12th ed. New York: McGraw-Hill, 2007: Figure 18-59.)

What is the most likely diagnosis?

Aortic stenosis. Figure 6-3 shows narrowing of the aortic valve opening, which would appear larger in a normal patient. Calcified aortic valves are due to advanced age; however, in adolescents they are typically caused by bicuspid valves.

What factors increase the risk of this condition?

Aortic stenosis is commonly associated with older age, male gender, hypercholesterolemia, rheumatic fever, and congenital bicuspid aortic valve.

What type of murmur is caused by this condition?

The murmur of aortic stenosis is a **systolic ejection murmur** at the right upper sternal border, radiating to the neck. Signs of a severely stenosed valve include peaking of the murmur late in systole, palpable delay of the carotid upstroke, soft second heart sound, and an S4 gallop, which is produced due to a hypertrophied left ventricle. The intensity of this murmur increases with squatting and leg raise due to an increased preload and decreases with hand-grip, the Valsalva maneuver, and standing up. Handgrip results in increased afterload, which causes a relative equalization among pressure in the aorta and the left ventricle (LV). The Valsalva maneuver and standing up decrease preload.

How is this condition associated with congestive heart failure (HF)?

Aortic stenosis implies narrowing of the aortic valve, causing resistance to outflow of blood. In severe stenosis (valve area $<$ 50% of normal size), the narrowed valve causes increased pressure to build up in the LV, leading to concentric left ventricular hypertrophy (LVH). Although the LV initially responds to the increased pressure by thickening its walls, the increasing wall stress eventually decreases LV function, leading to HF. LVH also compromises coronary blood flow during exertion and can lead to angina.

What complications are associated with this condition?

- **Angina**: Without intervention, 50% of patients with angina die within 5 years.
- **Syncope with effort**: 50% of patients die within 3 years.
- **Dyspnea on exertion**: 50% of patients die within 2 years.
- **Post-stenotic aortic dilation**: Dilation of aortic root due to high-pressure flow through the narrow valve increases the risk of aortic dissection.
- **A-fib**: 5%–6% of adults experience atrial fibrillation with mild to moderate aortic stenosis.
- **Infective endocarditis**: 10%–30% lifetime risk for those with a bicuspid aortic valve.

What is the treatment for this condition?

Valve replacement is recommended in patients with symptomatic, severe aortic stenosis, as 10-year survival rates after replacement are comparable with those of the normal population. Per 2014 ACC/AHA guidelines, the three Class I indications for aortic valve replacement in the setting of aortic stenosis are: (1) severe aortic stenosis with symptoms, (2) asymptomatic patients with severe aortic stenosis and LV ejection fraction $<$ 50%, and (3) severe aortic stenosis undergoing other cardiac surgery. Sodium restriction and cautious use of diuretics may be indicated in the setting of HF. Excessive volume depletion should be avoided to prevent hypotension.

CASE 3

A 58-year-old man comes to the physician complaining of occasional substernal chest pain that occurs with strenuous activity. He is obese and has a history of hypertension and diabetes mellitus. During the physical examination, he admits to eating most of his meals at fast-food restaurants. He also reports he has little time for exercise.

What is the most likely diagnosis?

Stable angina, characterized by substernal chest pain with exertion, is often secondary to atherosclerosis. Stable angina is chest discomfort that occurs only during activity and resolves within several minutes of activity cessation. Patients with stable angina have minimal or no chest pain at rest. Unstable angina, however, occurs at rest and increases in frequency, severity, or duration.

What risk factors increase a person's likelihood of developing this condition?

Hypertension, diabetes mellitus, advanced age, male sex, and hyperlipidemia are major risk factors for atherosclerosis. Family history and smoking are also risk factors. Obesity and lack of exercise have not been definitively linked to increased risk of atherosclerosis but can exacerbate other risk factors associated with its development. Note that exercise capacity, however, is an important prognostic factor in those with cardiovascular disease.

What is the pathophysiology of this condition?

Endothelial dysfunction, which begins in early childhood, results from inflammation. Major risk factors include hyperlipidemia, smoking, and hypertension. Foam cells, or lipid-laden macrophages, accumulate in the subendothelium and form fatty streaks. Smooth muscle cells migrate (via platelet derived growth factor [PDGF] and fibroblast growth factor [FGF], which are secreted by platelets, endothelium, and macrophages) and synthesize extracellular matrix proteins and collagen that form a fibrous cap around the lipid plaque. Progressive enlargement of the plaque causes extracellular matrix remodeling and smooth muscle cell death. This increases the likelihood of plaque rupture, which may then embolize and lead to vessel occlusion (see Figure 6-4).

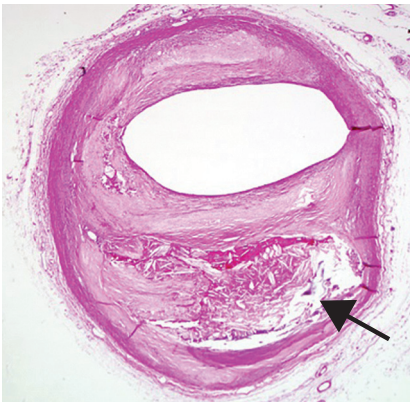


FIGURE 6-4. Cross-section of atherosclerotic coronary artery. Arrow points to the atheroma. (Reproduced with permission, from Le T, et al. *First Aid for the USMLE Step 1: 2019.* New York: McGraw-Hill, 2019.)

Which arteries are most commonly affected in cardiovascular disease?

Atherosclerosis preferentially affects the branching points of arteries or areas of turbulent blood flow, including the abdominal aorta, proximal coronary arteries, popliteal arteries, renal arteries, carotid arteries, and arteries of the circle of Willis.

What complications are commonly associated with this condition?

In addition to angina, other complications of atherosclerotic injury include aneurysms, myocardial infarction, stroke, ischemia (see Figure 6-5), and ischemic bowel disease.

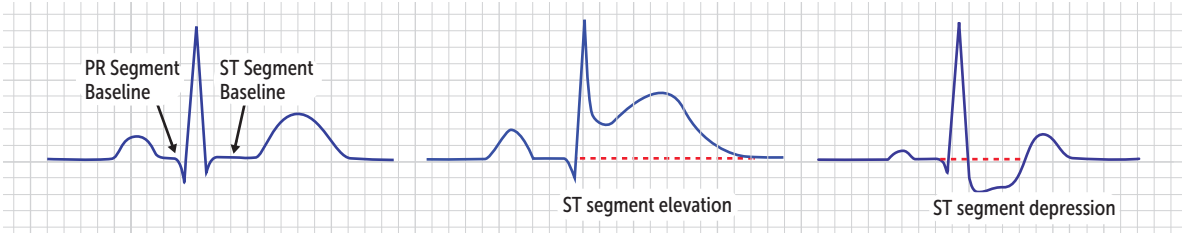


FIGURE 6-5. ECG showing ischemia. (Reproduced with permission from USMLE-Rx.com.)

What are the major forms of angina?

- **Stable angina**: Chest pain with exertion; responds to nitroglycerin.
- **Unstable angina**: Chest pain at rest secondary to thrombus with **incomplete** occlusion of a branch. May not completely respond to nitroglycerin; antithrombic agents and heparin may also be required. (Note that **complete** occlusion causes myocardial infarction.)
- **Vasospastic angina (previously termed Prinzmetal angina)**: Chest pain at rest, secondary to coronary artery vasospasm. Treatment includes calcium channel blockers.

CASE 4

A 58-year-old woman comes to the physician's office complaining of feeling lightheaded for the past week. She says she can feel her heart racing in her chest. She mentions she has been staying up late for the past few weeks because of her workload. Medical history reveals well-controlled diabetes mellitus. Physical examination reveals an anxious woman with pallor and mild diaphoresis. Cardiac examination reveals an irregularly irregular heartbeat. Vital signs are as follows:

Temperature: 36.1°C (97.0°F)
Respiratory rate: 22/min
Heart rate: 142/min
Blood pressure: 118/55 mm Hg
Glucose: 130 mg/dL

What is the likely diagnosis?

Atrial fibrillation.

What clinical and electrocardiographic abnormalities are commonly associated with this condition?

Lightheadedness, palpitations, anxiety, pallor, and diaphoresis are commonly associated with atrial fibrillation. Likewise, as in this patient, heart rate is elevated, and borderline hypotension is possible. Electrocardiogram (ECG) shows an absence of P waves, irregular R-R intervals, and tachycardia, as seen in this patient. Irregularly irregular uncoordinated atrial contractions can lead to tachycardia and stasis of blood in the left atrium; the development of a clot within the heart often ensues (see Figure 6-6).

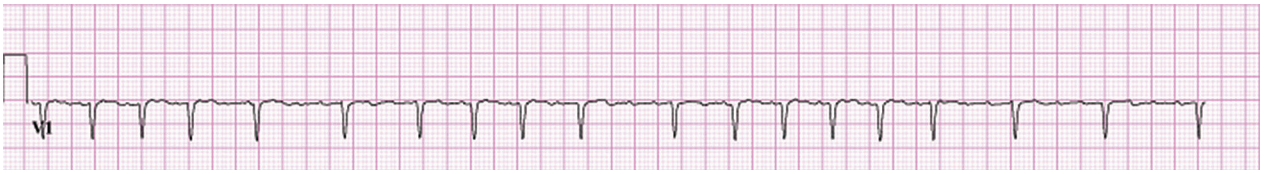


FIGURE 6-6. ECG strip in atrial fibrillation. (Reproduced with permission from USMLE-Rx.com.)

What is the treatment for this condition?

The patient's high heart rate needs to be slowed; to this end, β-blockers, calcium channel blockers, or digoxin are indicated. Metoprolol is a selective β_1-blocker that slows conduction through the atrioventricular node, thereby slowing heart rate. Cardioversion to a normal sinus rhythm may also be considered. However, care must be taken not to promote thromboembolism, which can occur if cardioversion is performed more than 48 hours after the onset of atrial fibrillation due to stasis of blood within the atrium. A transesophageal echocardiogram can screen for a left atrial thrombus, and the patient may be prescribed an anticoagulant such as warfarin for several weeks before cardioversion is attempted.

How is this condition managed?

Initially, the CHA_2DS_2-VAS_c score is calculated to assess stroke risk due to a-fib. A score of 2 or higher is considered moderate risk and anticoagulation treatment is recommended. Treatment options include heparin, warfarin, and novel oral anticoagulants (NOACs). Heparin is given intravenously and activates antithrombin III. Its effectiveness is determined by partial thromboplastin time (which reflects activity of the intrinsic pathway). Warfarin is given orally and impairs the synthesis of vitamin K–dependent clotting factors (II, VII, IX, X). It is monitored by prothrombin time (extrinsic pathway). NOACs, such as apixaban and rivaroxaban, are factor Xa inhibitors that have become increasingly popular in practice due to decreased bleeding risk and no requirement for PT or INR monitoring.

Why does paradoxical coagulation sometimes occur after starting warfarin therapy?

Warfarin also inhibits the synthesis of protein C and protein S. Because proteins C and S inhibit factors Va and VIIIa, a deficiency in these proteins promotes coagulation. Heparin has been commonly administered as a "heparin bridge" to prevent warfarin-induced skin necrosis.

CASE 5

A 50-year-old woman presents to her physician with a several-day history of fever, night sweats, chills, increasing dyspnea during her regular walks, and a 15-lb weight loss within the past 3 months. She also reports having had a transient weakness in her right arm approximately 2 weeks ago, which has spontaneously resolved. She denies chest pain, arthralgia, myalgia, or rash. Medical history and family history are unremarkable. Physical examination is notable for a fever of 38.4°C (101.2°F), a heart rate of 90/min, and a respiratory rate of 12/min. On cardiac auscultation, a loud split S1 and a diastolic third heart sound are present. Rales and increased tactile fremitus are present in both lung fields.

What is the most likely diagnosis?

Myxoma of the left atrium (see Figure 6-7). Most myxomas arise from the mural endocardium and measure 1–15 cm. Confirm diagnosis with an echocardiogram.

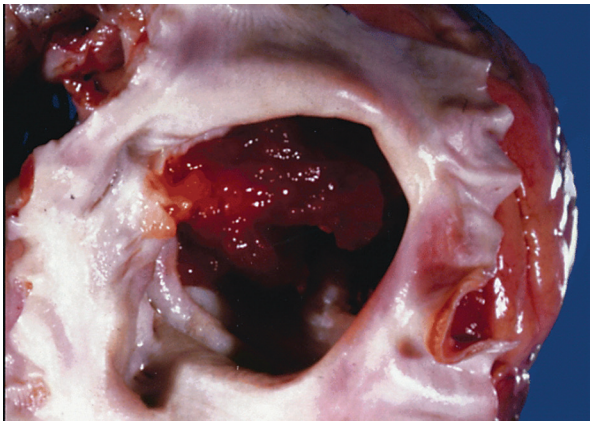


FIGURE 6-7. Cardiac myxoma. (Reproduced courtesy of The Armed Forces Institute of Pathology.)

What conditions should be included in the differential diagnosis?

- **Endocarditis**: Constitutional symptoms are common with atrial myxomas. However, this patient's transient right-arm weakness suggests embolization. This, combined with her fevers, chills, and sweats, makes infective endocarditis a possibility.
- **Vasculitis**: A peripheral vasculitis should be considered if the patient has arthralgia, myalgia, or rash, which occur in some patients with myxomas. Polyarteritis nodosa can cause multiple arterial aneurysms.
- **Transient ischemic attack** (TIA): Although not typically associated with constitutional symptoms, transient episodes of weakness or other neurological deficits may be secondary to TIAs caused by carotid artery plaque burden. Carotid ultrasound can exclude this possibility.
- The patient's rales and increased fremitus may represent atelectasis or consolidation at the lung bases.

What is the epidemiology of this condition?

Primary tumors of the heart are rare. Myxomas account for approximately 50% of benign tumors in the heart. The majority (75%) are located in the left atrium, although all chambers can be affected. The typical age of onset is 30–60 years. Familial occurrences have been reported in approximately 5% of cases via autosomal dominant transmission. These are associated with a younger age of presentation and higher rates of recurrence.

What complications may result from this condition?

Complications from left atrial myxomas can be categorized as follows:

- **Embolization** occurs in 40%–50% of cases with tumor fragments dislodging to distal organs (eg, brain, kidneys, or extremities).
- **Infection** is rare but may lead to further complications with embolization.
- **Obstruction** of the mitral or pulmonary venous orifices may occur, resulting in pulmonary hypertension and right heart failure.

How can the results of the cardiac examination be explained?

Splitting of S_1 is accentuated as the tumor is extruded from the mitral orifice. P_2 can also be louder if the tumor obstructs the mitral orifice or pulmonary venous return. The third heart sound is produced by the tumor "plopping" within the atrium during diastole.

CASE 6

A 55-year-old man comes to his physician for a follow-up visit, after being hospitalized 2 weeks earlier for an inferior wall myocardial infarction (MI). The patient has a history of coronary artery disease. His ECG is shown in Figure 6-8.

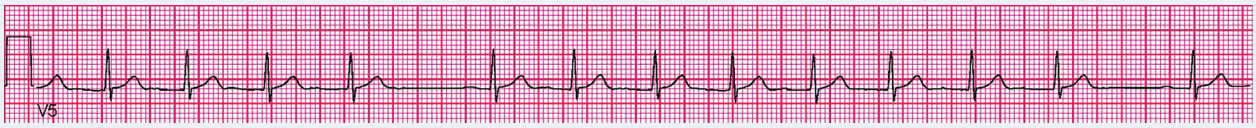


FIGURE 6-8. (Reproduced with permission from USMLE-Rx.com.)

What pathology does the ECG in Figure 6-8 depict?

Second-degree atrioventricular (AV) block type I, also known as **Mobitz type I block** or **Wenckebach block**. Progressive lengthening of the PR interval from one beat to the next is seen until finally a beat is dropped (a P wave is not followed by a QRS complex), as seen in Figure 6-8.

What is the pathophysiology of this condition?

Second-degree AV block type I occurs secondary to impaired conduction at the level of the AV node, such that atrial impulses fail to reach the ventricles. Given the location of the patient's prior MI, it is possible that it may have compromised the conductive ability of his AV node. An MI involving the right coronary artery may disrupt blood supply to the sinoatrial (SA) node and atrioventricular (AV) node. (Note that the AV node artery is typically a branch off the dominant coronary artery, which most commonly is the RCA; however, occasionally it can branch from the L circumflex.) By contrast, involvement of the left anterior descending coronary artery causes infarction of the His-Purkinje system.

How is this condition classified?

In **first-degree block**, the PR interval is prolonged, but there are no missed beats (a QRS complex follows every P wave) (see Figure 6-9A).

In **second-degree block**, there is intermittent failure of AV conduction. In a **Mobitz type I block**, the PR interval progressively lengthens until a beat is dropped (see Figure 6-8). In a **Mobitz type II block**, there is a sudden loss of impulse conduction without a corresponding change in PR interval. Mobitz type II may progress to more serious arrhythmias such as complete heart block (see Figure 6-9B).

In **third-degree block** (also known as **complete heart block**), there is no conduction via the AV node; atrial impulses do not reach the ventricles, and the ventricles beat at their intrinsic pace (see Figure 6-9C). On ECG, this is reflected as P waves and QRS complexes occurring independently of each other. Note that Lyme disease can cause third-degree heart block.

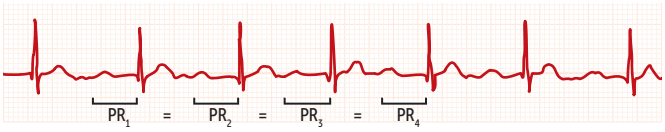


FIGURE 6-9A. First-degree AV block. The PR interval is fixed and is longer than 0.2 seconds, or five small blocks. (Reproduced with permission from Le T, et al. *First Aid for the USMLE Step 1: 2019.* New York: McGraw-Hill, 2019)

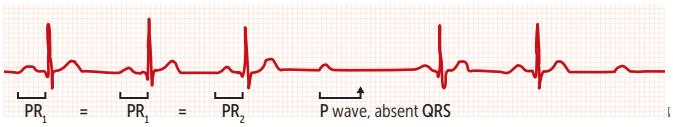


FIGURE 6-9B. Mobitz type II second-degree heart block. The PR interval is constant until the dropped beat. (Reproduced with permission from Le T, et al. *First Aid for the USMLE Step 1: 2019.* New York: McGraw-Hill, 2019.)

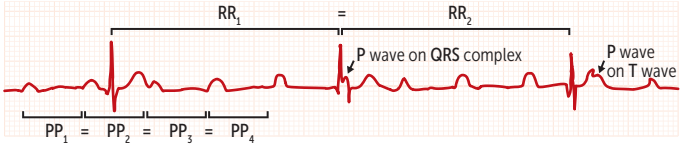


FIGURE 6-9C. Third-degree heart block. The P-P interval is uniform (lower double arrows) and the R-R interval is uniform (upper double arrows), but the P waves and QRS complexes are disassociated. (Reproduced with permission from Le T, et al. *First Aid for the USMLE Step 1: 2019.* New York: McGraw-Hill, 2019.)

What is the treatment for this condition?

Often, no treatment is necessary in asymptomatic patients with a second-degree Mobitz type I block. In symptomatic patients, atropine or isoproterenol may be used, or a pacemaker may be required. In contrast, patients with type II or type III heart block are often treated with pacemakers.

CASE 7

A 56-year-old man with a history of hypertension and hyperlipidemia presents to the ED 2 hours after the sudden development of crushing chest pressure and pain radiating to his jaw and left arm. His ECG shows ST elevations in the precordial leads, and his cardiac troponin levels are elevated. He undergoes cardiac catheterization, which reveals an occlusion in his left anterior descending (LAD) coronary artery.

Which area of the heart is affected by this obstruction?

The LAD runs along the anterior interventricular (IV) groove and supplies the anterior right and left ventricles as well as the anterior IV septum. The LAD is the most common coronary artery to become occluded.

From what vessel does the LAD originate?

The left main artery bifurcates, in most people, to the LAD and the circumflex artery (see Figure 6-10).

What are the branches of the right coronary artery (RCA), and what territories do they supply?

The **RCA** first travels in the atrioventricular (AV) groove, then wraps around the inferior border of the heart to the posterior IV groove. In 80% of people, the **SA nodal artery** is the first branch of the RCA. Other branches of the RCA include the right marginal, posterior descending (in 80% of people), and AV nodal arteries.

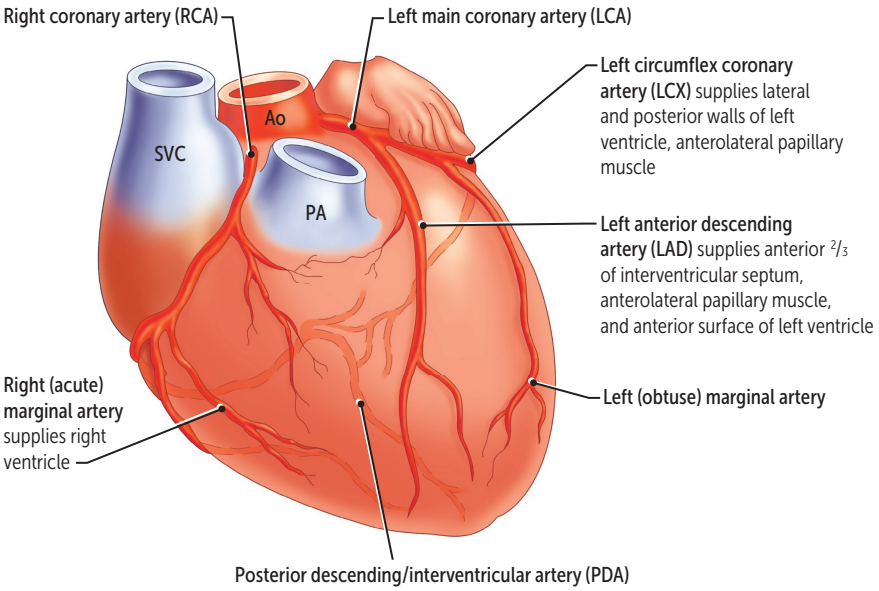


FIGURE 6-10. Coronary artery anatomy. (Reproduced with permission from USMLE-Rx.com.)

During which part of the contraction cycle do coronary arteries fill?

The coronary arteries have maximal blood flow during diastole and minimal flow during systole. This is due to their location above the cusps of the aortic valve, which obstructs flow into the coronary arteries when the valve opens during systole.

What biomarkers indicate myocardial injury?

Cardiac troponin I and T are sensitive and specific markers of damage to the heart.

Creatine kinase (CK) is an enzyme that is found in muscle tissue throughout the body and may become elevated from damage to muscle cells. Elevated CK levels are not specific to myocardial infarction (MI) and may be seen in drug-induced myopathies, rhabdomyolysis, myocarditis, and myositis (dermatomyositis, polymyositis).

CK-MB is an isoenzyme of CK that composes 3%–5% of the total CK and is expressed in higher levels in cardiac muscle. CK-MB is sensitive and specific for myocardial injury; however, skeletal muscle injury can increase CK-MB slightly as well. Troponins are the preferred method to detect myocardial injury.

What is the timing of biomarker release after myocardial injury?

CK levels rise within 4–8 hours, peak at 12–24 hours, and return to baseline within 36–48 hours. It is therefore a good measure of reinfarction.

Troponin I and T may be detected as early as 2 hours after MI but usually rise by 6 hours, peak at 12 hours, and return to baseline by 7–10 days, making the test useful to identify patients with delayed presentations of MI.

CASE 8

A 2-week-old baby boy is seen in the pediatrician's office for a well-baby checkup. His mother states that he has been lethargic and hasn't been feeding well. There were no complications with the pregnancy, and on discharge the baby was doing well. On physical examination, the baby's femoral pulses are weak and delayed bilaterally. Blood pressure readings on his lower extremities are decreased in comparison to the upper.

What is the most likely diagnosis?

Coarctation of the aorta occurs two to five times more often in males than in females.

In this condition, which part of the aorta is typically affected?

In the majority of cases, the lesion is in the descending aorta, distal to the origin of the left subclavian artery and in the periductal region. Disease course depends on the degree of obstruction after ductal closure, the presence of collateral circulation, and any associated cardiac anomalies. Less severe forms are characterized by an isolated aortic narrowing and the presence of adequate collateral flow. These forms progress gradually and become symptomatic between the second and third decades of life. Severe, symptomatic disease in early infancy (< 10 days of age) occurs if the coarctation is associated with additional cardiac anomalies and/or inadequate collateral flow to compensate for ductal closure. Figure 6-11 shows the anatomic features of aortic coarctation.

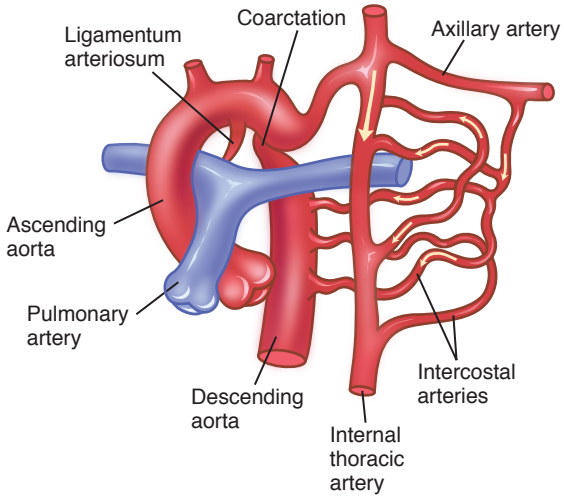


FIGURE 6-11. Coarctation of aorta—compromised flow to descending aorta causing shunting to intercostal arteries (rib notching). (Reproduced with permission from USMLE-Rx.com.)

What is the characteristic finding on physical examination?

Auscultation over the chest and/or back may reveal a midsystolic ejection murmur. A continuous murmur over the chest may also be heard in older individuals who have developed collateral circulation. Weak, delayed pulses in the lower extremities are also characteristic of coarctation.

What chromosomal abnormality is associated with this condition?

Coarctation of the aorta is associated with Turner syndrome (45,XO). Note that congenital bicuspid aortic valves can also be associated with Turner syndrome.

What findings on physical examination, ECG, and x-ray of the chest often develop over time in patients with this condition?

Many patients develop hypertension of the upper extremities with weak, delayed femoral pulses. If the coarctation is proximal to the point of division of the left subclavian artery, the systolic pressure in the right arm may be greater than that in both the lower extremities and the left arm. Patients may complain of headaches due to hypertension, and if left untreated, acute cerebral hemorrhage can occur.

Left ventricular hypertrophy is a common finding on ECG.

X-ray of the chest often shows an indented aorta, which is referred to as the "3 sign" and/or notching of the inferior surfaces of the ribs, usually around 7 years of age. This notching is the result of increased blood flow through the intrathoracic and intercostal vessels, which serve as collateral circulation.

CASE 9

A 2-day-old baby is observed to have purpuric skin lesions (see Figure 6-12). His mother recently emigrated from a developing country. Her pregnancy is notable for a flulike illness involving a maculopapular rash of her face and body several weeks after her last menstrual period. Physical examination of the neonate reveals a low birth weight, cataracts, and a grade II/VI harsh crescendo-decrescendo systolic murmur most audible at the left upper sternal border with radiation to the axilla and back. Laboratory testing demonstrates thrombocytopenia.

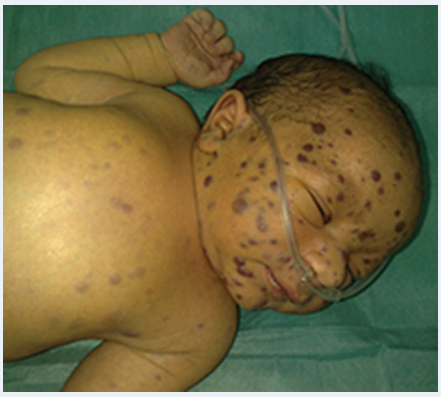


FIGURE 6-12. (Reproduced with permission from Benmiloud S, et al. *Pan Afr Med J.* 2012;13:23.)

What is the most likely diagnosis?

This constellation of clinical findings, including cardiac manifestations, a "blueberry muffin" rash (as seen in Figure 6-12), and the maternal history strongly suggest congenital rubella syndrome (CRS). Rubella virus (RV) is an RNA virus of the Togaviridae family, and it is associated with an 85% risk of congenital defects if acquired in the first 12 weeks of pregnancy. Other infections acquired in utero that can present with rash and ocular findings can be recalled with the **ToRCHeS** acronym: **T**oxoplasmosis, **o**ther infections, **R**ubella, **C**ytomegalovirus infection, **He**rpes simplex, and **S**yphilis. Infections that have a similar appearing rash to rubella include measles, roseola, scarlet fever, varicella-zoster virus (VZV), and mononucleosis.

What laboratory test in the neonate can help confirm this diagnosis?

Viral culture of nasal secretions or monthly serology testing for anti-rubella IgM antibody with rising titers can establish a laboratory CRS diagnosis.

What cardiac anomalies are associated with the murmur seen in this patient?

In this patient, the location of the murmur at the left upper sternal border and radiation into the lung fields strongly suggest pulmonary valve or pulmonary artery stenosis, which are common in CRS. A supravalvar or peripheral pulmonary artery stenosis is more likely in this case given the radiation and the absence of a systolic click, which would indicate an obstructed or dysplastic valve. Another common cardiac anomaly of CRS is patent ductus arteriosus. Failure of the ductus arteriosus to close produces a continuous machine-like murmur across the precordium. Prostaglandin E_2 is responsible for maintaining the patent ductus arteriosus; therefore, nonsteroidal anti-inflammatory drugs such as indomethacin are a treatment option.

What other symptoms are common in patients with this condition?

Primary rubella infection early in pregnancy results in defective organogenesis. The classic permanent abnormalities include cataracts, retinopathy, heart defects, and sensorineural deafness. Transient abnormalities include meningoencephalitis, thrombocytopenia with or without purpura, and bony radiolucencies. Since CRS is a persistent infection, more abnormalities, such as developmental difficulties and progressive panencephalitis, can occur.

What is the treatment for this condition?

Since no therapy currently exists for CRS, the focus is on prevention through vaccination. Rubella vaccine contains live, attenuated rubella virus and therefore is contraindicated in pregnant women. Rubella has been eliminated in the United States and Scandinavia but persists elsewhere because of inadequate vaccination programs.

CASE 10

A 75-year-old nonsmoking male, status–post recent abdominal surgery suddenly develops calf muscle pain in his left lower extremity (LLE). His hospitalization since his surgery 3 days ago has been unremarkable. The patient's medical and family histories reveal no cardiovascular disease or malignancy. On physical examination, he is afebrile and is not in acute distress. His LLE is swollen and mildly erythematous. The skin is warm to the touch and intact throughout. Homans sign (pain on passive dorsiflexion of the foot) is negative. His right lower extremity is unremarkable. Relevant laboratory test results are as follows:

Partial thromboplastin time (PTT): 28 seconds
Prothrombin time (PT): 12 seconds
International normalized ratio (INR): 0.9

What is the most likely diagnosis?

Deep venous thrombosis (DVT) is most common in the lower extremities. Hospitalized patients are at high risk for DVT and the associated complications of pulmonary embolism. Risk of DVT is higher in surgical patients than medical patients and is particularly high for patients who have had hip or knee surgery. Homan sign has a low sensitivity and specificity, so although it is negative, the clinical picture still points towards DVT. The most specific clinical sign for DVT is edema.

How is this condition diagnosed?

The level of D-dimer, a fibrin degradation product, is often elevated in DVT; however, it is not used to diagnose DVT. Assays for D-dimer are highly sensitive and have a low false-negative rate in **symptomatic** patients. A negative D-dimer test, therefore, may exclude DVT in low-risk patients. D-dimer can also be used to monitor anticoagulation treatment and DIC; however, it must be kept in mind that D-dimer levels can mildly increase in pregnancy, inflammatory conditions, and liver disease, so D-dimer levels can exclude diagnoses rather than confirm them. In DVT-prevalent populations (eg, surgical patients), additional tests may be used to diagnose or confirm DVT, such as deep venous ultrasonogram with examination for flow abnormalities (that would be present with a thrombus). Other tests include MRI and venography.

In what other conditions is D-dimer elevated?

D-dimer may be elevated in a number of inflammatory conditions, including liver disease, autoimmune disease, malignancy, surgery, and in elderly patients. D-dimer therefore has a low specificity for DVT.

What are the risk factors for this condition?

Risk factors of DVT are described by the Virchow triad. **Stasis** may increase secondary to surgery, immobility, paresis, increasing age, heart failure, pregnancy, or obesity. **Vessel injury** may result from smoking, prior DVT, catheterization, or varicose veins. Numerous hereditary conditions result in **hypercoagulability**. Other hypercoagulable states include malignancy, estrogen therapy, acute medical illnesses, inflammatory bowel disease, and nephrotic syndrome.

What conditions should be included in the differential diagnosis?

Numerous conditions can mimic DVT, including the following: muscle strain or tear, lymphedema, venous valvular insufficiency, popliteal cysts, and cellulitis.

What is the anatomy of the major deep veins in the lower extremities?

The anterior tibial, posterior tibial, and peroneal veins converge at the lower popliteal fossa to form a single popliteal vein. The popliteal vein continues medially to become the superficial femoral vein. The deep femoral vein runs laterally and joins the superficial femoral and great saphenous vein in the femoral canal to form the common femoral vein. Thrombus formation in the superficial veins of the legs (thrombophlebitis) has a low risk of thromboembolism or pulmonary embolism formation and thus is not routinely treated with anticoagulation.

CASE 11

A 50-year-old African-American man presents to his physician complaining of worsening dyspnea on exertion, orthopnea, and paroxysmal nocturnal dyspnea. His medical history is notable for an anterior myocardial infarction (MI) 15 months ago. A holosystolic murmur is audible, particularly at the apex, along with a diastolic rumble. ECG demonstrates left ventricular hypertrophy and deep ($>$ 1 mm), broad Q waves in V_1, V_2, and V_3. Echocardiography shows increased chamber volume, depressed ejection fraction (EF), and thinning of the left ventricular walls.

What is the most likely diagnosis?

Dilated cardiomyopathy (DCM) is defined as a left ventricular (LV) EF $<$ 40% and a ventricular chamber with increased diastolic and systolic volumes. In this patient, it is likely of ischemic etiology. DCM is a major cause of congestive heart failure in young people. Males and African-Americans are at an increased risk for DCM.

What are causes of this condition?

There are many causes of DCM, but they can be broadly categorized as primary or secondary. **Primary** causes of DCM include idiopathic or genetic factors. **Secondary** causes of DCM include ischemia, hypertension, valvular disease, drugs (alcohol, cocaine, doxorubicin), infectious disease (Chagas disease, coxsackievirus), vitamin B deficiency, and postpartum state.

What typical signs and symptoms are associated with this condition?

DCM results in depressed systolic pump function and the typical symptoms of myocardial failure, as seen in this patient. Enlargement of the ventricle dilates the annulus and displaces the papillary muscles. This can result in the holosystolic murmur of mitral regurgitation. The subsequent increase in early diastolic atrium-to-ventricle flow results in the diastolic rumble. Prior MIs are characterized by deep, broad Q waves. The presence of Q waves in the precordial leads suggests an old anterior MI.

What is the pathogenesis of this condition?

After an MI, it is hypothesized that the reduced peripheral (particularly renal) perfusion leads to fluid retention in an attempt to increase cardiac output. This ultimately results in cardiac remodeling. Figure 6-13 shows the relationship between renin-angiotensin and autonomic nervous system activation and cardiac myocyte cell death.

What is cardiac remodeling?

Following MI, necrotic muscle cells are replaced by proliferating fibroblasts and collagen deposition. The development of scar tissue in the myocardium thins the ventricle walls, reshapes the ventricle, and ultimately adversely affects contractility. To maintain organ perfusion, one mode of compensation is via cardiac hypertrophy, which varies depending on a predominantly pressure- or volume-overloaded system. Concentric hypertrophy develops due to pressure overload, whereas eccentric hypertrophy, which can occur with an MI, is due to volume overload. The difference between the two is how the cardiac sarcomeres align. The sarcomeres in concentric hypertrophy align in parallel whereas those in eccentric hypertrophy align in series. Eccentric hypertrophy primarily leads to ventricular dilation; however, wall thickness is also increased. Note that cardiac hypertrophy can be physiological. Aerobic exercise can lead to eccentric hypertrophy, and static exercise can cause concentric hypertrophy.

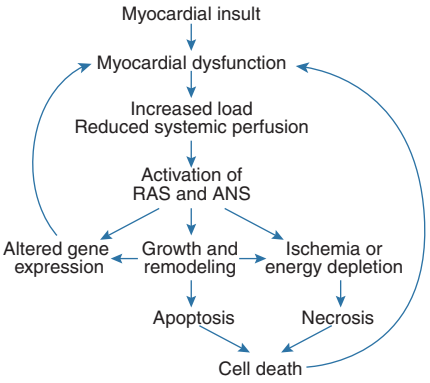


FIGURE 6-13. The renin-angiotensin system and autonomic nervous system in the progression to myocardial failure. (Modified, with permission, from Fuster V et al. *Hurst's The Heart,* 11th ed. New York: McGraw-Hill, 2004: 1892.)

What is the treatment for this condition?

Angiotensin-converting enzyme inhibitors and β-blockers are appropriate in all patients with reduced ejection fractions, whether or not they are symptomatic (Class I indication), because they slow the remodeling process and reduce myocardial workload, respectively. In so doing, they improve cardiac output and reduce mortality. Diuretics may be used in volume-overloaded patients. In some cases, anticoagulation may be required, as there is a predilection for thrombi to form in a dilated cardiac chamber. Digitalis may also improve the EF and decrease heart failure–associated hospitalizations; however, it has not been shown to decrease mortality. Aldosterone antagonists have been shown to provide a mortality benefit in patients with severe heart-failure symptoms.

CASE 12

A 30-year-old man is evaluated in the ED for a 24-hour history of chest pain, difficulty breathing, and chills. He denies any history of medical problems. On physical examination, he appears ill. His temperature is 40°C (104°F), his blood pressure is 90/50 mm Hg, and his heart rate is 110/min. Cardiac examination reveals a 3/6 diastolic murmur, but the patient denies any history of a murmur. ECG results are normal. Gram stain of a peripheral blood smear shows gram-positive cocci in clusters.

What is the most likely diagnosis?

Acute infective endocarditis caused by *Staphylococcus aureus*. The man's new heart murmur suggests a possible valvular lesion as the source of infection. In this case, a Gram stain that demonstrates gram-positive organisms in clusters suggests staphylococci.

Which valvular structure is most commonly affected in this condition?

In the general population, endocarditis most frequently involves the mitral valve (see Figure 6-14). Common organisms include staphylococcal and streptococcal species. In intravenous (IV) drug users, however, the tricuspid valve is most commonly involved. In these cases, venous blood contaminated by nonsterile venipuncture crosses the tricuspid valve first.

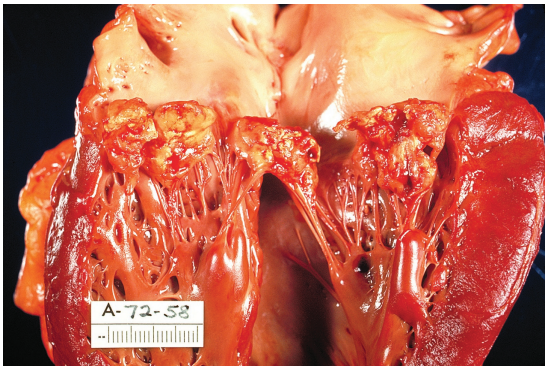


FIGURE 6-14. Bacterial vegetations on mitral valve. (Reproduced courtesy Centers for Disease Control and Prevention/Dr. Edwin P. Ewing, Jr.)

What other microorganisms are associated with this condition?

Acute endocarditis develops in previously normal valves; *S aureus*, *Neisseria gonorrhoeae*, and *Streptococcus pneumoniae* are common culprits. **Subacute endocarditis** is diagnosed in previously abnormal or damaged valves and is often secondary to previous rheumatic fever. Common causes of subacute endocarditis are *Streptococcus viridans*, *Staphylococcus epidermidis*, enterococci, *Candida*, and HACEK groups *(Haemophilus, Aggregatibacter, Cardiobacterium, Eikenella, Kingella*—found in the oropharyngeal regions).

What are other types of valvular vegetations, and what diseases are they associated with?

Libman-Sacks endocarditis occurs with systemic lupus erythematosus, which is believed to result from autoimmune damage to cardiac valves. **Nonbacterial thromboembolic endocarditis** can occur with the hypercoagulable state in cancer. **Rheumatic fever endocarditis** develops acutely and does not lead to valvular destruction.

What characteristic of this microbe confers resistance to antibiotics?

Penicillin resistance by *S aureus* develops through the secretion of penicillinase (a β-lactamase), which inactivates penicillin. Vancomycin resistance develops through the acquisition of a gene that changes the vancomycin binding site from a D-ala-D-ala sequence to D-ala-D-lac on bacterial cell wall precursors. Loss of the binding site results in resistance to vancomycin.

What are the complications of this condition?

A serious complication of endocarditis is embolization of valvular vegetations. Embolization to the brain, liver, kidneys, and bone may lead to abscess and may have profound neurological and physiological effects. Small pieces of vegetations may embolize peripherally, leading to Roth spots (retinal hemorrhages), Janeway lesions (nontender hemorrhagic lesions on palms or soles), Osler nodes (tender lesions on palms or soles), and Splinter hemorrhages (subungual) (See Figure 6-15).

What is the treatment for this condition?

The best treatment for infective endocarditis is IV antibiotics targeted at the causative agent.

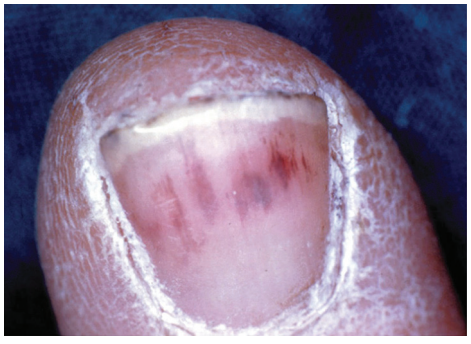


FIGURE 6-15. Splinter hemorrhages. (Reproduced with permission from USMLE-Rx.com.)

CASE 13

A 61-year-old man with chronic sinusitis and a family history of autoimmune disorders presents to his physician with cough and hemoptysis of 3 weeks' duration. He also complains of frequently becoming short of breath. Nasal mucosal biopsy shows an antibody binding intracellular proteinase-3 diffusely throughout the cytoplasm (antineutrophil cytoplasmic antibodies, C-ANCA). Urinalysis reveals hematuria with RBC casts.

What is the most likely diagnosis?

Granulomatosis with polyangiitis (formerly known as Wegener granulomatosis). Necrotizing granulomatous vasculitis of small- and medium-sized vessels leads to manifestations in the kidney and lungs (see Figure 6-16).

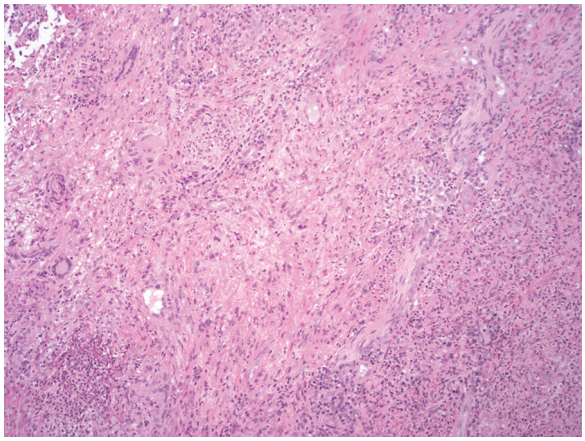


FIGURE 6-16. Lung biopsy shows a classic necrotizing granuloma in the lung with surrounding lymphocytes, plasma cells, macrophages, and occasional giant cells. (Reproduced with permission from USMLE-Rx.com.)

What laboratory test can help establish the diagnosis?

The presence of C-ANCA is associated with granulomatosis with polyangiitis, which must be differentiated from **Goodpasture syndrome**, an autoimmune disorder that also presents with hemoptysis and renal disease (see Table 6-1). Instead of C-ANCA antibodies, Goodpasture syndrome features anti–glomerular basement membrane antibodies (anti-GBM).

TABLE 6-1. Distinguishing Features of Granulomatosis with Polyangiitis and Goodpasture Syndrome

Feature	Wegener	Goodpasture
Antibody	ANCA	GBM
Renal biopsy	Leukocytoclastic vasculitis	Linear deposits among basement membrane
Organ involvement	All organs	Lung and kidney

What are the likely findings on gross pathology of the kidney?

Renal involvement in granulomatosis with polyangiitis commonly manifests as a pauci-immune or type III rapidly progressive glomerulonephritis. Immunofluorescence reveals no antibodies or immune complex deposition. By contrast, Goodpasture syndrome shows linear deposition of anti-GBM antibodies.

If this patient also had severe renal dysfunction, which treatment should be avoided?

Methotrexate, although therapeutic, can be nephrotoxic in patients with granulomatosis with polyangiitis. Preferred treatments include other immunosuppressants such as cyclophosphamide and corticosteroids.

What other findings are common in patients with this condition?

Perforation of the nasal septum (the so-called "saddle-nose" deformity; see Figure 6-17), chronic sinusitis, mastoiditis, cough, hemoptysis, hematuria, and RBC casts are common findings in patients with granulomatosis with polyangiitis. See Table 6-1 for the distinguishing features of granulomatosis with polyangiitis and Goodpasture syndrome.

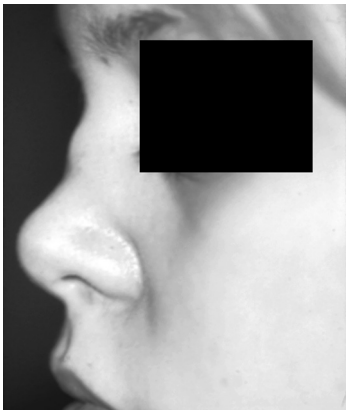


FIGURE 6-17. Nasal septum perforation in granulomatosis with polyangiitis. (Reproduced, with permission, from Imboden J, et al. *Current Diagnosis & Treatment: Rheumatology, 3rd ed.* New York: McGraw-Hill, 2013.)

CASE 14

A 65-year-old woman with a 60-pack-year smoking history comes to her primary care physician after 3 months of shortness of breath and dry cough. Until recently, she was able to walk the four blocks to her local grocery store without shortness of breath; however, now she is able to walk only one block before having to stop and rest. She has been waking from sleep with difficulty breathing and feels uncomfortable lying flat in bed. Her physical examination is notable for crackles at the lung bases. There is no evidence of hepatosplenomegaly or jugular venous distention.

What is the most likely diagnosis?

Left heart failure (LHF) is evidenced by orthopnea, paroxysmal nocturnal dyspnea, and dyspnea on exertion. Pure left-sided heart failure would not cause edema. Since LHF is usually associated with some degree of RHF, it can then manifest with mild edema.

What symptoms help differentiate right heart failure from left heart failure?

Right heart failure is characterized by compromised venous return. This can manifest as ascites, significant edema of the lower extremities, jugular venous distention $\geq$ 3 cm (or central venous pressure $\geq$ 8 cm), and hepatosplenomegaly secondary to liver and spleen congestion.

What is the pathophysiology of this patient's condition?

LHF can be divided into systolic and diastolic dysfunction. Systolic dysfunction refers to a significant decrease in ejection fraction, which can be caused by myocardial infarction and dilated cardiomyopathy. Diastolic dysfunction refers to decreased end diastolic volume, or an inability for adequate filling, due to hypertrophied or stiff cardiac muscle. It can be caused by hypertension, valvular heart disease, and hypertrophic cardiomyopathy. The ejection fraction in diastolic dysfunction is typically normal. In both mechanisms, congestion develops, causing backflow of blood and overall decrease in systemic tissue perfusion. Note that the signs and symptoms of systolic vs. diastolic heart failure are indistinguishable.

What does the Frank-Starling curve demonstrate about normal cardiac physiology?

The Frank-Starling curve, as illustrated in Figure 6-18, demonstrates how the stroke volume increases with an increase in the amount of blood filling the ventricles of the heart (ventricular end diastolic volume). In a normally functioning heart, from a resting state (point A), more blood returning to the left ventricle will cause an increase stroke volume, maintaining normal systolic function (point B).

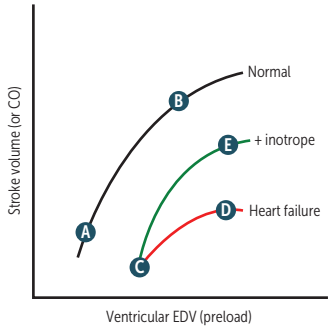


FIGURE 6-18. Frank-Starling curve. (Reproduced with permission from USMLE-Rx.com.)

How does the Frank-Starling curve change in heart failure?

Severe heart failure results in decreased contractility, resulting in a flatter Frank-Starling curve than with a normal heart, as illustrated using a red curve in Figure 6-18. In this state of decreased contractility, the stroke volume does not significantly increase as a normal heart would, despite continued increase in ventricular end diastolic volume. From point C to D, the ventricular end diastolic volume has increased significantly, but the stroke volume has essentially remained unchanged. As the heart is unable to maintain an adequate stroke volume, blood begins to pool in the ventricles, causing the classic symptoms of heart failure.

How would adding a diuretic or a positive inotropic drug affect the Frank-Starling curve?

Adding a diuretic and decreasing the overall fluid volume from the patient would decrease ventricular end diastolic volume as shown by the change from point D to C. Adding a positive inotropic drug increases the heart's contractility, which would steepen the curve once again and cause a shift from C to E. At point E, the patient's heart is able to maintain adequate stroke volume and cardiac output in the face of increased ventricular end diastolic volume.

This patient is at risk for which other conditions?

As described above, the congestion causes backflow of blood into the lungs, which can subsequently lead to pulmonary edema and RHF. The most common reason for RHF is due to LHF. On histologic examination, pulmonary edema will show "heart failure cells" or hemosiderin-laden macrophages. Pulmonary edema manifests by the symptoms orthopnea and paroxysmal nocturnal dyspnea. Additionally, peripheral edema, atrial fibrillation, pre-renal azotemia, and hypoxic encephalopathy can ensue.

CASE 15

A 51-year-old man comes to the physician's office for a routine physical examination. At his last examination 3 years ago, he was advised to modify his lifestyle because his blood pressure was 144/87 mm Hg. At the current visit, his blood pressure is 150/95 mm Hg. The patient is overweight (body mass index 28 kg/m2), and he has smoked one pack of cigarettes per day for the past 30 years.

What additional symptoms would indicate an emergent situation?

Blood pressure goals in most patients are < 130/80 mm Hg; the goal is lower in patients with diabetes or other comorbid conditions. Hypertensive urgency is characterized by severely elevated blood pressure (systolic > 180 mm Hg or diastolic > 110 mm Hg) **without** evidence of end-organ damage. Hypertensive emergencies are characterized by severely elevated blood pressure **with** signs of end-organ damage, including mental status changes, stroke, myocardial infarction, and renal failure.

What is the primary treatment for this condition?

Lifestyle modification is attempted before pharmacologic therapy is undertaken. This includes moderate dietary sodium restriction, weight reduction in obese patients, avoidance of smoking and excess alcohol intake, increased fruit and vegetable intake, and regular aerobic exercise.

What is the initial pharmacologic therapy of choice for this condition?

Current guidelines recommend that angiotensin-converting enzyme inhibitors (ACE-I), angiotensin receptor blockers (ARB), calcium channel blockers (CCB), and thiazide diuretics can all be used as potential first-line agents in non–African-American persons without diabetes or chronic kidney disease. In African-American patients, thiazide diuretics or CCB alone or in combination are initially recommended. In diabetic patients, ACE-I or ARB alone or in combination with other antihypertensive medications is first line.

What are the mechanism of action and major toxicities of angiotensin-converting enzyme (ACE) inhibitors?

ACE inhibitors, such as captopril and lisinopril, are particularly useful when comorbidities such as diabetes mellitus with microalbuminuria and left heart failure coexist with hypertension. These drugs work by inhibiting ACE, thereby reducing levels of angiotensin II and preventing inactivation of bradykinin (a vasodilator). Toxicities include cough, angioedema, taste changes, hypotension, fetal renal damage, rash, and hyperkalemia. Angiotensin II receptor blockers such as losartan have a decreased incidence of cough as an adverse effect.

What are the mechanisms of action and major toxicities of β_1-adrenergic blockers?

β_1-Selective blockers (acebutolol, betaxolol, esmolol, atenolol, and metoprolol) are particularly useful in decreasing mortality after ischemic events and in patients with congestive heart failure. They work by decreasing chronotropy, inotropy, and dromotropy, thereby slowing the heart rate and decreasing blood pressure. Although β1-specific antagonists have fewer respiratory adverse effects than nonspecific β-blockers (such as propranolol), major adverse effects include bradycardia, congestive heart failure, atrioventricular block, sedation, sleep alteration, and impotence.

What is chronotropy, inotropy, and dromotropy? (see Table 6-2)

TABLE 6-2. Chronotropy, Inotropy, and Dromotropy

	Definition	Positive	Negative
Chronotropy	*Frequency* of impulses from SA to AV node	Increases heart rate	Decreases heart rate
Inotropy	Cardiac *contraction* force	Increases stroke volume	Decreases stroke volume
Dromotropy	*Speed* of impulses from SA to AV node	Increases heart rate	Decreases heart rate

What are the mechanisms of action and major toxicities of calcium channel blockers?

Calcium channel blockers such as nifedipine (which is more specific for vasculature than verapamil and diltiazem) block voltage-dependent L-type calcium channels of smooth and cardiac muscle, thereby reducing muscle contractility. They are particularly useful when hypertension is not adequately controlled with the above agents. Major toxicities include cardiac depression, peripheral edema, flushing, dizziness, and constipation.

CASE 16

A previously healthy 16-year-old boy presents to the ED because of difficulty breathing and substernal chest pain radiating to the neck and shoulder while he was playing soccer. He is now feeling much better. He denies any drug or cigarette use and is not aware of any medical problems in his family, except for two uncles who died suddenly in their youth. Physical examination reveals a heart rate of 70/min, blood pressure of 124/80 mm Hg, and respiratory rate of 12/min. Heart sounds are notable for a normal S1 and normally split S2, along with a murmur. His point of maximum impulse is enlarged and anteriorly displaced. The precordial tracings from his ECG are shown in Figure 6-19.

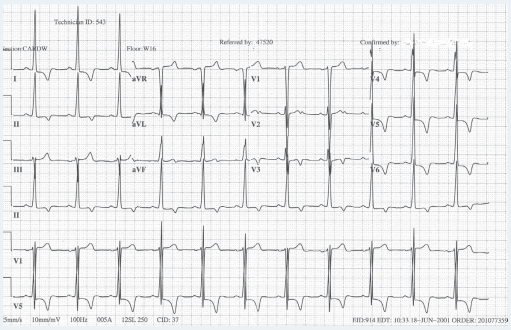


FIGURE 6-19. (Modified, with permission, from Fuster V, et al. *Hurst's The Heart,* 12th ed. New York: McGraw-Hill, 2007: Figure 30-9.)

What is the most likely diagnosis?

Hypertrophic cardiomyopathy (HCM) is suggested by the patient's age, symptoms, family history of sudden death (a common presentation in young people with HCM), murmur, and ECG findings. It is characterized by the overgrowth of myocardium with myocardial disarray (see Figure 6-20).

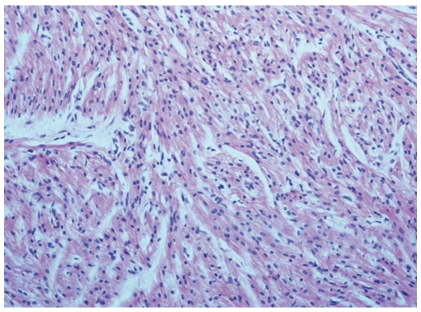


FIGURE 6-20. Hypertrophy of myocytes and cellular disorganization (disarray) of the left ventricle. (Reproduced with permission of Mecchia D, et al. Sudden death of an infant with cardiac, nervous system and genetic involvement – a case report. *Diagn Pathol*. 2013;8:159.)

What is the epidemiology and etiology of this condition?

Epidemiology: HCM is believed to be the most common genetic cardiovascular disorder. Its overall prevalence is estimated to be 1:500 to 1:1000. No gender preference is observed, and clinical manifestation varies by age. Hypertrophic cardiomyopathy is also associated with Friedreich ataxia.

Etiology: Multiple mutations that affect the cardiac sarcomere have been associated with HCM, many of which are transmitted in an autosomal dominant pattern.

How should the ECG findings in Figure 6-19 be interpreted?

The ECG shows normal sinus rhythm. These ECG findings suggest significant left ventricular hypertrophy, as indicated by the deep S wave in V_1 and tall R wave in V_5 or V_6 (ie, S wave in V_1 + R wave in V_5 or $V_6 \geq 35$ mm). In athletic young patients, high voltage in the R and S waves may not be abnormal; however, patients with HCM have more marked evidence of left ventricular hypertrophy than healthy individuals. ST-segment depression with T-wave inversion in V_4 to V_6 may suggest lateral infarction, given their presence only in these lateral leads. Note that these findings should be taken with caution because there are many different criteria (Cornell, Modified Cornell, Sokolow-Lyon, Romhilt-Estes) to diagnosis LVH.

What is the classic murmur associated with this condition?

The classic murmur is due to left ventricular outflow tract obstruction caused by the hypertrophic septum within a shrunken ventricular cavity. A systolic, crescendo-decrescendo murmur most audible at the left sternal border that ends shortly before S_2 is often heard. This murmur decreases with squatting and increases with standing or with low-volume states such as dehydration. The murmur of HCM is enhanced by maneuvers that worsen the obstruction below the aortic value and diminished by maneuvers that increase venous return, thus distending the left ventricle and decreasing the degree of stenosis. A mitral valve (MV) regurgitation murmur may also be heard, as the MV leaflets can be pulled into the outflow tract in midsystole.

What major classes of pharmacologic agents may benefit this patient?

β-Adrenergic antagonists are used to decrease heart rate, myocardial oxygen consumption, and outflow tract gradient and to increase diastolic filling time. Calcium channel blockers are used to decrease inotropy and chronotropy and improve diastolic relaxation. Verapamil is preferred because it acts primarily on the heart rather than the blood vessels and so has minimal effects on the afterload.

CASE 17

A 3-year-old boy is brought to his pediatrician by his mother because he has had a high fever for the past 5 days. Physical examination reveals bilateral injected conjunctivae, palmar erythema, oral mucositis, an inflamed red tongue (see Figure 6-21), cervical lymphadenopathy, and erythema on the soles of his feet.

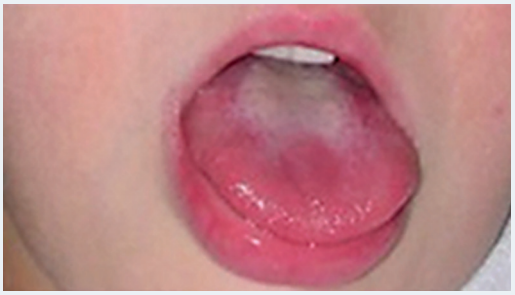


FIGURE 6-21. (Reproduced with permission from Stagi S, et al. *Ital J of Pediatr.* 2014;40:24.)

What is the most likely diagnosis?

Kawasaki disease (mucocutaneous lymph node syndrome). The diagnosis is made based on the presence of a fever lasting > 5 days and at least four of the following five key clinical features: changes of the oral cavity and lips, such as cracked or erythematous lips; strawberry tongue (see Figure 6-21); nonspecific erythematous rash that may be morbilliform, maculopapular, or target-like, which characteristically appears on the trunk before spreading to involve the extremities, perineum, and face (see Figure 6-22); nonpurulent bilateral conjunctivitis; changes in the extremities (erythema of hands and feet or desquamation of hands and toes) and cervical lymphadenopathy.

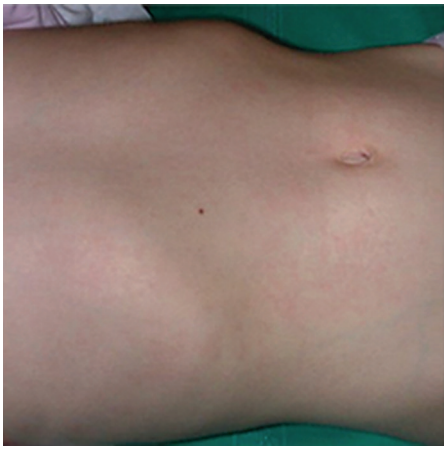


FIGURE 6-22. Kawasaki disease rash on torso. (Reproduced with permission from Stagi S, et al. Kawasaki disease in a girl with Turner syndrome: A remarkable association. *Ital J Pediatr*. 2014;40:24.)

What is the pathophysiology of this disease?

This acute autoimmune disorder is characterized by necrotizing, systemic vasculitis of small and medium-sized vessels as well as veins. Although the exact cause is unknown, it is believed to be triggered by infection, evidenced by the fact that Kawasaki disease usually does not occur prior to the age of 6 months, a period of life in which maternal antibodies still circulate in the infant.

Which patients are most commonly affected?

Kawasaki disease is most common in children 6 months to 5 years old. Individuals of Asian ancestry are more often affected.

What is the treatment for this condition?

High-dose aspirin and intravenous immunoglobulin G are the preferred treatment. Remember that in other cases of pediatric fevers, aspirin would be contraindicated due to the risk of Reye syndrome (a rapidly progressive encephalopathy). Steroids are used only after failure of first-line treatment. Patients should be treated as promptly as possible to prevent acute complications, including coronary aneurysm, myocardial infarction, severe heart failure, and hydrops of the gallbladder.

Which other infectious diseases commonly present as palmar and solar erythema?

Syphilis, Rocky Mountain spotted fever, meningococcemia, and coxsackievirus A infection can also present as palmar and solar erythema.

CASE 18

A 62-year-old diabetic woman with a 50-pack-year history of smoking and a history of atrial fibrillation and myocardial infarction comes to the ED with "excruciating" abdominal pain that began suddenly, awaking her from sleep. For the past several months, she has experienced abdominal pain after eating, leading to an unintentional weight loss. She denies surgical history except an appendectomy when she was a teenager. However, she states that she is currently being evaluated for pain in her legs that occurs when she is walking. On physical examination, she appears very uncomfortable, and her abdomen is slightly distended with hypoactive bowel sounds. She has extreme tenderness to light palpation in the midepigastric area. She has no rebound or guarding. She denies changes in bowel habits, but her stool is heme positive.

What is the most likely diagnosis?

The patient's severe gastrointestinal symptoms that are out of proportion to the physical signs elicited suggest acute mesenteric ischemia, injury to the small intestine due to inadequate blood supply. Given the sudden onset and her history of atrial fibrillation, this is most likely a thrombotic event. Atrial fibrillation increases the risk for a thrombus because irregular contractions can slow blood flow or cause pooling, which can create blood clots, which can break free and travel into other arteries. Ischemia affecting the **small bowel** initially presents with severe pain; peritoneal signs develop later. Peritoneal signs point to inflammation of the peritoneum (peritonitis) and include physical exam findings such as rebound tenderness, tenderness to percussion, and involuntary guarding. Ischemic colitis, injury, and inflammation of the **large bowel** due to ischemia, is less painful and typically presents with hematochezia.

What composes the arterial supply of the intestines?

The superior mesenteric artery (SMA) supplies part of the duodenum and part of the head of the pancreas (the territory of inferior pancreaticoduodenal artery), jejunum, ileum, ascending colon, and proximal two-thirds of the transverse colon. The inferior mesenteric artery (IMA) supplies the hindgut, which includes the distal third of the transverse colon, the descending colon, the sigmoid colon, and the rectum. This is schematically shown in Figure 6-23.

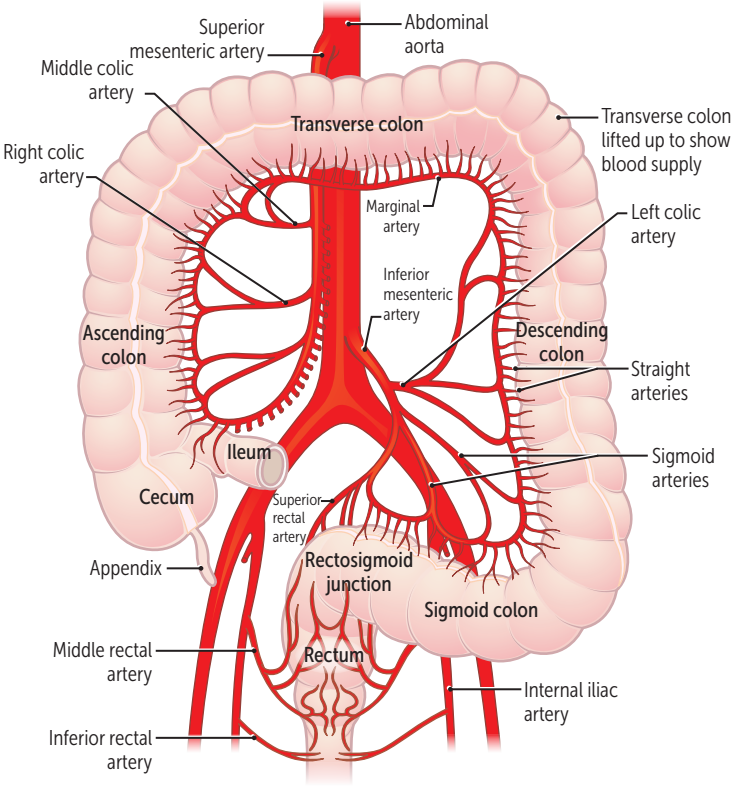


FIGURE 6-23. Arterial supply to the intestines. (Reproduced with permission from USMLE-Rx.com.)

What is the treatment for this patient?

Blood flow must be restored urgently. Thrombolytic medications may resolve the thrombus but also predispose the patient to severe gastrointestinal bleeding upon reperfusion. Hence, a surgical approach is favored (thrombectomy, bypass). In addition, any necrotic segments of the intestine must be surgically removed.

CASE 19

A 45-year-old man presents to his physician for a routine health maintenance visit. He reports that he has experienced intermittent heart palpitations. He denies any chest pain, dyspnea on exertion, or syncope. On physical examination, the patient appears well and in no distress. His blood pressure is 110/79 mm Hg. Auscultation of his chest while sitting reveals a late systolic click associated with a high-pitched, late systolic murmur. The systolic click occurs closer to S_1 with standing. His ECG is normal; a transesophageal echocardiogram shows a thin leaflike structure entering the inferior left atrium during systole.

What is the most likely diagnosis?

Mitral valve prolapse (MVP), a condition found in 0.6%–2.4% of the population, is the most common valvular heart disease. Most cases are asymptomatic and discovered incidentally. However, left atrial enlargement may occur if the prolapse is associated with a mitral regurgitation, which increases the amount of blood in the left atrium. Left atrial enlargement can result in occasional benign supraventricular arrhythmia that the patient perceives as palpitations. Men and women are affected equally. MVP is defined by the echocardiographic measurement of the superior displacement of one or both mitral leaflets into the left atrium (LA).

What is the pathogenesis of this condition?

MVP is multifactorial in origin with an autosomal dominant pattern of inheritance in some families. It can occur as a result of changes within the valvular tissue, geometric disparities between the left ventricle and mitral valve, and connective tissue disorders, such as Marfan syndrome (prevalence of 91%) and Ehlers-Danlos syndrome (6%).

How does standing and squatting affect the timing of the systolic click?

In MVP, the systolic click represents the sudden tensing of the mitral valve as the leaflets prolapse into the left atrium during systole (see Figure 6-24) and occurs when the left ventricle reaches a critical volume during ventricular contraction (this "click" sound is best illustrated by comparing it to the sound a parachute makes when it suddenly opens). Standing decreases the end-diastolic volume (EDV) by reducing systemic afterload and venous return, thereby allowing the critical volume to be reached earlier. The click therefore is heard closer to S_1. In contrast, squatting increases the EDV. The click is thus heard closer to S_2.

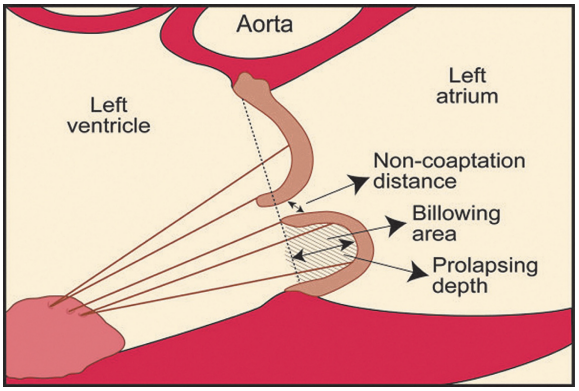


FIGURE 6-24. The shaded region, labeled "billowing area," depicts abnormal prolapse of the mitral valve leaflet during systole, causing the "click" sound upon auscultation. (Reproduced with permission from Sénéchal M, et al. Relation of mitral valve morphology and motion to mitral regurgitation severity in patients with mitral valve prolapse. *Cardiovasc Ultrasound.* 2012;10:3.)

What are the major complications of this condition?

MVP typically has a benign prognosis. A poorer prognosis is more likely in male, elderly patients with a systolic murmur, thickened and redundant mitral leaflets, or left atrial or ventricular hypertrophy. The most common complication is infective endocarditis as the surface of the mitral valve is damaged, allowing bacteria to more easily colonize the irregular scarred surfaces. Other complications of MVP include severe mitral valve regurgitation, and cerebrovascular ischemic events. Risk stratification by clinical examination and echocardiography is necessary.

CASE 20

A 56-year-old woman presents to the ED complaining of severe pain in her lower jaw and neck that has developed over the past hour. She describes the pain as a pressure that is not relieved by rest or by changes in position. She took ibuprofen at home without relief. She also complains of nausea that began shortly before the onset of jaw and neck pain. On further questioning, she admits to a "heavy" feeling in her chest, which she describes as a squeezing or crushing sensation. She is profusely diaphoretic. An ECG is performed and shown in Figure 6-25.

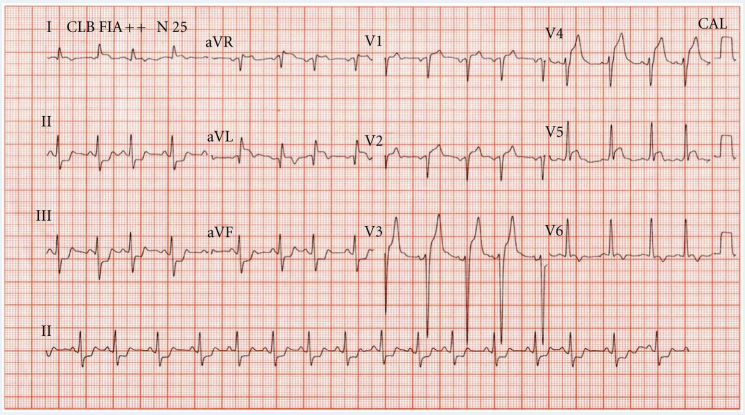


FIGURE 6-25. (Reproduced with permission from Nakazone MA, et al. *Cas Rep Med*. 2010;2010:830583.)

What is the most likely diagnosis?

Acute myocardial infarction (AMI) most often results from a thrombotic event in a coronary artery due to plaque rupture. Myocardial tissue dies (infarction) if perfusion is not reestablished and can be visualized as ST segment elevations in continous leads on an ECG (see Figure 6-25).

How does diabetes affect this patient's presentation?

Typical myocardial infarctions feature crushing chest pain that may radiate to the arms, back, or jaw. However, since patients with diabetes are prone to develop neuropathies, pain signals from the heart may not be relayed to the brain effectively, resulting in myocardial infarctions without chest pain or atypical pain patterns. A special instance in all patients regardless of diabetes is the inferior MI, caused by an occlusion of the right coronary artery. It commonly presents with abdominal discomfort but no chest pain.

What serum markers are useful in making this diagnosis?

Serum cardiac markers such as creatinine kinase-MB fraction (CK-MB) and cardiac-specific troponin I (cTnI and cTnT), are released into the blood at varying times in response to cardiac tissue necrosis after AMI. **cTnI**, which is more specific than the other markers for AMI, is used within the first 4 hours, and cTn1 levels may remain elevated for 7–10 days. **CK-MB** levels peak about 20 hours after the onset of coronary artery occlusion and usually return to baseline within 48 hours.

What complications are associated with this condition? (see Table 6-3)

TABLE 6-3. Post-MI Complications

Complication	Time of occurrence
Cardiogenic shock, heart failure, ventricular arrhythmia	0-24 hours
Postinfarction fibrinous pericarditis	1-3 days
Papillary muscle, septal, or free-wall rupture	3-14 days
Dressler syndrome, ventricular aneurysm with risk of thrombus	2 weeks to several months

CASE 21

A 2-month-old boy is brought to his physician because of poor feeding since discharge from the hospital on his second day of life. The mother reports that he seems to tire easily. His medical history is notable for an uncomplicated 38-week gestation and a normal, spontaneous vaginal delivery. On physical examination, the patient is small for his age but otherwise appears well and is breathing comfortably without cyanosis. Palpation reveals a hyperdynamic precordium and widened pulse pressures with bounding peripheral pulses. A grade III/VI continuous, "machine-like" murmur that peaks at the second heart sound is audible over the left sternal border and below the left clavicle.

What is the most likely diagnosis?

Patent ductus arteriosus (PDA) is indicated by the characteristic continuous "machine-like" murmur and physical examination.

What is the purpose of the ductus arteriosus?

The ductus arteriosus (DA) typically originates from the origin of the left pulmonary artery to connect to the lower aspect of the aortic arch at the origin of the left subclavian artery. Before birth, it shunts blood away from the pulmonary vasculature (right-to-left shunt), because the lungs are fluid-filled and do not provide oxygenation. Patency is maintained during fetal life by the low arterial oxygen tension and circulating prostaglandins produced largely by the placenta. Upon birth, blood pressure in the pulmonary circulation drops because pulmonary vascular resistance decreases and systemic vascular resistance increases, reversing the blood flow through the DA.

What is the pathogenesis of this condition?

The DA typically closes within 2–3 days of birth and becomes the ligamentum arteriosum. This spontaneous closure occurs from a combination of factors, including the increased partial pressure of oxygen secondary to lung-mediated oxygenation, the removal of the vasodilatory effects of prostaglandin E_2 (PGE_2) derived from the placenta, and a decreased number of PGE_2 receptors. Inadequate closure of the DA results in a PDA and permits a left-to-right blood shunt that increases volume load of the left ventricle and the pulmonary arteries. In some congenital heart conditions that require a PDA in order to maintain adequate oxygenation of tissues (called ductus-dependent), PGE_2 is intentionally given to keep the DA open.

What is the prognosis of this condition?

The additional stress on the heart and lungs derived from the left-to-right shunt eventually results in left ventricular hypertrophy and ultimately heart failure, vascular damage, and pulmonary hypertension. Regardless of size, a PDA also increases the risk for infective endocarditis. Pharmaceutical closure can often be achieved with a prostaglandin inhibitor, such as indomethacin. Otherwise, a surgical or catheter-based closure may be required.

CASE 22

A 47-year-old man presents to the ED after experiencing substernal chest pain. The pain is worsened with inspiration and is relieved only when he leans forward. He says he recently recovered from an upper respiratory infection. Cardiac examination reveals a leathery friction rub and distant heart sounds. An ECG is shown in Figure 6-26.

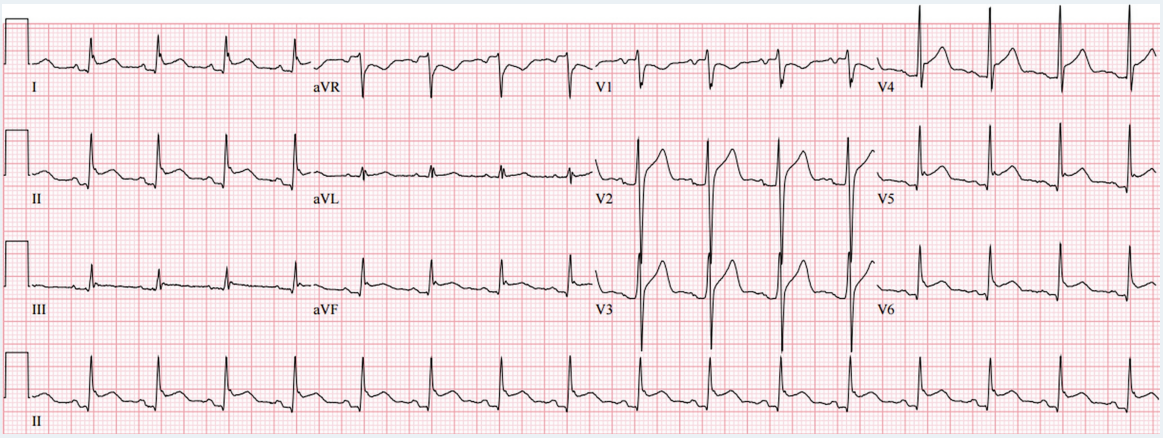


FIGURE 6-26. (Reproduced with permission from Fuster V, et al., eds. *Hurst's The Heart*. 14th ed. New York: McGraw-Hill, 2017.)

What is the most likely diagnosis?

Pericarditis often presents with diffuse ST-segment elevation (as seen in Figure 6-26), positional chest pain, and friction rub. The latter is due to inflammation of the pericardium, resulting in decreased production of lubrication. The typical friction rub has three phases (atrial contraction, ventricular contraction, and ventricular relaxation).

What is an ECG likely to show?

Classic findings of pericarditis include diffuse ST-segment elevations and PR-segment depression (see Figure 6-26). This is in contrast to the ST-segment elevations in some MIs, in which the elevations are limited to ischemic regions (contiguous leads). Likewise, the J point (where the QRS complex transitions into the ST segment) is usually a smooth curve in pericarditis but abrupt in transmural infarction, allowing distinction when multivessel infarction is suspected.

How is this patient's condition classified?

There are three types of pericarditis: serous, fibrinous, and hemorrhagic. Risk factors for the development of **serous pericarditis** include systemic lupus erythematosus, rheumatoid arthritis, and uremia. Preceding viral infection is also a possible cause of serous pericarditis, as is the case in this patient. Risk factors for **fibrinous pericarditis** include uremia, myocardial infarction (Dressler syndrome), and rheumatic fever. Risk factors for **hemorrhagic pericarditis** include tuberculosis and malignancy.

Which physical examination and ECG findings are suspicious for cardiac tamponade in this patient?

Tamponade is the compression of the heart by fluid in the pericardium, which inhibits diastolic filling, reducing the amount of blood available for the heart to pump (reduced cardiac output). This results in systemic hypotension due to reduced cardiac output and elevated jugular venous pressure due to inadequate drainage of blood from the jugular vein into the right atrium. The fluid around the heart also causes distant, or muffled, heart sounds. **Pulsus paradoxus**, a decrease in arterial blood pressure by $>$ 10 mm Hg during inspiration, is also a sign of tamponade. Inspiration normally causes a slight drop in arterial blood pressure of $<$ 10 mm Hg. This occurs because inspiration causes the intrathoracic pressure to become more negative, which causes expansion of pulmonary vasculature, causing blood to pool in the lungs and decreasing return to the left side of the heart. The negative intrathoracic pressure also increases systemic venous blood return to the right side of the heart, causing a slight bulge of the septum to the left. Both of these factors act to decrease left heart filling, which decreases stroke volume and ultimately decreases arterial blood pressure by a slight amount. In normal conditions, the septum only bulges slightly due to the physiologic pressure gradient between the right and left sides of the heart. However, in cardiac tamponade, external pressure on the heart causes pressure between the right and left to equalize, allowing a more drastic bulging of the septum. The more severe bulging causes a more dramatic decrease in left ventricular filling and stroke volume, decreasing arterial blood pressure by more than the normal 10 mm Hg during inspiration. **Electrical alternans**, a beat-to-beat variation in the amplitude of the QRS complex, may also be noted.

CASE 23

A 35-year-old woman presents to her physician complaining of fatigue and fever. She has lost 7 kg (15 lbs) over the past 2 months and also reports occasional abdominal pain, headaches, and muscle pain. On physical examination, her blood pressure is 154/92 mm Hg. Retinal examination reveals cotton-wool spots, and skin examination is notable for palpable purpura on her right calf (see Figure 6-27). Laboratory studies showed an erythrocyte sedimentation rate of 121 mm/h. An enzyme-linked immunosorbent assay (ELISA) is positive for hepatitis B surface antigen antibodies.

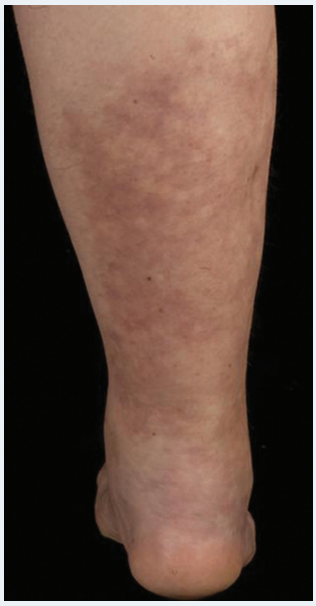


FIGURE 6-27. (Reproduced with permission from Ahmed S, et al. *J Med Case Reports.* 2011;5:450.)

What is the most likely diagnosis?

This patient has polyarteritis nodosa with palpable purpura and other common symptoms such as weight loss, inflammatory markers, and evidence of vasculitis in her retina.

What is the pathophysiology of this disease?

Polyarteritis nodosa is an autoimmune disorder characterized by segmental, transmural inflammation of small- and medium-sized arteries due to necrotizing immune complexes. On angiography, the segmental inflammation appears as a "string of pearls." Vessels supplying the kidneys, heart, liver, and gastrointestinal tract are most often involved.

What laboratory test can help establish the diagnosis?

The presence of perinuclear antineutrophilic cytoplasmic antibody (P-ANCA) correlates with disease activity. P-ANCAs are more commonly seen in small-artery disease. Furthermore, antibody testing against hepatitis B may strengthen the diagnosis, as approximately 30% of cases of polyarteritis nodosa are associated with this infection.

What other small to medium vasculitides could this patient have?

Churg-Strauss syndrome is a variant of polyarteritis nodosa characterized by eosinophilia and asthma. Autoantibodies mostly target blood vessels in the lungs, but in the late stage other organ systems can become involved (including the skin). **Granulomatosis with polyangiitis** features ANCAs that damage blood vessels in the upper respiratory tract and kidney. However, it can also involve joints, skin, and the gastrointestinal tract.

What complications may be seen in this patient's condition?

Inflammation of the small and medium-sized arteries induces a local state of hypercoagulability. This may lead to thromboses and subsequent ischemia or infarction of distal tissues. Unfortunate individuals have suffered strokes and heart attacks, but ischemia is possible in any organ system. Damaged arteries are at risk for aneurysms. Treatment with prednisone and cyclophosphamide produces remission or even cure in approximately 85% of affected individuals and prevents these complications.

CASE 24

A 33-year-old woman who recently immigrated to the United States from India presents to her physician complaining of profound shortness of breath. Over the past few weeks, she has been progressively unable to walk up a flight of stairs without stopping to catch her breath. For the past few nights, she has been waking up suddenly, gasping for air. She also notes that she has recently been unable to fit into her dress shoes. The patient says she is generally healthy, leads an active lifestyle, and takes no medication except for vitamin supplements. Her medical history is significant only for a 2-week hospitalization when she was a teenager for fever, sore throat, and joint pain. On physical examination, her blood pressure is 110/80 mm Hg, heart rate is 100/min, and respiratory rate is 24/min. Jugular venous distention is noted, as are diffuse wheezes and rales at both lung bases. There is edema of her ankles bilaterally. Heart auscultation reveals a low-pitched, diastolic murmur with an opening snap, heard best at the apex. X-ray of the chest is normal with the exception of congestion of the pulmonary vasculature.

What is the most likely diagnosis?

This patient has rheumatic heart disease. Mitral stenosis (fish-mouth buttonhole deformity) is often seen in patients with previous rheumatic fever infection. This disease primarily affects the mitral and aortic valves; involvement of tricuspid and pulmonary valves is rare. This condition is not commonly seen in the United States.

What hemodynamic changes occur in the heart in this condition?

Left **atrial** diastolic pressure increases in cases of mitral stenosis because the left atrium must pump against a small, stiff valve. This can increase pulmonary hydrostatic pressure, leading to pulmonary congestions and edema. Eventually, right heart failure ensues.

What pathogen is responsible for the underlying infection in this condition?

Rheumatic heart disease is a result of group A β-hemolytic streptococci infection. Valvular heart disease, as in this patient, often occurs many years after the acute infection. Antistreptolysin O antibodies are often seen in patients long after the acute infection resolves.

What is the treatment for this condition?

Cautious use of diuretics and sodium restriction to relieve pulmonary congestion is recommended. Surgery for valve replacement may be indicated for patients with severe symptoms. Prophylactic antibiotics for endocarditis are indicated for all invasive procedures, including dental work. Because rheumatic heart disease worsens with each recurrent episode, long-term continuous antimicrobial therapy is used to prevent future group A strep infections.

CASE 25

A 69-year-old woman consults her physician because she recently experienced a brief episode of blurred vision in her right eye when reading the newspaper. The episode resolved spontaneously after approximately 20 minutes. On further questioning, she reports she has recently started to have headaches over her right temple, which worsen at night, especially when she lies on her right side. She also states that she can no longer eat large meals because her jaw muscles tend to get tired; instead, she has to eat frequent small meals.

What is the most likely diagnosis?

Biopsy of the temporal artery reveals temporal arteritis. Temporal arteritis may present with skip lesions, so obtaining an adequate length of the artery during biopsy is important for diagnosis. An elevated erythrocyte sedimentation rate and elevated C-reactive protein levels are nonspecific markers associated with temporal arteritis.

Which histopathologic features are associated with this condition?

Temporal arteritis is a systemic vasculitis of large- and medium-sized vessels. It is not restricted to the temporal artery. Mononuclear infiltrates in vessel walls and frequent giant cell formations are expected findings (see Figure 6-28).

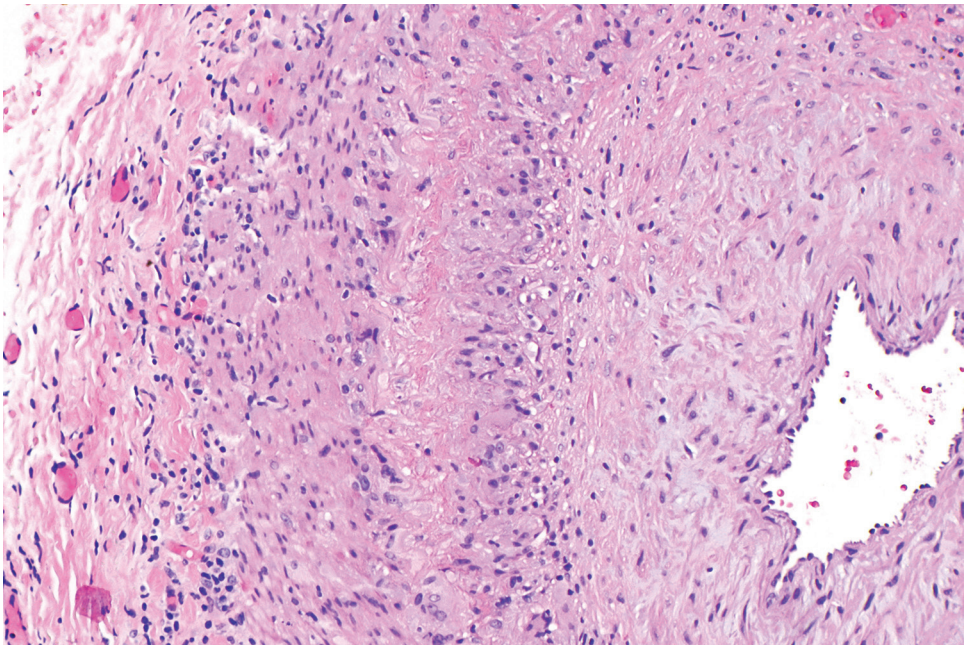


FIGURE 6-28. Histology of temporal arteritis showing mononuclear infiltrates and giant cells. (Reproduced courtesy of Dr. Michael Bonert.)

What is the treatment for this condition?

Corticosteroids should be started as soon as possible. Nonsteroidal anti-inflammatory drugs can be given for pain.

What complications are associated with this condition?

Without treatment, blindness in one or both eyes due to involvement of the ophthalmic artery or posterior ciliary arteries is the most common complication. Patients may also have fever, fatigue, new-onset headache, and jaw or arm claudication. More serious complications, such as thoracic aneurysm, occur less frequently. Additionally, temporal arteritis is often associated with **polymyalgia rheumatica**, a syndrome that features pain and stiffness in muscles and joints of the hips, shoulders, and neck. It is thought to have an autoimmune etiology.

CASE 26

A 13-month-old adopted boy is brought to the pediatrician by his mother, who reports that he hyperventilates and becomes blue around his lips and in his fingertips after crying, eating, or any exertion. She has also noticed he tends to squat when he gets these symptoms, which causes him to "pink up" again.

What is the most likely diagnosis?

Tetralogy of Fallot (TOF) (cyanotic congenital heart disease known as "blue baby syndrome") presents as dyspnea on exertion, such as feeding or crying. The four anatomic findings in TOF are as follows:

- Pulmonary stenosis
- Right ventricular hypertrophy
- Overriding aorta (deviation of the origin of the aorta to the right)
- Ventricular septal defect (VSD)

Exertion results in systemic vasodilation, which lowers left-sided resistance, thereby increasing the right-to-left shunting of blood. Bypass of oxygen exchange in the lungs causes hypoxia and cyanosis. Squatting significantly increases systemic (left-sided) resistance, reducing the amount of blood shunted, and alleviates symptoms.

Which developmental defect is responsible for this condition?

In TOF, the infundibular septum (the portion of the septum adjacent to the outflow tracts) is anteriorly and superiorly displaced during development, leaving a hole in the ventricular septum (see Figure 6-29). This displacement also causes pulmonary stenosis by blocking flow to the pulmonary artery; the result is increased pressure on the right side of the heart and right ventricular hypertrophy.

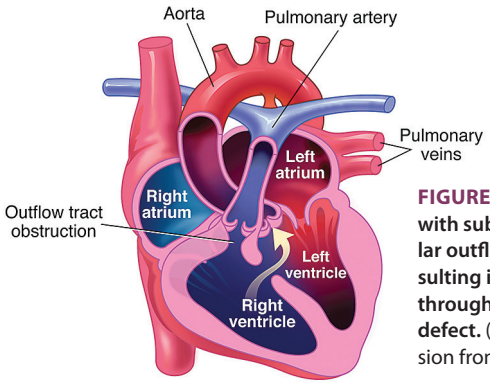


FIGURE 6-29. Tetralogy of Fallot, with substantial right ventricular outflow tract obstruction resulting in right-to-left shunting through the ventricular septal defect. (Reproduced with permission from USMLE-Rx.com.)

What is the characteristic radiologic finding in this condition?

X-ray of the chest typically shows a boot-shaped heart (see Figure 6-30), due to right ventricular hypertrophy and the absence of a pulmonary artery shadow above the left side of the heart. An echocardiogram with Doppler mode shows the altered pattern of blood flow.

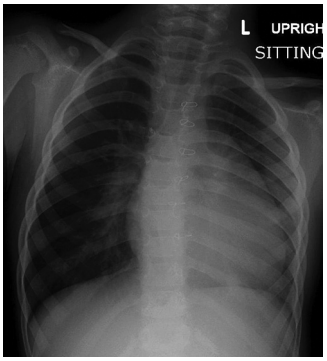


FIGURE 6-30. X-ray of the chest of a child with Tetralogy of Fallot. (Reproduced courtesy of Dr. James Heilman.)

What additional physical finding is commonly associated with this condition?

Clubbing of the fingers may appear in adults (see Figure 6-31) secondary to chronic hypoxemia. It is believed that the lungs secrete growth factors in patients with chronic hypoxia, resulting in abnormal tissue growth that first becomes evident in the distal phalanges. Table 6-4 compares cyanotic heart diseases.

TABLE 6-4. Cyanotic Heart Diseases

Decreased pulmonary flow	Increased pulmonary flow
Tetralogy of Fallot	Transposition of great arteries
Tricuspid atresia	Truncus arteriosus
Pulmonary atresia	Total anomalous pulmonary venous
Ebstein anomaly	Total anomalous pulmonary venous return (TAPVR)

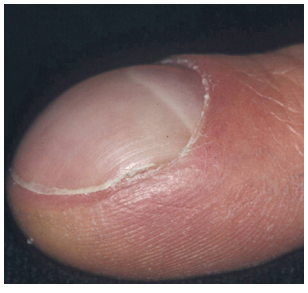


FIGURE 6-31. Clubbing of the fingers. (Reproduced, with permission, from Wolff K, et al. *Fitzpatrick's Dermatology in General Medicine,* 7th ed. New York: McGraw-Hill, 2008; Figure 87-31.)

CASE 27

A term baby girl with a cleft palate is found to have bluish discoloration of her lips while being examined in the well-baby nursery. Her caretakers report that she tires easily during feeding. Her prenatal history is notable for the lack of prenatal care. Physical examination reveals tachycardia and tachypnea, but she is afebrile. Her S2 heart sound is single and loud. An early systolic ejection click is audible at the left sternal border. Her hips are maintained in flexion, and her extremities are warm and well perfused.

What is the most likely diagnosis?

Truncus arteriosus (TA) accounts for 1% of congenital cardiac malformations. It is also associated with DiGeorge syndrome, as is the case in this patient.

What is the characteristic anatomy in this condition?

The TA is the embryologic precursor that normally separates into the aorta and pulmonary artery by formation of the spiral septum. Persistent TA is caused by failure of the spiral septum to develop and thereby failure of aorta and pulmonary artery to septate. Normally, neural crest cells that are present in the TA grow in a spiral formation, separating the two outflow tracts and forming the intertwined aorta and pulmonary artery. If this septum fails to form, a single outflow tract persists (see Figure 6-32A). A ventricular septal defect (VSD) is always present; lack of a VSD in the setting of TA is incompatible with life and results in stillbirth. Instead of separate aortic and pulmonary valves, there is one truncal valve with two to six leaflets (leading to the characteristic absence of S2 splitting). Surgical repair of these defects is required for survival (see Figure 6-32B).

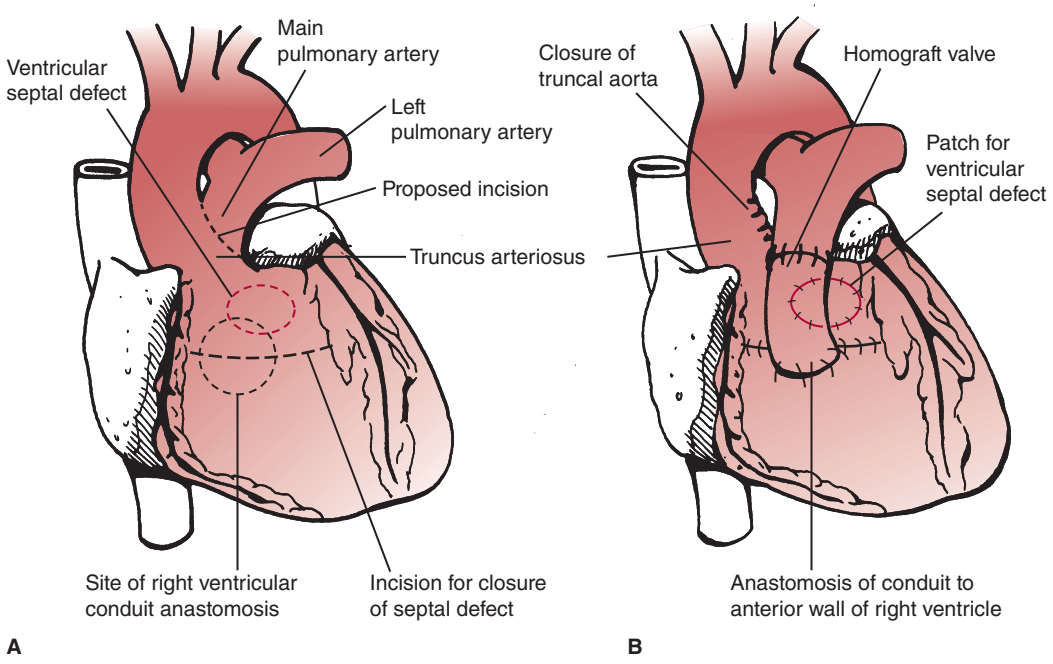


FIGURE 6-32. Truncus arteriosus. (A) The main pulmonary artery arises from the truncus arteriosus downstream to the truncal valve. A ventricular septal defect is present. (B) The main pulmonary artery is incised from the truncus. The ventricular septal defect is closed with a patch. A valved conduit is sutured to the anterior wall of the right ventricle and the distal pulmonary artery. (Reproduced with permission from Doherty GM, ed. *Current Diagnosis & Treatment: Surgery*, 14th ed. New York: McGraw-Hill; 2014.)

What are the reasons for this patient's symptoms?

The clinical presentation depends on the amount of pulmonary flow. High pulmonary flow ultimately increases arterial oxygen saturation, reducing risk of cyanosis. However, this patient likely has low pulmonary flow; this results in central cyanosis and earlier presentation with congestive heart failure, which is indicated by the tachycardia and respiratory distress.

CASE 28

A 65-year-old man presents to the ED complaining of a sudden onset of substernal chest pain that radiates to his shoulder. It began while he was watching TV on his couch. He describes that the paramedics administered nitroglycerin spray, which alleviated his chest pain for about 20 minutes, but then the pain returned. When examined in the ED, the patient states that he has had similar pain with exercise in the past, but it always vanished with rest. A troponin test is negative.

What is the most likely diagnosis?

Chest pain that occurs at rest is commonly seen in unstable angina, subendocardial infarction, and transmural infarction. However, only unstable angina presents without damage to the myocardium, and hence does not produce a troponin leak. In this condition, the flow of a coronary vessel is limited to the extent that it cannot meet the metabolic demand of the heart, but it does not cause death of myocardial tissue. Rest and dilation of the coronary vessels (nitroglycerin) improve the pain. Given his history of coronary heart disease, unstable angina is most likely.

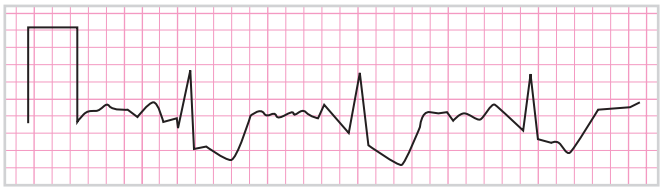
What is the mechanism of action of nitroglycerin?

Nitrates undergo denitration that results in the liberation of nitric oxide (NO) in vivo. NO activates guanylyl cyclase, thereby increasing cyclic guanosine monophosphate (cGMP) concentrations and stimulating cGMP-dependent protein kinases. In smooth muscles, this results in the dephosphorylation of myosin light chains and inhibition of calcium entry and increases potassium channel activity. This ultimately leads to vasorelaxation. Clinically, this leads to a reduction in preload (venous relaxation) and a reduction in afterload (some arterial relaxation). The vasodilatory effect is more pronounced on the venous system. As the heart operates at lower pressures, myocardial oxygen demand is also reduced. Furthermore, nitroglycerin dilates coronary vessels, improving myocardial oxygenation. If combined with a phosphodiesterase inhibitor such as sildenafil (commonly used for the treatment of erectile dysfunction), life-threatening hypotension may result.

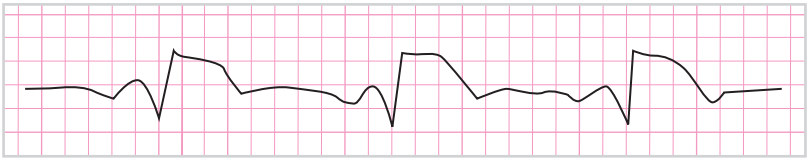
How can ECG studies differentiate among ischemia, subendocardial infarction, and transmural infarction?

Inverted T waves and pathologic Q waves occur once the infarction progresses (see Figure 6-33A). The cardiac blood supply runs along the surface of the heart, providing adequate perfusion to the epicardium but not to the deeper endocardium in the event of a subtotal occlusion. As a result, the epicardial side of the myocardium remains viable while the endocardial side is starved of nutrients. Subendocardial infarctions appear as inverted T waves without ST-segment changes on ECG.

Stable and unstable angina pectoris lead to ST-segment **depression** in at least two contiguous leads (see Figure 6-33B). Transmural infarction features ST-segment **elevation** $>$ 1 mm in at least two contiguous leads.



A



B

FIGURE 6-33. ECG changes in (A) ischemia and (B) transmural infarction.

CASE 29

A 22-year-old man comes to his physician for a routine preemployment physical examination. He is healthy and takes no medications. However, he admits he has recently experienced a few episodes of shortness of breath, dizziness, and palpitations. Physical examination is unremarkable. However, the patient's ECG is notable for a shortened PR interval (< 0.12 sec); a prolonged QRS complex (> 0.12 sec); and a slurred, slow-rising onset of the QRS complex (known as a delta wave; see Figure 6-34).

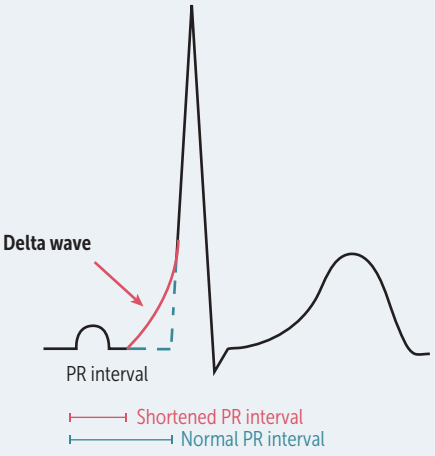


FIGURE 6-34. (Reproduced with permission from USMLE-Rx.com.)

What is the most likely diagnosis?

Wolff-Parkinson-White (WPW) syndrome (also known as preexcitation syndrome). The delta wave shown in Figure 6-34 is a highly tested and unique ECG finding for WPW syndrome. Lown-Ganong-Levine syndrome is a similar preexcitation syndrome but can be distinguished from WPW syndrome by its absence of a delta wave.

What is the pathophysiology of this condition?

In a normal heart, the only excitatory pathway between the atria and ventricles is the atrioventricular (AV) node. In WPW, the presence of an abnormal band of myocytes creates an accessory conduction pathway, distinct from the AV node, between the atrial and ventricular systems. Because the myocytes contain sodium channels, whereas the AV node has calcium channels, excitation often progresses faster through the accessory pathway than the AV node.

Why is the PR interval on ECG shortened in this condition?

The PR interval is the interval between atrial excitation (the P wave) and ventricular excitation (the QRS complex). Thus, it is analogous to the conduction time through the AV node. It is shortened in WPW syndrome because AV conduction occurs via a faster, accessory pathway (frequently, the bundle of Kent), which bypasses the AV node.

What would be the consequences if this patient developed atrial fibrillation?

The consequences would be potentially lethal. Atrial fibrillation has an atrial rate of up to 300 excitations/min. In a normal heart, the AV node is still refractory when subsequent depolarizations arrive and maximally allows a ventricular rate of approximately 150 depolarizations/min. However, the accessory pathway has a short refractory period and may transmit excitatory impulses at their atrial rate. Ventricular contraction at up to 300/min does not allow enough time for ventricular filling, and sudden cardiac death occurs.

Why are class II and class IV antiarrhythmic drugs not useful in this condition?

Class II and IV antiarrhythmic agents, the β-blockers and calcium channel blockers, may not be useful in patients with WPW syndrome because they increase AV node refractoriness and decrease AV node conduction velocity. They do not slow conduction over accessory pathways and may even shorten the refractory period for accessory pathways. This may increase ventricular response to atrial fibrillation or flutter, causing hemodynamic collapse. Instead, quinidine, disopyramide, and procainamide may be used to control arrhythmias in this syndrome.

What is the treatment for this condition?

For most patients with WPW syndrome, electrophysiologic ablation is performed to ablate the accessory pathway. Cure is achieved in 90% of cases with no need for medication.

7
Endocrine

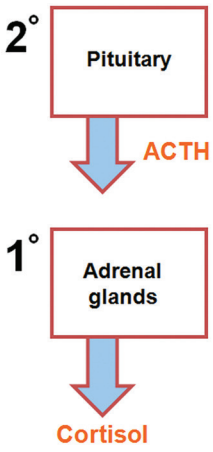
CASE 1

A 40-year-old woman visits her physician because of fatigue and weakness, which she has experienced for several months. She says she often feels lightheaded when she first gets out of bed in the morning or stands suddenly, with some changes in her vision during these episodes as well. Review of symptoms is positive for frequent headaches, nausea, and vomiting. Her vital signs are notable for a blood pressure of 125/75 mm Hg seated and 105/60 mm Hg standing. Physical examination reveals several patches of hyperpigmentation on the skin, primarily in her palmar creases, mucous membranes, and nailbeds. Relevant laboratory findings are as follows:

Sodium: 126 mEq/L (135–145 mEq/L)
Bicarbonate: 19 mEq/L (18–22 mEq/L)
Potassium: 5.2 mEq/L (3.5–5.0 mEq/L)
Cortisol: 4.3 mg/dL
Chloride: 97 mEq/L

What is the most likely diagnosis?

Addison disease, or primary adrenal insufficiency, is suggested by the clinical history of weakness and orthostatic hypotension (drop of systolic by 20 mm Hg or diastolic by 10 mm Hg, going from seated to standing) and by the signs of hyperpigmentation, hyponatremia, hyperkalemia, and a low serum cortisol level. The adrenal insufficiency seen in Addison disease classically spares the medulla; thus levels of epinephrine and norepinephrine should remain intact. Differentiation between primary and secondary adrenal insufficiency can be seen in Figure 7-1.



1° versus 2° adrenal insufficiency	
1° adrenal insufficiency = Addison disease	**2° adrenal insufficiency**
↑ K^+ (from aldosterone deficiency)	Normal K^+ (no aldosterone deficiency)
↑ ACTH causing hyperpigmentation	↓ ACTH so no hyperpigmentation
Eosinophilia	No eosinophilia
Hyponatremia may be present	

FIGURE 7-1. Primary versus secondary adrenal insufficiency. (Reproduced with permission from USMLE-Rx.com.)

What are common etiologies of this disease?

Most cases of Addison disease are idiopathic or autoimmune related (see Figure 7-1). Other causes include the following:

- Disseminated intravascular coagulation
- **Waterhouse-Friderichsen syndrome** (hemorrhagic necrosis of the adrenal gland, classically due to *Neisseria meningitidis*)
- Granulomatous diseases such as tuberculosis
- HIV infection
- Metastasis
- Trauma
- Latrogenic vascular disorders

What is the cause of this patient's metabolic abnormalities?

Adrenal insufficiency causes a deficiency of cortisol. Hyponatremia, hyperkalemia, and a low bicarbonate level can result from low aldosterone levels associated with primary adrenal insufficiency.

How would this patient's cortisol level change if she were administered adrenocorticotropic hormone (ACTH)?

The cortisol level should not change appreciably since ACTH production is already increased, as the site of disease is at the adrenal gland itself, also known as a primary adrenal insufficiency. This is suggested by the **hyperpigmentation**, which is secondary to increased melanocyte-stimulating hormone (MSH), due to the attempt of the pituitary gland to overcome the cortisol deficiency by increasing ACTH production. ACTH and MSH both come from the same precursor molecule, pro-opiomelanocortin (POMC), so any process that would increase ACTH production should conversely also result in an MSH elevation.

What are the secondary and tertiary forms of this condition?

Secondary adrenal insufficiency is caused by decreased ACTH secretion by the pituitary gland. Administration of ACTH results in a cortisol response. This syndrome does not cause hyperpigmentation as levels of MSH are not elevated. **Tertiary adrenal insufficiency** is caused by a decrease in corticotropin-releasing hormone (CRH) production by the hypothalamus.

CASE 2

A 4-year-old girl with a history of ambiguous genitalia is brought to her pediatrician for a check-up. The child's blood pressure is found to be 130/89 mm Hg. Physical examination is notable for clitoral enlargement, partial labial fusion, and scant pubic and axillary hair growth. Laboratory tests reveal the following:

Sodium: 142 mEq/L (135–145 mEq/L)
Potassium: 3.1 mEq/L (3.5–5.0 mEq/L)
Chloride: 102 mEq/L (95–105 mEq/L)
Bicarbonate: 25 mEq/L (18–22 mEq/L)

What enzyme-deficiency does this patient have?

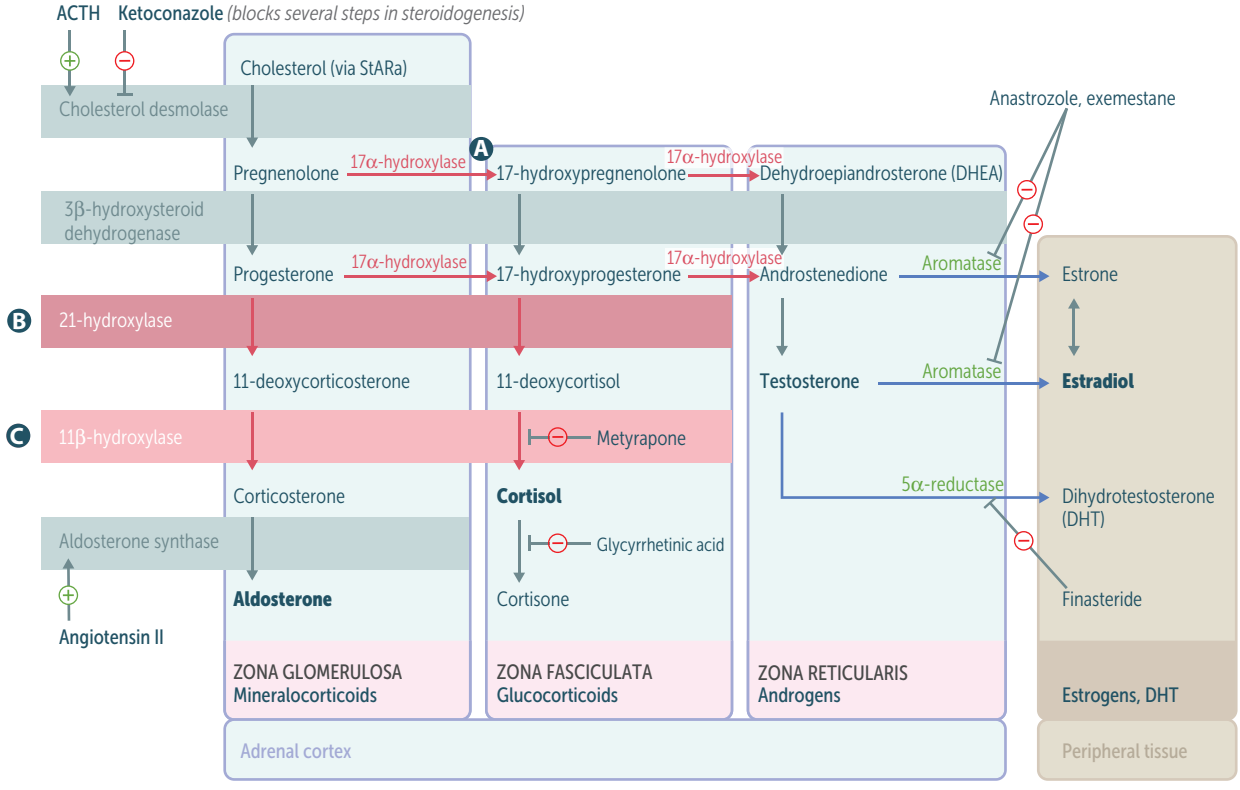
11β-Hydroxylase deficiency is suggested by the constellation of hypertension, virilization, such as increased muscle bulk, male pattern hair, and a deeper voice (in females), low renin, and mild hypokalemia.

What is the mode of inheritance of this condition?

Inheritance is autosomal recessive, with mutations in the *CYP11B1* gene. All the congenital adrenal hyperplasias are inherited in an autosomal recessive manner.

How is this condition differentiated from a more common, but similar, enzyme deficiency?

21β-Hydroxylase deficiency presents with hypotension, hyperkalemia, increased renin activity, and mild hyponatremia. Both deficiencies present with virilization in females or precocious puberty in males. A review of adrenal steroid synthesis is shown in Figure 7-2.



Congenital adrenal hyperplasias

A = 17α-hydroxylase deficiency. ↓ sex hormones, ↓ cortisol, ↑ mineralocorticoids. Cx = **HYPER**tension, hypokalemia; phenotypically female but no maturation.

B = 21ß-hydroxylase deficiency. Most common form. ↓ cortisol (increased ACTH), ↓ mineralocorticoids, ↑ sex hormones. Cx = masculinization, female pseudohermaphroditism, **HYPO**tension, hyponatremia, hyperkalemia, ↑ plasma renin activity, and volume depletion. Salt wasting can lead to hypovolemic shock in the newborn.

C = 11ß-hydroxylase deficiency. ↓ cortisol, ↓ aldosterone and corticosterone, ↑ sex hormones. Cx = masculinization, **HYPER**tension (11-deoxycorticosterone acts as a weak mineralocorticoid).

FIGURE 7-2. Adrenal steroid synthesis. (Reproduced with permission from Le T, et al. *First Aid for the USMLE Step 1: 2019*. New York: McGraw-Hill, 2019.)

How does this enzyme deficiency result in hypertension?

11β-Hydroxylase converts 11-deoxycorticosterone into corticosterone, and 11-deoxycortisol into cortisol. 11β-Hydroxylase deficiency causes a lack of cortisol and aldosterone. However, the precursor 11-deoxycortisone can still act as a weak mineralocorticoid and cause hypertension through exerting its effects on electrolyte reabsorption, exhibited in this case as hypokalemia.

What is the treatment for this condition?

Dexamethasone or hydrocortisone can be used to replace the missing corticosteroid. The lowest effective dose should be used to avoid the Cushingoid adverse effects of glucocorticoids, including bone demineralization and growth retardation.

CASE 3

A 36-year-old woman with no significant medical history presents to her primary care physician with a 6-month history of amenorrhea, weight gain, and excessive facial hair growth. She denies any recent diet or medication changes. The patient also complains that over the past 6 months she has developed increased difficulty with combing her hair as well as climbing stairs. Her vital signs are notable for a pulse of 80/min and blood pressure of 148/90 mm Hg. Physical examination reveals a well-developed hirsute female with truncal obesity, abdominal striae, and peripheral edema. Relevant laboratory findings are as follows:

Sodium: 140 mEq/L
Bicarbonate: 25 mEq/L
Potassium: 3.4 mEq/L
Chloride: 92 mEq/L
Glucose: 225 mg/dL

What is the most likely diagnosis?

Cushing syndrome results from excess glucocorticoids, either from increased cortisol production or exogenous glucocorticoid therapy. Features of excess glucocorticoids can be seen in Figure 7-3. Common causes include the following:

- Exogenous corticosteroids (most common)
- ACTH-secreting pituitary adenoma (**Cushing disease**)
- Adrenal hyperplasia/adenoma/carcinoma
- Adrenocorticotropic hormone (ACTH)-producing tumor (small cell lung cancer, bronchial carcinoids, etc.)

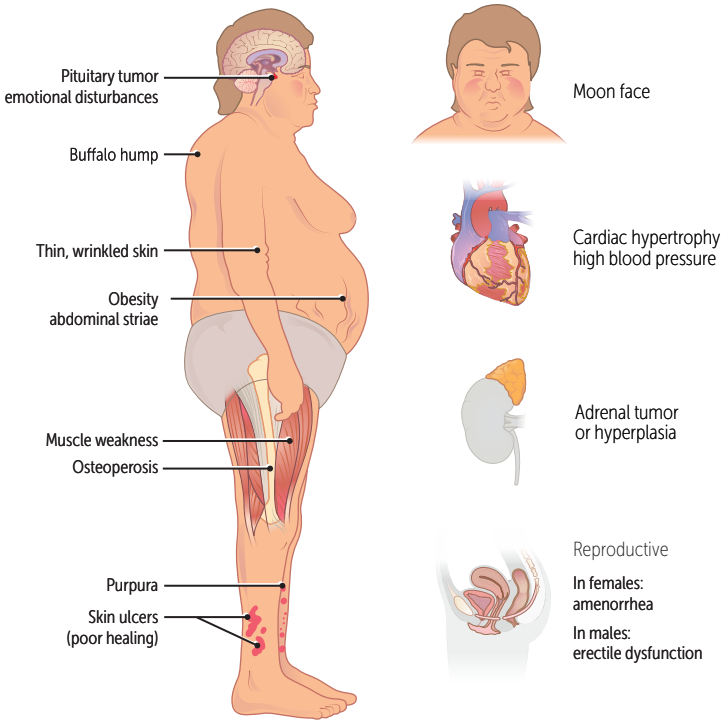


FIGURE 7-3. Clinical features of Cushing syndrome. Of note, an enlarged sella turcica will only be seen in Cushing disease. (Reproduced with permission from USMLE-Rx.com.)

What laboratory tests can help confirm the diagnosis?

Screening tools for Cushing syndrome or glucocorticoid excess include the following:

- 24-hour urine free cortisol test. Elevated cortisol level indicates hypercortisolism.
- Dexamethasone suppression test. A normal result is a decrease in cortisol after administration of low-dose dexamethasone. In glucocorticoid excess due to Cushing disease, low-dose dexamethasone will not suppress cortisol levels.

After identifying elevated cortisol levels, what diagnostic tests help define the source of the hormonal abnormality?

The next best test to order would be serum ACTH.

- High ACTH: Pituitary adenoma or an ectopic ACTH-producing neoplasm.
- Low ACTH: Adrenal tumor/hyperplasia or exogenous glucocorticoid administration.
- A **high-dose dexamethasone suppression test** can differentiate between a pituitary adenoma and an ectopic ACTH-producing tumor. Pituitary adenomas are suppressed by high-dose ACTH, whereas ectopic ACTH-producing tumors usually are not.

What are the treatments for this condition?

The treatment for adrenal tumors is surgery. Treatments for nonresectable tumors or hyperplasia are as follows:

- Ketoconazole: Inhibits glucocorticoid production via 17–20 desmolase.
- Metyrapone: Reversibly inhibits 11β-hydroxylase in the steroid synthesis pathway.
- Aminoglutethimide: Limits the synthesis of steroids by inhibiting p450scc (side-chain cleaver), which blocks the conversion of cholesterol to pregnenolone.

What is the regular cycle of cortisol levels in the body?

Cortisol levels peak in the early morning (approximately 8 am) and reach their lowest levels at midnight. Basal body temperature fluctuates with the cortisol cycle (see Figure 7-4).

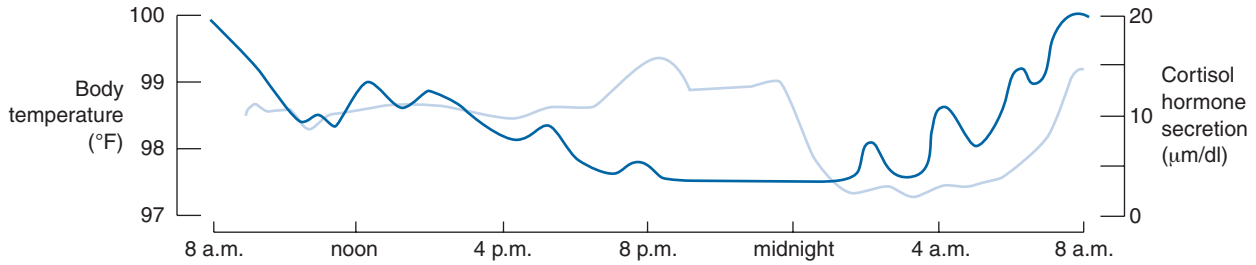


FIGURE 7-4. Cortisol and basal body temperature. Light blue line represents temperature. Darker blue line represents cortisol. (Reproduced with permission from USMLE-Rx.com.)

CASE 4

A previously healthy 30-year-old woman visits her physician complaining of a racing heart, sweating, weight loss, and tremulousness. She appears anxious, and on further questioning reports that her anxiety and restlessness have begun to cause problems at her workplace. She has no prior psychiatric history. Her vital signs reveal a heart rate of 130/min and a blood pressure of 135/90 mm Hg. Physical examination reveals moist skin, fine body hair, and bilateral bulging of her eyes (see Figure 7-5).

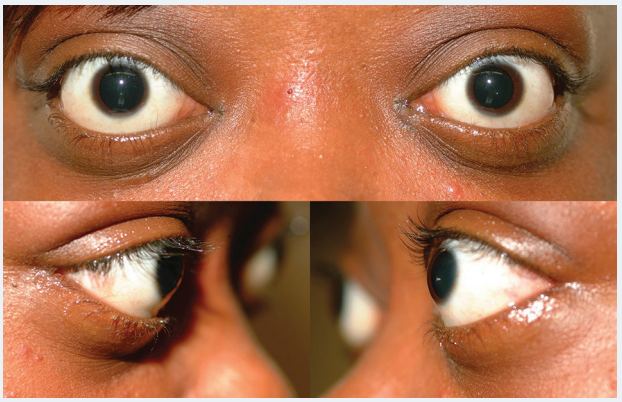


FIGURE 7-5. (Reproduced with permission from USMLE-Rx.com.)

What is the most likely diagnosis?

Graves disease.

What demographic group does this condition typically affect?

Graves disease occurs eight times more frequently in women than men. The disease rarely occurs before adolescence as patients typically present between the ages of 20–40 years old. Females tend to present later, typically around the ages of 30–60 years old. Proptosis (as seen in Figure 7-5) is a common sign.

What is the pathophysiology of this condition?

It is caused by autoimmune-induced hyperthyroidism. Immunoglobulins, specifically IgGs, mimic thyroid-stimulating hormone (TSH) and activate the TSH receptor.

What are other common causes of hyperthyroidism?

- **Iatrogenic**: Exogenous thyroid hormone medication.
- **Silent thyroiditis**: Inflammation of the thyroid gland, which progresses from hyperthyroidism to hypothyroidism.
- **Struma ovarii**: Ovarian neoplasm (mature teratoma) that contains thyroid tissue.
- **Subacute thyroiditis**: Inflammation of the thyroid gland thought to be secondary to viral infection, commonly resulting in a solitary "cold" nodule seen on RAI uptake scans.
- **Toxic adenoma**: Benign thyroid neoplasm.
- **Toxic multinodular goiter** (Plummer disease): Enlarged thyroid gland containing multiple active nodules that produce thyroid hormone (called "hot" nodules because of their increased uptake on radioactive iodine scans.)
- **Hydatidiform mole/Choriocarcinoma**: alpha subunit of β-hCG can lead to excess thyroid receptor stimulation and subsequent hyperthyroidism

Note: Infiltrative ophthalmopathy and pretibial myxedema are seen only in hyperthyroidism caused by Graves disease.

What are the treatments for this condition?

Graves disease can remit and recur. Effective treatment includes thyroidectomy (subtotal vs. total), thyroid-inhibiting medications, or radioactive iodine ablation (radioactive iodine is taken up by, and then destroys, hyperfunctioning thyroid tissue). Medications such as propylthiouracil (PTU) and methimazole inhibit iodine organification and coupling in the thyroid. PTU and steroids also inhibit the peripheral conversion of T4 to T3. PTU and methimazole are associated with agranulocytosis (may present as sore throat), a life-threatening reaction to the medication that necessitates withdrawal of treatment.

What is thyroid storm?

Thyroid storm is an acute, life-threatening surge of thyroid hormone in the blood, usually precipitated by surgery, trauma, infection, acute iodine load, or long-standing hyperthyroidism. Manifestations include tachycardia ($>$ 140/min), heart failure, fever, agitation, delirium, psychosis, stupor, and/or coma. Gastrointestinal symptoms may also be present. Treatment is aggressive, as patients are treated with PTU (preferred over methimazole as it blocks the peripheral conversion of T4 to T3), IV esmolol, corticosteroids, and possibly high-dose potassium iodide.

CASE 5

A worried mother brings her 12-year-old son to the pediatrician with concerns that he is growing too quickly. Both she and the patient's father are relatively short, as are other members of the family. The patient, an avid Little League player, complains only that his baseball cap, mitt, and shoes do not fit any more. On physical examination, the patient is above the growth curve for his age and has large hands and feet, frontal bossing of the cranium, prominent jaw, and coarse facial features with oily skin. Lab tests reveal a fasting glucose of 131 mg/dL.

What is the most likely diagnosis?

Gigantism, which is caused by excess growth hormone (GH). In adults, the long bone epiphyses are fused (ie, growth plates), and the disease is called acromegaly. In older patients, physical changes may go unnoticed until hats, gloves, and shoes no longer fit.

What is the pathophysiology of this condition?

The most common cause of gigantism, or any excess amount of GH, is from a pituitary adenoma secretion. A genetic component of the disease is suggested by the high levels of GH seen in **McCune-Albright syndrome** and multiple endocrine neoplasia type I. Multiple endocrine neoplasia type 1 (MEN1) is also associated with pituitary neoplasias, parathyroid hyperplasia, and pancreatic malignancies.

How is GH produced?

GH, along with prolactin, is produced and stored in the acidophilic cells of the anterior pituitary. Basophilic cells in the anterior pituitary can be recalled with the mnemonic **B-FLAT**: **B**asophils: **F**SH, **L**H, **A**CTH, and **T**RH.

How is secretion of GH controlled?

GH is released in a **pulsatile** fashion. Secretion is controlled by the hypothalamus (see Figure 7-6). GHRH stimulates GH production. Somatostatin interferes with its effect on the pituitary. GH then increases the release of Insulin-like growth factor-1 (IGF-1), which exerts negative feedback to inhibit GH secretion. At puberty, the frequency and amplitude of GH secretory pulses increase because of gonadal hormones. The combination drives the "growth spurt."

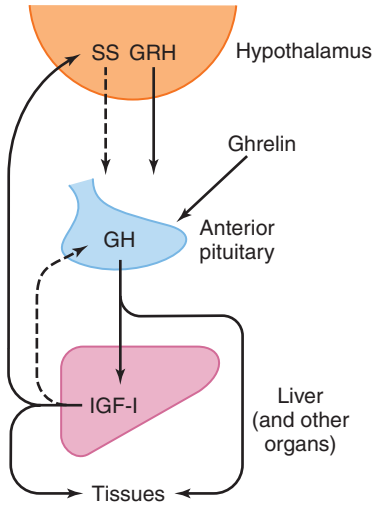


FIGURE 7-6. Feedback control of growth hormone secretion. Solid arrows represent positive effects and dashed arrows represent inhibition. GH, growth hormone; GHRH, growth hormone–releasing hormone; IGF-I, insulin-like growth factor-I; SS, somatostatin. (Reproduced with permission from Barrett KE, et al. eds. *Ganong's Medical Physiology Examination & Board Review* New York, NY: McGraw-Hill, 2018.)

How is this condition diagnosed?

Excess GH production is diagnosed by physiologic testing and brain imaging.

- **Screening**: The best screening test for excess GH secretion is a measurement of serum IGF-1 levels. IGF-1 levels are a more reliable indicator of GH excess than GH levels because IGF-1 remains constant throughout the day, whereas GH fluctuates.
- **Confirmatory test**: The diagnosis of GH excess can be confirmed with an oral glucose suppression test. In normal patients, GH levels are suppressed after the administration of a glucose load. In patients with gigantism or acromegaly, GH values may rise, remain unchanged, or suppress only partially.
- **Imaging**: MRI of the pituitary gland may reveal adenoma as the source of excess GH secretion.

CASE 6

A 62-year-old woman presents to her physician with a month-long history of vague abdominal pain, constipation, and nausea and vomiting. She also has experienced diffuse bone pain over the past month, which she attributed to "just getting old." The patient also complains of decreased attentiveness as well as generalized fatigue. Physical examination reveals diffuse abdominal tenderness. Relevant laboratory findings are as follows:

Sodium: 140 mEq/L
Calcium: 11.2 mg/dL
Chloride: 110 mEq/L
Bicarbonate: 26 mEq/L
Potassium: 4.0 mEq/L
Phosphate: 1.8 mg/dL
Blood urea nitrogen/creatine: 20:1.2 mg/dL

What is the most striking laboratory finding?

Hypercalcemia. Common causes of hypercalcemia are:

- Malignancy (typically see highly elevated levels, ie, > 14 mg/dL)
- Intoxication with vitamin D
- Sarcoidosis (increased levels of 1α-hydroxylase)
- Hyperparathyroidism (most commonly a single hyperfunctioning gland, can also see generalized parathyroid hyperplasia)
- Milk-alkali syndrome

In outpatients, hyperparathyroidism is the most common cause of hypercalcemia; in inpatients, malignancy is the most common cause.

How is calcium regulated in the body?

- **Parathyroid hormone** (PTH) stimulates osteoclasts to resorb calcium from bone; increases calcium reabsorption in the distal convoluted tubules of the kidney; increases production of 1,25-$(OH)_2$ vitamin D by the kidney; and decreases renal reabsorption of phosphate.
- **Vitamin D** promotes calcium reabsorption from bone and the small intestine.
- **Calcitonin** inhibits osteoclast activity, thereby decreasing reabsorption of calcium from bone. In normal calcium homeostasis, calcitonin is likely not as significant.

The patient is found to have elevated PTH and normal creatine. How does this help explain her clinical presentation?

The patient has primary hyperparathyroidism (see Table 7-1), as evidenced by high PTH, high calcium, and normal renal function. To recall the symptoms of hypercalcemia, use the following mnemonic: **bones** (osteopenia, fractures), **stones** (kidney stones), **groans** (anorexia, constipation), and psychiatric **overtones** (weakness, fatigue, altered mental status). Primary hyperparathyroidism is most commonly due to a singular parathyroid adenoma, whereas secondary hyperparathyroidism is primarily seen in the setting of chronic renal failure.

TABLE 7-1. Comparison of Primary, Secondary, and Tertiary Hyperparathyroidism

Hyperparathyroidism	Calcium	Phosphorus	PTH	1,25-$(OH)_2$ vitamin D
Primary	↑	↓	↑	May be ↑
Secondary	↓	↑	↑	↓
Tertiary	↑	Often ↑	↑	May be ↓

(Reproduced with permission of USMLE-Rx.com.)

What is the treatment for acute, severe forms of this condition?

Hydration. If the electrolyte abnormality persists, a loop diuretic can be used (to increase calcium excretion). If needed, calcitonin and bisphosphonates can also be prescribed.

What is the long-term treatment for this patient?

Parathyroidectomy. In the setting of a solitary adenoma, the affected gland can be removed, whereas in cases of parathyroid hyperplasia 3.5 glands are typically removed.

CASE 7

A 52-year-old woman presents to the clinic with several months' history of generalized weakness, cold intolerance, and weight gain. Physical examination reveals alopecia, a thick and beefy tongue, myxedema, and delayed deep tendon reflexes. Her heart rate is 55/min and her blood pressure is 100/70 mm Hg. She is not taking any medications. Relevant laboratory findings are as follows:

Free thyroxine (T_4): 0.31 ng/dL
Thyroid-stimulating hormone (TSH): 31 μU/mL
Cholesterol: 230 mg/dL

What is the most likely diagnosis?

The patient's cold intolerance, weight gain, myxedema, fatigue, prolonged relaxation phase of deep tendon reflexes, and low free T_4 with high TSH suggest primary hypothyroidism.

What is the most common cause of this condition?

Hashimoto thyroiditis (autoimmune destruction of the thyroid gland). Patients are typically positive for **antithyroid peroxidase (antithyroglobulin) antibodies**. Microscopic analysis of tissue typically shows inflammatory infiltrate mixed with intact glandular tissue (see Figure 7-7). Additional causes of hypothyroidism include Riedel thyroiditis, subacute thyroiditis, and silent thyroiditis. The prevalence of Hashimoto thyroiditis is increased in patients with other autoimmune disease such as vitiligo.

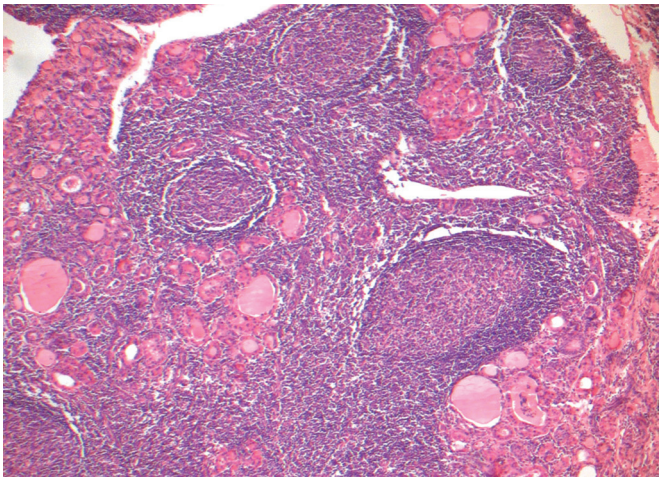


FIGURE 7-7. Hashimoto thyroiditis. Heterogenous pattern with nodules of lymphocytic or mixed inflammatory infiltrate in some areas and intact functioning glandular tissue with normal-appearing colloid in other areas under light microscopy. (Reproduced with permission from USMLE-Rx.com.)

What endocrine disorder is associated with low free T_4 and low serum TSH levels?

Low T_4 levels in the setting of low or normal TSH levels imply **secondary hypothyroidism**, the most common cause of which is **hypopituitarism**. Other manifestations of hypopituitarism include sexual dysfunction and diabetes insipidus.

What is the treatment for this condition?

Levothyroxine (synthetic T_4 hormone). Levels of T_4 typically take 4–6 weeks to reach steady state after initiation of therapy, and patients are monitored via TSH levels.

How are thyroid hormones produced and metabolized?

Iodine is essential for the production of thyroid hormones in the follicular cells of the thyroid gland. Following T_4 production in the thyroid gland, deiodinases in the peripheral tissues convert T_4 to the active form, T_3, as well as the inactive form, rT_3.

What are the primary functions of thyroid hormones in the peripheral bloodstream?

The role of T_3 in the body can be remembered by the **4B**s: **B**rain maturation, **B**one growth (synergism with GH), **β**-adrenergic effects (increased β_1 receptors in the heart), and increasing the **B**asal metabolic rate (via increased Na^+-K^+ ATPase activity).

CASE 8

A 14-year-old Hispanic-American boy with a family history of obesity and hypertension presents to the pediatrician for a mandatory school physical examination. He has no medical complaints. Social history is notable for a sedentary lifestyle. His diet consists of pizza, sandwiches, potato chips, and two 12-oz sodas daily. Physical examination reveals a male with an abdominal circumference > 40 inches. His body mass index is 36 kg/m^2, pulse is 100/min, and blood pressure is 140/95 mm Hg. Skin examination reveals velvety, darkly pigmented patches in the skin folds at the nape of his neck and axilla (see Figure 7-8).

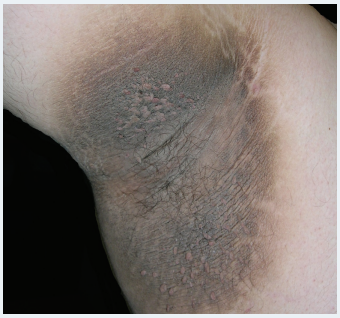


FIGURE 7-8. (Reproduced courtesy of Dr. Richard Usatine.)

What is the most likely diagnosis?

Metabolic syndrome, also known as dysmetabolic syndrome, syndrome X, and insulin resistance syndrome.

What are the diagnostic criteria for this condition?

The National Cholesterol Education Program Adult Treatment Panel III defines metabolic syndrome as the presence of any three of the following five traits:

- Abdominal obesity (male > 40 inches; female > 35 inches)
- Hypertriglyceridemia (≥ 150 mg/dL)
- High-density lipoprotein (HDL) cholesterol (male < 40 mg/dL; female < 50 mg/dL)
- Blood pressure ≥ 130/85 mm Hg
- Fasting glucose ≥ 100 mg/dL

What do the skin findings represent?

Acanthosis nigricans (see Figure 7-8) is a common physical sign of insulin resistance, particularly in Hispanics and African-Americans, and is commonly manifested in the neck, axilla, and groin. It may be due to high levels of circulating insulin or insulin-like growth factor receptors in the skin. Other conditions with acanthosis nigricans include **polycystic ovarian syndrome** and some visceral **malignancies**.

What is insulin resistance?

Insulin resistance (IR) is the state in which endogenous or exogenous insulin produces a less-than-expected biological effect. Patients have elevated blood glucose with normal to elevated insulin levels. Today, IR is nearly universal in obese individuals and is correlated with amount of intra-abdominal fat. Several mechanisms of IR in obesity have been proposed:

- Insulin receptor downregulation
- Intracellular lipid accumulation
- Increased free fatty acids that impair insulin action
- Cytokines and "adipokines," which modify the effect of insulin

Treatment with metformin can be initiated to increase insulin responsiveness. Other interventions include aggressive lifestyle modification, cholesterol management, and BP control.

What further complications are associated with this condition?

Patients with metabolic syndrome are at increased risk for coronary artery disease, cardiac-related mortality, and development of type II DM (5× increased risk).

What class of drugs should be avoided in patients with this condition?

Atypical antipsychotics, such as clozapine or olanzapine, are associated with the metabolic syndrome, particularly weight gain and hypertriglyceridemia. Even for patients without weight gain, the effect on serum triglycerides increases the risk for adverse cardiovascular events.

CASE 9

A 40-year-old woman presents to her physician with a 2-month history of hoarseness and occasional palpitations and headaches. Her blood pressure is 170/90 mm Hg. Physical examination reveals a lump at the base of her neck. Results of biopsy of the mass are shown in Figure 7-9. Laboratory values are significant for hypercalcemia. Family history is not contributory, as the patient is adopted.

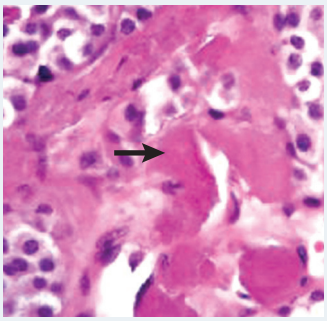


FIGURE 7-9. (Reproduced with permission from USMLERx.com.)

What is the most likely diagnosis?

Multiple endocrine neoplasia (MEN) type IIA, or Sipple syndrome, is characterized by medullary carcinoma of the thyroid, pheochromocytoma, and hyperparathyroidism (due to either hyperplasia or tumor). Medullary carcinoma of the thyroid is characterized by nests of cells in amyloid stroma and commonly secretes calcitonin, which can be helpful in making the diagnosis. Figure 7-9 shows the lobular pattern of growth of this tumor. Table 7-2 presents MEN types.

TABLE 7-2. MEN Types

	Type I	Type IIA	Type IIB
Inheritance	Autosomal dominant	Autosomal dominant	Autosomal dominant
Neoplasms	Pancreatic islet cell tumors (Zollinger-Ellison, insulinoma, VIPoma) Parathyroid hyperplasia Pituitary adenomas	Medullary thyroid cancer Parathyroid hyperplasia Pheochromocytoma	Medullary thyroid cancer Mucosal neuroma Pheochromocytoma
Body habitus			Marfanoid

What genetic screening tests can help confirm the diagnosis?

The presence of the *RET* oncogene mutation in the setting of medullary carcinoma is diagnostic for MEN IIA. A variant of the *RET* mutation is also seen in MEN IIB.

What additional laboratory tests are important to obtain?

- Calcitonin and carcinoembryonic antigen levels: medullary carcinoma
- PTH and calcium levels: parathyroid hyperplasia or adenoma
- Urinary and plasma levels of catecholamines and catecholamine metabolites (vanillylmandelic acid, metanephrine, and normetanephrines): pheochromocytoma

If this patient has the *RET* mutation, what is the probability that her children will develop this condition?

MEN IIA is an autosomal dominant disease. Therefore, the probability of her children having the mutation is 50%, assuming that the child's father is unaffected.

CASE 10

A 35-year-old woman presents to her primary care physician complaining of recent episodes of weakness and tingling in her extremities, as well as some muscle aches in both of her legs. She also complains of polyuria, nocturia, and polydipsia. Prior blood pressures have been steadily normal over the past years, but upon measuring today, the patient has a blood pressure of 160/100 mm Hg. Repeat measurement later in the visit confirms this reading. Laboratory studies reveal a serum sodium level of 147 mEq/L, a potassium level of 2.8 mEq/L, and very low serum renin activity.

What is the most likely diagnosis?

Primary hyperaldosteronism, as suggested by the patient's history and her hypertension, hypernatremia, and hypokalemia. Approximately 30%–60% of cases are due to solitary adrenal adenomas in the zona glomerulosa, the aldosterone-secreting layer of the adrenal cortex, which is known as Conn syndrome. Bilateral hyperplasia of the zona glomerulosa can also result in symptoms similar to Conn syndrome.

How is aldosterone regulated?

Renin, produced by the **juxtaglomerular cells** of the kidney, cleaves **angiotensinogen** (produced by the liver) to form **angiotensin I**. Angiotensin I, in turn, is cleaved by angiotensin-converting enzyme to form **angiotensin II**. In response to volume contraction, **angiotensin II** becomes a potent stimulator of aldosterone synthase, a key enzyme in aldosterone synthesis. Other key stimuli of aldosterone secretion include decreased plasma sodium and increased plasma potassium. This is in contrast to the other steroids synthesized in the adrenal that are primarily regulated by ACTH.

Another patient presents with similar symptoms, but his laboratory tests show increased serum renin activity. What are the most likely diagnoses?

Hypertension has a variety of causes. Approximately 95% of patients with hypertension have primary or "essential" hypertension, which has no identifiable cause. The remaining patients have secondary hypertension, which is caused by an identifiable underlying etiology such as extra-adrenal hyperstimulation of aldosterone secretion (see Table 7-3). In a patient with similar symptoms but an elevated renin level, one should explore the possibility of renal artery stenosis, CHF, cirrhosis, or nephrotic syndromes.

Table 7-3. Causes of Secondary Hypertension

Etiology	Description	Management
Renal artery stenosis	Typically $<$ 25 or $>$ 50 years of age with new-onset hypertension (HTN). Includes fibromuscular dysplasia and atherosclerosis.	Consider ACE-Is in unilateral disease **only**. Angioplasty and stenting are typically reserved for patients who fail medical therapy.
Pheochromocytoma	Adrenal gland tumor that secretes catecholamines (eg, norepinephrine and epinephrine). Leads to episodic headache, sweating, and tachycardia.	Surgical resection of the tumor, only after treatment with both α-blockers and β-blockers. Note, it is vital that β-blockade is achieved first as use of α-blockade beforehand will lead to hypertensive emergency.
Conn syndrome	Most commonly secondary to aldosterone-secreting adrenal tumor. Causes triad of HTN, hypokalemia, and metabolic alkalosis.	Surgical resection of the tumor.
Cushing syndrome	Due to ACTH-producing pituitary tumor, ectopic ACTH-secreting tumor, or excess cortisol secretion by adrenal tumor. May also be caused by exogenous steroid exposure.	Surgical resection of the tumor, with coinciding removal of exogenous steroids.
1° renal disease	Typically unilateral renal parenchymal disease.	Treatment with ACE-Is, which function to slow progression of disease.

Given the patient's serum potassium level, what are the most likely findings on ECG?

Typical ECG findings include prominent U waves, flattened T waves, and ST-segment depression (see Figure 7-10).

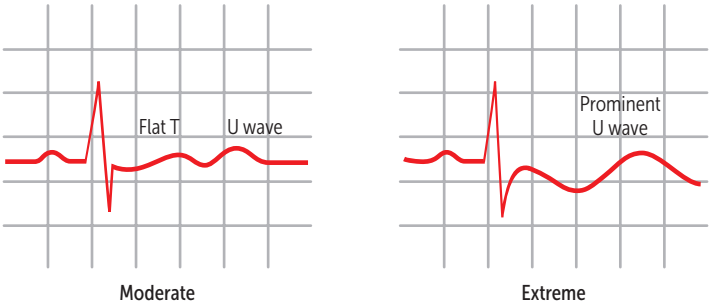


FIGURE 7-10. U waves in ECG resulting from hypokalemia, thus increasing risk for torsades de pointes and other arrhythmias. Moderate (left) and extreme (right) variations shown. (Modified with permission of USMLE-Rx.com.)

What is the treatment for this condition, and what are the adverse effects?

If a solitary, aldosterone-secreting adrenal adenoma is found, surgical resection (adrenalectomy) is indicated. Bilateral adrenal hyperplasia is treated medically with an aldosterone antagonist such as spironolactone. Major adverse effects of spironolactone are due to its antiandrogen effects, including gynecomastia, loss of libido, menstrual irregularities, and impotence. Another aldosterone antagonist, eplerenone, may be used instead of spironolactone as it has fewer sexual adverse effects.

CASE 11

A 10-year-old girl is brought to her pediatrician for a workup of new-onset seizures. The patient had been in her usual state of health until 3 months ago, when she developed numbness and tingling in her fingertips and frequent muscle cramps. Last week, she had a grand mal seizure. CT scan of the head at that time revealed no intracranial lesions. Physical examination reveals a well-nourished female with short stature and shortened fourth and fifth digits. Tapping on her cheek elicits rapid facial muscle contractions. Relevant laboratory findings include the following:

Calcium: 7 mg/dL
Phosphate: 6 mg/dL
Parathyroid hormone (PTH): 100 pg/dL

What is the most likely diagnosis?

Pseudohypoparathyroidism (type 1a) is characterized by renal unresponsiveness to PTH. A genetic cause of this disorder results from a mutation in the *GNAS1* gene, which codes for a G_s-a_1 protein of adenylyl cyclase. McCune-Albright hereditary osteodystrophy is also present in type 1a pseudohypoparathyroidism, and some patients have growth hormone–releasing hormone resistance.

What would hypocalcemia with a low serum PTH level suggest?

Primary hypoparathyroidism, usually caused by accidental removal or injury of the parathyroid glands during thyroid surgery, causes decreased PTH levels, which results in decreased serum calcium levels. Other causes of hypoparathyroidism include autoimmune, congenital (DiGeorge syndrome), and infiltrative diseases (hemochromatosis, Wilson syndrome).

What are Chvostek and Trousseau signs?

Chvostek sign (twitching of ipsilateral facial muscles upon tapping of the facial nerve just anterior to the ear) and Trousseau sign (carpal contractions provoked by inflating a blood pressure cuff above systolic blood pressure for more than 3 minutes) are signs of hypocalcemia.

How is the serum calcium level regulated?

Serum calcium is regulated by PTH and vitamin D (see Figure 7-11). PTH has two major sites of action: bone and kidney. In bone, PTH increases bone turnover, liberating calcium, as well as phosphate. In the kidney, PTH increases enzymatic formation of 1,25-$(OH)_2$-cholecalciferol from vitamin D, phosphate excretion, and calcium reabsorption. The active form of vitamin D stimulates calcium and phosphate absorption in the gut as well as bone resorption.

Albumin has an important relationship with serum calcium: 45% of serum calcium is found free-floating in its ionized form, 40% is typically bound to circulating albumin, and 15% is bound to inorganic/organic anions. Measured serum levels of calcium may be inaccurate if serum albumin is low (starvation states, cirrhosis, etc.) and thus must be corrected by the following equation:

$$Ca^{2+} = \text{Total serum } Ca^{2+} + 0.8\,(4 - \text{serum albumin})$$

Blood pH also has an important effect on the albumin/calcium relationship as protons bind the same site on albumin as does calcium. Decreasing blood pH (acidosis) will "kick off" Ca ions, leading to hypercalcemia, and the opposite is true, with alkalosis leading to increased binding sites on albumin and subsequent hypocalcemia.

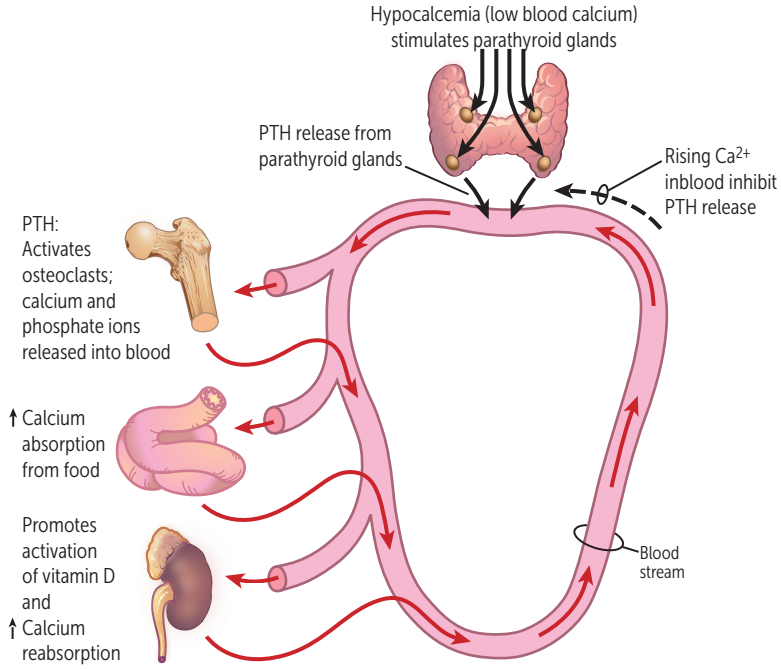


FIGURE 7-11. Vitamin D and parathyroid hormone. (Reproduced with permission from USMLE-Rx.com.)

Where is PTH synthesized?

PTH is synthesized in the chief cells of the parathyroid glands.

What are the other physiologic effects of hypocalcemia?

In addition to muscle cramping, paresthesias, and convulsions, low calcium levels also may prolong the QT interval on ECG. It is important to identify patients with prolonged QT intervals as it is a risk factor for serious cardiac arrhythmias, including torsades de pointes. By contrast, patients with hypercalcemia have a shortened QT interval. It is also important to note that both blood pH and albumin levels can affect measured serum calcium, as an increased pH will lead to increased binding of albumin to Ca and a subsequent relative hypocalcemia.

CASE 12

A 50-year-old woman presents to the ED complaining of 2 hours of vertigo, headache, palpitations, blurry vision, and diaphoresis. She has a history of occasional tension headaches but no significant cardiac history. She does not smoke and has no history of hypertension. At presentation her blood pressure is 200/140 mm Hg, her heart rate is 120/min, and she is afebrile. Her skin is sweaty and flushed. Noncontrast imaging of the brain is negative for blood or other mass lesions. Her blood pressure is stabilized pharmacologically. Laboratory testing reveals increased plasma metanephrine and normetanephrine levels. Results of a serum thyroid-stimulating hormone test are within normal limits. Twenty-four-hour urine catecholamines and meta/normetanephrines are elevated.

What is the most likely diagnosis?

Pheochromocytoma is a catecholamine-secreting tumor of chromaffin cells of the adrenal medulla.

What are the key steps in epinephrine catabolism?

Catecholamines are substrates for monoamine oxidase (MAO) and catechol-O-methyltransferase (COMT) (see Figure 7-12). Epinephrine can undergo two paths of catabolism. In the first, COMT converts epinephrine into metanephrine, which MAO then converts into 3-methoxy-4-hydroxymandelic acid. In the second, MAO converts epinephrine into dihydroxymandelic acid, which COMT then converts into 3-methoxy-4-hydroxymandelic acid (the same product as the first pathway).

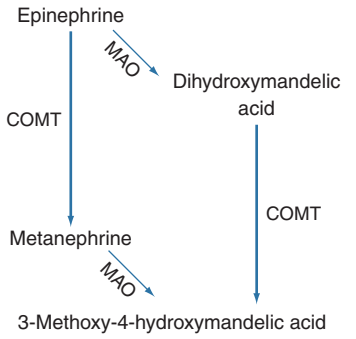


FIGURE 7-12. Epinephrine catabolism. (Modified with permission from USMLE-Rx.com.)

What receptors do catecholamines act on to produce hypertension?

Catecholamines act on α_1 and β_1 receptors. Activation of α_1 receptors contracts vascular smooth muscle, and activation of β_1 receptors in the heart increases heart rate, conduction velocity, and contractility.

During removal of an adrenal gland, the surgeon must secure the adrenal vasculature, especially the adrenal vein. How is the blood supplied to the adrenal gland?

The arterial blood supply to the adrenal gland can be variable, with blood supply from the superior suprarenal artery originating from the inferior phrenic artery, the middle suprarenal artery originating from the aorta, and the inferior suprarenal artery originating from the renal artery. The adrenal gland typically has a dominant vein, which empties into the left renal vein (left adrenal gland) and the inferior vena cava (right adrenal gland).

What is the probability that this patient's condition is malignant?

Approximately 10%. Remember the "**rule of 10s**" for pheochromocytomas: **10%** are malignant, **10%** bilateral, **10%** extra-adrenal, **10%** calcify, and **10%** are pediatric. The most common site of extra adrenal involvement is the organ of Zuckerkandl, which is usually located at the root of the inferior mesenteric artery.

What is the structure and function of the adrenal gland?

The adrenal gland is composed of the cortex and medulla, each with its own secretory products. The zones of the adrenal cortex can be remembered with the mnemonic, "**the deeper you go, the sweeter it gets**": salt-related hormones (aldosterone) from the zona glomerulosa, sugar-related hormones (cortisol) from the zona fasciculata, and sex-related hormones (testosterone, DHEAS) in the zona reticularis. The adrenal medulla produces catecholamines such as epinephrine and norepinephrine.

What is the importance of treatment order for this condition?

Patients must be given irreversible α-blockers (phenoxybenzamine) first, followed by β-blockers. The α-blockade must be achieved first, as premature β-blockade could lead to hypertensive crisis.

CASE 13

A 32-year-old woman is postpartum day 4 after delivery of her fourth child. The delivery was complicated by massive hemorrhage. She desires to breast-feed, but her breast milk has not come in (normally it begins 24–48 hours postpartum). She breast-fed all of her other children without delay. In addition, she complains of intense fatigue, mental sluggishness, lightheadedness, and a racing heartbeat. On physical examination she is pale, diaphoretic, and weak. Vital signs are as follows:

Temperature: 36.2°C (97.1°F)
Pulse: 100/min supine, 115/min sitting, and 130/min standing
Blood pressure: 90/70 mm Hg supine, 80/60 mm Hg sitting, and 70/50 mm Hg standing

What is the most likely diagnosis?

Sheehan syndrome.

What is the likely cause of this condition?

This patient's massive hemorrhage during pregnancy likely led to ischemia and necrosis of the pituitary gland. The pituitary becomes physiologically hypertrophied during pregnancy, which leads to an increased risk of ischemic injury.

What hormones are secreted by the pituitary gland?

The pituitary gland can be separated into anterior and posterior components. The anterior pituitary (adenohypophysis) is derived from ectoderm and produces follicle-stimulating hormone (FSH), luteinizing hormone (LH), adrenocorticotropic hormone (ACTH), growth hormone, thyroid-stimulating hormone, melanotropin, and prolactin. (Know the role of each of these hormones.) The posterior component (neurohypophysis) is derived from neuroectoderm and produces antidiuretic hormone and oxytocin. Oxytocin is required for lactation and contraction of the uterus.

What are the clinical manifestations of this condition?

The most common presentation of this condition is failure of lactation. Other symptoms, due to the loss of other pituitary hormones, include weakness, lethargy, cold insensitivity, genital atrophy, and menstrual disorders. These symptoms may occur immediately following the postpartum hemorrhage but can also develop years after the initial event.

What is the significance of the patient's vital signs?

The patient displays orthostatic hypotension, defined as a systolic blood pressure decrease of at least 20 mm Hg systolic (or a diastolic blood pressure decrease of 10 mm Hg) within 3 minutes of standing. There is a compensatory increase in heart rate to maintain peripheral perfusion. The cause of hypotension in this patient is loss of cortisol (via decreased ACTH), which is required for maintenance of peripheral vascular tone. This is a medical emergency, as the patient is at risk for vascular collapse, for which the patient should be treated with exogenous glucocorticoids.

What other signs and symptoms can be expected in this patient?

Other endocrine signs and symptoms can occur secondary to the loss of pituitary hormones such as TSH (weakness, lethargy, cold insensitivity), FSH/LH (genital atrophy, menstrual irregularities, loss of sexual hair), prolactin (failure to lactate), as well as general anorexia/weight loss. Lifelong hormone replacement is required.

CASE 14

A 45-year-old man presents to the clinic complaining of increased urination and associated confusion, lethargy, and deep muscle cramps that he localizes to his lower extremities. The patient states that he believes these all began about a couple months ago after he fell off a roof during work and hit his head. He was cleared at the hospital for any acute intracranial bleed but states that these symptoms have been getting progressively worse since the fall. He has never experienced anything like this prior to this recent onset and is not currently taking any medications. Physical examination is grossly negative and lower extremity strength is 5/5 bilaterally. A comprehensive metabolic panel (CMP) demonstrates a sodium of 131 mEq/L. Urinalysis demonstrates an osmolality of 75 mOsm/kg and a urinary sodium level of 45 mEq/L. Further analysis shows abnormally low uric acid, normokalemia, and a blood pH of 7.41.

What is the most likely diagnosis?

In the setting of hypoosmolar urine and increased urinary output of sodium, this patient is most likely suffering from syndrome of inappropriate antidiuretic hormone (SIADH) secretion. This is the most common cause of euvolemic hyponatremia. The lab findings, coupled with symptom onset following head trauma, points towards this etiology. ADH works by exerting its effect on the distal convoluted tubule and collecting duct of the nephron. Other causes of hyponatremia can be found in Table 7-4.

TABLE 7-4. Common Causes of Hyponatremia, Sorted by Volume Status

Sodium Imbalance: Hyponatremia			
Diagnosis	**Causes**	**Clinical manifestations**	**Treatment**

Serum Na^+ concentration < 136 mEq/L	**Hypovolemia:**
	• Renal losses:
	  • Diuretics
	  • Osmotic diuresis
	• Extrarenal losses:
	  • GI losses from nausea/vomiting/diarrhea
	  • Third-spacing in burns, pancreatitis, etc.
	Euvolemia:
	• SIADH
	• Glucocorticoid deficiency
	• Hypothyroidism
	• Primary polydipsia
	Hypervolemia:
	• Renal: acute and chronic renal failure, nephritic syndrome
	• Extrarenal: cirrhosis, heart failure
		• Mainly central nervous system (CNS) dysfunction
		• Manifestations depend on severity, rapidity, cause of the hyponatremia
		• Early symptoms: altered personality, headache, lethargy, confusion
		• In more severe cases (serum $Na^+ < 115$ mEq/L) stupor, neuromuscular hyperexcitability, seizures, coma, and death can result
			• Most serious complication of treatment is iatrogenic cerebral osmotic demyelination from overly rapid or inappropriate Na^+ correction
			• Slow correction at rate of 0.5-1 mEq/L/h
			Goals:
			• Restrict free water intake in all patients, especially in euvolemia
			• Hypovolemia requires adequate fluid resuscitation with isotonic fluids
			• Hypervolemia may require loop diuretics, dialysis, and treatment of underlying disorder, in addition to water restriction

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What are other causes of this condition?

SIADH is classically associated with central nervous system (CNS) disease, whether from head injury or tumor, but it can also be associated with a variety of other causes. Some other etiologies of SIADH include:

- Pulmonary disease (sarcoidosis, chronic obstructive pulmonary disease (COPD), pneumonia)
- Ectopic tumor production/paraneoplastic syndrome (small cell lung cancer)
- Drugs (antipsychotics, selective serotonin reuptake inhibitors , nonsteroidal anti-inflammatory drugs, carbamazepine)

What are the likely laboratory findings?

Lab findings consistent with SIADH primarily revolve around urinalysis. Typically, urine osmolality is $>$ 50–100 mOsm/kg in the setting of serum hypo-osmolarity ($<$ 275 mOsm/kg). These patients must also have no physiologic reason for increased ADH, such as congestive heart failure (CHF), cirrhosis, or hypovolemia. Urinary sodium is also typically increased, with values $>$ 40 mEq/L commonly seen. Other lab values seen in SIADH include decreased levels of uric acid, physiologically normal levels of potassium, and a normal acid-base level.

What is the treatment for this condition?

Treatment of SIADH is primarily accomplished through fluid restriction and addressing the underlying cause. Care must be taken when correcting the patient's hyponatremia if severe, as overambitious correction can lead to central pontine myelinolysis. Adverse effects of sodium correction can be remembered with the mnemonics **"low to high and the pons will die"** (central pontine myelinolysis) and **"high to low and the brain will blow"** (cerebral edema).

CASE 15

A 13-year-old girl presents to her pediatrician 2 weeks after an upper respiratory infection with a complaint of a "lump in her neck." Physical examination demonstrates a round, freely mobile, slightly tender midline mass that elevates with swallowing and protrusion of her tongue. The remainder of the examination is within normal limits. Her birth and developmental history are unremarkable.

What is the most likely diagnosis?

Thyroglossal duct cyst.

What is the differential diagnosis for this condition?

The differential for benign midline neck masses is vast, including thyroglossal duct cysts, dermoid cysts, sebaceous cysts, ectopic thyroid tissue, midline branchial cleft cysts (usually are lateral), lipomas, and lymphadenopathy.

Hint: If the question describes a **lateral** neck mass in a patient with a webbed neck, shield chest, short stature, and coarctation of the aorta, think Turner syndrome. The neck mass is likely to be a **cystic hygroma**.

How does the thyroid gland form during development?

The thyroid is derived from **endoderm** at the **foramen cecum**, the junction between the developing anterior and posterior tongue. The thyroid descends to its final position over the trachea by the seventh week of gestation, and its pharyngeal connection forms a stalk called the thyroglossal duct (see Figure 7-13).

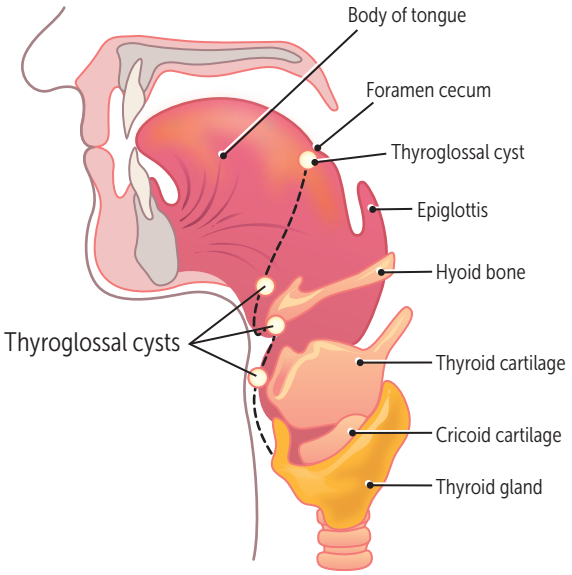

FIGURE 7-13. Thyroglossal cysts along thyroid route of descent. (Reproduced with permission of USMLE-Rx.com.)

What is the pathophysiology of this condition?

The thyroglossal duct should degenerate by the 10th week of gestation. However, in some individuals, cystic remnants of the tract remain. Most never become clinically relevant. However, many cysts are detected in patients with recent upper respiratory tract infections, either because infection leads to cyst inflammation, or simply because the cysts are found incidentally on examination of the neck.

What is the most common location of this mass?

Thyroglossal duct cysts are in close relation to the hyoid bone and the thyrohyoid membrane. More than 50% are at the level of the hyoid bone within 2 cm of the midline.

What is the most common site of ectopic thyroid tissue?

It is commonly found in the tongue (**lingual thyroid**). If ectopic foci of thyroid tissue will be surgically removed, it must first be confirmed that the ectopic tissue is not the only thyroid tissue the patient has, as thyroid hormone is necessary for survival.

What is the name of the surgical procedure to treat this condition?

Sistrunk procedure. It involves dissection of the cyst and its tract, with removal of the body of the hyoid bone. Incomplete resection, specifically of the hyoid bone, can lead to high rates of recurrence.

CASE 16

As part of Federal Aviation Administration requirements, a 55-year-old pilot presents for a complete checkup. Upon examination of the patient's neck, the physician notes a firm nodule in the right upper lobe of the thyroid that remains fixed with swallowing. Ultrasound-guided fine-needle aspiration (FNA) reveals ground-glass cytoplasm, inclusion bodies, and calcifications.

What is the most likely diagnosis?

Papillary thyroid cancer.

What is the prevalence of this condition?

Thyroid cancer represents approximately 1% of all human cancers. **Papillary** thyroid cancer is the most common type (~85%). Other types include **follicular** (~10%), **medullary** (5%), and **anaplastic** (1%). Papillary and follicular types make up the well-differentiated thyroid cancers, whereas the medullary and anaplastic types are considered poorly differentiated.

How is this condition diagnosed?

Careful physical examination, serum thyroid function tests, ultrasound, and FNA of the thyroid.

The first diagnostic step is measuring thyroid-stimulating hormone (TSH) levels. The next step is imaging of the mass with ultrasound and/or radioactive iodine scans. In a patient with a functional nodule that produces thyroid hormone, TSH levels are expected to be suppressed. These functional or "hot" nodules (called "hot" because of their appearance on radioactive iodine scanning) are rarely malignant and thus do not necessitate biopsy. By contrast, a patient with a nonfunctional thyroid mass (called a "cold" nodule) requires biopsy to evaluate for malignancy.

What characteristic features of this condition are likely to be seen on excisional biopsy?

There is no single pathognomonic feature of papillary thyroid cancer. However, the combination of "**ground-glass**" cytoplasm, "**Orphan Annie**" inclusion bodies, prominent nuclei with clefts and grooves, and calcified **psammoma bodies** (see Figure 7-14) point to the diagnosis.

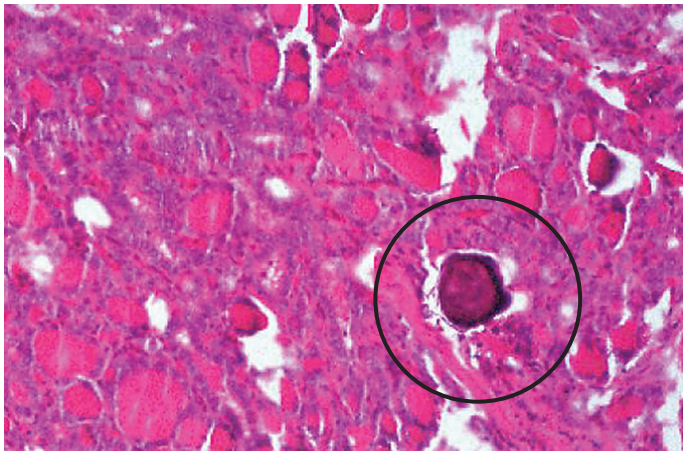

FIGURE 7-14. Psammoma body in papillary thyroid cancer. (Reproduced with permission from USMLE-Rx.com.)

What are the risk factors for this condition?

- Male gender (although women are more likely to have thyroid nodules, a thyroid nodule in a man is more likely to be cancerous)
- Age younger than 20 years or older than 60 years
- Prior **radiation exposure** (eg, acne treatment as a child, victims of Hiroshima, and frequent flyers)
- Medical or family history of thyroid cancer (especially medullary thyroid cancer)

What is the treatment for this condition?

Total thyroidectomy (with/without lymph node dissection) and postoperative radioactive iodine ablation is indicated. The radioactive iodine is necessary to destroy microsatellites of disease that may have been left behind at surgery. Lumpectomy and lobectomy are no longer recommended in the surgical management of thyroid cancer.

CASE 17

A 77-year-old man is brought to the clinic by a concerned neighbor to evaluate a large neck mass. According to the neighbor, the patient lives alone and keeps to himself. The neighbor has noticed that the neck mass has enlarged over several months. Meanwhile, the patient has lost approximately 5.4 kg (12 lb) and has developed a noticeable tremor when he reaches for his morning paper or walks his dog. Vital signs reveal a resting heart rate of 134 beats/min that is irregularly irregular and a blood pressure of 145/100 mm Hg. On physical examination, the man is thin with a large goiter containing many palpable nodules. Exophthalmos and pretibial myxedema are absent. Thyroid function tests reveal elevated free thyroxine (T_4) and barely detectable thyroid-stimulating hormone levels.

What is the most likely diagnosis?

Plummer disease (also known as toxic multinodular goiter) (see Figure 7-15) is the second most common cause of hyperthyroidism in the Western world after Graves disease and the number one cause among the elderly and in endemic areas of iodine deficiency. This is not to be confused with the uncommon **Plummer-Vinson syndrome** (esophageal web plus iron deficiency anemia).

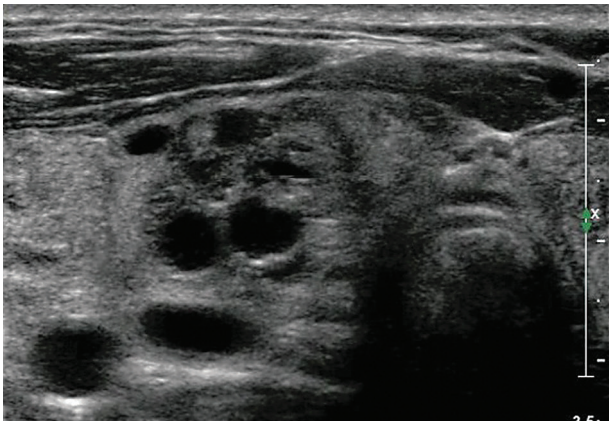

FIGURE 7-15. Multinodular goiter. Transverse ultrasound showing enlarged thyroid gland, which is almost entirely replaced by multiple hyperechoic and hypoechoic nodules. (Reproduced with permission from USMLE-Rx.com.)

How does the physical examination help establish a differential diagnosis?

Patients with Graves disease typically have a diffusely enlarged painless goiter rather than a multinodular goiter. Exophthalmos, pretibial myxedema, and acropachy (thickening of peripheral tissues), characteristic of Graves disease, are absent in Plummer disease. Subacute thyroiditis (also known as de Quervain thyroiditis) presents with an enlarged **painful** goiter, neck pain, and fever, frequently after a viral illness such as mumps or coxsackievirus. The erythrocyte sedimentation rate is typically elevated, and the condition resolves with time and use of nonsteroidal anti-inflammatory drugs.

What are the signs and symptoms of local compression by a neck mass?

- **Symptoms**: Dysphagia (difficulty swallowing), dysphonia (hoarseness), and dyspnea (difficulty breathing).
- **Signs**: Stridor (typically biphasic), tracheal deviation, superior vena cava syndrome. (Pemberton sign is engorgement of the facial and neck veins upon simultaneous raising of the arms overhead, secondary to superior vena cava compression at the thoracic inlet.)

What will a radioactive iodine scan likely show?

A thyroid scan with radioactive iodine or Tc ^{99m} will likely show **patchy uptake**, with multiple "**hot**" **nodules** interspersed among areas with decreased uptake. A "hot" nodule means that the activity of the thyroid tissue in that area is elevated. Patients with Graves disease have homogenously high uptake on thyroid scan, whereas patients with thyroiditis (de Quervain or silent lymphocytic thyroiditis) have low uptake on thyroid scan. In general, nodules containing thyroid cancer tend to be "cold" nodules and should be biopsied via fine-needle aspiration.

What is the treatment for this condition?

Given the size of his goiter, signs of local compression, and symptoms of hyperthyroidism, total **thyroidectomy** should be performed. This will alleviate the symptoms of hyperthyroidism in approximately 90% of cases and will rapidly relieve the compression. Preoperatively, the patient should be treated with **antithyroid medication** (such as methimazole) and **β-blockers** to render him euthyroid and to alleviate the atrial fibrillation. β-blockers will also decrease the peripheral conversion of T_4 to T_3.

CASE 18

A mother brings her 7-year-old son in to see the pediatrician. She says the boy has been less active, stating that he frequently must take naps and that he has also begun wetting his bed again, something he had stopped doing 2 years ago. Chart review reveals that within the past year the child's weight dropped from the 75th percentile to the 50th percentile even though he has been eating and drinking more than usual, the mother reports. Relevant laboratory findings include the following:

WBC count: 11,400/mm^3
Chloride: 100 mEq/L
Blood urea nitrogen: 14 mg/dL
Sodium: 132 mEq/L
Creatinine: 1.2 mg/dL
Potassium: 5.0 mEq/L
Glucose: 350 mg/dL

What is the most likely diagnosis?

Autoimmune destruction of pancreatic β-islet cells resulting in insulin deficiency, leading to type 1 diabetes mellitus (DM). Antibodies such as anti-GAD (glutamic acid decarboxylase) and anti-islet cell can help confirm the diagnosis. Common presenting symptoms include polydipsia, polyphagia, weight loss, and polyuria (osmotic diuresis secondary to glycosuria).

What are the two types of this condition?

Type 1 DM is characterized by absolute insulin deficiency; **type 2 DM** is characterized by insulin resistance and increased insulin levels. Type 1 DM typically presents in thin individuals younger than 30 years of age. Type 2 DM typically affects obese individuals older than 40 years of age (although it is increasingly seen among younger obese individuals). Both types of diabetes can result in retinopathy, nephropathy, and neuropathy. There is a relative weak genetic predisposition seen in type 1 DM (50%), whereas type 2 DM has a strong genetic predisposition (90% among identical twins). Type 1 DM is associated with the HLA genotypes DR3 and DR4 (HLA class II – MHC), and type 2 diabetes has no association with the HLA genotypes (see Table 7-5).

TABLE 7-5. MHC II Loci and Diseases Associated With Each

Disease	Classic DR association
Myasthenia gravis	DR 2
Celiac disease	DR 3
Rheumatoid arthritis	DR 4
Type I diabetes	DR 4

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What is diabetic ketoacidosis (DKA)?

DKA is a life-threatening complication of uncontrolled type 1 DM. In the absence of insulin, increased levels of fatty acids are delivered to the liver, where ketogenesis occurs (see Figure 7-16). Ketogenesis results in increased circulating blood levels of ketone bodies (β-hydroxybutyrate > acetoacetate), thus lowers the pH of the blood. Presenting symptoms include Kussmaul respirations, abdominal pain, dehydration, and nausea/vomiting. Patients may have a sweet/fruity/alcoholic odor to their breath (due to exhaled acetones).

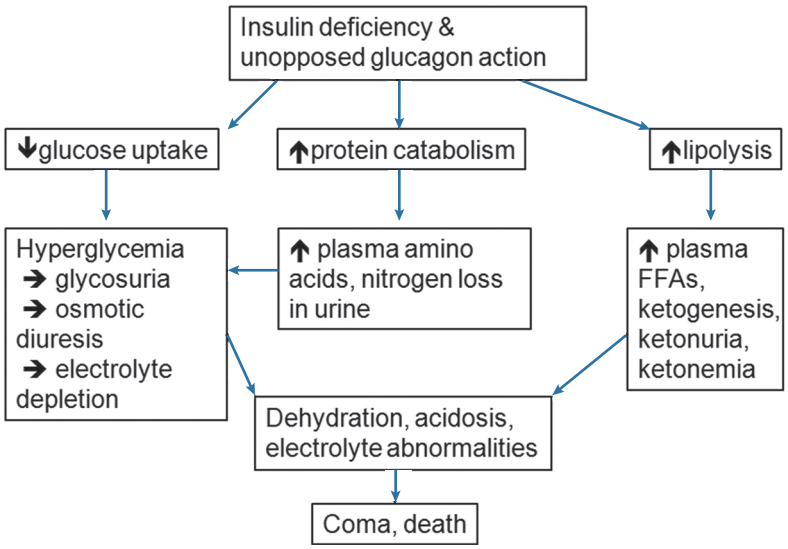

FIGURE 7-16. Insulin deficiency flow chart. (Modified with permission from USMLE-Rx.com.)

What is the treatment for DKA?

Acute DKA requires rapid fluid resuscitation with normal saline, followed by the administration of intravenous insulin and repletion of depleted electrolytes, especially potassium. Administration of bicarbonate to correct the acidic blood pH is usually not recommended unless the acidosis is severe (typically < 6.9). Once patients reach a glucose level of 250 mg/dL, glucose is added to the treatment, such that hypoglycemia does not occur. Following an episode of DKA, lifelong insulin replacement is required for patients diagnosed with type 1 DM. Oral hypoglycemic agents are effective in type 2 DM but not in type 1.

What electrolyte abnormalities are frequently associated with DKA?

DKA is associated with depletion of total body potassium stores through osmotic diuresis. Serum potassium levels may appear normal or elevated even though total body potassium stores are low; this is because intracellular potassium is shifted into the extracellular space in exchange for hydrogen ions to buffer the effects of metabolic acidosis. Treatment of DKA with insulin drives potassium back into cells, and patients undergoing treatment for DKA can thus become profoundly hypokalemic. Patients may also have their Mg and PO^4 stores depleted in addition to the hypokalemia.

CASE 19

A 30-year-old African-American woman with a history of hypertension presents to her new primary care physician for a physical examination. She claims to be in good health but has noticed she is urinating more frequently and has had several urinary tract infections in the past year. Her family history is significant for coronary artery disease, cerebrovascular accidents, and diabetes in multiple first-degree relatives. Her heart rate is 70/min and her blood pressure is 140/90 mm Hg. Physical examination is notable for morbid obesity (body mass index: 48 kg/m^2), and a urine dipstick reveals 2+ glycosuria.

What is the most likely diagnosis?

Non-insulin-dependent (type 2) diabetes mellitus (NIDDM).

What are the diagnostic criteria for this condition?

- Random plasma glucose > 200 mg/dL with symptoms or
- Fasting plasma glucose > 126 mg/dL on two separate occasions or
- Plasma glucose > 200 mg/dL 2 hours after a glucose tolerance test (75 g load) or
- HbA_{1C} > 6.5% (may necessitate repeat testing to confirm unless unequivocal hyperglycemia is also present)

What is the production and structure of insulin?

Insulin is originally produced as pre-proinsulin in the pancreas. During posttranslational processing, a signal peptide is removed, producing proinsulin. Proinsulin contains two polypeptide chains connected by two sulfhydryl bonds (cysteine to cysteine) and a **C-peptide**. In the conversion from proinsulin (the zymogen) to active insulin, the C-peptide is cleaved off (see Figure 7-17). Synthetic insulin lacks the C-peptide. Therefore, measuring C-peptide is useful in patients in whom surreptitious insulin injection is suspected (factitious hypoglycemia).

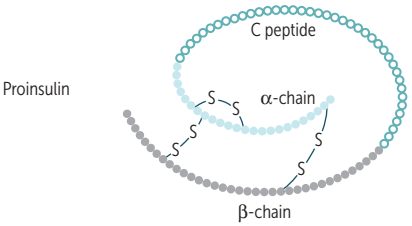

FIGURE 7-17. Structure of human insulin. (Reproduced with permission from Le T, et al. *First Aid for the USMLE Step 1: 2019*. New York: McGraw-Hill, 2019.)

How does insulin exert its effects on organs?

The insulin receptor is a heterodimer of α and β subunits. The β subunit is a **tyrosine kinase**. When insulin binds, this subunit autophosphorylates itself, leading to activation of downstream signaling cascades. Insulin stimulates glucose storage as glycogen in the liver, triglyceride storage in adipose tissue, and amino acid storage as protein in muscle. It also promotes upregulation of the GLUT4 receptor, thus leading to increased utilization of glucose in muscles for energy (see Figure 7-18).

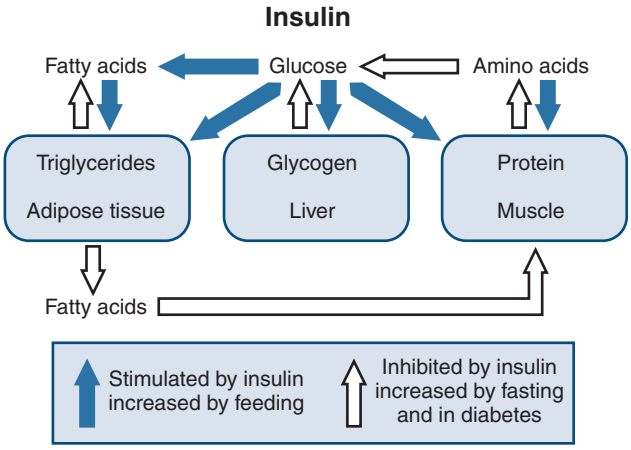

FIGURE 7-18. Actions of insulin on human tissues. (Modified with permission from Brunton LL, et al. *Goodman & Gilman's The Pharmacological Basis of Therapeutics,* 11th ed. New York: McGraw-Hill, 2006: 1621.)

What is the treatment for this condition?

Nonpharmacologic treatments such as diet, weight reduction, and exercise must be employed, as increased adipose tissue is strongly associated with the development of insulin resistance. However, these have limited long-term success. Pharmacologic treatment for type 2 DM includes **oral hypoglycemic agents**. Only in refractory cases is insulin added to the regimen (Table 7-6 lists common drugs for both type 1 and type 2 DM). Tight glucose control markedly reduces microvascular (retinopathy and nephropathy) and neurologic complications of DM. The goal is a hemoglobin A_{1c} level of $< 7\%$.

Table 7-6. Common Pharmacologic Agents for the Treatment of Type 1 and 2 Diabetes Mellitus

Drug Classes	Action	Clinical Use	Toxicities
Insulin: Lispro (rapid-acting) Aspart (rapid-acting) Regular (rapid-acting) NPH (intermediate) Glargine (long-acting) Determir (long-acting) Degludec (ultra long-acting)	Bind insulin receptor (tyrosine kinase activity). Liver: ↑ glucose stored as glycogen. Muscle: ↑ glycogen and protein synthesis, K^+ uptake. Fat: aids TG storage.	Type 1 DM, type 2 DM, gestational diabetes, life-threatening kyperkalemia, and stress-induced hyperglycemia.	Hypoglycemia, hypersensitivity reaction (very rare), lipodystrophy.
Biguanides: Metformin	Inhibit hepatic gluconeogenesis and the action of glucagon, by inhibiting mGPD. ↑ glycolysis, peripheral glucose uptake (↑ insulin sensitivity).	Oral. Can be used in patients without islet function. May promote weight loss.	Most grave adverse effect is lactic acidosis (contraindicated in renal failure), GI upset, B_{12} deficiency.
Sulfonylureas: First generation: Tolbutamide Chlorpropamide Second generation: Glyburide Glimepiride Glipizide	Close K^+ channel in β-cell membrane, so cell depolarizes → triggering of insulin release via ↑ Ca^{2+} influx.	Stimulate release of endogenous insulin in type 2 DM. Require some islet function, so useless in type 1 DM.	Weight gain, 1st generation: disulfiram-like effects, 2nd generation: hypoglycemia.
GLP-1 analogs: Exenatide, liraglutide	↑ insulin, ↓ glucagon release.	Type 2 DM, may aid in weight loss.	Nausea, vomiting, pancreatitis.
DPP-4 inhibitors: Linagliptin, saxagliptin, sitagliptin	Inhibit DPP-4 enzyme that deactivates GLP-1. ↓ glucagon release, gastric emptying. ↑ glucose-dependent insulin release, satiety.	Type 2 DM, usually used after patients have failed metformin or sulfonylureas.	Mild urinary or respiratory infections, weight neutral.
Meglitinides: Nateglinide Repaglinide	Close K^+ channel in pancreatic β cell membrane → cell depolarizes → insulin release via ↑ Ca^{2+} influx (different binding site than sulfonylureas).	Type 2 DM, may be used as monotherapy or with other medications.	Hypoglycemia (↑ risk with renal failure), weight gain.
Amylin analogs: Pramlintide	↓ glucagon release, ↓ gastric emptying, ↑ satiety.	Type 1 DM and type 2 DM, may promote weight loss, typically used in conjunction with other medications.	Hypoglycemia (in setting of mistimed prandial insulin), nausea.
Glitazones/ thiazolidinediones: Pioglitazone Rosiglitazone	↑ insulin sensitivity in peripheral tissue. Binds to PPAR-γ nuclear transcription regulator.	Used as monotherapy in type 2 DM or combined with other agents.	Weight gain, edema, hepatotoxicity, CV toxicity Delayed onset of actions (weeks).
α-glucosidase inhibitors: Acarbose Miglitol	Inhibit intestinal brush-border α-glucosidases. Delayed sugar hydrolysis and glucose absorption lead to ↓ postprandial hyperglycemia.	Used as monotherapy in type 2 DM or in combination with above agents.	GI disturbances. Avoid in significant renal impairment.
SGLT2 inhibitors: Dapagliflozin, canagliflozin, empagliflozin	Block reabsorption of glucose in PCT.	Type 2 DM, may aid in weight loss.	Glycosuria, UTIs, vulvuvaginal candidiasis, hypotension.

(Modified with permission from Le T, et al. *First Aid for the USMLE Step 1: 2019.* New York: McGraw-Hill, 2019.)

CASE 20

A 55-year-old woman with a history of external neck radiation therapy as a child presents to her physician for her yearly checkup. Physical examination reveals a firm nodule in the neck. Ultrasound confirms several bilateral thyroid nodules; the largest nodule measures 1.5 cm in the left lobe. Biopsy of the nodule confirms the presence of papillary carcinoma. Two weeks later, the patient undergoes total thyroidectomy.

Care must be taken during thyroidectomy not to remove all functioning parathyroid gland tissue. How many parathyroid glands are there?

Most people (85%) have four parathyroid glands. However, 13%–15% of people have more than four glands, and less than 2% of people have fewer than four glands. After undergoing a total thyroidectomy, patients require lifelong thyroid hormone replacement.

What is the embryologic origin of the parathyroid glands?

The superior parathyroid glands are derived from the fourth pharyngeal pouch. The inferior parathyroids are derived from the third pharyngeal pouch. Most ectopic sites are derived along the embryologic descent path (eg, carotid sheath and mediastinum), with the inferior parathyroids having a more variable presentation of location.

What layers of muscle are encountered during a thyroidectomy?

- Platysma (facial nerve innervation)
- Cervical fascia
- Sternohyoid (a flat, "strap" muscle)
- Sternothyroid (a flat, strap muscle)
- The other two strap muscles (thyrohyoid and omohyoid) are not commonly encountered during routine thyroidectomy.

What nerves in this region are particularly at risk during thyroidectomy?

Damage to the **recurrent laryngeal nerve**, which innervates all intrinsic laryngeal musculature except for the cricothyroid in the tracheoesophageal groove results in a hoarse voice. The external laryngeal branch of the superior laryngeal nerve accompanies the superior thyroid artery, and therefore, care must be taken while ligating this artery during surgery (see Figure 7-19). It is spared by ligating the artery close to the gland. Damage results in changes in pitch (primarily resulting in a lower-pitched voice) as this nerve innervates the cricothyroid muscle, a muscle responsible for the tensing of the vocal folds.

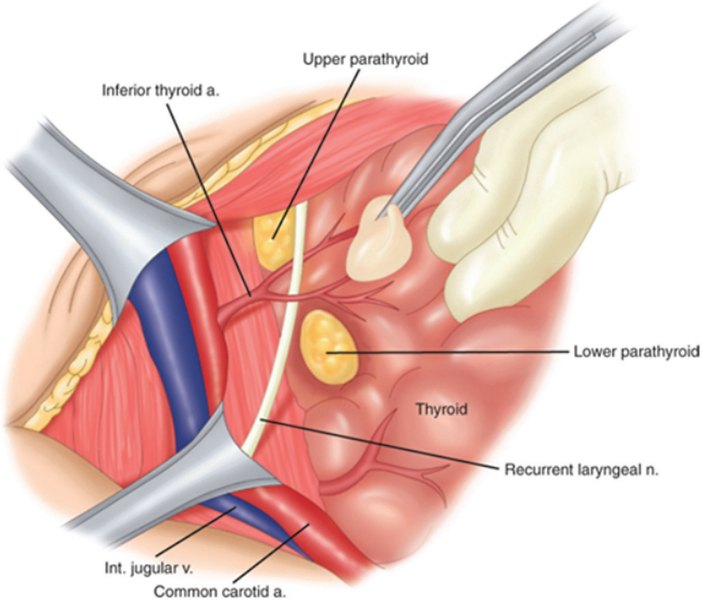

FIGURE 7-19. Pathway of left recurrent laryngeal nerve. a, artery; v, vein; n, nerve. (Reproduced with permission from Brunicardi F, et al. eds. *Schwartz's Principles of Surgery*, 10th ed. New York: McGraw-Hill, 2015.)

What are some other causes of hypothyroidism?

- Autoimmune (Hashimoto thyroiditis)
- Alcohol
- Drugs (amiodarone and lithium)
- Infection (de Quervain thyroiditis)

8
Gastrointestinal

CASE 1

A 45-year-old man presents to his doctor's outpatient office complaining of difficulty swallowing for the past several months. Solid foods have been most difficult for him to swallow for the past 4 months, but recently liquids have also become problematic. He often has chest discomfort after eating and occasionally regurgitates bits of undigested food. Patient denies any recent weight loss, fever, or night sweats. His physical examination, including an abdominal and cervical lymph node exam, are unremarkable.

What is the most likely diagnosis?

Achalasia, which is a motility disorder caused by destruction of the neurons within the myenteric (Auerbach) plexus. The myenteric plexus can be found between the circular and longitudinal layers of the muscularis externa (note the submucosal plexus is located within the submucosa). The ineffective myenteric plexus results in impaired relaxation of the lower esophageal sphincter (LES) and loss of smooth muscle peristalsis in the lower two-thirds of the esophagus. It is thought that nitric oxide oxide–producing inhibitory neurons are lost in the myenteric plexus.

What condition should be considered in an immigrant patient with this presentation?

Chronic **Chagas** disease, caused by the parasite *Trypanosoma cruzi* (transmitted by the reduviid bug), is indistinguishable from idiopathic forms of achalasia and should be considered in patients from endemic areas (eg, Central and South America). In chronic Chagas disease, patients can develop megaesophagus (this term describes the increased intraluminal diameter of the esophagus). These patients can also suffer from dilated cardiomyopathy.

What other conditions can present with dysphagia?

It is important to differentiate odynophagia from dysphagia in a patient presenting with complaints related to swallowing. Dysphagia describes difficulty swallowing, while odynophagia describes pain with swallowing. Globus refers to the sensation of a lump in the throat. Diagnoses to consider with a patient who complains of dysphagia (difficulty swallowing) include esophageal diverticula, rings, webs, diffuse esophageal spasm (DES), and cancer. Patients with DES present with dysphagia (solids and liquids) and substernal chest pain. Regurgitation will not be present. DES involves changes in the myometrium and not the LES.

The esophagus has four layers: mucosa, submucosa, muscularis, and serosa. Increases in intraluminal pressure within the esophagus can create pulsion diverticula. These are false diverticula whose walls consist only of mucosa and submucosa, which herniate through the muscular layer. Zenker diverticulum is the most common type and occurs with a posterior outpouching of the mucosa and submucosa through the cricopharyngeal muscle in the upper portion of the esophagus. Patients present with dysphagia and regurgitation of food, halitosis (bad breath), and aspiration. Epiphrenic diverticula are thought to form in a similar way but at the distal esophagus. Traction from mediastinal inflammation or motility disorders can create true diverticula whose walls also include a muscular layer. These mainly occur in the mid-esophagus.

Esophageal rings and webs are structures that can partially occlude the esophageal lumen and cause dysphagia. Schatzki rings are the most common type of esophageal ring. They are mucosal structures that occur at the squamocolumnar junction.

Esophagitis describes an inflammation of the esophagus that can cause both dysphagia and odynophagia but predominately causes odynophagia. It commonly occurs in patients who are immunosuppressed. The causal agents are usually viral (such as herpes simplex virus , cytomegalovirus) and fungal (such as Candida). Medication-induced esophagitis is another common etiology of the disorder.

What imaging or testing can help confirm this diagnosis?

A barium swallow is often the initial diagnostic approach to dysphagia. In a barium swallow, the patient swallows contrast medium while being video imaged radiographically. A barium swallow demonstrates a "bird's beak" appearance of the esophagus that can be diagnostic for achalasia (a partially occluding tumor can also create similar radiographic findings) (see Figure 8-1). Esophageal manometry reveals complete absence of peristalsis and failure of the LES to relax after swallowing, confirming the diagnosis.

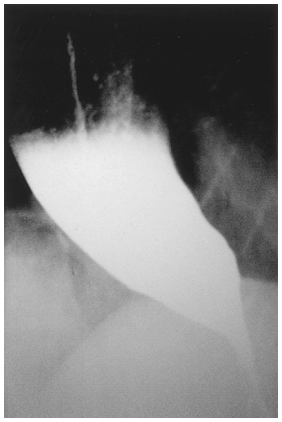

FIGURE 8-1. "Bird's beak" appearance of the esophagus in achalasia. (Reproduced with permission from Lalwani AK. *Current Diagnosis & Treatment in Otolaryngology—Head & Neck Surgery,* 2nd ed. New York: McGraw-Hill, 2008: 489.)

What is the treatment for this condition?

Trials of calcium channel blockers and nitrates are initially used to increase relaxation of the affected area. However, if trials fail, other treatment options are available. Pneumatic dilation of the LES provides effective but temporary relief in most patients and may need to be repeated. Surgical myotomy is also effective. In nonsurgical candidates, injections of botulinum toxin in the LES are also used.

CASE 2

A 40-year-old woman with a history of hyperlipidemia presents to her primary care physician with an hour history of severe epigastric pain that radiates to the back. The patient also complains of decreased appetite, nausea, and vomiting small amounts of yellow-sour fluid. On physical exam, patient is jaundiced and tender to palpation in the epigastric region. Laboratory results are as follows: Serum amylase: 521 U/L. Serum lipase: 643 U/L (normal < 160 U/L). CT of abdomen is shown in Figure 8-2.

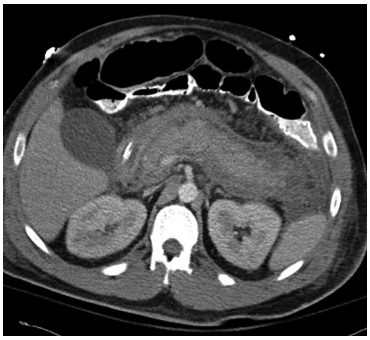

FIGURE 8-2. (Reproduced with permission from USMLE-Rx.com.)

What is the most likely diagnosis?

Acute pancreatitis.

What are the potential causes of this condition?

Acute pancreatitis occurs when pancreatic enzymes (trypsinogen, chymotrypsinogen, and phospholipase A) are activated in pancreatic tissue rather than in the lumen of the intestine, resulting in the autodigestion of pancreatic parenchyma. The most common causes are **G**allstones (the most common etiology) and **E**tOH. Other causes include **I**diopathic, **T**rauma, **S**teroids, **M**umps, **A**utoimmune diseases, **S**corpion stings, **H**ypercalcemia/**H**ypertriglyceridemia, **E**RCP, and certain **D**rugs (sulfa drugs; nucleoside reverse transcriptase inhibitors , including didanosine and possibly stavudine) (mnemonic: **I GET SMASHED**).

How is this condition diagnosed?

In this patient, the significantly elevated amylase and lipase levels are sensitive and specific for acute pancreatitis. Diagnosis of pancreatitis requires at least two of the following:

1. Elevated lipase (more specific) or amylase three times the upper limit.
2. Characteristic findings of acute pancreatitis on CT, such as the edema seen around the pancreas in Figure 8-2.
3. Acute onset of severe epigastric pain that radiates to the back.

What are the possible complications of this condition?

Complications that can occur are sepsis, acute peripancreatic fluid collection, pancreatic pseudocyst formation, and acute necrotic collection. Necrotic collection can be infected or sterile. Other complications include diffuse intravascular coagulopathy, diffuse fat necrosis, adult respiratory distress syndrome, and hypocalcemia.

What is the differential diagnosis? (Think other causes of epigastric pain.)

Cholelithiasis refers to the presence of gallstones in the gallbladder. Choledocholithiasis refers to the presence of stones within the biliary ducts themselves. Stones in either location can become impacted more distally in the biliary tree causing obstruction and stasis of bile flow. Local inflammation and infection naturally follow stasis, resulting in either cholecystitis (stone impacting cystic duct), cholangitis (stone impacting common bile duct), or gallstone pancreatitis (stone impacting distal bile duct beyond its junction with the pancreatic duct). Significant elevations in lipase and amylase distinguish gallstone pancreatitis from these other biliary pathologies.

Peptic ulcer disease (PUD) can present similarly with epigastric patient, but the pain is intermittent and recurrent in patients with typical history (such as proton pump inhibitor use, NSAIDS, *Helicobacter pylori* infection, etc.)

A perforated viscus can also present with epigastric pain. In this situation, a luminal structure (eg, small bowel) within the GI tract perforates, allowing air (and other contents depending on area of perforation) into the peritoneal cavity. Inflammation and infection of the peritoneal cavity follows. Pancreatitis can be differentiated by a lack of peritoneal signs (guarding, rebound, etc.) and a significantly elevated amylase and lipase.

Acute coronary syndrome should be considered in patients 50 years of age or older with upper abdominal pain and associated risk factors.

What is the treatment for this condition?

Most cases (85%–90%) are self-limited and resolve within 4–7 days of the start of treatment. Typical treatment for acute pancreatitis includes aggressive intravenous fluid resuscitation, bowel rest and nutritional support, and pain management. Antibiotics may be used in complicated cases with infected necrotic tissue or extrapancreatic infections. Patients who developed complications may require other complication-specific treatments.

CASE 3

A 42-year-old man presents to his doctor for a checkup. He has not seen a physician in several years. He has a history of alcohol abuse and 40 pack-year history of smoking. On review of systems, the patient reports petechiae and increased bruising for the past 6 months. He has also had a loss of appetite and 20 lbs weight loss during this time. Physical examination reveals a malnourished white male who appears older than his stated age. He is jaundiced with temporal wasting, mild gynecomastia, palmar erythema, spider angiomas, and edema of the lower extremities. The abdomen distended with shifting dullness. Laboratory findings are as follows:

WBC count: 3200/mm^3
Hemoglobin: 9.8 g/dL
Platelets: 90,000/mm^3
Blood urea nitrogen (BUN): 36 mg/dL
Creatinine (Cr): 1.5 mg/dL
Albumin: 2.5 g/dL
Partial thromboplastin time (PTT): 40 seconds
Prothrombin time (PT): 20 seconds
Alanine aminotransferase (ALT): 50 U/L
Aspartate aminotransferase (AST): 120 U/L

What is the most likely diagnosis?

Alcoholic cirrhosis of the liver. Findings include ascites, palmar erythema, lower extremity edema, and gynecomastia, and can suggest a diagnosis of liver failure. The moderately elevated transaminase levels suggest a chronic process (loss of large numbers of hepatocytes limit dramatic elevations seen in an acute hepatic pathologies). Further indicators of chronicity include decreased albumin, elevated PT and PTT, thrombocytopenia, and decreased hematocrit. PT may be better at evaluating cirrhosis than PTT because it assesses the activity of factor VII. This factor has a shorter half-life than clotting factors involved in the internal (PTT) pathway; therefore, PT will better reflect recent changes in clotting factor synthesis. Most etiologies of liver damage create more significant increases in ALT than AST. Nevertheless, in alcohol-induced hepatic injury, AST levels often exceed ALT levels in ratios of 2 to 1 (mnemonic: **Shots for AST**).

What are the causes of this patient's gynecomastia, petechia, and easy bruising?

The liver normally degrades estrogen. In liver failure, circulating serum levels of estrogen are higher, causing gynecomastia and palmer erythema. Spider angiomas are also caused by elevated estrogen in cirrhotic patients. Thrombocytopenia was classically believed largely to occur secondary to splenic sequestration; however, decreased hepatic synthesis and secretion of thrombopoietin (TPO) does result in decreased thrombopoiesis. This explains the patient's petechia.

How does ascites form?

Ascites refers to a pathological buildup of fluid in the peritoneal cavity. The most common cause is cirrhosis. Portal hypertension is prerequisite for ascites formation; however, many other factors contribute. In particular, systemic vasodilation and reduction in systemic vascular resistance (SVR) contribute to activation of endogenous vasoconstrictors, including the renin-angiotensin-aldosterone system (RAAS). This allows for sodium and water retention.

The pathophysiology underlying systemic vasodilation in cirrhosis is controversial; however, it is thought to involve increased levels of circulating vasodilators, including nitric oxide, either due to increased synthesis or decreased clearance. Regardless, this has vast potential implications. Vasodilation within the pulmonary microvasculature, for example, is thought to be the underlying mechanism of hepatopulmonary syndrome, in which patients with chronic liver disease present with dyspnea and hypoxemia.

Synthetic deficiencies also contribute to ascites formation by resulting in decreased circulating proteins including albumin. This causes a shift in the Starling equation as plasma oncotic pressure decreases, allowing H2O to extravasate out of the intravascular space. Physical signs of ascites on abdominal exam can include shifting dullness, bulging flanks, and a fluid wave.

What do the laboratory findings reveal about renal function?

Elevated BUN and Cr levels (BUN:Cr ratio $>$ 20) suggest prerenal acute kidney injury (AKI). In cirrhosis, portal hypertension elicits splanchnic vasodilation and results in hypoperfusion of the kidneys. This can create a "prerenal picture" with compensatory activation of endogenous vasoconstrictors, including the renin-angiotensin-aldosterone system. In the setting of end-stage liver disease, prolonged hypoperfusion to the kidneys can cause intense renal vasoconstriction and renal failure unresponsive to volume loading. This is known as hepatorenal syndrome.

CASE 4

A 25-year-old woman presents to her physician with an 8-hour history of abdominal pain. It began as dull periumbilical pain but is now sharp and located in the right lower quadrant (RLQ). She also reports nausea, loss of appetite, and subjective fever. She denies changes in urination or bowel habits, dysuria, or recent sick contacts. Her last menstrual period was 3 weeks ago. Vital signs are as follows: heart rate of 122/min, respiratory rate of 16/min, temperature of 38.8°C (102°F), SpO_2 of 96%. On exam, the abdomen is exquisitely tender throughout with positive Rovsing and rebound tenderness. Psoas and obturator signs are present. Relevant laboratory findings are as follows:

WBC count: 18,000/mm^3
β-Human chorionic gonadotropin (β-hCG): Negative
Urinalysis: Negative for blood, WBCs, leukocyte esterase, and protein

What is the most likely diagnosis?

Appendicitis. It is important to note that appendicitis presenting with classic signs and symptoms can be diagnosed clinically. Delayed appendectomy increases the likelihood of perforation. Contrast-enhanced abdominal CT has good sensitivity and specificity and can be a good tool for diagnosis. Figure 8-3 presents an abdominal CT with contrast showing appendicitis. The arrow indicates the location of the inflamed appendix.

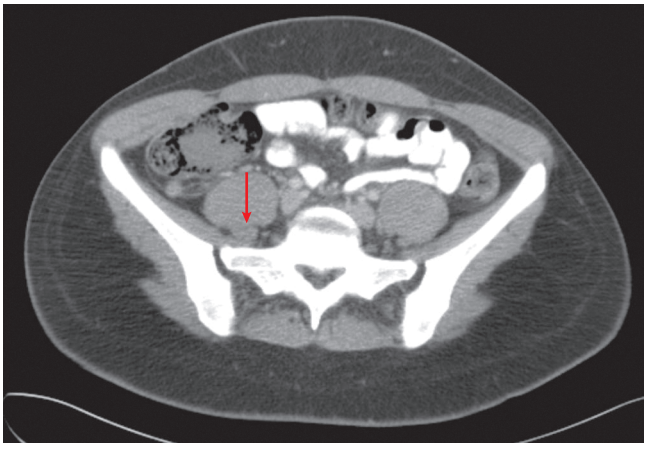

FIGURE 8-3. CT of abdomen in appendicitis. (Reproduced with permission from USMLE-Rx.com.)

What is the differential diagnosis for this patient?

- **Female reproductive**: ectopic pregnancy (very unlikely with negative β-hCG), pelvic inflammatory disease (PID), and ovarian torsion, ruptured Graafian follicle
- **Gastrointestinal**: Crohn disease (can initially present without changes in bowel habits), peptic ulcer disease, Yersinia enterocolitica infection
- **Urinary and renal**: Urinary tract infections (UTIs) usually present with frequency, urgency, and dysuria, accompanied by abnormal urinalysis. Cystitis presents similarly with the potential addition of suprapubic tenderness. Pyelonephritis presents with urinary symptoms and flank pain.

What is the pathophysiology of this condition?

Appendicitis is thought to originate from **obstruction** of the appendix. This may occur through lymphoid hyperplasia (younger patients) or an impacting fecalith (older patients). Other causes of obstruction can include infectious processes, tumors, foreign bodies, etc. Obstruction results in distension, increasing intramural pressure and compromising vascular and lymphatic flow. Ischemia and necrosis follow. This process allows for bacterial proliferation as the appendix becomes necrotic. Increasing intraluminal pressures and compromise of the appendix wall's structural integrity (due to ischemia and necrosis) can lead to perforation and subsequent peritonitis.

What is the McBurney point?

The **McBurney point** is one-third the distance from the right anterior superior iliac spine to the umbilicus; it is where the pain from acute appendicitis classically localizes once there is peritoneal irritation. During an abdominal exam, palpating this area will cause an increase in pain.

What other physical exam findings can be seen in this condition?

Rovsing sign describes pain being localized to the RLQ when the left lower quadrant (LLQ) is palpated in abdominal examination. Psoas sign refers to RLQ pain elicited by extension of the right lower extremity (RLE) at the hip. It is associated with a retrocecal appendix. Obturator sign describes RLQ pain elicited by flexion of the RLE at the hip and knee followed by internal rotation at the hip. This sign is associated with a pelvic appendix.

Which antibiotics are effective in this condition?

Enteric (gram-negative rods) and anaerobic organisms can commonly cause infection in acute appendicitis. Antibiotic choices are based on coverage of these organisms and the presence or absence of perforation. Ampicillin and sulbactam, piperacillin/tazobactam, second-generation cephalosporins and carbapenems are some of the antibiotics that may be used depending on disease severity and antibiotic resistance of the causative bacteria.

What is the treatment for this condition?

Surgical appendectomy is the treatment for acute appendicitis. Intravenous fluid resuscitation and empiric antibiotics are presurgical interventions. In cases when surgery is not possible, antibiotics can be used to improve survival despite not being curative. Patients with appendiceal abscesses can be treated with antibiotics and image-guided percutaneous drainage.

What are some possible complications with this condition?

The major complication is when the appendix ruptures due to the increased intraluminal pressure causing leakage of intraluminal contents (bacteria) into the peritoneal cavity.

CASE 5

A 42-year-old woman is brought to the ED by her husband due to severe abdominal pain. She has been having abdominal pains after eating for the past 2 days. On further questioning, she has had fever, nausea, and vomiting. Past medical history is pertinent for an unknown hematological disorder that resulted in a splenectomy. Vital signs are notable for a temperature of 38.9°C (102°F), heart rate of 135/min, blood pressure of 102/50 mm Hg, and respiratory rate of 24/min. On physical examination, she is overweight, diaphoretic, jaundiced, and confused. Abdominal examination reveals tenderness and guarding in the right upper quadrant without peritoneal signs.

What is the most likely diagnosis?

Cholangitis is an infection of the bile ducts secondary to ductal obstruction (see Figure 8-4). Most commonly, the common bile duct is obstructed by a gallstone. Other causes include strictures, biliary cancer, and infection (eg, with the Chinese liver fluke, *Clonorchis*).

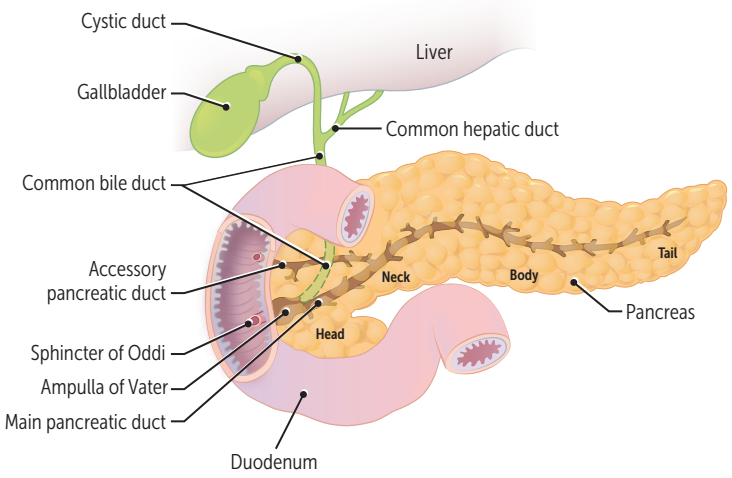

FIGURE 8-4. Anatomy of the biliary tree. (Reproduced, with permission, from Le T, et al. *First Aid for the USMLE Step 1: 2019.* New York: McGraw-Hill, 2019.)

How does the physical examination help confirm the diagnosis?

Charcot triad describes the classic presentation of acute cholangitis with abdominal pain, jaundice, and fever. Patients with severe disease can develop Reynolds pentad, which refers to the findings of altered mental status and hypotension in addition to those of Charcot triad (fever, jaundice, and abdominal pain).

What risk factors in this patient's history predisposed her to this condition?

The patient likely has underlying choledocholithiasis (stones in the biliary tree). The **4 F**'s (**F**at, **F**ertile, **F**orty, and **F**emale) refer to risk factors for the development of cholesterol gallstones. This patient, however, also has hereditary spherocytosis (HS). HS is an autosomal dominant disorder in which RBC membrane proteins which anchor the plasma membrane (including spectrin or ankyrin) to the cells cytoskeleton are altered, compromising membrane stability. Patients with HS are predisposed to developing bilirubinate stones due to chronic hemolysis. These stones are radiopaque. The high iron content from the hemolyzed red blood cells may also help these stones to be visualized on x-ray.

What laboratory findings are expected?

- WBC count will be elevated as a cellular response to infection.
- Conjugated hyperbilirubinemia will be present. Indirect bilirubin is elevated in this case because of red cell lysis in the setting of hereditary spherocytosis. Direct bilirubin is elevated because of inappropriate excretion in the setting of obstruction.
- Alkaline phosphatase, secreted by the mucosal cells of the biliary tree, but not specific to biliary obstruction, will be elevated.
- γ-glutamyl transferase, secreted by the mucosal cells of the biliary tree, will be elevated, but is also nonspecific as a marker of biliary obstruction.
- Positive blood cultures are consistent with the patient's systemic signs of infection.

What is the treatment for this condition?

This patient is displaying severe symptoms, so every effort should be made to relieve the obstruction and decompress the biliary tree. Endoscopic retrograde cholangiopancreatography (ERCP) is the tool of choice, as it is both diagnostic and therapeutic.

CASE 6

A 3-day-old white girl is brought to her pediatrician because she is "yellow, weak, floppy, and sleeps all the time." Physical examination reveals a jaundiced infant with scleral icterus. She is arousable but lethargic with hypotonia. Relevant laboratory findings are as follows:

Total bilirubin: 34 mg/dL
Direct bilirubin: Undetectable
ALT: 12 U/L
AST: 10 U/L
Coombs test: Negative

What is the most likely diagnosis?

Crigler-Najjar (CN) syndrome.

What is the pathophysiology of this condition?

Crigler-Najjar syndrome is a rare, inherited disorder of bilirubin metabolism, resulting from mutations in the uridine diphosphoglucuronic glucuronosyltransferase (*UGT1A1*) gene. *UGT1A1* codes for the UDP-glucuronosyltransferases (UGT) enzyme, which catalyzes the conjugation bilirubin and glucuronic acid. Conjugated (direct) bilirubin is more water-soluble than unconjugated (indirect) bilirubin and is excreted as bile. In Crigler-Najjar syndrome, the activity of UGT is decreased or absent (CN-II and CN-I respectively) (see below). Unconjugated bilirubin results, depositing throughout the body, as evidenced in this patient by jaundice and scleral icterus. In neonates, unconjugated bilirubin can cross the blood-brain barrier (BBB) and cause bilirubin-induced neurological dysfunction (BIND). Untreated BIND can cause chronic, permanent neurological dysfunction known as kernicterus—or even death.

What are the two subtypes of this condition, and how do they differ in severity?

- **Crigler-Najjar type I** (CN-I): Glucuronyl transferase activity is completely absent, which results in severe disease and poor long-term prognosis in absence of liver transplantation.
- **Crigler-Najjar type II** (CN-II): Glucuronyl transferase activity is present but low. Patients with this form of the disease have a much better prognosis than those with type 1. CN-II is also known as **Arias syndrome**.

This patient is at risk for what life-threatening complication?

In this vignette, the baby is described as "floppy," suggesting some level of BIND. **Kernicterus** refers to the permanent neurological disorder that results for BIND. Unconjugated bilirubin crosses the immature neonatal BBB and deposits in the gray area, damaging basal ganglia. Uncontrolled, BIND can cause irreversible damage, resulting in kernicterus. Generally, cognitive function remains relatively spared but movements disorders, hearing loss, and gaze abnormalities are common.

What is the treatment for this condition?

In CN-I, liver transplantation is the only definitive treatment. Phototherapy and plasmapheresis may limit BIND and kernicterus. In CN-II, hyperbilirubinemia often responds to phenobarbital. Clofibrate can be used as an alternative to phenobarbital.

What are other hereditary hyperbilirubinemias?

Gilbert syndrome is a more common and asymptomatic inherited disorder of UGT. In Gilbert syndrome, unconjugated bilirubin results from decreased production of UGT due to mutations in the promotor region of the *UGT1A1* gene. Ineffective hepatic uptake of bilirubin has also been implicated as a potential cause of Gilbert syndrome. Patients are generally asymptomatic in absence of fasting, illness, or other stresses.

Dubin-Johnson syndrome (DJS) is a rare, autosomal recessive defect in the excretion of conjugated bilirubin into the bile canaliculi. A loss of function mutation in the *ABCC2* gene, which normally codes for the multidrug resistance protein 2 (MRP2), results in the inability to transfer conjugated bilirubin across the canalicular membrane. MRP2, also called canalicular multispecific organic anion transporter 1 (*cMOAT*), is an ATP-binding cassette (*ABC*) transporter found in the apical/canalicular membrane of hepatocytes and normally functions to excrete conjugated bilirubin into the bile canaliculi. DJS is benign and results in a grossly **black liver**, possibly due to accumulation of pigments composed of epinephrine metabolites within lysosome. Patients with DJS are usually asymptomatic but can present with icterus or vague abdominal pain.

Rotor syndrome is a rare, autosomal recessive defect caused by mutations in the *SLCO1B1* and *SLCO1B3* genes (solute carrier organic anion transporter). A defect in these genes results in infective reuptake by distal hepatocytes and a decreased excretion of conjugated bilirubin into the bile. Rotor syndrome is clinically similar to DJS but **lacks** the characteristic black liver.

CASE 7

A 64-year-old woman presents to her physician complaining of LLQ abdominal pain for the past 2 days. The pain is described as sharp and constant. The patient also complains of nausea but denies vomiting. She had a similar episode last year that required her to be admitted to the hospital. The patient has a history of chronic constipation, and her last bowel movement was 6 days ago. Her only medication is one baby aspirin per day. On physical examination, she is febrile to 38.6°C (101.5°F), with a blood pressure of 110/70 mm Hg, heart rate of 125/min, and respiratory rate of 18/min. A digital rectal exam does not show hemorrhoids or anal fissures, but guaiac stool test is positive. Relevant laboratory findings are as follows:

WBC count: 14,400/mm^3
Hemoglobin: 12 g/dL
Hematocrit: 37%
Platelets: 250,000/$mm^{3,}$
Sodium: 136 mEq/L
Chloride: 100 mEq/L
Potassium: 4.3 mEq/L
Bicarbonate: 24 mEq/L
Creatinine: 1.1 mg/dL
BUN: 14

What is the most likely diagnosis?

Diverticulitis (inflamed diverticula).

Which of the clinical signs and symptoms help confirm the diagnosis?

Signs and symptoms can vary depending on severity. LLQ abdominal pain and tenderness is common. Nausea/vomiting (N/V), low-grade fever, tachycardia, and an elevated WBC count can also be present.

Diverticulosis is a prerequisite to diverticulitis and refers to a herniation of the colonic mucosa and submucosa through its muscular layer. Since the walls of colonic diverticula lack a muscular layer, they are considered false diverticula. Diverticula become inflamed in diverticulitis and can result in perforations. Diverticulosis is mainly symptomatic but can present with painless bleeding.

What are some diseases that also present with bright red blood per rectum?

Hemorrhoids may present as rectal bleeding. External hemorrhoids are painful while internal hemorrhoids are painless. Anal fissures can also present with bright red blood (BRB). Patients also tend to complain of pain during defecation. Occasionally, massive GI bleed with short transit time can also cause BRB per rectum.

What tests can help confirm the diagnosis?

Radio imaging of the abdomen is needed to rule out perforation, which would be indicated by the presence of free air within the peritoneal cavity (a surgical emergency in which an area of lucency provides evidence of free air). Radiographic findings can include bowel wall thickening, fistulas, and/or abscesses (see Figure 8-5). Colonoscopy and barium enema are contraindicated in acute diverticulitis and may cause perforation.

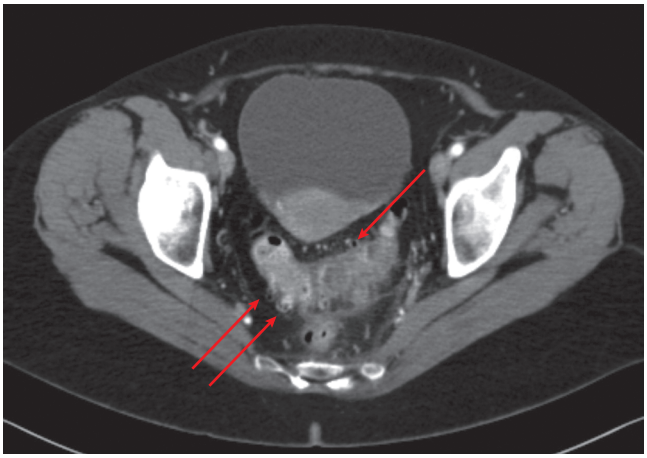

FIGURE 8-5. Diverticulitis. Axial contrast-enhanced CT shows inflammatory stranding in the fat surrounding multiple diverticula in the sigmoid colon. (Reproduced with permission from USMLE-Rx.com.)

What are the risk factors for this condition, and what steps can prevent recurrence?

Advanced age, chronic constipation, previous diverticulosis, and aspirin use all heighten the risk for diverticular disease. A high-fiber diet and adequate hydration reduce the risk of developing diverticula and subsequent diverticulitis.

What is the treatment for this condition?

Uncomplicated diverticulitis can be treated with antibiotics (such as ciprofloxacin and metronidazole) targeting gram-negative rods and anaerobic organisms. Adequate analgesia is used to control abdominal pain during acute diverticulitis. A follow-up colonoscopy should be performed after acute symptoms resolve in order to rule out cancer. Cases of diverticulitis complicated by abscess, fistula formation, perforation, or obstruction may require additional therapy, including surgical intervention.

CASE 8

Four hours after noneventful delivery, a full-term neonate regurgitates breast milk after the mother begins feeding him. The delivery was uncomplicated. The pregnancy was complicated by gestational polyhydramnios. On exam the abdomen is distended. The physician cannot place a nasogastric tube, and an x-ray produces the image shown in Figure 8-6.

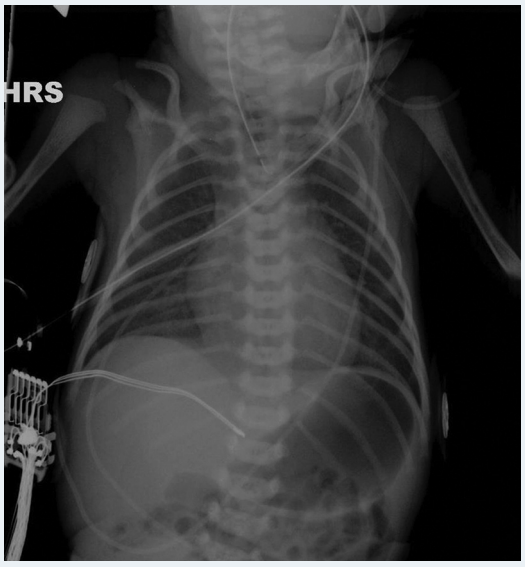

FIGURE 8-6. (Reproduced with permission from USMLE-Rx.com.)

What is the most likely diagnosis?

Esophageal atresia (EA) with tracheoesophageal fistula (TEF). EA with distal TEF variant shown in Figure 8-7 below accounts for 84% of cases.

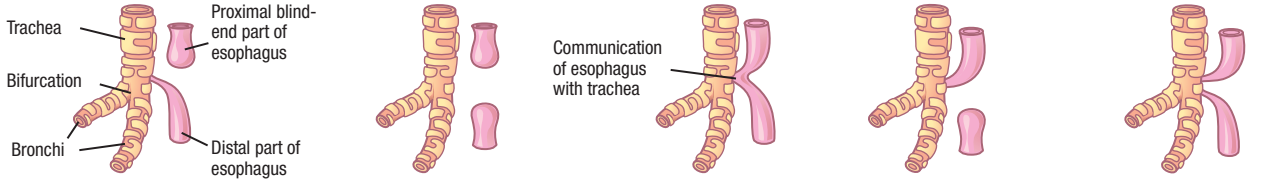

FIGURE 8-7. Five types of tracheoesophageal fistula. (Reproduced with permission of USMLE-Rx.com.)

What is the mechanism of polyhydramnios?

Normally, the fetus swallows amniotic fluid in utero. The fluid is absorbed by the infant's GI tract and contributes to its development. Swallowed amniotic fluid is eliminated through the fetal urinary system. In EA, the fetus is unable to swallow amniotic fluid, resulting in accumulation and polyhydramnios. Polyhydramnios can also result from disorders of the urinary tract, as in neonatal Bartter syndrome.

What is the embryonic origin of this condition?

The **foregut** gives rise to both the trachea and esophagus. In a complex and yet to be fully understood process, the respiratory system emerges from the foregut endoderm and the proximal structures (ie, trachea) separate from those of the GI system (ie, esophagus). Particular mechanisms by which EA and TEF are formed remain controversial. It is likely that various abnormalities along this developmental pathway cause different formations that ultimately create EA and/or TEF.

What congenital condition can be associated with polyhydramnios and bilious vomiting?

Duodenal atresia, which has an increased incidence in infants with trisomy 21 (Down syndrome). Duodenal atresia is believed to result from the failure of recanalization of the duodenum during fetal development. During pregnancy, polyhydramnios, dilated bowel, and/or ascites may be found. On radiograph, a classic "double-bubble" picture may be seen. This occurs due to air filling the stomach and proximal duodenum (see Figure 8-6). Bilious vomiting indicates gastrointestinal obstruction distal to the ampulla of Vater.

This patient should be screened for what other congenital abnormalities?

Up to half of EA cases are associated with other congenital abnormalities. Two associated congenital syndromes are VACTERL and CHARGE.

VACTERL	***CHARGE***
Vertebral anomalies	**C**oloboma
Anal atresia	**H**eart defects
Cardiovascular anomalies	**A**tresia of the choanae
Tracheoesophageal fistula	**R**etardation of mental and/or physical development
Esophageal atresia	**G**enital hypoplasia
Renal anomalies	**E**ar abnormalities
Limb defects	

What is the treatment for this condition?

EA with TEF is treated with surgical repair that may be carried out in stages.

CASE 9

A 42-year-old obese woman presents to the urgent care facility with a sudden onset of right upper quadrant and epigastric pain that began 8 hours earlier. The pain is steady in nature, worsened by eating, and radiates to the right shoulder. Vitals are as follows: Temperature of 37.4°C (99.4°F), heart rate of 98/min, respiratory rate of 22/min, blood pressure of 144/82 mm Hg, weight of 98 kg (216 lb), and height of 162 cm (5.31 ft). Physical examination reveals inspiratory arrest with deep palpation of the right upper quadrant. Relevant laboratory findings are as follows:

Total bilirubin: 2.6 mg/dL
Direct bilirubin: 1.8 mg/dL;
Cr: 1.05 mg/dL
Alkaline phosphatase (ALKP): 420 U/L
GGT: 95 U/L
AST: 54 U/L
ALT: 60 U/L

What is the most likely diagnosis?

Cholelithiasis refers to the presence of gallstones within the gallbladder. **Choledocholithiasis** refers to the presence of gallstones in the bile ducts. Gallstone disease, secondary to cholesterol stones, is common in the United States. It can be asymptomatic or manifest as a spectrum of disorders, which include biliary colic, cholelithiasis, choledocholithiasis, cholecystitis, cholangitis, gallstone pancreatitis, and gallstone ileus. Biliary colic is intermittent, usually resolving within a few hours; however, it is often recurrent and can progress to cause other gallstone pathologies. The constant pain for 8 hours duration, in combination with elevated direct bilirubin, ALKP, and GGT, are suggestive of choledocholithiasis in this case.

What physical signs of this condition does the patient exhibit?

Boas sign is a radiation of pain from the inflamed gallbladder to the right shoulder. This physical sign occurs because the inflamed gallbladder begins to irritate the phrenic nerve, and the pain to the right shoulder is referred pain.

Murphy sign is the arrest of inspiration with deep palpation in the right upper quadrant. This physical sign is generated when the gallbladder comes in contact with the examiner's hand as the abdominal organs are shifting down during inspiration.

What type of stones can affect the biliary tree?

Cholesterol gallstones are most common in the United States and occur when bile is supersaturated with cholesterol, allowing stones to precipitate. **Pigmented gallstones** commonly occur in patients who have hemolysis (eg, sickle cell disease, thalassemia, etc.). They can occur secondary to bile duct/gallbladder infection, hemolysis, or impaired hepatic processing of bilirubin.

What is the pathophysiology of the patient's pain?

Gallstones produce dull, poorly localized visceral pain by obstructing the ampulla of Vater or the cystic duct, causing distention of the gallbladder and irritation of surrounding structures.

Infection with which bacteria may result from this condition?

Choledocholithiasis can cause obstruction and biliary stasis, compromising defense mechanisms that normally prevent bacteria within the duodenum from ascending into the biliary tree. As such, these bacteria can infect the biliary tree causing **cholangitis**. *Escherichia coli*, *Enterobacter*, *Klebsiella*, *Enterococcus*, and anaerobes are commonly implicated in infection of the biliary tree secondary to obstruction (ie, cholangitis).

Which structures are adjacent to the gallbladder?

The **gallbladder** lies within the gallbladder fossa, which is a depression in the inferior surface of the liver. The **cystic duct** originates at the neck of the gallbladder and connects with the common hepatic duct to form the common bile duct. The common bile duct joins with the pancreatic duct and terminates at the **ampulla of Vater**, where bile is excreted into the duodenum. The sphincter of Oddi is found here and can regulate bile excretion.

CASE 10

A 65-year-old male immigrant from Japan presents with a 2-year history of abdominal pain and early satiety, which have become progressively worse. He has lost 9.07 kg (20 lbs) over the course of his abdominal pain. He denies any dysphagia, odynophagia, or diarrhea. He does have a 40-pack year smoking history but denies any alcohol use.

What is the most likely diagnosis?

In an older individual with significant weight loss and nonspecific symptoms, cancer should be high on your differential. In this patient without significant trouble swallowing or eating but still complaining of early satiety, geography, and smoking history, gastric carcinoma is the most likely diagnosis. Gastric carcinoma is frequently diagnosed as PUD, but an endoscopy with multiple biopsies would confirm the diagnosis.

What risk factors are associated with this condition?

- Infection with *Helicobacter pylori*.
- Japanese heritage.
- Chronic gastritis.
- Smoking.
- Diets high in nitrosamines (ie, smoked, cured, or pickled foods) commonly found in East Asia, the Andes, Scandinavia, and eastern Europe.
- Pernicious anemia and type A blood (associated with gastritis).
- Family history.
- Previous gastric surgery.

What will the biopsy findings reveal?

Adenocarcinoma is the most common type of gastric cancer, and its hallmark is **signet-ring cells** on histopathology (see Figure 8-8). Other signs include **linitis plastica**, or "**leather-bottle stomach**," which is a diffusely infiltrative cancer and portends a worse prognosis. Polypoid carcinoma involves a mass projecting into the stomach and superficial spreading type provides the most favorable prognosis. It is also important to rule out **gastric lymphoma**, which is frequently associated with *H pylori* and may regress without surgery if the bacteria can be eradicated.

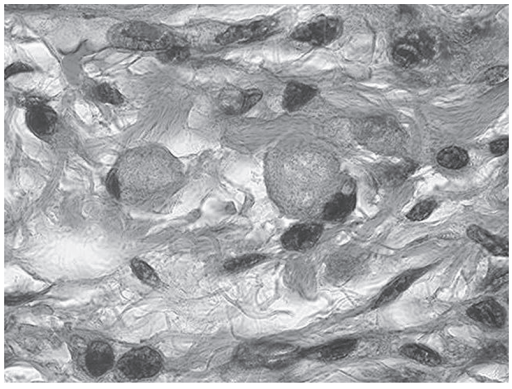

FIGURE 8-8. Signet-ring appearance of cells. Image shows the fairly uniform tumor cells with abundant intracytoplasmic mucin, which pushes the nuclei to the side, giving the cells their typical signet-ring appearance. (Reproduced with permission from USMLE-Rx.com.)

How does this condition spread?

Gastric cancer metastasizes by direct extension through the gastric wall and the lymphatic system and via peritoneal spread. Spread of gastric cancer has unique names depending on the location of the spread. Krukenberg tumor is metastasis to the ovary in females, Blumer shelf is metastasis to the rectum, Sister Mary Joseph node is metastasis to the periumbilical lymph node, Irish node to the axilla, and Virchow node to the left supraclavicular fossa.

Why does this patient suffer from dyspareunia and dyschezia?

These symptoms result from metastasis via peritoneal spread to the **pouch of Douglas** (the rectouterine cul-de-sac). This may be felt on rectal examination as an anterior rectal wall mass or a "**Blumer shelf**." Gastric carcinoma metastasis to the ovary is called a **Krukenberg tumor**.

CASE 11

A 66-year-old woman presents to her physician with epigastric pain, history of nausea, and diarrhea for 3 days. Her medical history is complicated by type 2 diabetes, hypertension, erosive esophagitis, and chronic peptic ulcer disease. She takes several medications, including a β-blocker. CT of the abdomen reveals a 2 × 2-cm mass in the head of the pancreas. Relevant laboratory findings are as follows:

Gastric pH: < 2.0
Serum gastrin: 1500 pg/mL
Hematocrit: 26%
Basal gastric acid output: > 15 mEq/h

What is the most likely diagnosis?

Gastrinoma, a gastrin-secreting, non–β islet cell, neuroendocrine tumor of the pancreas or duodenum. These tumors cause gastric hypersecretion of hydrochloric acid (HCl), which results in severe ulcers disease and diarrhea. Zollinger-Ellison syndrome (ZES) describes the clinical manifestations of gastrin hypersecretion secondary to gastrinoma.

What role does gastrin play in the stomach?

Gastrin is a peptide hormone released by G cells in response to vagal stimulation via gastrin-releasing peptide (GRP). Conversely, somatostatin suppresses gastrin secretion by G cells. Gastrin stimulates the cholecystokinin-2 of the stomach. Gastrin stimulates histamine release from ECL cells. Gastrin and histamine act synergistically to stimulate parietal cell HCl secretion by binding to CCK2 and H2 receptors respectively.

A hydrogen-potassium ATPase transports a proton (H^+) across the parietal cell apical/luminal membrane in exchange for a potassium ion (K^+). Its activity is stimulated by increases in Ca^{2+} and cAMP resulting from histamine and gastrin binding at the basolateral membrane. Other signals that stimulate hydrogen-potassium ATPase activity are acetylcholine from direct vagus stimulation. Somatostatin, secretin, gastric inhibitory peptide (GIP), vasoactive intestinal peptide (VIP), PPIs, and prostaglandins inhibit the ATPase.

What test can further support the diagnosis?

Serum gastrin levels are used to diagnose ZES. Levels > 1000 pg/mL with gastric pH < 5 establish the diagnosis but may not be present in all ZES patients. In these patients, the secretin stimulation test may be useful. Here secretin is administered and would be expected to inhibit gastrin production in patients without gastrinoma. Gastrinomas, however, respond oppositely and increase gastrin secretion in response to secretin. The test therefore differentiates between the presence of a gastrinoma and other potential causes of hypergastrinemia. Patients with ulcer disease should also be tested for *H. pylori* infection, a common cause of the disease. PPI use can also cause **mild** gastric acid hypersecretion.

What are the two most common neuroendocrine tumors?

Insulinoma (usually benign) is the most common neuroendocrine tumor. Gastrinoma (can be malignant) is the second most common.

What are the signs and symptoms of this condition?

- Increased fasting gastrin level.
- Ulcers in unusual locations such as the proximal jejunum.
- Gastroesophageal reflux disease.
- Diarrhea.
- Nausea/vomiting.
- Epigastric pain.
- Weight loss.

With what syndromes is this condition commonly associated?

Zollinger-Ellison syndrome (ZES) is characterized by a classical triad of severe peptic ulcer disease, gastric acid hypersecretion, and presence of non-β cell gastrin producing tumors.

Multiple endocrine neoplasia type I (MENI) is a genetic syndrome with an increased risk of parathyroid, pituitary, and pancreatic (such as gastrin-secreting) adenomas.

What is the treatment for this condition?

Surgical resection is often used in patients who have local disease without metastasis. Chemotherapy may be used in those with metastatic disease. Medical treatments involve the use of proton pump inhibitors and octreotide. Octreotide is a somatostatin analog with a longer half-life and has similar effects on decreasing gastric acid secretion.

CASE 12

A 45-year-old man presents to his physician complaining of retrosternal chest pain. He says that it occurs after eating and is associated with a sour taste in his mouth. He complains of coughing that typically occurs at night after he lies down. The patient has had these symptoms for several years, but they have been worsening over the past 3 months.

What is the most likely diagnosis?

Gastroesophageal reflux disease (GERD), potentially complicated by Barrett esophagus (see Figure 8-9).

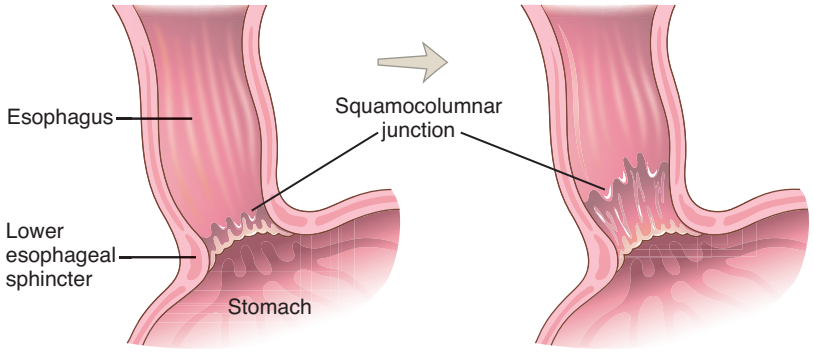

FIGURE 8-9. Barrett esophagus shown on the right. The columnar epithelium of the stomach has advanced superiorly in response to reflux of gastric contents into the distal esophagus. (Reproduced with permission from USMLE-Rx.com.)

What is the differential diagnosis for this patient's symptoms?

There are a few diagnoses that may present similarly to GERD. These include coronary artery disease, peptic ulcer disease, acute cystitis, diffuse esophageal spasm, and other esophageal motility disorders.

What are the expected findings on endoscopy?

Endoscopy reveals an upward shift of the squamocolumnar junction (also known as the Z line). The shift is due to metaplasia. The normal nonkeratinized stratified squamous epithelium of the esophagus has undergone metaplasia to gastric columnar epithelium (see Figure 8-10). This occurs in response to chronic gastric acid exposure secondary to incompetence of the LES. Barrett esophagus is a precancerous condition that requires regular surveillance by endoscopy and biopsy.

Patients with Barrett esophagus are at greatly increased risk for what other condition?

Compared to the general population, patients with Barrett esophagus are 30 times more likely to develop esophageal adenocarcinoma (lifetime risk: ~ 5%). Less commonly, esophageal strictures may also develop as the aforementioned chronic injury induces scar formation. Collagen can deposit and contract over time, creating an obstruction and resulting in dysphagia.

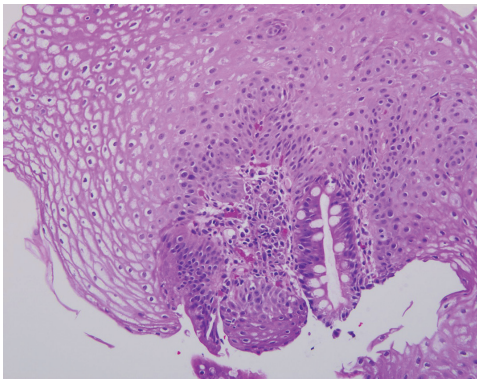

FIGURE 8-10. Barrett esophagus. The distal squamous mucosa has undergone metaplasia to become columnar epithelium with goblet cells (intestinal epithelium) in response to chronic acid exposure. This process is a well-recognized precursor to the development of esophageal adenocarcinoma. (Reproduced with permission from USMLE-Rx.com.)

What are the common treatments for this condition?

Patients are to begin lifestyle modifications, including elevation of the head of the bed, dietary restrictions, and weight loss, which are often used in conjunction with medical therapy. Patients are also given a trial of proton pump inhibitor (PPI). If symptoms persist after the trial, testing for *Helicobacter pylori* is appropriate. *H pylori* is treated with treatment with triple therapy (PPI, amoxicillin, clarithromycin).

What factors increase the risk of developing esophageal cancer?

Barrett esophagus is the major risk factor for **esophageal adenocarcinoma**. As mentioned above, cells superior to the squamocolumnar junction undergo metaplasia from squamous cells to columnar cells. Alcohol and cigarette smoking are major risk factors for esophageal squamous cell carcinoma. Risk factors for esophageal cancer include conditions that may be remembered with the mnemonic **ABCDEF**: **A**chalasia/**A**frican-**A**merican male, **B**arrett esophagus, **C**orrosive esophagitis/**C**igarettes, **D**iverticuli (ie, Zenker diverticulum), **E**sophageal web/**E**tOH, and **F**amilial.

CASE 13

A 35-year-old man presents to his physician with erectile dysfunction, decreased libido, achy joints, polydipsia, urinary frequency, and polyuria. His wife also notes that he looks like he has a tan, despite it being January. On physical examination, his skin appears bronze in color. Relevant laboratory studies are as follows:

Blood glucose: 242 mg/dL
Serum iron: 1200 mg/dL
Transferrin saturation: 99%

What is the most likely diagnosis?

Hemochromatosis is a disease of excessive iron accumulation, which leads to tissue damage. The classic triad of hemochromatosis is as follows:

- (Pigmented micronodular) cirrhosis.
- Diabetes mellitus.
- Skin pigmentation.

The last two symptoms give this disease the nickname "**bronze diabetes**."

How is this condition inherited?

Several types of hereditary hemochromatosis (HH) have been described and involve mutations of different genes. Type 1 (classic) hemochromatosis is an **autosomal recessive** disease caused by a defect in the ***HFE*** gene of chromosome 6p and is, therefore, also called HFE-related hemochromatosis.

What is the pathophysiology of this condition?

Regardless of the genetic type, hereditary hemochromatosis causes iron overload via impairment of Hepcidin activity or synthesis. Hepcidin has an important role in iron regulation, including the absorption of iron from the gut. In HH the inhibitory role of hepcidin on iron absorption from the GI tract is lost. Excess iron subsequently accumulates and causes tissue damage. Organs that can be affected include:

- Liver, leading to **cirrhosis**. Liver biopsy typically shows extensive hemosiderin deposits within the hepatocytes and Kupffer cells (specialized macrophages). Hemosiderin and other iron-containing compounds stain with **Prussian blue**.
- Pancreas, leading to **diabetes mellitus**.
- Heart, leading to restrictive **cardiomyopathy** and congestive heart failure.
- Joints, leading to arthritis and **arthralgias** (secondary to chondrocalcinosis).
- Gonads, leading to **hypogonadism**.

What is the treatment for this condition?

Treatment involves repeated phlebotomy and an iron chelation using agents such as deferoxamine. Diet regulation and specific treatments for potential organ damage may also be used. Wilson disease is treated with chelating drugs such as penicillamine.

How is this condition differentiated from Wilson disease?

Wilson disease is a disorder of copper metabolism. It involves an accumulation of copper within the liver. The transport disorder also causes an impairment of copper incorporation into the enzyme ceruloplasmin, resulting in a decrease in ceruloplasmin levels. Excess copper can accumulate in the liver, brain, and cornea. In the brain, copper mainly deposits in basal ganglia of putamen and globus pallidus, giving rise to the term **hepatolenticular degeneration**. Like hemochromatosis, patients are at risk for developing hepatocellular carcinoma. Wilson disease is characterized by **ABCCCD**:

- **A**sterixis.
- **B**asal ganglia degeneration (parkinsonian features, choreiform movements, and hemiballismus).
- **C**orneal deposits (in Descemet membrane, which can cause Kayser-Fleischer rings)
- **C**irrhosis
- **C**eruloplasmin decrease
- **D**ementia and other mental status disturbances.

CASE 14

A 34-year-old man with a history of alcohol and drug abuse comes to the ED complaining of nausea and vomiting. He notes no recent change in diet or lifestyle and has been in a monogamous relationship for the past year. Physical examination reveals a fever of 38.3°C (101°F), a heart rate of 80/min, and a respiratory rate of 18/min. Scleral icterus is present, and there is tenderness in the right upper quadrant and midepigastric region. Workup is negative for gonorrhea and chlamydia. Relevant laboratory findings are as follows:

ALT: 1310 U/L
AST: 1200 U/L
Alkaline phosphatase: 98 U/L
HBsAg: Negative
HBeAg: Negative
Anti-HBeAg antibody: Positive
Anti-HBcAg antibody: Positive
Anti-HBsAg antibody: Negative

What is the most likely diagnosis?

Acute hepatitis B virus (HBV) infection.

What laboratory findings support the diagnosis?

Hepatitis can have many causes, including alcohol, viral infection, ischemia, congestive heart failure, or toxins such as acetaminophen or aflatoxin. The history of intravenous (IV) drug abuse, and equal and significant transaminitis (AST and ALT > 1000 U/L), suggests acute hepatitis from a viral etiology. By contrast, in alcoholic hepatitis, AST is typically elevated more than ALT (at ratios > 2:1) but does not usually rise above 1000 U/L.

The patient is in the "**window phase**" of HBV infection, which occurs after HBsAg has disappeared but before anti-HBsAg antibody is detectable. This conclusion is supported by the presence of anti-HBeAg and anti-HBcAg antibodies. The HBeAg and anti-HBcAg antibodies are predominantly IgM during the window phase. The patient is not a chronic carrier as he is negative for HBsAg. He is also not highly infectious as HBeAg (a marker of viral replication) is negative. In a vaccinated or immune patient, anti-HBsAg would be positive with a negative HBsAg and negative anti-HBcAg antibody. Figure 8-11 shows the serological findings in acute hepatitis B infection in relation to time.

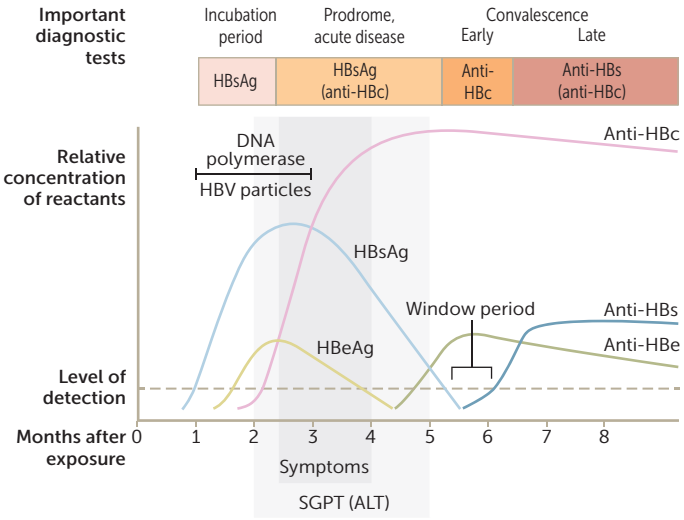

FIGURE 8-11. The serological findings in acute hepatitis B infection in relation to time. (Reproduced with permission from USMLE-Rx.com.)

What percentage of patients with an acute form of this condition progress to a chronic form?

Less than 10% of adults with acute HBV infection develop chronic hepatitis, whereas approximately 90% of affected neonates develop the chronic disease.

What are the treatments for the chronic form of this condition?

- Lamivudine (3TC) is phosphorylated into a nucleotide analog and leads to termination of viral DNA synthesis.
- α-Interferon, an endogenous cytokine, has a high efficacy but can be expensive and has side effects (headache, nausea/vomiting, liver/renal toxicity with chronic use).
- Adefovir is a nucleotide analog of adenosine monophosphate and therefore stops DNA replication. It is often used in cases of lamivudine-resistant chronic hepatitis.

CASE 15

A medical student accidently sticks himself while attempting to recap a needle while drawing blood from a patient. The patient he was treating is known to have chronic, active hepatitis C virus (HCV) infection. The student has blood drawn for antibody testing, which is found to be negative for anti-HCV antibody. Four weeks later, the medical student is still negative for anti-HCV antibody, but at 13 weeks, results of antibody testing are positive.

Was the third antibody test falsely positive? Why or why not?

No, this student has acute HCV infection. It takes weeks to months for the body to develop an antibody response to HCV. The two prior negative tests indicated only that he did not have a pre-existing HCV infection or prior exposure.

What other laboratory findings are typically found in patients with this condition?

Significant transaminitis (elevated AST and ALT) is common and secondary to intracellular enzymes release from hepatocyte damage. HCV RNA may also be detectable in the serum by reverse transcriptase–polymerase chain reaction (PCR).

What is the course of this condition?

Most patients with acute HCV infection are asymptomatic. Approximately 25% of patients will become jaundiced. The patient may have flu-like symptoms lasting 2–12 weeks. Although only a small percentage of people exposed to HCV by needlestick will develop acute hepatitis, 60%–80% of those who develop acute hepatitis will develop chronic infection. **Chronic infection** has a variable but slowly progressive course, with approximately 20% of patients developing cirrhosis. Excessive alcohol consumption further increases the risk of cirrhosis in this patient population.

What are the treatments for this condition?

A combination of ribavirin and pegylated α-interferon induces remission in approximately 40% of chronic, active HCV cases. Ribavirin is a guanosine analog that inhibits viral mRNA synthesis. Pegylated α-interferon is an endogenous cytokine that induces antiviral host enzymes and causes significant flu-like symptoms. Ledipasvir/sofosbuvir combination therapy is a newer treatment that can be curative. High costs of this treatment limit its availability.

CASE 16

A 55-year-old alcoholic male with known chronic hepatitis C infection presents with weight loss and ascites. Physical examination reveals spider angiomas, palmar erythema, and hemorrhoids. The liver edge is nonpalpable. Axial CT scan shows a heterogeneous mass in the right lobe of the liver (see Figure 8-12).

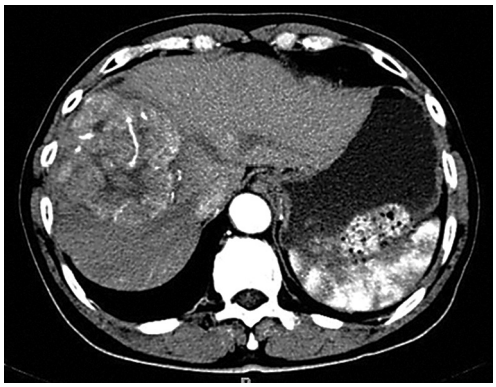

FIGURE 8-12. (Reproduced with permission from UMSLE-Rx.com.)

What is the likely diagnosis?

Hepatocellular carcinoma (HCC), also known as hepatocarcinoma. The CT in Figure 8-12 shows a mass in the right lobe of the liver. Once the mass is located by the CT, a biopsy is done to confirm the diagnosis.

What risk factors are associated with this condition?

- Cirrhosis.
- Chronic hepatitis B and C infection.
- Aflatoxin (produced by *Aspergillus flavus*).
- Heavy metal disorders with liver deposition (Wilson disease, hemochromatosis).
- α_1-Antitrypsin deficiency.

What serum marker may help diagnose this condition?

α-Fetoprotein (AFP). However, this is not specific for HCC, as elevated serum AFP can also occur in other liver diseases, pregnancy, and germ cell tumors. CEA levels may be elevated when the peritoneum is involved.

How can the physical examination findings be explained?

The patient has functional hyperestrogenemia. The liver is responsible for the degradation of estrogen and is ineffective in carrying out this process in cases of liver dysfunction. High levels of circulating estrogens can lead to spider angiomata, palmar erythema, testicular atrophy, and gynecomastia

The patient also has portal hypertension secondary to cirrhosis. This leads to development of collateral circulation to bypass the obstructed liver, resulting in:

- Esophageal varices.
- Caput medusae (dilation of superficial epigastric veins).
- Internal hemorrhoids (nontender as opposed to external hemorrhoids, which can result from constipation)

What nutritional deficiencies are likely to be present in this patient?

Alcoholics may be deficient in several vital nutrients, but the most common are thiamine (vitamin B_1), vitamin B_{12}, folate, calcium, and magnesium. In addition to lacking consumption of nutrient-containing foods, chronic alcoholics can suffer from pancreatic dysfunction, resulting in malabsorption of nutrients.

What role does thiamine play in the metabolism of carbohydrates and amino acids?

Thiamine is present in cells as thiamine pyrophosphate (TPP), which is necessary for the metabolism of pyruvate to acetyl-CoA, and α-ketoglutarate to succinyl-CoA in the process of aerobic cellular respiration. Thiamine is also used for the oxidative decarboxylation of branched-chain amino acids (leucine, isoleucine, and valine) and the pentose-phosphate shunt.

Why must patients with alcoholism receive thiamine whenever glucose-containing intravenous fluids are given?

This is done to prevent **Wernicke encephalopathy**. Thiamine is necessary for the metabolism of glucose. Thiamine deficiency can cause damage to areas of the brain, including the mammillary bodies. This is proposed to occur through oxidative damage, mitochondrial injury, and promotion of pro-apoptotic processes. If glucose is administered without correcting for thiamine deficiency, the mammillary bodies can be necrotic in a hemorrhagic process that causes irreversible damage. The triad of Wernicke encephalopathy is **confusion**, **ataxia**, and **ophthalmoplegia** (nystagmus). **Korsakoff syndrome** is a permanent condition with a similar etiology and is characterized by both retrograde and anterograde amnesia with confabulation.

CASE 17

An otherwise healthy 28-hour-old boy born at 39 weeks' gestation to a G3P2 mother is noted to have yellowed skin over his entire body. A complete blood count reveals a slightly low hematocrit but normal WBC and platelet counts. Other relevant laboratory findings are as follows:

Direct bilirubin: 0 mg/dL
Serum total bilirubin: 19 mg/dL
Direct Coombs test: Weakly positive
Mother's blood type: O+
Infant's blood type: B+

What is the most likely diagnosis?

Hyperbilirubinemia due to RBC lysis caused by maternal anti-B antibodies (immunoglobulin G) in the infant's blood. Remember, IgG antibodies can cross the placenta while IgM is too large and cannot. Specific IgG antibodies that may cross include the anti-Kell and anti-Rhc, which may cause hemolytic disease of the newborn. Anti-Lewis antibodies are an IgM subtype and thus inconsequential.

There are two types of neonatal jaundice: physiologic and pathologic. Physiologic jaundice is considered to be normal and can arise 72+ hours after delivery. If there is any appreciation of jaundice 24–36 hours after birth, it is considered pathologic, and there is some mechanism causing the jaundice to occur more quickly than normal. Pathologic jaundice should be further subdivided into unconjugated vs. conjugated. Unconjugated (as in this case) may be due to maternal antibodies attacking neonatal RBCs (Rh disease, anti-Kell, hemolytic disease of newborn, etc.), intrinsic RBC deficiencies, or extrinsic causes as in sepsis or Crigler-Najjar syndrome. Unconjugated causes are more worrisome as an acute cause due to kernicterus may result from too high bilirubin concentrations on the brain. Conjugated causes include TORCH infections, Hepatitis A/B, or drugs.

The patient is given phototherapy. Why is this effective?

Phototherapy irreversibly converts unconjugated bilirubin into lumirubin, which is similar to conjugated bilirubin. This conversion allows for a more soluble form of bilirubin, which can diffuse out into the bile and urine.

The patient is given a blood transfusion for his anemia. What ABO blood types should the packed RBC donor and the plasma donor be to minimize hemolysis upon transfusion?

The RBC donor should be type O to avoid hemolysis of donor cells by maternal anti-B antibodies in the infant's blood. The plasma donor should be type B or AB, so that the plasma will not contain anti-B antibodies, which would be incompatible with the infant's blood.

Which drugs, when ingested by the mother, increase the baby's risk of kernicterus?

Drugs that are highly bound to albumin—such as aspirin, ceftriaxone, and sulfa-based drugs—may displace bilirubin from albumin, thus increasing the level of neurotoxic free bilirubin in the blood and leading to the development kernicterus.

Despite phototherapy, the infant's total serum bilirubin climbs to 26 mg/dL. An infusion of albumin followed by an exchange transfusion is ordered. Why is this treatment effective?

Infused albumin binds free bilirubin, helping to draw extravascular bilirubin from tissues into the blood, which will then be removed by the exchange transfusion.

A 10-day-old previously healthy, breastfed neonate becomes jaundiced. What is the differential diagnosis?

Breast-milk jaundice and breast-feeding jaundice sound the same, but their mechanisms are quite different. In breast-milk jaundice, the breast milk itself causes an interruption of the conjugation of bilirubin, causing the infant to be jaundiced. Treatment includes switching the infant to formula, which should clear up the jaundice hue of the child. In breast-feeding jaundice, the pathophysiology is the quantity of breast milk (aka the baby is not feeding enough) that causes the body to reabsorb the bilirubin it would otherwise excrete. The treatment here is to increase the amount of feedings. Both types are an example of physiologic, unconjugated neonatal jaundice.

CASE 18

A 26-year-old man presents with a 6-month history of abdominal pain and increasingly frequent bloody diarrhea. He has had an unintentional loss of 5.4 kg (12 lb) over 6 months and now complains of joint and lower back pain. He reports that his father had similar complaints, and recently his 40-year-old uncle was diagnosed with colon cancer. Physical examination reveals diffuse voluntary guarding, no rebound tenderness, no masses, and no rectal fistulas. Colonoscopy reveals inflamed mucosa with friable pseudopolyps from the rectum to the splenic flexure.

What is the most likely diagnosis?

An inflammatory bowel disease. In this case, ulcerative colitis (UC) is more likely than Crohn disease (CD) because of the genetic component, gender of the patient, associated joint/lower back pain, and gross appearance.

How can these two conditions be differentiated from one another?

Table 8-1 compares CD with UC.

Table 8-1. Crohn Disease Versus Ulcerative Colitis

Characteristic	Crohn disease	Ulcerative colitis
Involvement	Any part of the GI system from mouth to anus. Terminal ileum most common.	Involves the rectum in all cases. Can involve colon partially or fully.
Histology	Transmural inflammation with skip lesions	Mucosa and submucosa; continuous involvement (no skip lesions)
Features	Skip lesions, fistulae, noncaseating granulomas	Crypt abscess, tenesmus, usually bloody diarrhea, pseudopolyps
Surgery	Not curative as in UC	Total colectomy is curative
Extra-intestinal symptoms	Uveitis, arthritis, ankylosing spondylitis, erythema nodosum, pyoderma gangrenosum, aphthous ulcers	Sclerosing cholangitis, toxic megacolon, jaundice, uveitis, arthritis, skin lesions
Cancer risk	Less	More
Serologic Markers	ASCA+	p-ANCA+

What extraintestinal manifestations are possible in this patient?

Extraintestinal manifestations in UC relate to its association with **HLA-B27**: ankylosing spondylitis, reactive arthritis (ie, arthritis, uveitis, urethritis), primary sclerosing cholangitis, and pyoderma gangrenosum. Patients with primary sclerosing cholangitis have an even greater risk of colorectal cancer (CRC).

What further screening is recommended for the future?

There is a significantly increased risk of CRC among patients with UC. The risk depends on duration and extent of disease, especially at 8–10 years after onset of symptoms. Patients should undergo colonoscopy and biopsy approximately 8 years after first diagnosis and, if negative, undergo a repeat examination every 1–3 years thereafter. Figure 8-13 shows an image from a colonoscopy.

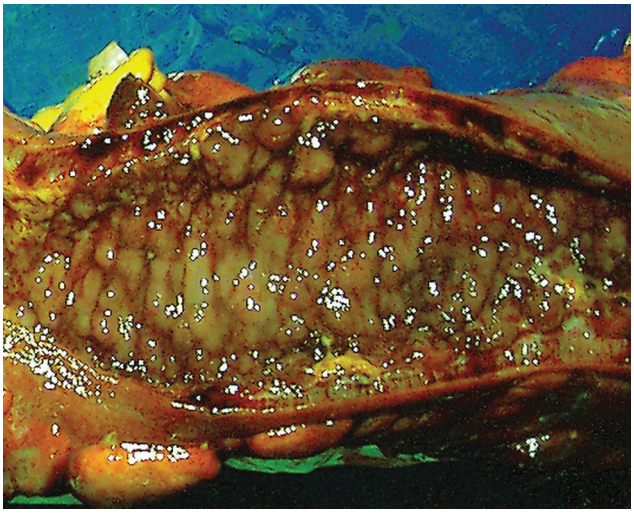

FIGURE 8-13. Ulcerative colitis. Hemorrhagic mucosa and pseudo-polyps with surrounding ulceration. 43-year-old man with long-standing history of bloody diarrhea and abdominal pain. (Reproduced with permission from USMLE-Rx.com.)

CASE 19

A worried mother rushes her 2-year-old son to the clinic after finding a large amount of bright red blood in his diaper. She notes that over the past week the child has been intermittently extremely irritable, curling into a ball with his legs pulled to his chest. His irritability resolves after vomiting (bilious) or passing a small stool. On examination, the child's vital signs are within normal limits, and he is in no apparent distress. Dried blood is noted at the anus. He is slightly uncomfortable with abdominal palpation, although no masses are appreciated.

What is the most likely diagnosis?

Intussusception is the telescoping of one portion of the bowel (often at the ileocecal junction) into another. This process can lead to luminal obstruction and vascular compromise.

What are the common causes of this condition?

- Anatomical causes include Meckel diverticulum (pediatric patients) or polyp/tumor (usually older males).
- Infectious causes include adenovirus, rotavirus vaccine, enteric bacteria.
- Vasculitic causes include Henoch-Schönlein purpura.

What is the embryonic origin of a Meckel diverticulum?

A Meckel diverticulum is the most common congenital abnormality of the small intestine, resulting from failure of the **vitelline duct** to close. The role of the vitelline duct is to connect the developing midgut to the yolk sac. Normally, the duct closes and obliterates by approximately 7 weeks' gestation.

What are the classic characteristics of a Meckel diverticulum?

Meckel diverticulum classically follows the "**rule of 2s**":

- Occurs in **2%** of the population, the majority of which are > **2** years of age.
- Complications develop in **2%** of patients.
- Male: ratio is **2:1**.
- Found within **2** feet of the ileocecal valve.
- Length is **2** inches long.

What explains the patient's temperament on presentation?

Intussusception makes the child irritable. The classic presentation on the boards will be an inconsolable child with a sausage-like palpable abdominal mass and "currant-jelly" stools. Children may appear completely well between episodes of obstruction. Patients often curl into a ball in an effort to reduce the intussusception. A barium enema can be both diagnostic and therapeutic.

What is the cause of the bright red rectal bleeding?

The two most common tissue types found in a Meckel diverticulum are gastric (80%) or pancreatic (~20%). The heterotopic gastric tissue releases gastric enzymes into the surrounding sensitive intestinal mucosa, which can lead to ulceration, pain, and bleeding.

Is a Meckel diverticulum a true or false diverticulum?

This is a true diverticulum, in that it involves all layers of the intestinal wall (see Figure 8-14). Treatment for Meckel diverticulum includes surgery by either laparotomy or laparoscopy. The surgeon needs to not only resect the diverticulum but also any ectopic glands to prevent any bleeding or recurrent bleeding.

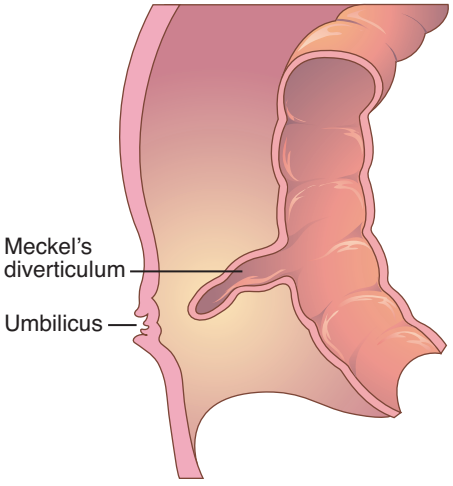

FIGURE 8-14. Meckel's diverticulum. (Reproduced with permission from USLME-Rx.com.)

CASE 20

A 75-year-old woman presents to the ED after passing two bright red, plum-sized clots of blood per rectum. There was no stool passed with the clots. The patient denies any abdominal discomfort or cramping but states she becomes lightheaded upon standing. She also reports being very constipated over the past few months. She takes one 81-mg aspirin per day. In the ED, her hematocrit is 28%, and her blood pressure is 110/70 mm Hg supine and 80/50 mm Hg standing.

Where is the likely origin of the blood?

The blood is most likely from the lower gastrointestinal (GI) tract. A general rule for cases involving GI bleed is the color and consistency of the blood. In the vast majority, an upper-GI bleed (considered to be at level of duodenum or higher) will have time to transmit through the entire GI system. This causes the blood to be broken down and turned into what is termed melena, or black/tarry. **Hematemesis** (bright red blood or coffee-grounded blood) is also considered an upper-GI bleed. On the other end, a lower-GI bleed is often after the duodenum and is bright red in color. **Hematochezia** is the medical term attached to a lower-GI bleed. A positive occult blood test can occur anywhere along the GI tract.

What conditions should be considered in the differential diagnosis in upper- vs. lower-GI bleed?

- Upper-GI bleed
  - Peptic ulcer disease
  - Esophageal varices, Mallory-Weiss tear, gastric varices
  - Neoplasm (not rapid bleeding)
- Lower-GI Bleed
  - Diverticulosis
  - IBD (Crohn, UC)
  - Colorectal carcinoma, ischemic colitis

What is the most likely cause of this patient's bleeding?

Diverticulosis. The most common causes of acute lower-GI bleeding are diverticulosis (33%), cancers/polyps (19%), colitis/ulcers (18%), angiodysplasia (8%), and anorectal hemorrhoids (4%). By 85 years of age, approximately 65% of the population has diverticula. Hemorrhoids should be suspected in a younger patient.

What is the pathophysiology of this condition?

Diverticulosis occurs when **diverticula** form, exposing the surrounding arterial vasculature to injury and causing thinning of the media. This predisposes to rupture, arterial bleeding, and rapid loss of blood per rectum. This is in contrast to **angiodysplasia**, which can cause venous intestinal bleeding. An interesting association is that angiodysplasia is associated with aortic stenosis, both conditions mainly affecting the elderly population. Although most diverticula form in the left colon, right-sided diverticula are more likely to bleed. Risk factors for diverticular formation include nonsteroidal anti-inflammatory drugs, lack of dietary fiber, older age, and constipation.

What is the initial diagnostic test for this condition?

Colonoscopy can be both diagnostic and therapeutic. The urgency of colonoscopy is based on the amount of blood produced and surrogate markers of the briskness of the bleed such as blood pressure and orthostatic hypotension. Additional tests include radionuclide imaging (radiologic monitoring of radionuclide-tagged red blood cells to determine site of bleeding) and mesenteric angiography.

CASE 21

A 56-year-old woman presents to her primary care physician complaining of significant pruritus of her skin. She has tried multiple over-the-counter skin lotions and creams with no effect. On physical examination, extensive excoriations on her extremities, slight scleral icterus, and xanthelasma are found. Initial laboratory tests reveal the following:

AST: 40 IU/L
ALT: 40 IU/L
Direct bilirubin: 1 mg/dL
Total bilirubin: 2 mg/dL
Alkaline phosphatase: 540 U/L
γ-Glutamyl transferase (GGT): 80 U/L

What is the most likely diagnosis?

Primary biliary cirrhosis (PBC) is a presumed autoimmune disease with destruction (inflammation and necrosis) of the **intrahepatic** bile ducts.

What are the signs and symptoms of this condition?

The most common symptoms are fatigue (65%) and pruritus (55%) in a woman 40–60 years of age. Jaundice and xanthelasma are fairly rare (~10%).

What laboratory tests support the diagnosis?

Most patients are diagnosed by routine laboratory tests: increased alkaline phosphatase, GGT, and bilirubin (total and direct). AST and ALT are characteristically normal.

What additional laboratory tests should be ordered?

Antimitochondrial antibodies should also be ordered. There may also be an increase in the erythrocyte sedimentation rate and serum **immunoglobulin M** levels.

What other conditions may be present in patients with this condition?

Other autoimmune diseases, such as **scleroderma**, **Sjögren syndrome**, and **rheumatoid arthritis** may coexist with PBC. Up to 50%–75% of patients with PBC present with sicca syndrome—dry eyes (xerophthalmia) and dry mouth (xerostomia)—commonly seen among Sjögren patients.

What is the treatment for the patient's pruritus?

Antihistamines.

What is the treatment for the patient's underlying condition?

Ursodeoxycholic acid (ursodiol). Methotrexate may be added in severe cases.

How is this condition distinguished from primary sclerosing cholangitis?

Primary sclerosing cholangitis is more likely in males, affects both intrahepatic and extrahepatic bile ducts, shows negative antimitochondrial antibodies, and is associated with ulcerative colitis.

The classic description of endoscopic retrograde cholangiopancreatography findings of the bile ducts is "pearls on a string" or "bile lakes" (see Figure 8-15).

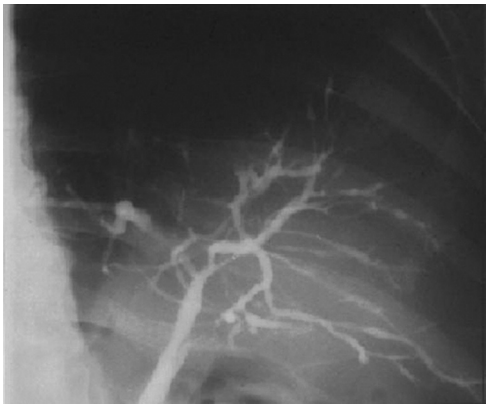

FIGURE 8-15. Biliary tree. Endoscopic retrograde cholangiopancreatography (ERCP) showing multiple strictures of primary sclerosing cholangitis. (Reproduced with permission from USMLE-Rx.com.)

CASE 22

A 53-year-old man with a history of hepatitis C virus (HCV) infection and cirrhosis presents to his physician with increasing jaundice, increased abdominal girth, weight loss, and early satiety. He says he is often fatigued and feels lightheaded when he stands. Laboratory testing reveals anemia, hyperbilirubinemia, and an increased serum α-fetoprotein level.

What is the most likely diagnosis?

Primary hepatocellular carcinoma (HCC). Incidence of HCC is increased in patients with HCV who develop cirrhosis. By contrast, patients who are infected with hepatitis B virus may develop HCC without cirrhosis.

What is the blood supply to the liver?

The liver is supplied by the portal vein (75% of blood flow) and hepatic artery. Branches of these vessels divide the liver into the left and right lobes. Efferent blood is carried from the hepatic vein to the inferior vena cava. Portal hypertension occurs when blood flow through the liver is obstructed, often due to cirrhosis.

How does the fetal blood supply to the liver differ from the adult blood supply?

The umbilical vein is the major blood supply to the fetal liver and provides nutrients to the developing fetus. The umbilical vein enters the fetus via the umbilicus and then joins the left portal vein. A small amount of placental blood perfuses the liver. Most placental blood, however, bypasses the liver via the ductus venosus and joins the left hepatic vein. The left hepatic vein then empties into the inferior vena cava and ultimately the right atrium. The umbilical vein and ductus venosus disappear 2–5 days after birth, becoming the **ligamentum teres** and **ligamentum venosum**, respectively.

What is the falciform ligament and where is it located?

During development, the **falciform ligament** connects the portion of the primitive foregut that will form the liver to the anterior abdomen at the umbilicus. This connection enables the umbilical vein from the placenta to enter its free border at the umbilicus and reach the portal vein at the porta hepatis. The falciform ligament on the anterior surface of the liver divides the liver into the left and right anatomic lobes.

Why does this patient have increased abdominal girth?

The increased abdominal girth is likely due to ascites, or excess peritoneal fluid, resulting from portal hypertension and a failing liver. In liver failure, albumin production falls, decreasing oncotic pressure within vessels. Transudative fluid leaves vessels as a result of the relative increase in hydrostatic pressure (Starling forces).

What calculation can differentiate transudative from exudative causes of ascites?

The serum-ascites albumin gradient (SAAG) = serum albumin minus albumin in ascites.
SAAG value > 1.1 g/dL = transudative cause; diagnosing portal hypertension with 97% accuracy.
SAAG value < 1.1 g/dL, exudative causes (eg, nephrotic syndrome, tuberculosis, and various cancers).

CASE 23

An 84-year-old man is hospitalized for a course of intravenous clindamycin to treat an abscess. One week later, he develops profuse heme-positive diarrhea, nausea, and malaise. The patient's temperature is 38.8°C (101.8°F). Physical examination reveals abdominal tenderness and distention. The WBC count is 19,000/mm^3 with a differential of 91% neutrophils, 7% monocytes, and 2% lymphocytes. Sigmoidoscopy reveals 0.2–2-cm raised, adherent, yellow plaques.

What is the most likely diagnosis?

This is a typical presentation of pseudomembranous colitis, which is notorious among hospitalized patients who receive **clindamycin**. Confirmatory findings include the presence of fecal leukocytes, anorexia, and dehydration. Even though clindamycin has been classically proven to cause pseudomembranous colitis, it is important to remember any antibiotic may cause *Clostridium difficile* (see below).

What is the causative organism of this condition?

Clostridium difficile. This anaerobic gram-positive rod becomes predominant in the bowel after normal flora have been killed off by broad-spectrum antibiotics, such as clindamycin, penicillins (especially ampicillin), and cephalosporins.

What is the underlying pathophysiology of this condition?

C difficile releases two exotoxins (**proteins A and B**) that bind to receptors on intestinal epithelial cells. These toxins cause sloughing of epithelial cells into the lumen and mucosal ulceration. A **pseudomembrane** forms, composed of inflammatory cells, proteins, and mucus (see Figure 8-16).

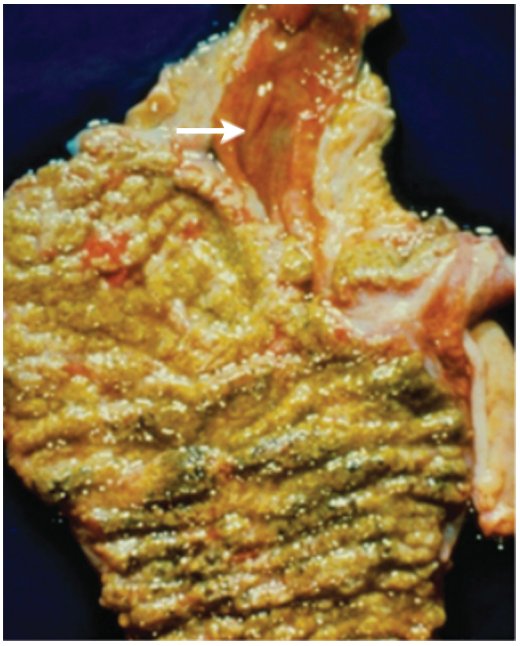

FIGURE 8-16. Autopsy specimen showing confluent pseudomembranes covering the cecum of a patient with pseudomembranous colitis. (Reproduced with permission from Kasper DL, et al. *Harrison's Principles of Internal Medicine,* 19th ed. New York: McGraw-Hill, 2014.)

What are other manifestations of infections with this organism?

Infection with *C difficile* can result in a broad spectrum of symptoms, ranging from asymptomatic to fulminant colitis. Antibiotic-associated diarrhea can be mild or profuse and can occur with or without colitis. The colitis itself can appear pathologically nonspecific or can demonstrate pseudomembranes. Fulminant colitis can result in **toxic megacolon (potentially lethal nonobstructive colonic dilation)** or even perforation.

What are the treatments for this condition?

Initial treatment strategy for this condition is the cessation of initiating antibiotic and, if needed, transition to another antibiotic (with less incidence of *C difficile* infections) to continue treatment of original infection. First-line treatment for *C difficile* is oral vancomycin, which can also treat severe *C difficile* enterocolitis. Oral medications are used instead of IV due to the fact that the antibiotic needs to be concentrated in the gut. IV vancomycin does not concentrate/is not excreted in the gut; thus, it is contraindicated in the treatment of pseudomembrane colitis. IV metronidazole may be used in the terminally ill patient with evidence of slowed gastric motility.

CASE 24

A 3-week-old white boy is brought to your clinic by his mother, who complains that the baby has intermittent bouts of projectile vomiting after meals. The mother also states that the child has been more lethargic than usual. On physical examination, the patient appears weak and has sunken eyes and poor skin turgor. He has fallen to the 25th percentile for weight. An olive-shaped mass is palpated in the right upper quadrant.

What is the most likely diagnosis?

Hypertrophic pyloric stenosis (see Figure 8-17).

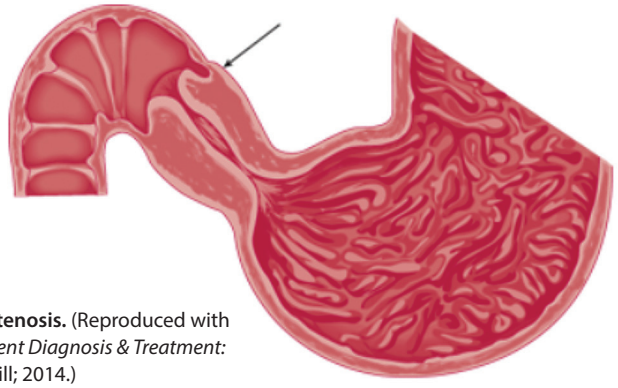

FIGURE 8-17. Hypertrophic pyloric stenosis. (Reproduced with permission from Doherty GM, ed. *Current Diagnosis & Treatment: Surgery*, 14th ed. New York: McGraw-Hill; 2014.)

What findings support this diagnosis?

This patient demonstrates the classic presentation of pyloric stenosis with immediate postprandial, **nonbilious**, often projectile vomiting ("the hungry vomiter") and a palpable olive-like mass in the epigastrium. **Firstborn white males** are 4× more at risk than other populations. Affected individuals usually present in the 3rd–8th weeks of life. Serum analysis will show hypochloremic, hypokalemic, metabolic alkalosis.

What are the typical laboratory findings in this condition?

Hypochloremic metabolic alkalosis from the loss of large amounts of gastric hydrochloric acid is seen with pyloric stenosis. Unconjugated hyperbilirubinemia may also be seen.

How is the diagnosis confirmed?

Diagnosis is straightforward when the "olive" is palpable. Otherwise, it may be difficult to distinguish this condition from gastroesophageal reflux without an ultrasound or upper gastrointestinal series. The latter may demonstrate an elongated pylorus ("**string sign**") with a tapered end ("**beak sign**").

What is the management for this condition?

The definitive management is surgery (pyloromyotomy).

Given appropriate management, what is the prognosis?

Patients can be expected to make a complete recovery, including return to normal weight and growth.

What other conditions are commonly associated with this condition?

Associated conditions include hiatal hernia, midgut volvulus, gastroesophageal reflux, and esophageal atresia.

CASE 25

A worried 24-year-old mother brings her 4-year-old daughter to the ED. She states the daughter has been ill for the past week with flu-like symptoms, including rhinorrhea, cough, headache, and nausea, which she has attempted to treat at home with at home medication. The child has been increasingly lethargic, and the mother found her barely responsive this morning. The child displays diminished consciousness and sluggish pupils. Kernig and Brudzinski signs are negative. She vomits multiple times in the ED and is admitted to the intensive care unit (ICU).

What is the most likely diagnosis?

Reye syndrome. Although extremely rare, this diagnosis is devastating if missed.

What drug did the mother likely administer to the patient?

Aspirin. Always suspect Reye syndrome in a child who has altered mental status, vomiting, and has suffered a recent viral illness.

What other laboratory findings are expected?

This patient is at risk for developing hepatic failure, cerebral edema, and death. Characteristic laboratory findings include the following:

- Severe transaminitis (aspartate aminotransferase and alanine aminotransferase $>$ 3000 U/L).
- Normal or slightly elevated bilirubin.
- Hypoglycemia.
- Hyperammonemia.
- Prolonged prothrombin time and international normalized ratio.
- Anion gap metabolic acidosis with mixed respiratory alkalosis.

What is the pathophysiology of this condition?

It is thought that salicylate metabolites during viral infection damage mitochondria and/or that susceptible individuals have an underlying polymorphism in mitochondrial function. **Mitochondrial dysfunction** leads to increased short-chain fatty acids, hyperammonemia, and cerebral edema, although the exact mechanism is unclear.

What is the association between the patient's recent flu-like symptoms and the current presentation?

Although the etiology of Reye syndrome is unknown, the condition typically occurs after a viral infection, particularly an upper respiratory tract infection, influenza, varicella, or gastroenteritis, and is associated with aspirin use during the illness.

What is a possible explanation for the child's change in mental status?

Cerebral edema is the likely cause. If cerebral edema can be controlled, the liver usually makes a full recovery. Therefore, ICU management is essential.

Options for controlling cerebral edema include the following:

- Mannitol (acts as an osmotic diuretic).
- Hyperventilation (reduces systemic carbon dioxide and leads to constriction of the cerebral vasculature).
- Barbiturates (reduces brain stem metabolism and therefore cerebral blood flow).
- Ventricular drainage (shunts cerebrospinal fluid).

Despite treatment, the patient dies. What pathologic findings are expected?

Microvesicular fatty change (steatosis) of the liver, kidneys, and brain may be seen on autopsy.

For what disease process is aspirin approved and is first line in treating pediatric patients?

Kawasaki disease is the only disease process for which aspirin is first-line treatment in the pediatric population.

CASE 26

A 3-month-old girl born prematurely has been maintained on parenteral nutrition since a length of her bowel was resected secondary to necrotizing enterocolitis when she was 2 weeks of age. The resected bowel included the ascending colon, ileum, and distal portion of the jejunum. She is unable to thrive on enteral feeding alone.

What condition explains the patient's inability to thrive solely on enteral feeding?

Short bowel syndrome due to extensive bowel resection leading to malabsorption.

After resection of the ileum, which specific molecules will be malabsorbed?

Vitamin B_{12} and **bile salts** are absorbed exclusively in the ileum and thus are deficient in short bowel syndrome.

The remainder of the patient's jejunum has adapted by increasing the number of cells in the villi, thereby lengthening the villi. What term describes this type of adaptation?

Adaptation that increases the number of cells within a tissue is known as **hyperplasia**. This is in contrast to **hypertrophy**, in which the cells increase not in number but in size.

During bowel transplantation, which branch(es) of the aorta must be identified and anastomosed to supply blood to the jejunum, ileum, and ascending colon?

- The **superior mesenteric artery** supplies blood to the intestine from the proximal jejunum to the proximal transverse colon.
- The **celiac trunk** supplies the stomach, liver, spleen, and duodenum.
- The **inferior mesenteric artery** supplies the distal transverse colon, descending colon, and sigmoid colon.

How might octreotide be used in this patient?

As a **somatostatin analog**, octreotide inhibits the release of gastrin. This reduces gastric secretions that would otherwise be in excess compared to the length of bowel and further impede absorption.

How will malabsorption of bile salts affect this patient's prothrombin time (PT) and partial thromboplastin time (PTT)?

Malabsorption of bile salts leads to an inability to properly absorb fat and fat-soluble vitamins (ADEK). PT and PTT both increase secondary to a lack of vitamin K, which is a necessary cofactor in the γ-carboxylation of multiple clotting factor glutamate residues.

In healthy individuals, where are the nutrients iron, folate, and B_{12} absorbed?

It is useful to remember the mnemonic "**Iron Fists Bro**" to indicate **I**ron is absorbed in the duodenum, **F**olate in the jejunum, and vitamin **B_{12}** in the ileum.

CASE 27

A 45-year-old man presents to the ED after vomiting approximately one-half cup of blood. Two days earlier, he began having nausea and colicky, nonradiating abdominal pain. He has an extensive history of alcohol abuse and currently drinks 8–10 beers a day. He has a medical history of pancreatitis and hematemesis, and he currently takes no medications. Digital rectal examination reveals dark, heme-positive stool.

What is the most likely diagnosis?

Upper gastrointestinal (GI) bleed.

What are the potential causes of this condition in this patient?

- **Esophagogastric varices** (collateral circulation in the case of portal hypertension).
- **Mallory-Weiss tears** of the esophageal mucosa (usually with a history of extensive retching before the onset of hematemesis).
- **Boerhaave syndrome** (complete rupture of the esophagus, usually with preceding retching).
- **Peptic ulcer disease** (cause of 55% of upper GI bleeds in all adults).
- **Tumors**.

What anatomic structure distinguishes an upper GI bleed from a lower GI bleed?

The **ligament of Treitz** marks the junction between the duodenum and the jejunum. Bleeding proximal to the ligament of Treitz is defined as an upper GI bleed.

If this patient had presented with BRB per rectum rather than dark stool, would the diagnosis change?

Not necessarily. A brisk upper GI bleed may also present with bright red blood per rectum, in which case there is insufficient transit time for breakdown of heme.

If the patient were previously diagnosed with esophageal varices, what medication may have been prescribed to prevent an upper GI bleed?

Nonselective **β-blockers** such as propranolol reduce blood flow in the portal system by creating unopposed α-adrenergic vasoconstriction of the mesenteric vessels. Because of the adverse effect of bronchoconstriction, patients with asthma, chronic obstructive pulmonary disease, and other pulmonary conditions must be carefully evaluated before use.

What is the management for this condition?

In cases of massive hematemesis, the first goal is intravenous fluid resuscitation and stabilization. **Nasogastric tube lavage** is indicated to prevent aspiration. It is also used to distinguish between upper and lower sources of GI bleeding and to identify high-risk lesions as sources of bleeding. Depending on the patient's condition, the next step could be either a diagnostic or therapeutic endoscopy.

CASE 28

A 37-year-old woman with a 20-year history of Crohn disease presents to her primary care physician complaining of fatigue. Physical examination reveals tachycardia (heart rate: 106/min), pale conjunctivae, angular cheilitis, and a beefy red tongue. Relevant laboratory findings include a hematocrit of 21% and an elevated mean corpuscular volume.

What is the most likely diagnosis?

Vitamin B_{12} deficiency.

What are the functions of the vitamin implicated in this condition, and how does its deficiency result in this presentation?

Vitamin B_{12} is a cofactor for methionine synthase, which catalyzes the transfer of a methyl group from *N*-methyltetrahydrofolate to homocysteine, producing tetrahydrofolate (TH_4) and methionine. Decreased production of TH_4 interferes with DNA synthesis required for hematopoiesis (see Figure 8-18A), resulting in megaloblastic anemia. Vitamin B_{12} is also a cofactor for methylmalonyl CoA mutase (see Figure 8-18B), an enzyme involved in the catabolism of odd-numbered fatty acid chains.

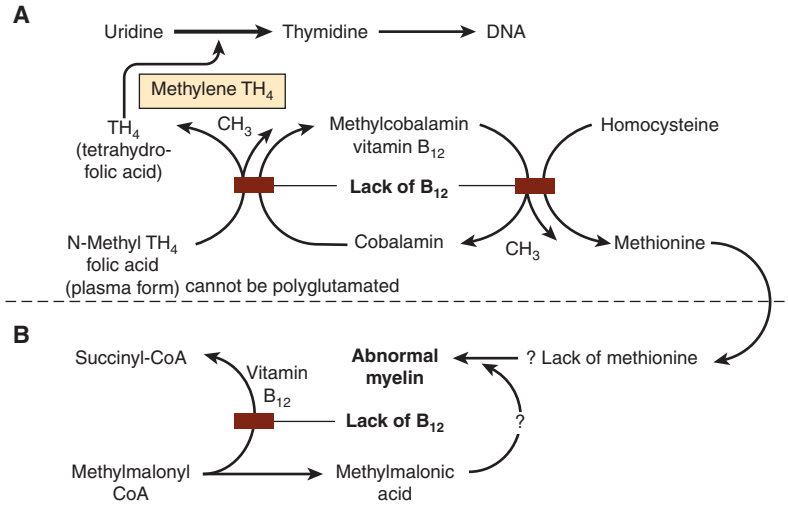

FIGURE 8-18. Role of cobalamin (vitamin B_{12}) and folic acid in nucleic acid and myelin metabolism. Lack of either cobalamin or folic acid retards DNA synthesis (A) and lack of cobalamin leads to loss of folic acid, which cannot be held intracellularly unless polyglutamated. Lack of cobalamin also leads to abnormal myelin synthesis, probably via a deficiency in methionine production (B). (Redrawn with permission from Hammer GD, et al. eds. *Pathophysiology of Disease: An Introduction to Clinical Medicine*, 7th ed. New York: McGraw-Hill; 2013.)

What are the possible causes of this patient's condition?

The most common cause of vitamin B_{12} deficiency is **pernicious anemia**, an autoimmune disorder in which **intrinsic factor**–producing gastric parietal cells are destroyed. Intrinsic factor is necessary for vitamin B_{12} absorption.

Other causes include malabsorption (eg, celiac sprue, enteritis, or *Diphyllobothrium latum* infection) and absence of the terminal ileum (as in Crohn disease or surgical resection). Vitamin B_{12} deficiency is rarely due to insufficient dietary intake. However, after several years, strict vegetarians are at risk, because the nutrient is found only in animal products.

For what other condition is this patient at risk?

B_{12} deficiency leads to subacute combined degeneration of the spinal cord, mostly affecting the posterior columns. Neurologic problems often manifest as paresthesias and ataxia. Over time, symptoms such as spasticity and paraplegia can develop. The exact role of vitamin B_{12} deficiency in this pathology is unclear. Neurologic symptoms are often irreversible.

What other vitamin deficiency can cause megaloblastic anemia?

Folic acid deficiency. Although there is an elevated level of serum homocysteine as in vitamin B_{12} deficiency, accumulation of methylmalonic acid (see Figures 8-18 A and B). and neurologic symptoms are not associated with folic acid deficiency.

CASE 29

A 47-year-old white man is brought to the ED by a policeman after being found wandering and incoherent on the streets. He has multiple watery bowel movements on arrival. Physical examination reveals a pigmented, scaling rash on his neck, arms, and hands, as well as glossitis.

What is the most likely diagnosis?

Vitamin B_3 (niacin) deficiency. This is commonly known as pellagra and is characterized by the **4 Ds**: **D**ementia, **D**iarrhea, **D**ermatitis, and eventually **D**eath.

What is the function of vitamin B_3?

Niacin is a precursor for oxidized nicotinamide adenine dinucleotide (NAD^+) and reduced nicotinamide adenine dinucleotide phosphate (NADPH). **NAD** helps carry reducing equivalents away from catabolic processes, such as oxidative phosphorylation. **NADPH** is used as a supply of reducing equivalents in anabolic reactions, such as the biosynthesis of steroids and fatty acids to maintain reduced glutathione, and in the oxygen-dependent respiratory burst of macrophages.

From what amino acid is vitamin B_3 derived?

Tryptophan.

What are the most likely causes of this presentation?

In developed nations, pellagra is seen most commonly in alcoholics (due to malnutrition). It can also be seen in patients with **Hartnup** disease (a disorder of tryptophan absorption) and carcinoid syndrome (in which there is increased conversion of tryptophan to serotonin). Isoniazid inhibits the conversion of tryptophan to niacin; therefore, patients receiving isoniazid are often prescribed niacin replacement. Figure 8-19 shows the conversion of tryptophan.

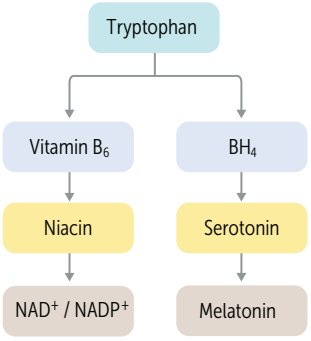

FIGURE 8-19. Conversion of tryptophan. (Reproduced with permission from USMLE-Rx.com.)

What are the symptoms of vitamin B_3 overdose?

Prostaglandin-mediated flushing is a symptom seen in overdose. Patients receiving niacin as a treatment for hypertriglyceridemia may experience this adverse effect. Prophylaxis with aspirin often prevents this reaction.

CASE 30

A 35-year-old woman presents to her physician complaining of several days of severe, gnawing epigastric pain. The pain is worse between meals and is somewhat relieved with milk, food, and antacids. She has had three peptic ulcers in the past 2 years. The pain is occasionally accompanied by diarrhea. She denies bloody stools or hematuria and does not use alcohol or tobacco. Upper endoscopy reveals prominent gastric folds and an erosion in the first portion of the duodenum. The patient's fasting gastrin level is 700 pg/dL.

What is the most likely diagnosis?

A history of recurrent peptic ulcers suggests Zollinger-Ellison (ZE) syndrome, in which there is hypersecretion of gastrin from a gastrinoma, resulting in high gastric acid output.

What are the common risk factors for peptic ulcer disease?

- *Helicobacter pylori* infection.
- Nonsteroidal anti-inflammatory drugs.
- Smoking.

With what endocrine disorder is this condition associated?

Approximately 20% of patients with ZE syndrome also have **multiple endocrine neoplasia** type I (Wermer syndrome). Such patients will also have parathyroid adenomas, resulting in hyperparathyroidism, and/or anterior pituitary tumors.

How is secretion of gastric acid normally regulated?

Gastric acid is secreted by *parietal cells* of the stomach in response to gastrin, acetylcholine (vagal input), and histamine (see Figure 8-20). Acid secretion is inhibited by somatostatin.

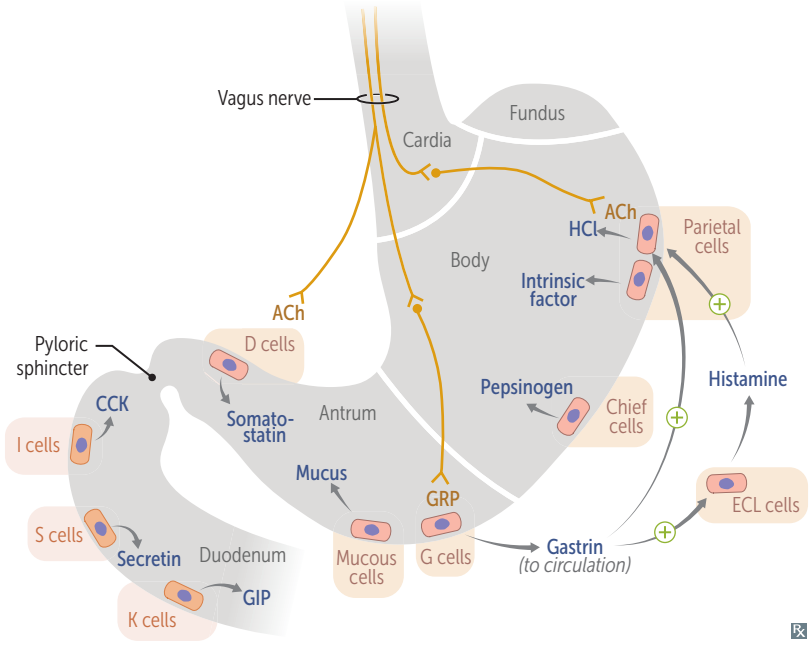

FIGURE 8-20. Gastrin increases secretion primarily through its effects on enterochromaffin-like (ECL) cells (leading to histamine release) rather than through its direct effect on parietal cells. (Reproduced with permission from Le T, et al. *First Aid for the USMLE Step 1: 2019.* New York: McGraw-Hill, 2019.)

What is the pathophysiology of this patient's diarrhea?

The voluminous acid secretion overwhelms the buffering capacity of pancreatic bicarbonate. Thus, pancreatic enzymes are inactivated in this acidic environment, impeding digestion. Excess acid also interferes with the emulsification of fats, leading to steatorrhea.

What are the treatments for this condition?

Surgical treatment involves resection of the gastrinoma (typically at the head of pancreas). Medical treatment uses proton pump inhibitors to suppress gastric acid secretion.

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9
Hematology and Oncology

CASE 1

A 27-year-old woman with a history of major depressive disorder and insomnia presents with severe abdominal pain, sudden onset 3 days ago. She has had similar attacks in the past, which she thought were due to menstruation. On physical examination, the patient has lower extremity hyporeflexia and generalized weakness, which is worse in the lower extremities. Urinalysis reveals urine that darkens on exposure to air and light. The porphobilinogen level is 110 mg/24 h (normal 0.0–1.5 mg/24 h).

What is the most likely diagnosis?

Acute intermittent porphyria (AIP).

What biochemical defect is responsible for this condition?

AIP is caused by a deficiency in **porphobilinogen deaminase** (also known as **hydroxymethylbilane synthase**), an enzyme required for heme production (see Figure 9-1). Acute accumulations of porphobilinogen cause patients to experience sudden abdominal pain and neuropsychiatric symptoms, including polyneuropathy and depression. These attacks are precipitated by factors that induce the activity of the upstream enzyme α-aminolevulinic acid (ALA) synthase, such as endogenous/exogenous gonadal steroids, drugs (sulfonamides, antiepileptics), alcohol, low-calorie diets, and stress.

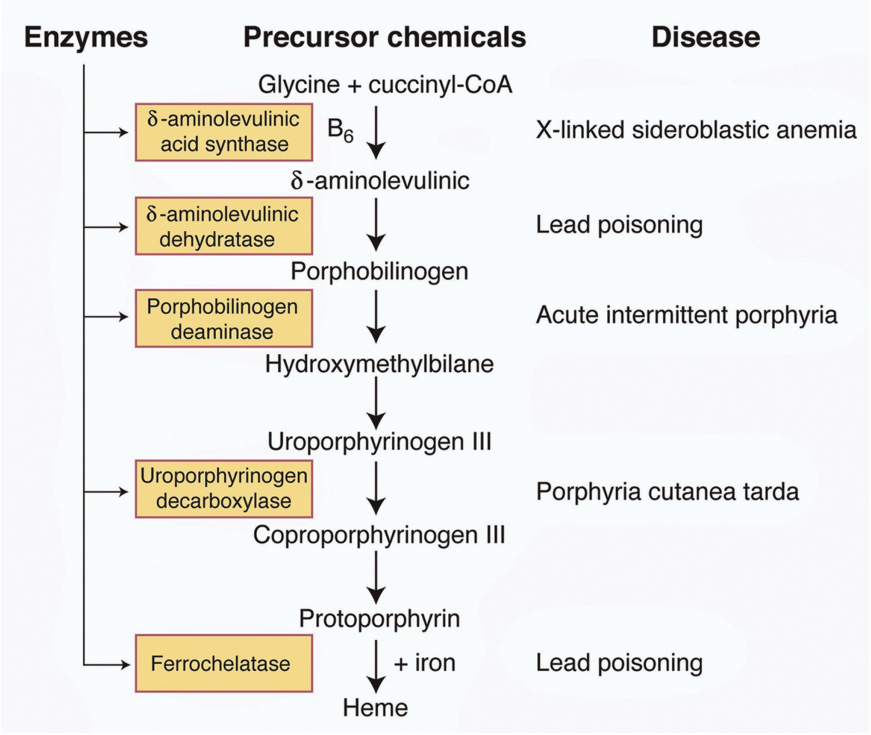

FIGURE 9-1. Heme synthesis. (Reproduced with permission from USMLE-Rx.com.)

What other condition should be considered if the patient has neurologic manifestations but no abdominal pain?

Ascending muscle weakness with hyporeflexia or areflexia is the classic presentation of **Guillain-Barré syndrome**. Though the high level of porphobilinogen is diagnostic of AIP in this patient, a lumbar puncture can be performed in uncertain cases; a finding of albuminocytologic dissociation (high protein, normal cell count) in the cerebrospinal fluid would point to Guillain-Barré syndrome as the diagnosis.

What is the treatment for this patient's condition?

In the acute setting, dextrose can be administered intravenously, as it is a repressor of ALA synthase. When a patient's symptoms are refractory to carbohydrate loading with dextrose, hemin may be used. Heme is the end product of the biosynthetic pathway and represses ALA synthase activity, thus reducing the severity of symptoms. Treatment of pain (supportive care) and monitoring for neurologic and respiratory compromise are essential. In terms of long-term care, dietary modifications should be considered in order to minimize ingestion of known triggers, such as alcohol.

CASE 2

The parents of a 4-year-old girl bring their daughter to the pediatrician because they are concerned about her fever, which has lasted for more than a week. Her parents have also noticed that she is less energetic and now walks with a limp. Physical examination is significant for hepatomegaly, scattered petechiae, and bruising over many surfaces of her body. Relevant laboratory finding are as follows:

Hemoglobin: 6 g/dL
White blood cell (WBC) count: 25,000/mm^3
Platelet count: 39,000/mm^3
Lactate dehydrogenase (LDH): 500 U/L

A peripheral blood smear is performed (see Figure 9-2).

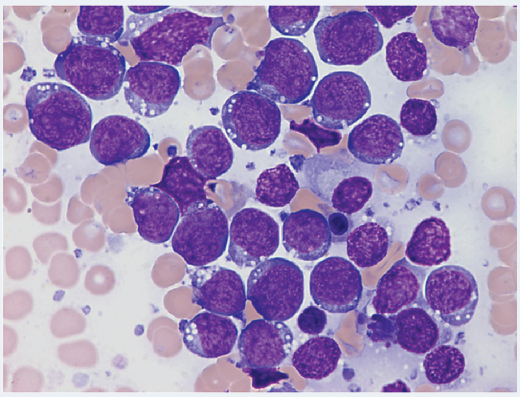

FIGURE 9-2. (Reproduced with permission from Kaushansky K, et al. eds. *Williams Hematology*, 9th. ed. New York: McGraw-Hill; 2016.)

What is the most likely diagnosis?

Acute lymphoblastic leukemia (ALL) is the most common malignancy of childhood. The classic presentation and laboratory findings include fever (the most common sign), fatigue, lethargy, bone pain, arthralgia, and elevated serum LDH.

What conditions should be considered in the differential diagnosis?

Idiopathic thrombocytopenic purpura (ITP) may be considered due to the low platelet count and the associated petechiae and purpura; however, ITP does not present with anemia or leukocytosis. Aplastic anemia is possible given the patient's symptoms and the marked anemia and thrombocytopenia; however, leukocytes should also be low in aplastic anemia, as it is characterized by pancytopenia. Infectious mononucleosis is another fitting diagnosis given the laboratory values, as viral infections cause a lymphocytosis and the splenomegaly of mononucleosis causes red blood cell and platelet sequestration; however, infectious mononucleosis almost always presents with pharyngitis and lymphadenopathy, which are absent in this patient. Finally, the peripheral blood smear (see Figure 9-2) shows a predominance of lymphoblasts (immature lymphocytes that are typically only seen in the bone marrow). This alone can rule out these other differential diagnoses.

What is the etiology of the physical examination findings?

In ALL, the white cell population expands and crowds out the normal marrow, causing anemia (fatigue, lethargy) and thrombocytopenia (easy bruising, petechiae). If the white cells invade the periosteum, a patient can also present with diffuse bone or joint pain. The most common symptom, fever, results from the excess number of white cells releasing pyrogenic cytokines. Painless enlargement of the scrotum and central nervous system symptoms may be a sign of more extensive extramedullary invasion. Finally, elevated LDH is a consequence of increased cellular turnover and is seen as a nonspecific feature of neoplasia.

What is the treatment for this condition?

Complex chemotherapy regimens are the standard, and the prognosis is very good. Recent advances in treatment have resulted in complete remission rates as high as 90% in children with ALL.

What genetic disorder is associated with this condition in children?

Trisomy 21 (Down syndrome).

CASE 3

A 67-year-old man presents to his physician with a 10-day history of fatigue, bleeding gums, cellulitis, and a recent weight loss of 9 kg (20 lb). On physical examination, the patient is pale but has no evidence of lymphadenopathy or hepatosplenomegaly. Results of a complete blood count are as follows:

WBC count: 18,300/mm^3 (75% blastocysts, 20% lymphocytes)
Hemoglobin: 9.1 g/dL,
Hematocrit: 29%
Platelet count: 98,000/mm^3

What is the most likely diagnosis?

Acute myelogenous leukemia (AML) is the most common acute leukemia in adults. The median age of diagnosis in the United States is 65 years.

What cells are affected in this condition?

AML is a neoplasm of myelogenous progenitor cells. The progenitor cells may appear as granulocyte precursors, monoblasts, megakaryoblasts, or erythroblasts.

What other symptoms are common in this condition?

Presenting symptoms are related to the pathophysiology of the disease. The thrombocytopenia manifests as epistaxis and petechiae, while the anemia can manifest as fatigue and shortness of breath. Gingival hyperplasia and leukemia cutis (skin infiltrates) are indicators of the extramedullary expansion of the leukemic cells. Finally, AML patients can present widespread thrombosis and bleeding as a manifestation of disseminated intravascular coagulation, occurring most classically with the **acute promyelocytic leukemia** (APL) subtype, though it may appear in other subtypes as well.

What are the likely bone marrow biopsy findings in this condition?

The proliferation of myeloblasts with characteristic eosinophilic, needle-like cytoplasmic inclusions, or **Auer rods**, is pathognomonic for AML (see Figure 9-3).

Auer rods represent collections of proteolytic enzymes within the leukemic cells. When released in large quantities, the enzymes can trigger the coagulation cascade and provoke disseminated intravascular coagulation, which is characterized by widespread thrombosis and bleeding.

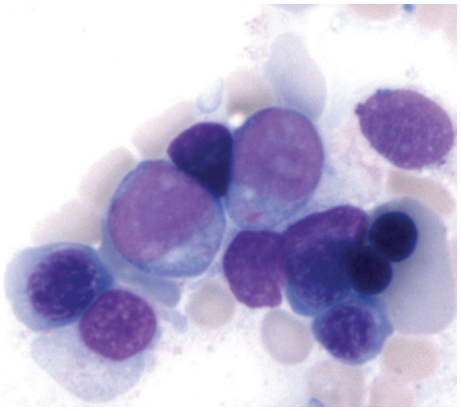

FIGURE 9-3. Auer rods in acute myelogenous leukemia. (Reproduced with permission from USMLE-Rx.com.)

How can genetic testing influence treatment?

Knowledge of the specific genetic abnormality a patient with AML has is critical for the diagnosis and treatment of their condition. For example, APL (formerly M3 AML) is a subtype of AML that is characterized by the t(15;17) chromosomal translocation and its associated fusion protein PML-RARα. It can be treated very effectively using all-*trans*-retinoic acid, a vitamin A derivative, which differentiates the less mature promyelocytes into the more mature neutrophils and induces the apoptosis of the excess leukemic cells.

Why is cellulitis commonly associated with this condition?

The leukemic expansion of white blood cells causes the population of mature white blood cells to shrink. The resulting neutropenia increases the susceptibility of the skin and soft tissue to infection.

CASE 4

A 27-year-old man is brought to the ED by ambulance after a motor vehicle accident. He was a restrained passenger in a two-car collision. He is complaining of left upper quadrant pain. On physical examination he appears restless and agitated, and he is noted to be tachycardic and tachypneic.

What organ is most likely injured in this case?

The spleen. It is an important organ in immune function and hematopoiesis. The primary function of the spleen is clearance of abnormal RBCs, microorganisms, and particulate matter from the bloodstream. Additionally, it is involved in hematopoiesis (extramedullary hematopoiesis) and synthesis of IgG, properdin, and tuftsin.

What is the normal size of this organ?

A normal spleen is nonpalpable. Spleens that are prominent and palpable below the costal margin are abnormal. Figure 9-4A is a CT scan of a man with splenic injury due to blunt trauma. This scan, obtained soon after contrast administration, shows multiple large lacerations of the spleen, hematoma, and perihepatic free fluid. Figure 9-4B, obtained after the contrast had cleared, more clearly shows a large laceration on the posterior surface of the spleen extending anteriorly to the hilum.

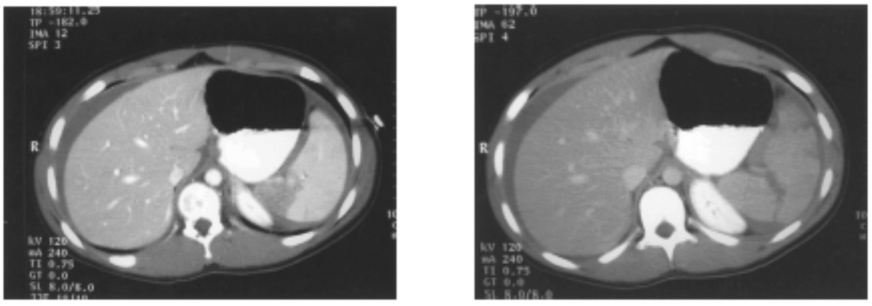

FIGURE 9-4. (A) CT of spleen early after contrast administration in a patient with blunt trauma to the spleen. (B) CT of spleen after contrast clears more clearly shows splenic laceration. (Reproduced, with permission, from Stone CK, et al. *Current Emergency Diagnosis & Treatment,* 5th ed. New York: McGraw-Hill, 2004: 471.)

What would you find on physical exam?

The spleen is located under the rib cage in the left upper quadrant of the abdomen, below the diaphragm. Therefore, during palpation, descent of an enlarged spleen is felt on inspiration.

Where is the most common site of referred pain in this injury?

Left shoulder and trapezius ridge tenderness (C3–C5 dermatomes, same as the roots of the phrenic nerve) may also be present as a result of subdiaphragmatic phrenic nerve irritation. Referred pain is due to subdiaphragmatic pooling of blood.

Why is a blunt injury to this organ so concerning?

The spleen is a highly vascular organ that filters up to 15% of the total blood volume per minute. The spleen can hold an average of 40–50 mL of RBCs in reserve and can pool significantly more blood. Therefore, severe blunt trauma or laceration of the spleen resulting in a rupture is so concerning because large amounts of blood can leak into the abdominal cavity, causing hemorrhagic shock and even death.

What is the major concern for a patient postsplenectomy?

The major concern is sepsis from encapsulated bacterial organisms. ***Streptococcus pneumoniae***, ***Neisseria meningitidis***, and ***Haemophilus influenzae*** vaccinations are essential since encapsulated organisms are usually cleared by the spleen. Vaccinations are usually given several weeks before splenectomy, if possible, or 2 weeks after in an emergent case. Antibiotic prophylaxis for dental procedures and empiric treatment for fever are also vital given the immunocompromised state of the asplenic patient.

CASE 5

A 14-year-old boy presents to his pediatrician with a laceration on his hand that has become badly infected. Upon questioning, the boy says he has felt fatigued for some time. Physical examination reveals pallor of the mucous membranes in addition to bleeding on the inside of his cheeks. Petechiae cover his body, and patches of purpura are present on his thighs, trunk, and arms. Relevant laboratory findings are as follows:

WBC count: 2000/mm^3
Hematocrit: 22%
Platelet count: 48,000/mm^3

What is the most likely diagnosis?

Aplastic anemia results from bone marrow failure or autoimmune destruction of myeloid stem cells, which leads to pancytopenia. Pancytopenia affects all cell lines, resulting in neutropenia, anemia, and thrombocytopenia, all of which are seen on a complete blood count.

What is the most likely cause of this patient's condition?

Most cases of aplastic anemia are idiopathic. Other possible causes include the following:

- **Viral agents** (eg, parvovirus B19, hepatitis viruses, HIV, Epstein-Barr virus).
- **Drugs** and **chemicals** (eg, alkylating and antimetabolite agents, chloramphenicol, insecticides, arsenic, and benzene)
- **Radiation**
- **Immune disorders** (eg, systemic lupus erythematosus, graft-versus-host disease)
- **Pregnancy**
- **Hereditary transmission (eg, Fanconi anemia)**

Note: The diagnosis is not considered aplastic anemia if tumor, fibrosis, or myelodysplasia is present, as the bone marrow failure is secondary to some other primary diagnosis.

What other test can help confirm the diagnosis?

A bone marrow biopsy can be performed to diagnose aplastic anemia. Normally, a biopsy of the bone marrow should show an equal predominance of the cells and fat. In contrast, the regenerative function is suppressed in aplastic anemia, so the marrow appears hypocellular (< 30% cellularity) and infiltrated with fat on biopsy, as seen in Figure 9-5.

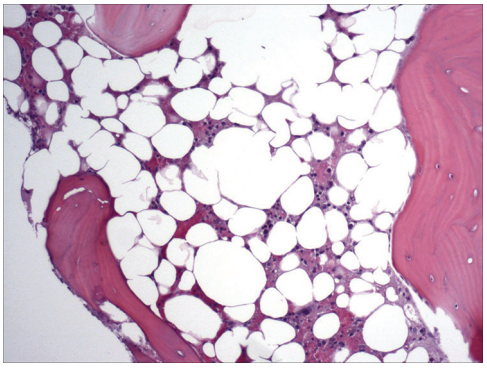

FIGURE 9-5. Biopsy of hypocellular bone marrow in aplastic anemia. (Reproduced with permission from USMLE-Rx.com.)

What is the treatment for this condition?

Initial treatment is to withdraw any possible toxic agent causing the condition. Since the patient is neutropenic and anemic, supportive care, including antibiotics for infection and blood transfusion if symptoms develop, is important. If the patient is found to have a fever, antibiotic coverage for *Pseudomonas* is recommended, as neutropenic fevers predispose patients to such infections. If testing reveals severe depression of one or several cell lines, definitive therapy, including stem cell transplantation or immunosuppression, is appropriate. If possible, transfusions should be avoided before bone marrow transplantation because of the risks of alloimmunization and graft rejection.

What is the difference between aplastic anemia and aplastic crisis?

Aplastic anemia refers to a complete bone marrow failure, resulting in pancytopenia. In contrast, aplastic crises are episodes of pure red cell aplasia; the white cell count and platelet count should be normal in an aplastic crisis.

CASE 6

A 66-year-old postmenopausal woman presents to her physician with complaints of fatigue, dyspnea, and dizziness. She says she craves chewing on ice cubes. Physical examination reveals tachycardia and pallor of the mucous membranes of her mouth. The cells on a peripheral blood smear are shown in Figure 9-6. Relevant laboratory findings are as follows:

Hemoglobin: 11 g/dL
Hematocrit: 30%
Reticulocyte count: 0.2%
MCV: 74 fL

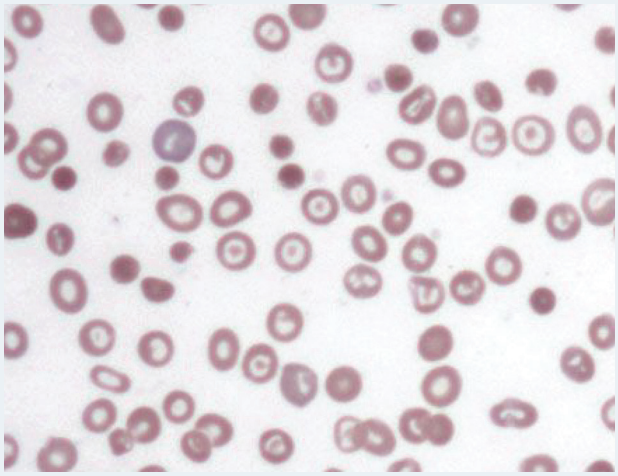

FIGURE 9-6. (Reproduced with permission from USMLE-Rx.com.)

What is the most likely diagnosis?

Iron deficiency anemia. The peripheral blood smear shows hypochromic RBCs, and the MCV reveals microcytosis. This diagnosis would be supported by laboratory studies demonstrating a **decreased iron concentration, increased total iron binding capacity,** and **decreased ferritin levels.** The cause for a patient's iron deficiency, however, needs to be further pursued. In addition, comorbid inflammatory conditions can raise serum ferritin, resulting in values within the normal range. The patient's craving for ice is one example of pica, defined as craving and chewing substances that have no nutritional value (ie, ice, clay, soil). A craving specifically for ice is often associated with iron deficiency anemia.

What factors can lead to this condition?

Causes of iron deficiency anemia include the following:

- Chronic blood loss (especially gastrointestinal blood loss secondary to colon cancer)
- Dietary deficiency (increased demand or decreased absorption)
- Intestinal hookworm infection (this is the most common cause worldwide and should be considered in patients who have immigrated from developing countries).

In general, in a postmenopausal woman and all men, one must look for GI blood loss in any newly diagnosed patient with iron deficiency anemia unless the cause of the iron loss is obvious (ie, recent trauma).

Why are total iron-binding capacity (TIBC) measurements important in this condition?

TIBC is high in iron deficiency anemia and low in anemia of chronic disease. Both illnesses have decreased serum iron levels. A low ferritin ($<$ 41 ng/mL) is sensitive and specific for iron deficiency anemia. The normal iron/TIBC ratio is typically 0.25–0.45, and levels $<$ 0.12 indicate iron deficiency. Anemia of chronic disease often has a normal iron/TIBC ratio because of the concomitant decrease of TIBC and serum iron.

This patient is at greatly increased risk for developing what other conditions?

While this patient's iron deficiency is moderate, patients with extreme cases of deficiency are at risk for Plummer-Vinson syndrome. This syndrome is characterized by atrophic glossitis, esophageal webs, and anemia.

What are the common causes of microcytic, hypochromic anemia?

Microcytic anemia results from either decreased hemoglobin production or faulty hemoglobin function. Common causes include iron deficiency, thalassemia, sideroblastic anemia, and lead poisoning.

CASE 7

A 45-year-old man presents to his physician for a regular checkup. He has no previous medical or surgical history. The patient is complaining of a sense of imbalance and that his feet feel slightly numb with occasional sensation of pins and needles. The patient has been eating a well-balanced diet and denies alcohol intake. As part of the checkup, the physician orders routine laboratory tests; relevant findings are as follows:

Hemoglobin: 11 g/dL
Hematocrit: 33%
Reticulocyte count: 0.2%
MCV: 120 fL

What is the most likely diagnosis?

The tests indicate a macrocytic anemia. However, macrocytic anemia is not a diagnosis in itself, and a cause for the anemia must be determined.

What other laboratory test can be used to determine the diagnosis?

In this patient we suspect vitamin B_{12} deficiency (megaloblastic anemias), given the high MCV and neurologic findings. In megaloblastic anemias, a peripheral blood smear reveals the presence of hypersegmented neutrophils (more than five nuclei) (see Figure 9-7).

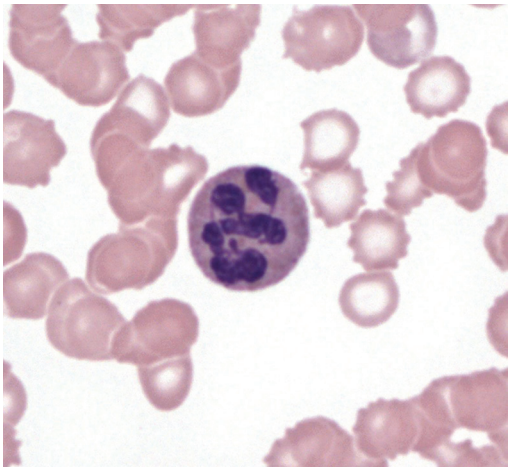

FIGURE 9-7. Hypersegmented neutrophil. (Reproduced with permission from USMLE-Rx.com.)

What are some possible etiologies for this condition?

Etiologies of macrocytic anemia include the following:

- Alcoholism
- Folate deficiency
- Vitamin B_{12} deficiency
- Hypothyroidism
- Myelodysplastic syndrome or myeloma
- Pharmaceutical agents (especially antimetabolites such as methotrexate or chemotherapeutic agents)

What findings distinguish vitamin B_{12} from folate deficiency?

- Vitamin B_{12} deficiency results in subacute combined degeneration of the dorsal columns of the spinal cord, causing loss of vibration and position sense. Also, methylmalonic acid is elevated in the urine of patients with B_{12} deficiency. In folate deficiency, there are **no neurologic findings** and no rise in methylmalonic acid levels in the urine.

CASE 8

A 4-year-old African-American girl is brought to her physician by her mother because she has been complaining of episodes of extreme pain and discomfort in her legs and lower back. On physical examination, she appears jaundiced and has a hematocrit of 23% and a hemoglobin level of 7 g/dL. Her mother reports she has family members who experienced the same symptoms.

What is the most likely diagnosis?

Sickle cell anemia.

What is the typical presentation of this condition?

Sickle cell anemia develops at approximately 6 months of age when hemoglobin S (HbS) replaces hemoglobin F (HbF). Painful crises, which are believed to be a result of hypoxic tissue injury from microvascular occlusions, often occur.

What is the pathophysiology of this condition?

HbS is the result of a single missense mutation in the β-globin gene of hemoglobin (negatively charged glutamate is replaced by neutrally charged valine and position 6). This makes hemoglobin susceptible to polymerization in conditions of low oxygen or dehydration (see Figure 9-8), dramatically reducing the flexibility of the RBC membrane. Any organ can be affected by the vascular congestion, thrombosis, and infarction caused by sickling cells, so patients tend to have multiple health problems. The combination of sickle cell anemia and thalassemia is common and can also result in sickle crises.

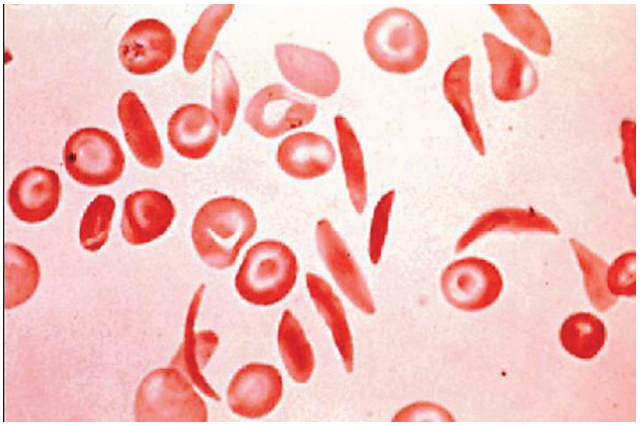

FIGURE 9-8. Sickle and target cells in the setting of sickle cell anemia. (Reproduced with permission from USMLE-Rx.com.)

What complications are common in patients with this condition?

- Painful (vaso-occlusive) crisis and chronic pain as the patient ages
- Aplastic crisis (cessation of erythropoiesis due to parvovirus B19 infection)
- Splenic sequestration crisis
- Autosplenectomy, which increases susceptibility to encapsulated organisms, like *Pneumococcus*
- Increased susceptibility to infections, especially osteomyelitis due to *Salmonella*
- Priapism
- Stroke
- Leg ulcers
- Acute chest syndrome (fat emboli, infection, and vaso-occlusion)
- Dactylitis
- Myocardial infarction; congestive heart failure
- Increased propensity for blood clots
- Iron overload from increased number of transfusions

What are the typical radiologic findings in this condition?

The marrow expansion caused by the profound anemia can lead to resorption of bone and subsequent new bone formation on the external aspect of the skull. This leads to a "crew-cut" appearance on skull radiographs.

What is the treatment for this condition?

Appropriate supportive care, including pain control and intravenous fluids, for acute sickle complications is the mainstay of therapy. Attention to the psychological impact of this disease, with social and psychiatric support, is essential to help patients deal with this disabling, painful disease. Additional medical therapy includes hydroxyurea, which increases HbF production, thereby reducing the number of cells with the potential to sickle. Exchange transfusion with normal RBCs may reduce the sickle RBC percentage and is used to treat the life-threatening complications of acute chest syndrome, stroke, and splenic sequestration.

CASE 9

A 32-year-old woman with systemic lupus erythematosus (SLE) presents to the ED reporting increased fatigue and lethargy for the past 3 months. On physical examination, she is afebrile and has mild splenomegaly. Laboratory test results are as follows:

Hemoglobin: 10.1 g/dL
Hematocrit: 30.6%
Reticulocyte count: 5%.

Figure 9-9 presents a peripheral blood smear. The direct and indirect Coombs tests are positive at 37°C (98.6°F) but not at 4°C (39.2°F).

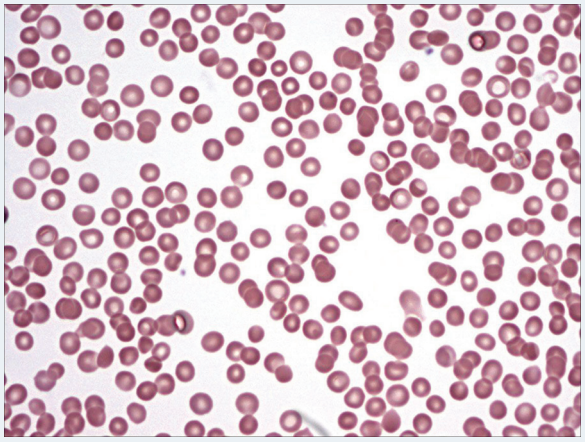

FIGURE 9-9. (Reproduced with permission from USMLE-Rx.com.)

What is the most likely diagnosis?

Warm autoimmune hemolytic anemia (WAIHA) secondary to SLE. The smear in Figure 9-9 demonstrates spherocytes, which can be found in warm autoimmune hemolytic anemias. They are characterized by a smaller, circular shape and often lack the central pallor of normal erythrocytes due to loss of the biconcave disc shape. Most cases of this condition are idiopathic or associated with autoimmune processes, lymphoproliferative disorders, or drugs.

What does the positive Coombs test indicate?

The positive Coombs test indicates the presence of antibodies against RBCs, which can cause intravascular or extravascular hemolysis. In an otherwise healthy patient, hemolysis will trigger reticulocytosis.

What is the difference between a direct and indirect Coombs test?

The Coombs reagent is an antihuman immunoglobulin that recognizes erythrocyte-bound immunoglobulins. In the direct Coombs test, a patient's blood is collected and directly incubated with the Coombs reagent; agglutination is considered a positive direct result and suggests that the patient has antibodies bound against her own red blood cells. In the indirect Coombs test, a patient's serum (which contains immunoglobulins) is collected and first incubated with a donor's red blood cells, and then the Coombs reagent is added; agglutination after addition of the Coombs reagent is a positive indirect result and suggests that the patient has antibodies against another person's red blood cells.

What are other causes of this condition?

The two most common causes are primary (idiopathic) and secondary due to such underlying conditions as autoimmune disorders, such as SLE. Medications (methyldopa, penicillin), lymphomas, and leukemias are also common triggers.

What is the pathogenesis of this condition?

WAIHA is typically an **IgG**-mediated process. IgG coats RBCs and acts as an opsonin for the RBCs to be phagocytosed by monocytes and splenic macrophages; this is *extravascular* hemolysis.
When medications are the underlying cause, the hapten model has been suggested, in which a drug binds the surface of an RBC and the immune system recognizes the pair as an antigen. Autoantibodies are produced and bind the RBC-drug pair, targeting the complex for extravascular hemolysis as well.

What is the other form of this condition?

Cold autoimmune hemolytic anemia is the other form, and it occurs when **IgM** antibodies bind RBCs at low temperatures, fix complement, and cause **intravascular** hemolysis. These cold agglutinins typically appear acutely following certain infections such as **mononucleosis** and ***Mycoplasma***. This disease is usually self-limited, but treatment-resistant forms exist. Clinical manifestations include pallor and cyanosis of distal extremities exposed to cold temperatures; this is secondary to vascular obstruction from complement deposition.

CASE 10

A 57-year-old nulliparous woman presents to her general practitioner concerned about a painless lump she has found in the right upper quadrant of her right breast. Her mother died of breast cancer at 60 years of age. Her medical history is significant for mild obesity, an early onset of menarche, and a late onset of menopause 3 years previously. She has noted some unilateral pain and dimpling of her right breast but has been scared to make an appointment with her physician. Laboratory tests show a serum calcium level of 9.7 mg/dL.

What is the likely diagnosis?

Breast cancer is the leading cause of cancer death in women, and the second leading cause of cancer overall in women. Most tumors develop in the upper/outer quadrant due to the greatest density of breast parenchyma in this location. There are many different types of breast cancer (see Table 9-1).

Table 9-1. Types of Breast Cancer

Type	Characteristics
Ductal carcinoma in situ.	Noninvasive, premalignant condition.
Invasive ductal carcinoma.	75% of invasive breast cancers.
Medullary, mucinous, and tubular breast cancer.	15% of invasive breast cancers.
Invasive lobular carcinoma.	10% of invasive breast cancers.
Phyllodes tumors, lymphomas, and sarcomas.	Rare invasive breast cancers.
Inflammatory carcinoma or Paget disease of the breast.	Not specific histologic types of cancer; rather, these are morphologic characteristics of breast cancer (induration, skin puckering, and erythema of the breast).

What is the pathophysiology of this patient's condition?

Breast cancer results from a transforming, or oncogenic, event that leads to clonal proliferation and survival of breast cancer cells. There are two general types of breast cancer: sporadic and hereditary. The events that trigger sporadic breast cancer are often unknown, but abnormalities in cell-cycle pathways, including HER-2, estrogen, and progesterone signaling, have been implicated. *BRCA1* and *BRCA2* genes have been linked to hereditary breast and ovarian cancer (HBOC) and are linked to defects in DNA mismatch repair. Notably, hereditary breast cancer only accounts for 5%–10% of all breast cancers diagnosed in the United States. This patient appears to have the sporadic type, supported by the late onset of diagnosis, increased hormone exposure from early menarche, late menopause, and obesity.

What risk factors are associated with an increased incidence of this condition?

The risks of developing breast cancer are largely tied to the amount of estrogen, a trophic hormone, the breasts are exposed to. Early menarche, late menopause, and nulliparity all represent increased numbers of menstrual cycles, and thus greater amounts of estrogen. Even postmenopausal women may be prone to breast cancer if they are obese because adipose tissue releases estrogen, or if they are being treated for menopausal symptoms with hormone replacement therapy. Other important risk factors include:

- Female gender.
- Alcohol intake.
- Breast density.
- Age.
- Family history (50%–70% of women carrying the *BRCA1* or *BRCA2* mutations develop breast cancer).
- Prior breast biopsy, particularly for lesions with atypia.
- Radiation exposure to the chest.

What are predictive and prognostic factors related to the treatment of this condition?

A predictive factor indicates whether a patient's particular variant of breast cancer will respond to a certain therapy. For example, if a tumor is positive for estrogen receptor (ER+), it will respond well to hormonal manipulation, and if it is positive for HER2/neu, it will respond well to monoclonal antibodies such as trastuzumab. On the other hand, a prognostic factor indicates the likely outcome in untreated patients based on the expected natural progression of the cancer. For example, the most important prognostic factor is lymph node involvement, indicating rapid progression of the disease when there is extensive involvement. "Triple negative" breast cancers (ER−, PR−, HER2/neu−) are another poor prognostic factor.

CASE 11

A 13-year-old boy is brought to his physician for increasing abdominal distention and pain that has lasted 7 days. Physical examination reveals decreased bowel sounds, tympany, and lower abdominal tenderness. CT scan of the abdomen shows a 6-cm mass involving the distal ileum. A biopsy of the mass is taken under radiographic guidance. The histologic sample shows sheets of intermediate-sized lymphoid cells with nonconvoluted nuclei and coarse chromatin along with many macrophages (see Figure 9-10).

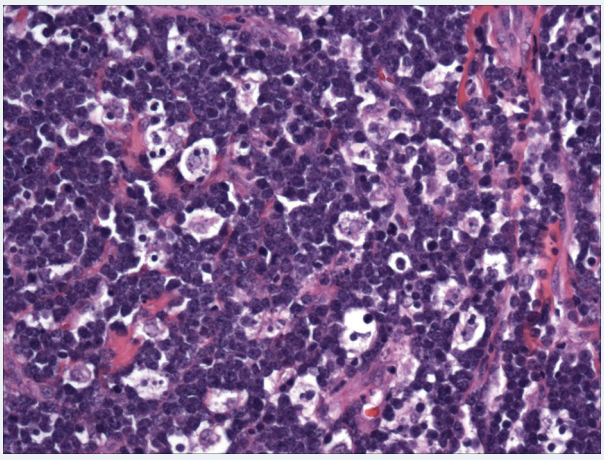

FIGURE 9-10. (Reproduced with permission from USMLE-Rx.com.)

What is the most likely diagnosis?

Burkitt lymphoma, a highly aggressive B-cell non-Hodgkin lymphoma. The "**starry-sky**" pattern on histology (see Figure 9-10) is classic for this condition and is characterized by dark neoplastic tumor cells with interspersed benign macrophages that are often referred to as "tingible body macrophages." Burkitt lymphoma of the gastrointestinal tract typically involves the ileocecum and peritoneum.

What are the three forms of this condition?

- The **sporadic** form, as described in this vignette, is the most common form in the developed world and appears in children and young adults as an abdominal mass.
- The **African/endemic** form, which is closely associated with Epstein-Barr virus (EBV) infection, is another type. In this type, the lymphoma typically presents as a maxillary or mandibular mass of the jaw.
- The **HIV-associated** form is the final type and may stem from reactivation of latent EBV virus in immunosuppressed patients. It typically arises in lymph nodes.

What is the typical cytogenetic change in this condition and what gene does it involve?

All forms of Burkitt lymphoma involve the *c-MYC* gene found on chromosome 8. The characteristic translocation is t(8;14), which places the *c-MYC* proto-oncogene adjacent to the immunoglobulin heavy-chain locus on chromosome 14, a locus that is physiologically highly expressed. This results in overexpression of *c-MYC*, a transcription factor that controls cellular metabolism, leading to increased cell growth. The tumor cells are typically CD20, CD10, and BCL-6 positive.

The heavy-chain locus of chromosome 14 is constantly transcribed because there is an ongoing physiological need for immunoglobulins. Thus, many lymphomas are associated with translocations involving this locus in order to take advantage of its high level of expression. For example, the t(14;18) translocation is classic for follicular lymphoma, allowing the Bcl-2 locus of chromosome 18 to be highly expressed. Bcl-2 is an antiapoptotic factor, and its overexpression permits the development of a tumor.

What is the treatment for this condition?

Endemic Burkitt lymphoma is treated with chemotherapy, but HIV-associated and sporadic Burkitt are not necessarily as readily treatable. Both HIV-associated and sporadic cases also commonly metastasize to the central nervous system, requiring CNS radiation and intrathecal chemotherapy for control.

What is tumor lysis syndrome?

Tumor lysis syndrome is due to the large amount of neoplastic cell death during treatment with chemotherapy, typically seen in the most rapidly growing cancers, such as Burkitt lymphoma. Laboratory analysis shows multiple metabolic complications, including hyperphosphatemia, hypocalcemia, hyperuricemia, and hyperkalemia, leading to acute renal failure. Allopurinol or rasburicase, aggressive hydration, and diuresis can be used to prevent these consequences.

CASE 12

A 35-year-old man presents to his primary care physician complaining of several months' history of watery diarrhea. He reports that the diarrhea is often "greasy-looking" but never bloody. On physical examination, the man's face is flushed, and his neck is covered by a blotchy, violaceous erythema. When asked about this flushing, the man says it has happened several times a day over the past few years, often while he is feeling stressed at work.

What is the most likely diagnosis?

Carcinoid syndrome (secretory) is the most likely diagnosis. Approximately 75%–80% of carcinoid syndrome cases arise from a small bowel carcinoid tumor. However, only approximately 10% of carcinoid tumors result in carcinoid syndrome (see Table 9-2 for signs and symptoms).

Table 9-2. Clinical Characteristics in Patients with Carcinoid Syndrome

Symptoms/Signs	At Presentation	During Course of Disease
Diarrhea	32%–93%	68%–100%
Flushing	23%–100%	45%–96%
Pain	10%	34%
Asthma/wheezing	4%–14%	3%–18%
Pellagra	0–7%	0–5%
None	12%	22%

(Adapted, with permission, from Kasper DL, et al. *Harrison's Principles of Internal Medicine*, 20th ed. New York: McGraw-Hill, 2018.)

What is the pathophysiology of this condition?

Carcinoid syndrome occurs only when sufficient concentrations of substances secreted by carcinoid tumors (derived from neuroendocrine cells) reach the circulation. Carcinoid tumors secrete serotonin and a variety of other gastrointestinal peptides, including gastrin, somatostatin, substance P, vasoactive intestinal polypeptide, pancreatic polypeptide, histamine, and chromogranin A. Carcinoid syndrome is unlikely to occur in intestinal carcinoid tumors unless liver metastases are present because the serotonin that is secreted into the portal vein will be metabolized in the liver. Lung carcinoid tumors, however, do not require metastases to present with carcinoid syndrome.

What type of cardiac involvement is typically seen in patients with this condition?

Right-sided valvular involvement occurs in 11% of patients initially and up to 41% during the course of the disease. Cardiac disease results from serotonin-mediated fibrosis in the endocardium, most commonly in the tricuspid valve. Most patients with cardiac involvement ultimately develop heart failure.

What vitamin deficiency is most commonly seen in this condition?

B_3 (niacin) deficiency. Tryptophan is the common precursor in both niacin and serotonin synthesis, so when carcinoid tumors drain tryptophan stores to produce serotonin, a niacin deficiency results and can present as diarrhea, dermatitis, and dementia, a triad collectively known as pellagra.

What laboratory test can help confirm the diagnosis?

Many conditions, such as menopause, as well as reactions to alcohol, glutamate, and calcium channel blockers, may cause flushing. However, flushing in conjunction with an increase in **5-hydroxyindoleacetic acid**, a metabolite of serotonin (5-HT, 5-hydroxytryptamine), on urinalysis occurs only in carcinoid syndrome.

What are the histological features of this condition?

Carcinoid tumors are neuroendocrine tumors and will appear as small, round, blue cells on biopsy, just like all neuroendocrine tumors. However, a unique feature is that the cells are often arranged into distinguishable rosettes.

What is the treatment for this condition?

If localization of a discrete carcinoid tumor is possible, surgical resection is the optimal therapy. For other cases, symptomatic management with the somatostatin analog octreotide is most beneficial.

CASE 13

A 55-year-old woman presents to her primary care physician for a routine physical. She reports an unintentional 14-kg (30-lb) weight loss and chronic fatigue. Abdominal examination reveals an enlarged spleen. Relevant laboratory findings are as follows:

Hemoglobin: 12.9 g/dL
Hematocrit: 38.1%
Mean corpuscular volume: 92 fL
WBC count: 167,000/mm^3
Platelet count: 625,000/mm^3

A peripheral blood smear shows many late granulocytic precursor cells, eosinophils, and basophils; relatively few metamyelocytes. Cytogenetic analysis reveals a t(9;22) translocation.

What is the most likely diagnosis?

Chronic myelogenous leukemia (CML) is likely, given the t(9;22) translocation coupled with the uncontrolled production of maturing granulocytes, platelets, and mild anemia (see Figure 9-11). This marked leukocytosis leads to **splenic enlargement**. Because basophilia is such an uncommon laboratory finding, its presence is a strong indicator of CML.

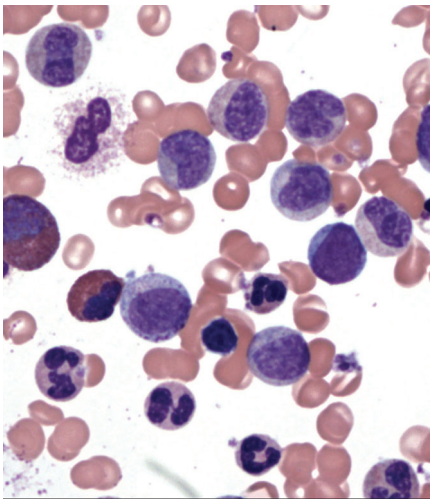

FIGURE 9-11. Chronic myelogenous leukemia, blood film. Leukemic promyelocytes, a basophilic myelocyte, and segmented neutrophils with increased nuclear material. (Reproduced with permission from USMLE-Rx.com.)

What is the differential diagnosis?

A leukemoid reaction may present very similar to this patient. It consists of a benign neutrophilia with an increase in granulocyte precursor cells in response to some sort of stress or infection, and it is considered a normal physiological response. Because the smears of these two conditions may appear very similar, the leukocyte alkaline phosphatase levels may be measured to distinguish the two; in CML, the levels are low, and in leukemoid reactions, the levels are high. The presence of basophilia and cytogenetic studies may also be used to distinguish the two.

What chromosomal abnormality is indicative of this condition and what is its product?

The translocation of the *BCR* gene on chromosome 22 with the *ABL* gene on chromosome 9 leads to the Bcr-Abl fusion product. This abnormality is called the **Philadelphia chromosome**, and it is considered pathognomonic for CML. It is important to note that it may also be seen in acute lymphoblastic leukemia, though its presence is a poor prognostic factor.

What is the pathophysiology of this condition?

This Bcr-Abl fusion protein results in a constitutively active Abl **tyrosine kinase** in the Ras/Raf/MEK/MAPK pathway. This leads to inhibition of apoptosis and unregulated cell division.

What is the targeted drug treatment for this condition?

Imatinib, a highly specific Bcr-Abl tyrosine kinase competitive inhibitor, has been the agent of choice and has radically changed the prognosis for CML patients. Dasatinib is a second-line treatment. Either treatment has shown a 90% cytologic remission rate. Though allogeneic bone marrow transplantation has been used for potential cure in the past, it is now used only in selected patients who fail to achieve cytogenetic remission with tyrosine kinase inhibitors.

What is a blast crisis?

Untreated CML inevitably progresses, usually in 3–5 years, to an accelerated phase and then a blast crisis in which additional genetic abnormalities accumulate, ultimately leading to acute myeloid (or 20% of the time lymphoid) leukemia. Peripheral smears will show a large percentage ($>$ 20%) of blast cells, consistent with an acute leukemia.

CASE 14

A 70-year-old man visits his primary care physician complaining of constant vague abdominal pain that has been increasing over the past month. He has noted recent weakness and weight loss, which he attributes to a decreased appetite. His father was diagnosed with colorectal cancer in his late fifties. The patient admits never having a colonoscopy and eats a diet high in fat and low in fiber. Rectal exam reveals a palpable mass and occult blood. Laboratory tests reveal that the patient's hematocrit is 28%.

What is the most likely diagnosis?

Colorectal cancer (CRC) is suggested by the symptoms of abdominal pain, anorexia, weight loss, palpable rectal mass, and anemia. Likewise, he has a family history of CRC at a relatively young age. CRC is the third-leading cause of cancer death in men (after lung and prostate cancer).

What risk factors are associated with this condition?

- Age > 50 years
- Lifestyle (alcohol, obesity, low-fiber and high-fat diet)
- Family history/syndromes (hereditary nonpolyposis CRC [HNPCC], familial adenomatous polyposis [FAP])
- Diabetes
- Inflammatory bowel disease
- Tumor suppressor gene and proto-oncogene changes

What are the guidelines for primary screening of this condition?

Screening for CRC is recommended between the ages of 50–75 (or younger for high-risk patients) and includes various modalities, such as fecal occult blood test (FOBT), colonoscopy, and flexible sigmoidoscopy. When someone has a positive FOBT, it is recommended to undergo colonoscopy to rule out polyps. If the colonoscopy is negative, annual colonoscopy is considered invasive and is not recommended; a follow-up colonoscopy in 10 years is the norm. A negative FOBT, on the other hand, requires no additional work-up until the next year, when a repeat stool test is recommended.

In high-risk patients, such as those with genetic risk factors (ie, familial adenomatous polyposis, hereditary nonpolyposis colorectal cancer), family history, and/or personal history of colorectal neoplasia, earlier and more frequent screening is recommended due to the early progression of the disease. For example, in patients with a first-degree relative with a history colorectal cancer, recommended screening should begin at age 40 or 10 years before the age at which the relative was diagnosed, whichever comes first.

What signs and symptoms are commonly associated with this condition?

Signs and symptoms of colorectal cancer include abdominal pain, anemia with low mean corpuscular volume (MCV) due to loss of iron through bleeding, bleeding/mucus per rectum, changes in bowel habits, weight loss, and tenesmus (the feeling of needing to pass stool with an empty rectal vault). Though symptoms may overlap between right- and left-sided colon cancers, right-sided or ascending cancers tend to grow as masses into the lumen of the colon and bleed, whereas left-sided or descending cancers tend to grow in a ring within the wall of the colon and obstruct the passage of stool.

What are the treatments for this condition?

Surgical treatment is usually the initial treatment of choice. Adjuvant chemotherapy will depend on tumor, node, and metastases (TNM) staging. While radiation therapy is not first line, it may be useful in patients for whom tumors cannot be surgically resected. Additionally, rapid advances are being made in targeted therapies used to treat colorectal cancer and both EGFR and VEGF inhibitors are approved for use in CRC disease; however, it is not an effective screening marker.

CASE 15

A 33-year-old African-American woman has been in the intensive care unit for 2 days after being admitted for treatment of a severe bacteremia. Her medical history is noncontributory. Physical examination reveals mucosal bleeding, oozing from intravenous access sites, and petechiae on her trunk and extremities. Laboratory tests reveal a prolonged prothrombin time (PT), activated partial thromboplastin time (aPTT), and bleeding time.

What is the most likely diagnosis?

Disseminated intravascular coagulation (DIC).

What is the pathophysiology of this condition?

DIC is a systemic process in which widespread activation of hemostasis causes thrombosis, and the excessive consumption of clotting factors results in hemorrhage (see Figure 9-12). This contrasts with localized hemostasis, which does not deplete coagulation factors.

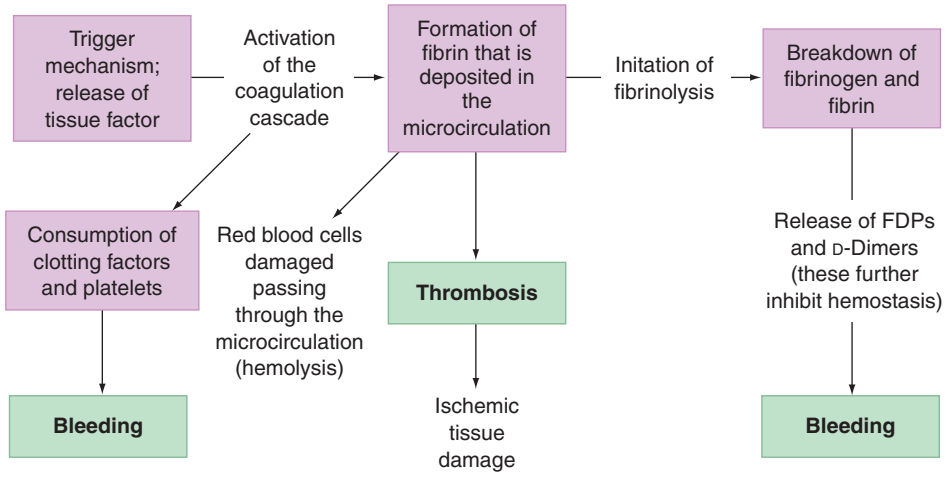

FIGURE 9-12. Pathophysiology of disseminated intravascular coagulation. (Reproduced with permission from Tintinalli JE, et al. *Tintinalli's Emergency Medicine: A Comprehensive Study Guide*, 8e; New York: McGraw-Hill; 2016.)

What are the common causes of this condition?

- Infectious causes include sepsis.
- Malignant causes include acute leukemia (especially acute myeloid leukemia) and other cancers (eg, prostate, causing a chronic DIC).
- Other causes include trauma, obstetric complications (eg, abruptio placentae, amniotic fluid embolism), and snake venom.

Which clotting factors are involved in the intrinsic, extrinsic, and common pathways?

The **intrinsic pathway** involves factors VIII, IX, XI, and XII, prekallikrein, and high-molecular-weight kininogen. The **extrinsic pathway** involves factor VII. The **common pathway** involves factors II, V, and X and fibrinogen (see Figure 9-13).

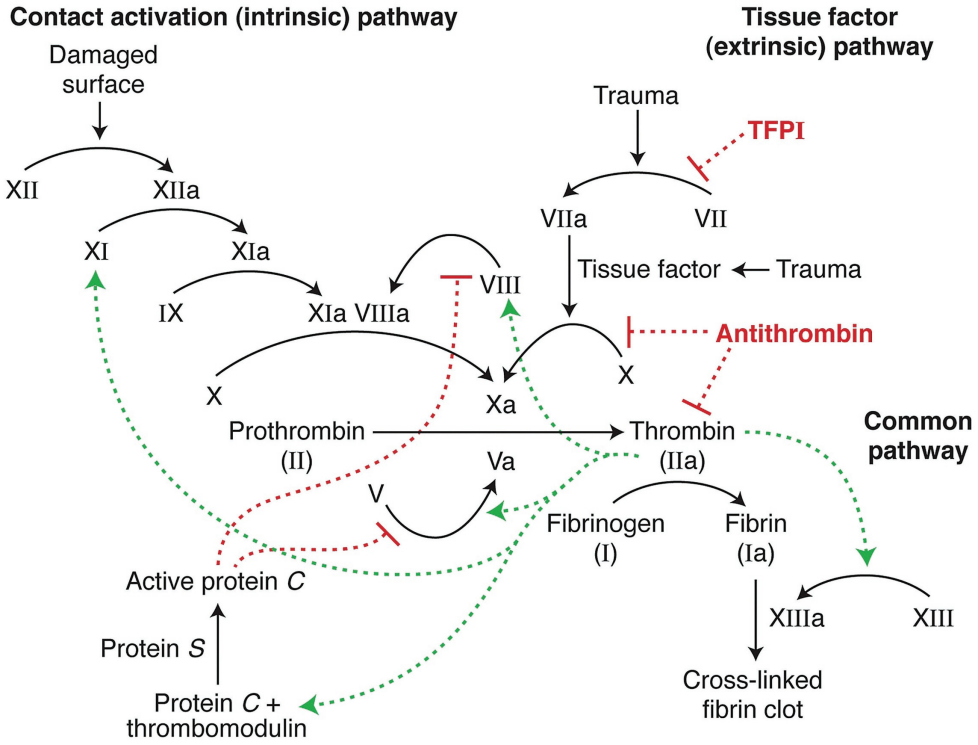

FIGURE 9-13. The clotting cascade. (Reproduced with permission from USMLE-Rx.com.)

Which laboratory tests help differentiate this condition from thrombocytopenia?

DIC is classically diagnosed from an elevated PT, elevated PTT, low fibrinogen, and high D-dimer. Bleeding time will also be low secondary to thrombocytopenia. Isolated thrombocytopenia would not show elevated coagulation tests.

What is the prognosis and treatment of this condition?

DIC mortality ranges from 40% to 80% when associated with sepsis, burns, or trauma. Treatment of the underlying condition causing DIC is essential. Hemodynamic support is the mainstay of acute treatment, but correction of coagulopathy with platelet or coagulation factor replacement may be necessary if there is a serious risk of bleeding (eg, recent surgery or fibrinogen $<$ 100 mg/dL). Fresh frozen plasma can be used to correct the PT/PTT while cryoprecipitate is used if the fibrinogen is $<$ 100 mg/dL.

CASE 16

A 56-year-old man presents to the ED complaining of a 1-day history of nausea and vomiting, with a 13.6-kg (30-lb) unintentional weight loss over the past few months. He noticed black specks in his emesis resembling coffee grounds. He reports early satiety with a decreased appetite, specifically for meat. He has no diarrhea, constipation, known sick contacts, or recent travel history but notes occasional fevers and chills with recent night sweats. Physical examination reveals that the patient is afebrile with a nontender, nondistended, soft abdomen with a firm epigastric mass. A stool test was performed and was guaiac positive, negative for ova and parasites. Relevant laboratory findings are as follows:

Hematocrit: 28%
Hemoglobin: 9 g/dL
WBC count: 9000/mm^3

What is the most likely diagnosis?

Gastric cancer. The diagnosis is definitively determined via esophagogastroduodenoscopy (EGD) and biopsy. The main finding on EGD is the development of linitis plastica, a diffuse thickening of the gastric wall that prevents expansion and leads to early satiety, a common complaint in patients with gastric cancer.

What risk factors are associated with this condition?

Risk factors for gastric cancer are as follows:

- ***Helicobacter pylori*** infection (causes intestinal metaplasia)
- Barrett esophagus (gastroesophageal junction adenocarcinoma)
- Diet (nitroso compounds and high salt intake)
- Smoking
- Low socioeconomic status
- Male gender (female reproductive hormones are protective)
- Obesity
- Previous gastric surgery
- Epstein-Barr virus infection (causing gastric lymphoma)

What signs and symptoms are commonly associated with this condition?

- Anorexia (especially for meat)
- Dysphagia (caused by lesions at the cardia of the stomach)
- Coffee-ground emesis (if bleeding tumor)
- Palpable epigastric mass
- Postprandial heaviness
- Vomiting (in cases of pyloric obstruction)
- Weight loss

If disease has metastasized:

- Intra-abdominal masses
- Virchow node (left supraclavicular node)
- Sister Mary Joseph node (periumbilical nodes)
- Krukenberg tumor (bilateral ovaries)

What are the typical laboratory findings in this condition?

Iron-deficiency anemia is present in 50% of patients.

What is the treatment for this condition?

Surgical resection may be achieved for early local disease. A combination of radiation and chemotherapy is often used along with resection in situations where the lesion is initially unresectable, or as adjuvant therapy post-surgery for node-positive disease.

CASE 17

A 42-year-old African-American man presents to the ED with sudden-onset shortness of breath. He complains of fatigue and weakness and says he saw blood in his urine for the first time this morning. He denies chest pain or palpitations and has no history of hypertension, coronary artery disease, or ischemic heart disease. He is being treated with trimethoprim-sulfamethoxazole for a urinary tract infection but has no other significant medical history. He denies alcohol or drug abuse. Physical examination reveals hepatosplenomegaly, mild scleral icterus, and tachycardia.

What is the most likely diagnosis?

Glucose-6-phospate dehydrogenase (G6PD) deficiency.

What is the pathophysiology of this condition?

G6PD protects cells from oxidative damage by converting nicotinamide adenine dinucleotide phosphate ($NADP^+$) to its reduced form (NADPH). NADPH carries electrons to reduce oxidized substances, such as oxidized glutathione. Reduced glutathione is required for cells to cope with oxidative stresses, such as those that are caused by ingestion of a sulfa drug (ie, trimethoprim-sulfamethoxazole) or dapsone. Patients with a deficiency in the G6PD enzyme lack reduced glutathione and are less able to cope with oxidant stressors. The unopposed oxidative stress causes the hemoglobin to precipitate into a Heinz body (see Figure 9-14), making the red blood cell more prone to hemolysis.

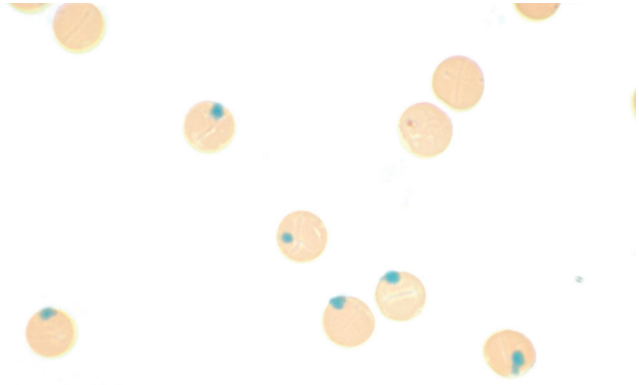

FIGURE 9-14. Heinz bodies, visualized with supravital stain. (Reproduced courtesy of Dr. Kristine Krafts.)

What are the typical peripheral blood smear findings in this condition?

Peripheral blood smear will likely reveal bite cells, the result of the spleen removing Heinz bodies from damaged red blood cells. Bite cells are otherwise normal-appearing red blood cells with a chunk, or "bite," missing from them. If the spleen is impaired, however, Heinz bodies may be present in the peripheral smear.

How is this condition acquired?

G6PD deficiency is an X-linked recessive trait, so it predominantly affects males. Heterozygous females are usually normal. Patients with G6PD deficiency are normal in the absence of oxidative stress. However, exposure to oxidative stress triggers the disease. G6PD in those with Mediterranean pedigrees results in favism, or hemolysis induced by the ingestion of fava beans.

What is the treatment for this condition?

Treatment is generally supportive with removal of the offending agent.

How are anemias classified in terms of cell volume?

- **Microcytic anemia** (MCV $<$ 80 fL) is caused by defects in heme or hemoglobin synthesis, iron deficiency, thalassemia, or lead poisoning.
- **Normocytic anemia** (MCV 80–100 fL) is caused by enzyme deficiency (such as G6PD or pyruvate kinase), blood loss (as from trauma), anemia of chronic disease, renal failure, or bone marrow aplasia.
- **Macrocytic anemia** (MCV $>$ 100 fL) can be caused by vitamin B_{12} or folate deficiency, warm or cold hemolysis, myeloma, liver disease, drugs that inhibit DNA synthesis, alcohol, and myelodysplasia.

CASE 18

A 67-year-old man presents to his physician with pain on swallowing and hoarseness. He has noted some swelling of the right side of his neck. The patient has smoked one pack of cigarettes per day since he was 15 years of age and drinks two beers nightly. Physical examination reveals a palpable neck mass and white plaques in his mouth.

What conditions should be considered in the differential diagnosis of a neck mass?

- **Congenital** causes of a neck mass include torticollis, thyroglossal duct cyst, brachial cleft cyst, cystic hygroma, dermoid cyst, and carotid body tumor.
- **Acquired** causes of neck mass include lymphoma, mononucleosis (Epstein-Barr virus/HHV4), other causes of lymphadenopathy, and cervical lymphadenitis.
- **Thyroid** causes include goiter (midline).
- **Malignant** causes include thyroid cancer (eg, papillary, medullary, follicular, or anaplastic types), lymphoma, and head or neck malignancy (eg, squamous cell or adenocarcinoma).

What is the most likely diagnosis?

Squamous cell tumor of the head and neck, given the patient's social history.

What risk factors increase this patient's likelihood of disease?

Tobacco and alcohol use are risk factors for both squamous cell tumors and adenocarcinoma of the head and neck. Human papillomavirus (HPV) infection is now becoming a more common risk factor in head and neck cancers, particularly in association with nonsmokers.

Which procedures can help confirm the diagnosis?

Diagnostic procedures include biopsy via fine-needle aspiration of the mass. The expected histological features on biopsy of a squamous cell tumor include accumulations of keratin, or "keratin pearls," and intercellular bridges representing desmosomes (see Figure 9-15). CT and/or MRI may also be useful to determine the stage and possible vascular involvement and resectability. If lymphoma is suspected, excisional biopsy should be performed.

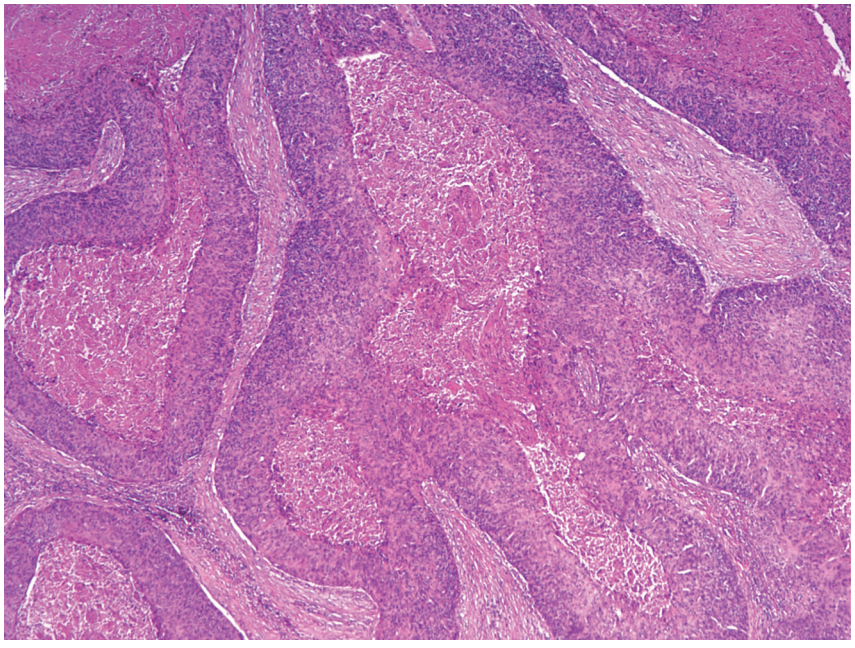

FIGURE 9-15. Squamous cell carcinoma of the larynx; central areas of keratinization, or pearls.
(Reproduced with permission from USMLE-Rx.com.)

Where are the lesions of this condition commonly located?

Head and neck cancers are typically found in the oral cavity, nasopharynx, larynx, oropharynx, and salivary glands.

What are the treatments for this condition?

Localized lesions are removed surgically or by radiotherapy. Palliative radiation is used for larger, more complex lesions. Combined chemotherapy and radiotherapy is the standard of care for advanced lesions.

CASE 19

A 55-year-old Caucasian man is brought to the ED after collapsing in a restaurant. He is conscious on arrival and claims he has not seen a doctor for many years. On physical examination, the patient appears jaundiced. An electrocardiogram (ECG) shows atrial fibrillation. Laboratory studies reveal an elevated serum glucose level and the following iron parameters:

Serum iron: 400 μg/dL
Transferrin: 150 μg/dL
Iron saturation: 85%
Ferritin: 2100 ng/mL

What is the most likely diagnosis?

Hereditary hemochromatosis (HH) is an autosomal recessive disease (with variable penetrance), resulting in excessive iron absorption. Excess iron gradually accumulates at a rate of approximately 0.5–1.0 g/year. Normal body iron content is approximately 3–4 g, and symptoms are noticeable at a body iron content exceeding 20 g. As a result, most men are not diagnosed until after 40 years of age, and women are not diagnosed until later due to iron loss in menstruation. Normal iron loss is 1 mg/day in men and 1.5 mg/day in menstruating women.

What is the pathophysiology of this condition?

Normally, iron homeostasis is achieved by regulating iron intake to compensate for losses through the skin, menses, pregnancy, and other processes. However, in HH, an autosomal recessive mutation in chromosome 6 (*HFE* gene) causes excessive iron to be absorbed through the intestine. This iron gradually deposits as hemosiderin throughout the body, particularly in the liver, skin, pancreas, joints, gonads, heart, and pituitary, which eventually leads to oxidative damage to these organs.

What signs and symptoms are commonly associated with this condition?

The classic triad in HH is cirrhosis, diabetes mellitus, and skin pigmentation, collectively referred to as "bronze diabetes." Other organs affected include:

- Heart: restrictive or dilated cardiomyopathy, conduction defects
- Joints: calcium pyrophosphate arthropathy (pseudogout), especially the metacarpophalangeal joints of the second and third digits
- Pituitary: hypogonadism (impotence in men), weakness/lethargy
- Gastrointestinal: increased risk of infection with *Yersinia enterocolitica*

What are the typical laboratory findings in this condition?

Iron saturation of > 60% in men or > 50% in women suggests HH 90% of the time. A cutoff of 45% for both men and women is typically used for simplicity. If you suspect hemochromatosis, genetic testing (a simple blood test) for the HH gene should be performed. Other typical laboratory findings include hyperglycemia, elevated liver enzyme levels, elevated serum iron levels, **decreased total iron binding capacity**, and **elevated ferritin levels**. A liver biopsy is not typically needed for diagnosis. If obtained, it will demonstrate intracellular accumulations of iron among widespread fibrosis (see Figure 9-16).

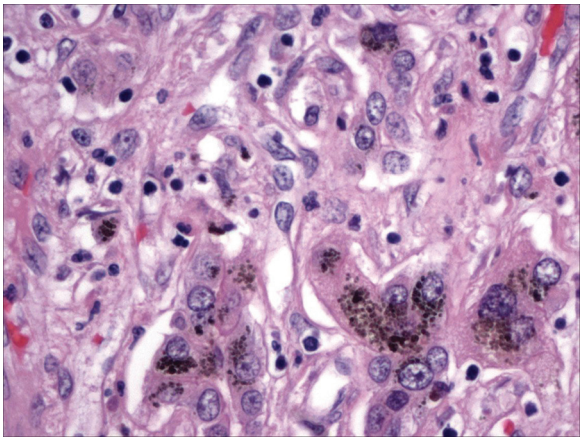

FIGURE 9-16. Liver biopsy. (Reproduced with permission from USMLE-Rx.com.)

What is the treatment for this condition?

Treatment for HH includes serial phlebotomy with the possible use of deferoxamine, an iron-binding agent, especially for patients with homozygous *HFE* mutations (C282Y) and iron overload. Compound heterozygotes with iron overload should also be treated. Deferoxamine can be used for severe iron overload or in those patients who cannot tolerate phlebotomy (eg, those with anemia or cardiac disease).

CASE 20

A 25-year-old man visits his primary care physician for a routine screening evaluation. He explains that he has been having fevers and drenching night sweats for the past 6 months. Additionally, he has been feeling increasingly tired and itchy over his entire body with no obvious explanation. On physical examination, the patient has lost 11 kg (25 lb) since his last visit and has a markedly enlarged nontender lymph node in his anterior cervical chain. A biopsy of this node is taken (see Figure 9-17).

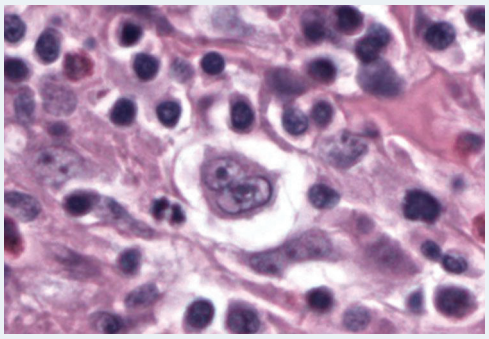

FIGURE 9-17. (Reproduced with permission from USMLE-Rx.com.)

What type of cell is depicted in Figure 9-17?

This is a Reed-Sternberg cell, characterized by large size, bilobed nucleus, and nucleolar inclusion bodies ("**owl's eyes**"). Classically, these cells, formed from germinal B cell centers, also display a common set of markers, including **CD15+ and CD30+** and are paradoxically negative for common B cell markers, including CD20.

What is the most likely diagnosis?

Hodgkin lymphoma. Most patients present with nontender asymptomatic palpable lymphadenopathy, often in the neck and supraclavicular area. Alternatively, many patients will present with a fairly large asymptomatic mediastinal mass on routine x-ray of the chest. Approximately one-third of patients experience fever, night sweats, weight loss, fatigue, and pruritus. There are five main classes of Hodgkin lymphoma (see Table 9-3).

Table 9-3. Five Main Types of Hodgkin Lymphoma

Type of Hodgkin	Relative prevalence	Histology, associations, and prognosis
Nodular sclerosis	Most common, especially among younger women	Fibrous bands dividing a lymph node into nodules; lacunar cells; carries a good prognosis
Lymphocyte-predominant	Uncommon	Lymphohistiocytic "popcorn cells"
Lymphocyte-rich	Uncommon	Reactive lymphocytes that comprise infiltrate; 40% of cases associated with Epstein-Barr virus
Lymphocyte-depleted	Least common	Very few lymphocytes, relatively plentiful Reed-Sternberg cells; associated with Epstein-Barr virus and HIV; poor prognosis
Mixed cellularity	Uncommon	Polymorphic infiltrate with plentiful Reed-Sternberg cells; 70% of cases associated with Epstein-Barr virus; associated with older age

What are B symptoms?

Classic B symptoms are unexplained weight loss, persistent or recurrent fevers, and drenching night sweats. These symptoms generally correlate with an advanced stage of disease and tumor burden and a slightly worse prognosis independent of stage.

What is the treatment for this condition?

More than 90% of patients with early-stage localized disease are cured with excision and localized radiotherapy. Patients with more advanced disease typically undergo the ABVD chemotherapy regimen consisting of doxorubicin (adriamycin), bleomycin, vinblastine, and dacarbazine. Cure rates for Hodgkin lymphoma are very high, even with advanced, stage 4 disease.

What is the difference between Hodgkin lymphoma and non-Hodgkin lymphoma?

While both Hodgkin and non-Hodgkin lymphomas can present with B symptoms, there are important distinctions. Hodgkin lymphomas are always B-cell lymphomas, involving Reed-Sternberg cells; non-Hodgkin lymphomas are usually B-cell lymphomas but may occasionally be comprised of T cells and have no characteristic cell on biopsy. Additionally, Hodgkin lymphomas tend to involve a single group of nodes and spread contiguously, while non-Hodgkin lymphomas spread erratically and involve multiple lymph nodes. Finally, Hodgkin lymphomas are likely to be associated with Epstein-Barr virus, whereas non-Hodgkin lymphomas tend to be related to HIV and other autoimmune conditions, such as *H pylori* gastritis, and have a worse prognosis.

CASE 21

An 11-year-old boy is brought to his physician because of frequent nosebleeds and "purple spots" on his body. He reports no recent history of trauma. Physical examination reveals petechiae and purpura on his arms, outer thighs, and ankles (see Figure 9-18).

A peripheral blood smear shows large platelets but no helmet cells or schistocytes. Results of a Coombs test are positive. Relevant laboratory findings are as follows:

Hemoglobin: 12.5 g/dL
Hematocrit: 36%
WBC count: 5000/mm^3
Platelet count: 11,000/mm^3
Bleeding time: 12 minutes
PT: 13 seconds
PTT: 25 seconds

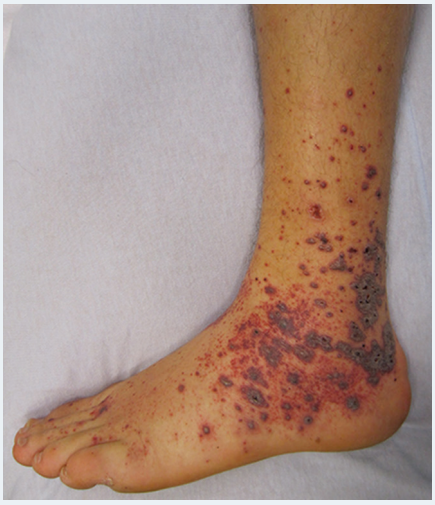

FIGURE 9-18. (Reproduced courtesy of Dr. James Heilman.)

What is the most likely diagnosis?

Idiopathic thrombocytopenic purpura (ITP), a disease that is associated with antiplatelet antibodies, is the most likely diagnosis. The patient presents with isolated thrombocytopenia (normal WBC and Hct), no coagulopathy, and given her age, ITP is the most common cause of thrombocytopenia.

What are the three main mechanisms of low platelet counts?

Thrombocytopenia may be caused by:

- Splenic sequestration (classically caused by sickle-cell disease, as RBCs and platelets become trapped in the spleen).
- Decreased production (stem cell failure, leukemia, aplastic anemia, EtOH, aspirin, clopidogrel).
- Increased destruction (ITP, thrombotic thrombocytopenic purpura, heparin, quinidine).

What clinical findings are commonly associated with this condition?

- ITP presents with mucous membrane bleeding, petechiae, and purpura (see Figure 9-18).
- Epistaxis (nosebleed) and easy bruising are characteristic of bleeding disorders in general. These symptoms are characteristic of platelet-related issues (ie, low quantity of platelets or poor quality of platelets); issues with coagulation factors, on the other hand, would present with bleeding into tissues (ie, hemarthroses, muscle hematomas, retroperitoneal hemorrhage).
- ITP in childhood usually develops after a viral infection or immunization and is self-limited.
- Adult ITP, in contrast, is often a chronic disease.

How is the etiology of this condition determined?

Thrombocytopenia can have a number of etiologies, which can be differentiated according to Figure 9-19.

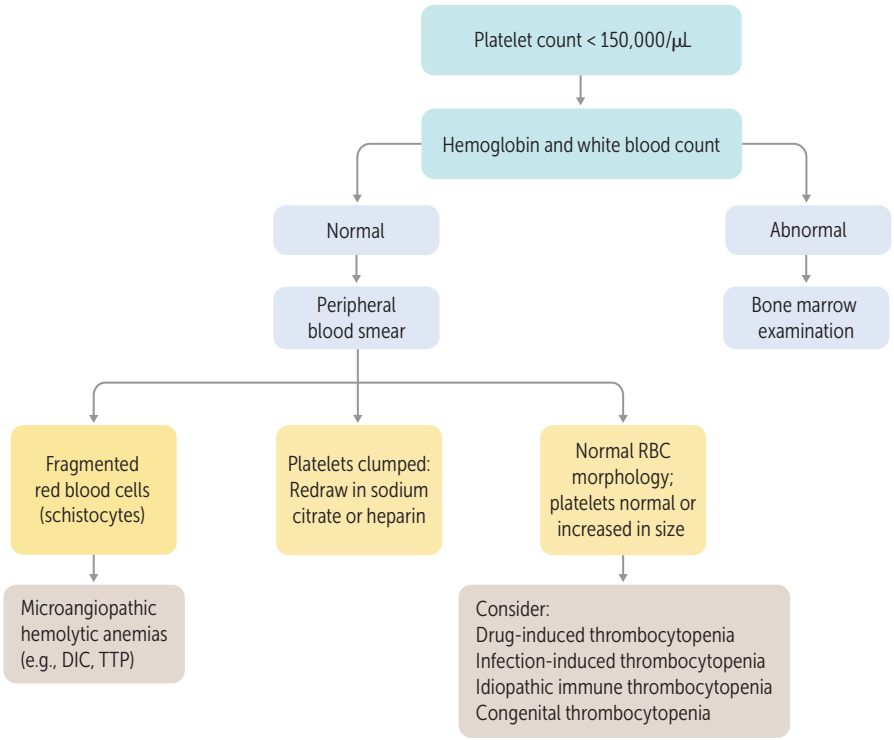

FIGURE 9-19. Algorithm for thrombocytopenia evaluation. (Reproduced with permission from USMLE-Rx.com.)

What are the treatments for this condition?

First-line treatment is high-dose steroids. Second-line treatment includes intravenous IgG, anti-Rh, splenectomy, or rituximab (anti-CD20). Thrombopoietin receptor agonists (romiplostim) have been shown to be highly effective in raising platelet counts for long-term control, but long-term safety data and cost of therapy are limiting factors in using these modalities as first-line therapy. Acute bleeding in ITP is treated with intravenous IgG followed by platelets and pulse methylprednisolone. It's important to note that treatment for ITP is controversial in children because many cases are self-limiting and may not require any form of treatment. In reality, treatment depends mostly on the severity of symptoms.

CASE 22

Upon presentation to his family physician, an 8-month-old boy is noted to have jaundice and dyspnea. Physical examination reveals tachycardia and splenomegaly. The mother recalls a long family history of "blood disease." A Coombs test is negative. Relevant laboratory findings are as follows:

Hemoglobin: 8.5 g/dL
Hematocrit: 29%
MCV: 85 fL
Mean corpuscular hemoglobin concentration (MCHC): 400 g/L

What is the most likely diagnosis?

Hereditary spherocytosis, an autosomal dominant form of hemolytic anemia.

What protein defect causes this condition?

RBC membrane defects are the result of mutations in **spectrin** or **ankyrin** (erythrocyte skeletal proteins). This results in a decreased membrane/volume ratio, which makes the cells more fragile. Therefore, a positive result on **osmotic fragility testing** is typically pathognomonic for the disease. Cells are trapped in the spleen, where they are destroyed.

What are the typical peripheral blood smear findings in this condition?

Small RBCs without central pallor (**spherocytes**) (see Figure 9-20) are seen on a peripheral blood smear.

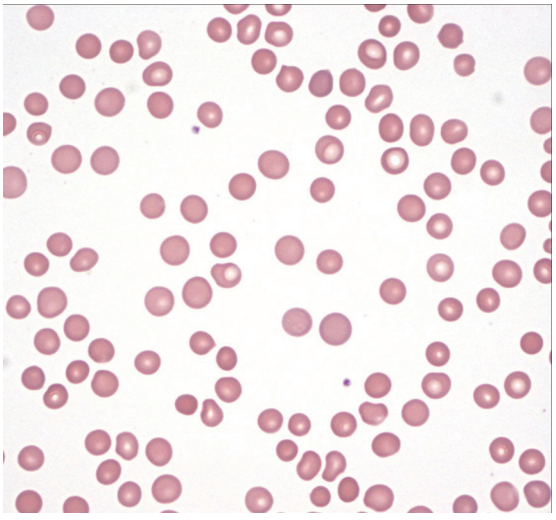

FIGURE 9-20. Spherocytosis. (Reproduced with permission from USMLE-Rx.com.)

What blood tests and findings can help establish the diagnosis?

- An osmotic fragility test may confirm the presence of fragile sphere-shaped RBCs.
- The MCHC is increased because of a reduction in membrane surface area in the setting of a constant hemoglobin concentration.
- MCV remains normal because the overall volume remains stable.
- High reticulocyte counts (5%–10%).
- Indirect bilirubin levels are elevated due to hemolysis.

What test could be used to differentiate this condition from autoimmune etiologies?

A direct Coombs test is used to distinguish hereditary spherocytosis from warm antibody hemolysis: Hereditary spherocytosis is Coombs negative, whereas warm antibody hemolysis is Coombs positive. A positive result on a **direct** Coombs test indicates the presence of antibodies on RBCs. A positive result on an **indirect** Coombs test indicates the presence of antibodies in the serum.

What are the treatments for this condition?

Splenectomy is curative and should be considered in patients with severe disease. Surgery also helps prevent gallstone formation. Folate supplementation can be useful.

CASE 23

A 60-year-old woman presents to her primary care physician for her annual physical examination. She says she has been feeling "down" and tired lately. Upon questioning, she also admits to some constipation, abdominal pain, joint pain, and muscle aches. She has worked at a factory for the last 30 years. Physical examination reveals blue pigmentation in her gum-tooth line. A peripheral blood smear reveals coarse basophilic stippling. Relevant laboratory findings are as follows:

Hemoglobin: 9.0 g/dL
Hematocrit: 26%
Mean corpuscular volume: 76 fL
WBC count: 5000/mm^3

What conditions can cause basophilic stippling?

Basophilic stippling (see Figure 9-21) may be caused by lead poisoning, hemolysis, or thalassemia. Laboratory tests, including a Coombs test, reticulocyte count, and hemoglobin electrophoresis, can help differentiate these conditions, as follows:

- In lead poisoning, Coombs test is negative, reticulocyte count is low, and hemoglobin electrophoresis is normal.
- In hemolysis, Coombs test is positive, reticulocyte count is elevated, and hemoglobin electrophoresis is normal.
- In thalassemia, Coombs test is negative, reticulocyte count is elevated, and hemoglobin electrophoresis is abnormal.

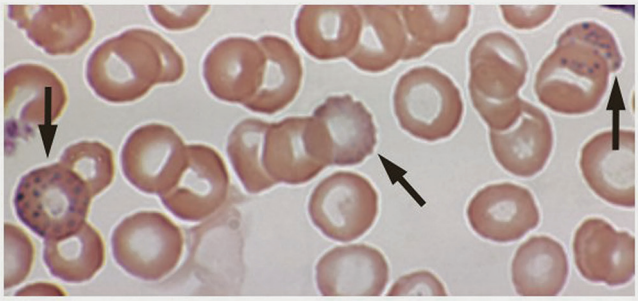

FIGURE 9-21. Peripheral blood film showing basophilic stippling of red blood cells (*arrows*) in a patient with elevated blood lead levels. (Reproduced courtesy of Fred H, et al. *Images of Memorable Cases: Case 81*. Open Stax CNX. January 31, 2018.)

What is the most likely diagnosis?

Lead poisoning is suggested by the blue pigmentation of the gums (**Burton lines**), microcytic anemia, and characteristic basophilic stippling. Most adult exposure to lead is occupational (factories, manufacturing, working directly with lead). In children, however, lead poisoning most commonly occurs orally (lead-based paint in the house, eating paint chips).

What are other common signs and symptoms of this condition?

Common signs and symptoms of lead poisoning include colicky abdominal pain; constipation; irritability; difficulty concentrating; depression/psychosis; decreased short-term memory; arthralgias and myalgias; headache; decreased libido; and peripheral neuropathy, often presenting as extensor weakness (eg, wrist drop) due to segmental demyelination and degeneration of motor axons.

What is the most likely cause of the patient's anemia?

Lead poisoning is an environmental cause of porphyria through inhibition of aminolevulinate dehydratase, which converts delta-aminolevulinic acid to porphobilinogen in one of the first steps of heme synthesis. It also inhibits ferrochelatase to inhibit the conversion of protoporphyrin IX to heme in the last step of synthesis. This impairment results in decreased hemoglobin production and a microcytic, hypochromic anemia.

What do increased serum lead levels and increased free erythrocyte protoporphyrin (FEP) levels indicate about the duration of this condition?

Increased serum lead levels indicate lead exposure within the past 3 weeks. FEP levels are a measure of intoxication in the past 120 days (the average lifetime of an RBC). Chelation therapy with succimer can be useful in severe cases after removing the source of the lead.

CASE 24

A 65-year-old woman presents to her physician with cough, hemoptysis, wheezing, and pain in her shoulder running down her arm. She has noted increased vocal hoarseness and weight loss over the past few months. She also has noted worsening shortness of breath when ascending or descending one flight of stairs. Sputum analysis reveals atypical cells. A complete blood count reveals her hematocrit is 25% and her WBC count is 12,000/mm^3.

What is the most likely diagnosis?

Lung cancer (with Pancoast syndrome). This condition is caused by a tumor of the upper lobe of the lung, which causes pain in the ipsilateral arm and Horner syndrome (ptosis, miosis, and ipsilateral anhidrosis). The tumor is often accompanied by ipsilateral pain or weakness/numbness in the ulnar distribution.

What are the major clinical features of this condition?

- Hoarseness (recurrent laryngeal nerve involvement)
- Neck or facial swelling (superior vena cava obstruction)
- Diaphragmatic paralysis (phrenic nerve involvement)
- Dyspnea (airway obstruction)
- Metastasis
- Paraneoplastic syndromes (Cushing syndrome, hypercalcemia, the syndrome of inappropriate secretion of antidiuretic hormone, clubbing [hypertrophic osteoarthropathy], and Lambert-Eaton syndrome)

What are the typical laboratory and imaging findings in this condition?

- Radiograph and CT typically reveal lung nodules (though not sensitive).
- Sputum analysis reveals atypical cells (not sensitive).
- Anemia of chronic disease (not sensitive).
- Definitive diagnosis requires a tissue biopsy and pathology results showing cancer cells.
- Positron emission tomography may be useful to evaluate lymph node involvement; this is critical for staging.

What are the primary pathologic types of this condition?

Non–small cell lung cancer (which is the most common type) includes the following:

- **Squamous cell carcinoma** accounts for 30% of lung cancers. It occurs centrally near the hilum; slower growth and cavitation are frequently seen.
- **Adenocarcinoma** accounts for 30% of lung cancers. These tumors may be mucus-secreting, as in acinar adenocarcinoma.
- **Bronchoalveolar carcinoma** occurs more often in nonsmokers and is often multifocal.
- **Large cell carcinoma**, which is rare.
- **Small cell carcinoma** accounts for 25% of lung cancers. These tumors occur centrally and are early to metastasize. They are sensitive to chemotherapy but frequently relapse.

What are the treatments for this condition?

Surgery is considered for lesions without distant metastasis if the patient has sufficient cardiopulmonary reserve. Radiotherapy is used to treat unresectable tumors. Adjuvant chemotherapy is also used with some patients undergoing surgery. For patients with metastatic disease, palliative chemotherapy is often used.

CASE 25

A 62-year-old African-American man comes to his physician complaining of fatigue, recent weight loss, and bone pain in his lower back. His medical history is unremarkable except for two recent attacks of pneumonia that were successfully treated. An x-ray of his spine reveals lytic lesions in the vertebral bodies. Relevant laboratory values are as follows:

Sodium: 140 mEq/L	Chloride: 106 mEq/L	Calcium: 14 mg/dL
Phosphate: 3.6 mg/dL	Magnesium: 1.8 mg/dL	Blood urea nitrogen (BUN): 15 mg/dL
Bicarbonate: 25 mEq/L	Potassium: 4.0 mEq/L	Creatinine: 2.0 mg/dL

What is the most likely diagnosis?

Fatigue, weight loss, bone pain, increased recent susceptibility to infection, and elevated serum calcium and creatinine levels suggest multiple myeloma.

What is the pathophysiology of this condition?

Multiple myeloma is a clonal proliferation of B cells that have differentiated into plasma cells. These mature B cells cause lytic lesions in the bones. These cells produce massive quantities of identical immunoglobulin molecules, usually IgG or IgA, that are either κ or λ light chain (κ more common than λ). Rarely, IgD or nonsecretory myeloma is diagnosed.

What renal complications are associated with this condition?

The large amount of **Bence Jones proteins** (free immunoglobulin light chains) found in the urine of patients with multiple myeloma causes azotemia. Other renal complications include inflammation with potential giant cell formation and metastatic calcification.

What other tests can confirm the diagnosis?

A complete blood count should be ordered. Patients with multiple myeloma may be anemic as a result of tumor cells overcrowding myeloid precursor cells. Electrophoresis with immunofixation will demonstrate **M protein**, the term given to the massively produced immunoglobulin. Urinalysis of a 24-hour collection may reveal the presence of a Bence Jones protein. Bone marrow biopsy shows a two- to four-fold increase in plasma cells; biopsy results are essential for the diagnosis of multiple myeloma. Other immunoglobulins may be low, which can add to the risk of infection. Due to hyperglobulinemia, RBCs on peripheral blood smear will clump in a **rouleaux formation** (see Figure 9-22).

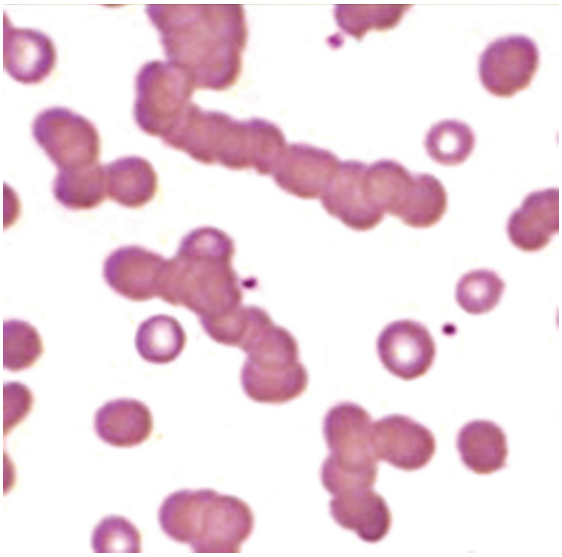

FIGURE 9-22. Rouleaux formation on peripheral blood smear. (Reproduced with permission from USMLE-Rx.com.)

What is MGUS?

Monoclonal gammopathy of undetermined significance (MGUS) is a precursor (premalignant) lesion if the M protein level is < 3 g/dL, there is $< 10\%$ plasma cells in the bone marrow, and there are no clinical manifestations of multiple myeloma present. The **CRAB** mnemonic can be used to remember the clinical characteristics that are **not** present in MGUS but **are** present in multiple myeloma: elevated **C**alcium, **R**enal failure, **A**nemia, and **B**one lesions. 25%–30% of those with MGUS go on to develop a lymphoproliferative disorder in their lifetime.

CASE 26

A mother brings her 4-month-old infant to the pediatrician because the child has had watery diarrhea almost daily for the past month. Previously a good eater, the baby is now refusing to feed and is irritable most of the time. On physical exam, a mass is palpated in his abdomen that is nontender, fixed, and firm.

What is the most common tumor in infants?

Neuroblastoma is a malignancy of the sympathetic nervous system that arises during embryonic development. In the embryo, **neuroblasts** (pluripotent sympathetic stem cells) invaginate and migrate along the neuraxis to the adrenal medulla, the sympathetic ganglia, and various other sites. Figure 9-23 shows a large neuroblastoma occupying the right flank in an older child. The site of disease presentation depends on the area of neuroblast migration.

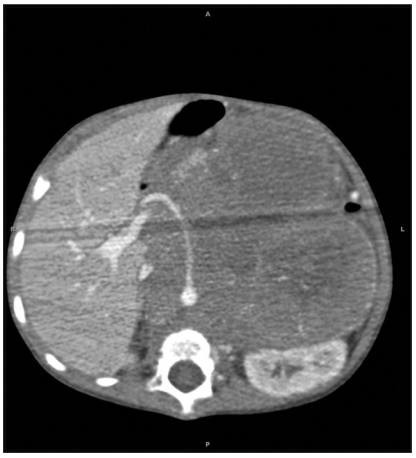

FIGURE 9-23. Neuroblastoma. Large, heterogeneously enhancing mass superior to the left kidney, displacing the left kidney and encasing the left renal artery. (Reproduced with permission from USMLE-Rx.com.)

What are the types of small, round, blue-cell tumors?

- Neuroblastoma is a common tumor of the adrenal medulla in children. It is characterized by homovanillic acid (dopamine breakdown product) present in urine. It is associated with the *N-myc* oncogene.
- Wilms tumor is the most common childhood renal malignancy and presents with flank mass and hematuria. It is associated with deletion of *WT1* on chromosome 11.
- Acute leukemia is caused by unregulated growth of leukocytes in the bone marrow.
- Mesothelioma is associated with smoking and asbestos exposure.
- Rhabdomyosarcoma is a tumor of skeletal muscle.
- Medulloblastoma is a highly malignant cerebellar tumor. It often compresses the 4th ventricle to cause hydrocephalus.
- Retinoblastoma is associated with 13q mutation of *Rb* gene.

What prognostic factors are important in this condition?

Tumor stage and the patient's age at diagnosis are the two most important prognostic factors. Patients with localized disease, regardless of age, have a favorable prognosis (5-year survival rate: 80%–90%). Overall, younger age at diagnosis carries a more favorable prognosis.

What are the likely biopsy findings in this condition?

Histologically, neuroblastoma presents as dense nests of small, round, blue tumor cells with hyperchromatic nuclei. Homer-Wright pseudorosettes are seen in 10%–15% of cases. These pseudorosettes are composed of neuroblasts surrounding neuritic processes and are pathognomonic for neuroblastoma. Rosette patterns on histology are found in tumors of the nervous system. Other cases include retinoblastomas (Flexner-Wintersteiner rosette), and ependymomas (true ependymal rosette).

What are the treatments for this condition?

For patients with localized disease, surgical excision is curative. For more advanced disease, treatment consists of surgical excision followed by chemotherapy. Chemotherapy for neuroblastoma consists of combination regimens, typically vincristine, cyclophosphamide, and doxorubicin. Other regimens include etoposide in combination with either cisplatin or carboplatin.

CASE 27

A 30-year-old woman comes to her physician complaining of a headache that has affected her intermittently for the past 6 months. The frontally located headache occurs on most days and is typically dull but sometimes piercing. Over the same time period, the woman has also had episodes of shaking and jerking in her right arm which last about a minute. She also reports an intermittent sensation of "pins and needles" in her right hand.

What is the most likely diagnosis?

Oligodendroglioma. These relatively rare, slow-growing tumors are responsible for 2%–4% of primary brain tumors. They occur with equal incidence in women and men. They originate from glial cells, which myelinate central nervous system axons. Seizures, often focal in nature, are the most common presenting symptom.

Where do the tumors of this condition typically occur?

Oligodendrogliomas almost always (92% of cases) occur supratentorially and are most often found in the frontal lobes. Lesions are typically peripheral. Most oligodendrogliomas arise in the cortex and extend into the white matter of the cerebral hemispheres.

What symptoms are typically associated with this condition?

The clinical presentation of oligodendrogliomas is typically attributable to compression of adjacent structures by the tumor:

- Headache
- Mental status changes
- Paresis
- Seizures

Because they are slow-growing tumors, they may have a more insidious presentation, whereas the anaplastic forms present with more rapid neurologic decline. Because the patient may be asymptomatic, oligodendrogliomas are often diagnosed incidentally.

What are the likely histologic findings in this condition?

"Fried egg" cells are typically seen on histologic section (see Figure 9-24). These cells have characteristic round nuclei with clear cytoplasm. The tumors often calcify (30% of cases), and calcifications may be apparent on histologic section.

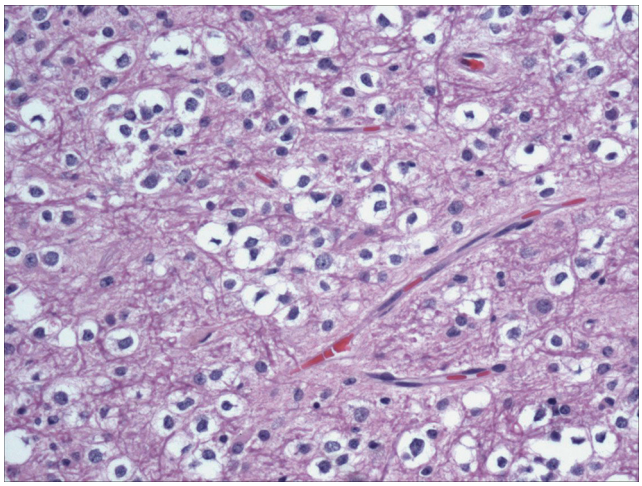

FIGURE 9-24. Oligodendroglioma with classic fried-egg tumor cells.
(Reproduced with permission from USMLE-Rx.com.)

What is the prognosis for patients with this condition?

About 50% of patients with oligodendrogliomas survive $>$ 5 years, and the 10-year survival rate is 25%–34%. Mortality increases with features of increasing nuclear atypia, necrosis, and mitosis. Some oligodendrogliomas contain astrocytic components and are termed **mixed gliomas**. Patients with highly anaplastic oligodendrogliomas have a median survival of $<$ 2 years.

CASE 28

A 49-year-old woman presents to her gynecologist because her menstrual periods have become less frequent. The patient also reports she has hair growing on her face and has developed mild acne, which she has not had since she was a teenager. On physical examination, the patient's abdomen is somewhat distended and there is a palpable mass on the left adnexum.

What is the most likely diagnosis?

A palpable adnexal mass in conjunction with abdominal swelling suggests ovarian cancer, which is often accompanied by ascites. The patient's irregular periods may simply be normal menopause, but the triad of irregular periods, facial hair, and acne suggest androgen excess. The **Sertoli-Leydig ovarian tumor** is an androgen-producing neoplasm that presents with hirsutism in 50% of patients.

From what cell line does the tumor involved in this condition originate?

The Sertoli-Leydig cell tumor is of sex cord–stromal origin. Tumors from this origin are relatively rare and account for only 5% of ovarian neoplasms. They consist of mixtures of stromal fibroblasts, granulosa cells, theca cells, and cells that resemble testicular Sertoli cells and Leydig cells.

What do Sertoli and Leydig cells produce?

- Sertoli cells contain aromatase and convert testosterone to estrogen. In men, follicle-stimulating hormone stimulates Sertoli cells in spermatogenesis.
- Leydig cells, which are stimulated by luteinizing hormone, secrete testosterone.

What other tumors have the same origin?

Other stromal ovarian tumors include:

- **Fibromas**, solid tumors consisting of cells that resemble fibroblasts
- **Thecoma** tumors, which contain fibroblasts plus lipid-containing cells
- **Granulosa cell** tumors, which consist of estrogen-secreting granulosa cells and may present with abnormal vaginal bleeding or endometrial hyperplasia

What are the likely histologic findings in this condition?

The Sertoli-Leydig cell tumor is usually composed of large cells with eosinophilic cytoplasm arranged into tubules and surrounded by a fibrous stroma (see Figure 9-25). Sertoli cells are found lining the tubules, and Leydig cells may be found in the stroma.

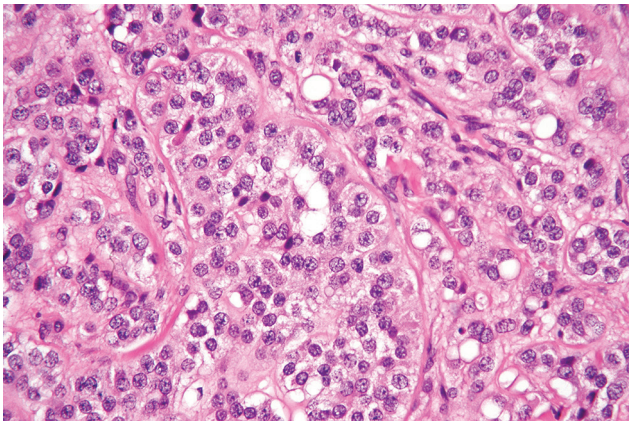

FIGURE 9-25. Sertoli-Leydig cell tumor with tubular histological findings. (Reproduced courtesy of Dr. Michael Bonert.)

What is the lymphatic drainage of the ovaries?

Like that of the testicles, the ovaries' lymphatic drainage is to the lumbar and para-aortic lymph nodes. The ovarian lymph vessels travel with the venous drainage in the broad ligament.

What is the treatment and prognosis of this condition?

These tumors are almost always benign and have an excellent long-term prognosis; treatment with unilateral oophorectomy is highly successful.

CASE 29

A 54-year-old diabetic African-American man presents to his primary care physician after his wife noted scleral icterus and a recent unintentional 11.4-kg (25-lb) weight loss. The patient denies abdominal pain. Physical examination reveals a mass in the right upper quadrant of the abdomen. Relevant laboratory findings are as follows:

Alkaline phosphatase: 127 U/L
Direct bilirubin: 6 mg/dL
Calcium: 10.6 mg/dL

What is the most likely diagnosis?

Pancreatic cancer.

What is the classic presentation of this condition?

The classic presentation of pancreatic cancer is painless jaundice. Weight loss, abdominal pain, and pruritus are also common.

What is the pathophysiology of this condition?

Pancreatic tumors form mostly in the head and neck of the pancreas from the endocrine and exocrine portions of the pancreas. The majority of pancreatic cancers are exocrine in origin. Tumors in the head and neck cause compression of the surrounding structure, most notably the common bile duct, causing obstructive jaundice.

What risk factors are associated with this condition?

- African-American race
- Cigarette smoking
- History of chronic pancreatitis
- History of diabetes mellitus
- Male gender
- Diet high in fried meats

What are the common sites of invasion for this condition?

Pancreatic cancer can invade the duodenum, the ampulla of Vater, and the common bile duct. Figure 9-26 shows a pancreatic adenocarcinoma, which appears as a large, heterogeneously enhancing mass at the head of the pancreas.

What is the most common form/location of this condition?

More than 80% of pancreatic tumors are adenocarcinomas, and 60% are found in the head of the pancreas. Notably, with pancreatic adenocarcinoma, the tumor marker CA19-9 is often elevated.

What are the common sites of metastasis?

Metastasis often begins in the regional lymph nodes and spreads to the liver or, less often, to the lungs. Pancreatic cancer can also directly invade the duodenum, stomach, and colon.

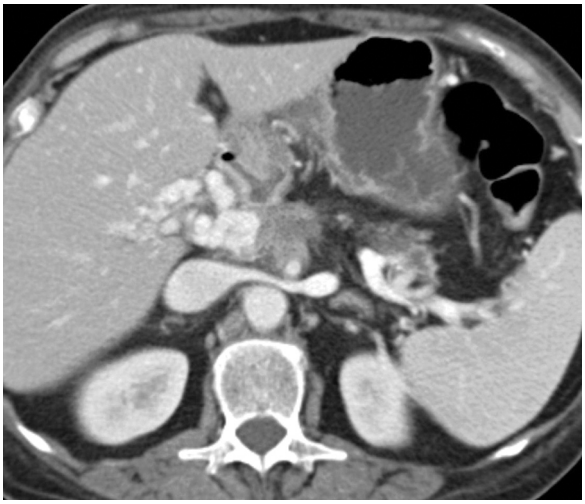

FIGURE 9-26. Pancreatic adenocarcinoma. Contrast-enhanced CT shows a soft tissue mass in the pancreatic head. Note the soft tissue encasement around the SMA. There is also a cavernous transformation of the portal vein. (Reproduced with permission from USMLE-Rx.com.)

With treatment, what is the prognosis of this condition?

Approximately 90% of patients die within 1 year of diagnosis; however, if resection of the cancer is possible and the cancer is caught in an early stage, 5-year survival increases to 30%. For a cancer in the head/neck of the pancreas, resection is performed with a Whipple procedure; for a cancer in the tail, resection is performed with a distal pancreatectomy. In a Whipple procedure, the stomach antrum, part of the duodenum, head of the pancreas, common bile duct, and gallbladder are removed. The remaining pancreas, common hepatic duct, and remaining stomach are all sewn into the jejunum.

CASE 30

An 8-month-old boy is brought to the pediatrician by his foster parents for a checkup. They become concerned when he continues to bleed after the heel-stick. They report that during his circumcision, he seemed to bleed for an extended amount of time as well. Physical examination is significant for multiple bruises on the child's knees and elbows. Relevant laboratory findings include a platelet count of 250,000/mm^3, a normal bleeding time, a PT of 12 seconds, and a PTT of $>$ 120 seconds.

What is the most likely diagnosis?

Hemophilia is due to deficiencies in the intrinsic coagulation pathway (factor VIII in hemophilia A, factor IX in hemophilia B, and factor XI in hemophilia C). Therefore, this disease is characterized by normal bleeding time, platelet count, and prothrombin time but an **elevated PTT**. Von Willebrand disease is the most common hereditary bleeding disorder. It is distinguished from hemophilia by its prolonged bleeding time and usually a modest prolongation of the PTT.

What are the variants of this condition?

- Hemophilia A: factor VIII deficiency
- Hemophilia B (Christmas disease): factor IX deficiency
- Hemophilia C: factor XI deficiency

Hemophilia B is clinically indistinguishable from hemophilia A. However, hemophilia A is 5–10 times more prevalent.

How is this condition inherited?

Hemophilia A and B are X-linked recessive disorders. Hemophilia C, a less common variant, is an autosomal recessive disorder.

What are the possible complications of this condition?

- Complications include deep and delayed bleeding into joints (hemarthrosis) and muscles (hematoma), and the gastrointestinal tract. The most concerning complications are bleeds in the central nervous system and oropharynx.
- Mucosal or cutaneous bleeding is uncommon and more characteristic of platelet dysfunction or von Willebrand disease.
- Transmission of blood-borne infection (specifically HIV and hepatitis C) through transfusion for excessive blood loss has been significantly reduced through modern screening technology and recombinant factors.

What are the treatments for this condition?

- Clotting factor concentrate replacements can be used to prevent bleeding and limit existing hemorrhage. Both monoclonal purified and recombinant factor VIII and IX exist.
- Fresh frozen plasma and whole blood transfusions are used in the acute setting (but they carry the risk of encouraging the development of inhibitor antibodies to factor VIII).
- In mild cases of hemophilia A, desmopressin, an ADH analog, transiently increases the factor VIII level.

How do platelet disorders differ from coagulation disorders?

Platelet disorders affect primary hemostasis, in which a temporary platelet plug is formed to stop a bleed. Therefore, when platelets are defective (qualitative problem) or deficient (quantitative problem), formation of the platelet plug will be delayed, which is reflected by an elevated bleeding time; PT and PTT, markers of the coagulation cascade, are unaffected. On the other hand, coagulation disorders affect secondary hemostasis, in which the primary platelet plug is reinforced through formation of an insoluble fibrin mesh using the various coagulation factors. Thus, when a factor is missing or being consumed too rapidly, the formation of the fibrin mesh is impaired, such that PT and/or PTT will be prolonged; bleeding time will be unaffected because the platelet plug forms without any issues. The findings are summarized in Table 9-4.

Table 9-4. Platelet Disorders vs. Coagulation Disorders

Disorder	Bleeding time	PT	PTT
Platelet disorders			
Defective Platelets Glanzmann thrombasthenia Bernard-Soulier syndrome	↑	—	—
Deficient Platelets Immune thrombocytopenic purpura Hemolytic uremic syndrome Thrombotic thrombocytopenic purpura	↑	—	—
Coagulation disorders			
Deficient Coagulation Factors Hemophilias A, B, C	—	↑	↑

CASE 31

During an annual physical examination, a previously healthy 70-year-old man mentions recent weakness and rib pain. His appetite has been good, and he has not experienced fevers, nausea, vomiting, or changes in bowel habits. Upon questioning, he also admits to experiencing extreme itchiness all over his body after showering or bathing. Physical examination reveals a palpable enlarged spleen. Results of a complete blood count are as follows:

WBC count: 10,000/mm^3
Hemoglobin: 22 g/dL
Hematocrit: 62%
Platelet count: 425,000/mm^3

What is the most likely diagnosis?

Polycythemia vera, also known as primary erythrocytosis. This patient's elevated hemoglobin concentration is a sign of an increased RBC count. An increased RBC mass ($>$ 32 mL/kg in women and $>$ 36 mL/kg in men) is diagnostic of polycythemia vera absent of secondary causes. Polycythemia vera is one of the myeloproliferative syndromes; other myeloproliferative syndromes include essential thrombocytosis, CML, and myeloid metaplasia. The increased RBC mass may cause engorgement of organs with blood, resulting in hepatomegaly or splenomegaly, as seen in this patient.

Levels of which hormone should be measured to establish the diagnosis?

Polycythemia vera may be primary or secondary in nature. **Erythropoietin** levels can help distinguish between the two:

- Erythropoietin levels will be decreased or normal in **primary polycythemia** (polycythemia vera). Because the production of erythrocytes is not being driven by high erythropoietin levels; the polycythemia is autonomous. In fact, erythropoietin may be decreased due to the negative feedback loop detecting high levels of erythrocytes and tissue oxygenation.
- In **secondary polycythemia**, increased erythropoiesis results from increased erythropoietin stimulation (eg, erythropoietin-secreting tumor, hypoxemia, altitude, or erythropoietin receptor mutations).

Which two types of carcinoma are associated with this condition?

Renal cell carcinoma and **hepatocellular carcinoma**. In a healthy adult, the kidneys produce a majority of the body's erythropoietin, and the liver is a secondary source.

What is a myeloproliferative disorder?

It is a disorder in which there is clinical expansion of multipotent hematopoietic stem cells. Isolated cell lines may be affected; if megakaryocyte expansion occurs, an essential thrombocytosis is seen.

How can an uncorrected ventricular septal defect (VSD) lead to this condition?

In patients with uncorrected VSD, atrial septal defect, or patent ductus arteriosus, blood is shunted from the left side of the heart to the right side, which exposes the pulmonary vasculature to systemic blood pressures. Over time, the pulmonary vasculature adapts by increasing pulmonary resistance, and blood flow through the shunt is reversed to flow from right to left. This reversal of flow is known as **Eisenmenger syndrome**. Right-to-left shunts cause hypoxemia and cyanosis, a potent stimulus for erythropoietin secretion and a cause of secondary polycythemia.

What are the treatments for this condition?

Phlebotomy can reduce the risk of blood clots in patients with polycythemia to that of the normal population. In high-risk patients (the elderly or those with a history of clots), hydroxyurea may be useful for controlling the hematocrit.

CASE 32

A 3-year-old boy is brought to the pediatrician by his parents who noticed that his right eye has turned "white" (see Figure 9-27). When they referred to earlier photographs, the child's eyes were normally colored. The boy denies any pain or irritation in his eyes, and he does not complain of loss of vision. The parents deny any trauma to the area, and there is no family history of ocular disease. On physical examination, the boy's extraocular movements are intact and symmetrical, his pupillary light reflexes are normal, and he has intact central and peripheral vision in both eyes. However, when he is asked to fixate at a point in distance, the boy's left eye deviates toward his nose (esotropia). Funduscopic examination reveals a chalky, white-gray retinal mass in the left eye.

FIGURE 9-27. (Reproduced with permission from Leila S, et al. *Pan Afr Med J*. 2016;25:131.)

What is the most likely diagnosis?

Leukocoria found in a young child (as seen in Figure 9-27) suggests retinoblastoma.

What conditions should be considered in the differential diagnosis?

Conditions that present similarly to leukocoria include the following:

- Congenital cataracts
- Developmental abnormalities of the vitreous/retina
- Inflammatory conditions

What is the pathogenesis of this condition?

Retinoblastoma results from mutations of both alleles of the *Rb* gene, on chromosome 13q14, which codes for a tumor suppressor protein. The Rb protein binds and sequesters transcription factors of the E2F family to prevent the G1-to-S phase transition. Loss of Rb thus promotes deregulation of this transition and increased growth.

What is the "two-hit hypothesis"?

The **two-hit hypothesis** (Knudsen hypothesis) suggests that two separate mutations are required for tumorigenesis involving a suppressor gene. In heritable disease, patients inherit a mutated germline allele from a parent and acquire a second somatic mutation later in development. This often causes bilateral and multifocal disease. In noninherited disease, two spontaneous mutations arise in a single retinal cell during development, causing unilateral, unifocal disease.

What secondary malignancies is this patient at risk of developing?

Osteogenic sarcoma, soft tissue sarcoma, and malignant melanoma commonly develop in patients with retinoblastoma. Metastatic spread occurs rapidly through direct infiltration or via the subarachnoid space, blood, and lymphatics.

What is the treatment for this condition?

The treatment of choice for retinoblastoma is enucleation of the affected eye; the goal is to remove a large portion of the optic nerve, as it is the most common path for metastasis to the brain. Other treatment options include external-beam radiation therapy, cryotherapy, and chemotherapy. With treatment, 5-year survival for retinoblastoma is $>$ 90%.

CASE 33

A 55-year-old woman presents to her physician complaining of a 2- to 3-month history of cough. The cough was initially nonproductive but has become progressively more productive of sputum and occasionally blood. She has a 50-pack-year history of cigarette smoking. Physical examination reveals marked decreased breath sounds on the right side, and an x-ray of the chest demonstrates hilar enlargement and a perihilar mass on the right side. The mass is biopsied, and the histologic specimen is shown in Figure 9-28.

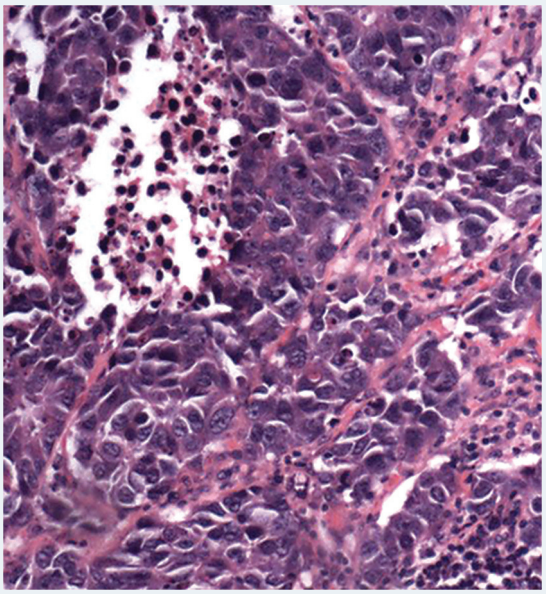

FIGURE 9-28. (Reproduced with permission from USMLE-Rx.com.)

What is the most likely diagnosis?

Small cell lung cancer (SCLC). SCLC often presents as a hilar or mediastinal mass.

What risk factors are associated with this condition?

Smoking is the major risk factor for the development of most lung cancers. Bronchoalveolar carcinoma, however, is not thought to be related to smoking. Exposure to other substances, including asbestos, polycyclic aromatic hydrocarbons, and ionizing radiation also increases the risk for SCLC.

What are the most common sites of metastasis for this condition?

SCLC metastasizes to virtually every organ in the body, usually early in the onset of disease. Brain metastases are common, with resulting neurologic deficits. Bone metastases result in bone pain or fractures and can cause spinal cord compression. Liver, supraclavicular lymph nodes, and adrenal metastases are also common.

What are the treatments for this condition?

Most patients with SCLC have unresectable disease at the time of presentation. In the rare patient with small peripheral lesions and no metastases, surgical resection may be an option. Treatment for SCLC involves chemotherapy, typically etoposide plus cisplatin, with or without radiotherapy. In patients who do not receive chemotherapy or radiation, mean survival is 6–17 months, while survival for treated patients can average $>$ 24 months.

What other syndrome is this patient at greatly increased risk for developing?

She is at risk for developing Lambert-Eaton myasthenic syndrome (a paraneoplastic syndrome). This condition, which is similar to myasthenia gravis, is caused by autoantibodies against the P/Q-type calcium channels in the presynaptic neuromuscular junction. It causes weakness of the proximal musculature, especially of the lower limbs. Cranial nerves are commonly affected, which often manifests as ptosis of the eyelids and diplopia.

CASE 34

A 19-year-old African-American woman presents to her primary care physician with pelvic pain and discomfort of a few months' duration. A bimanual pelvic examination reveals a large left adnexal mass. A subsequent CT scan confirms a 16-cm well-demarcated solid mass in this area. A stereotactic biopsy reveals primitive mesenchymal cells along with tissue suggestive of glands, bone, cartilage, muscle, and neuroepithelial cells.

What is the most likely diagnosis?

Teratoma, the most common type of germ cell tumor. The component tissues in a teratoma arise from all three germ layers and vary from immature to well differentiated (see Figure 9-29). Additionally, these tissues are foreign to the anatomic site in which they are found.

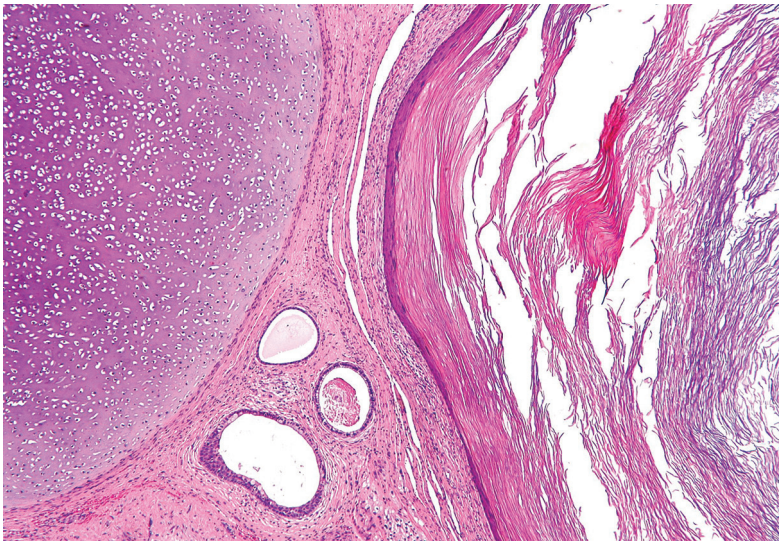

FIGURE 9-29. Low-magnification micrograph of a mature teratoma showing products of all three germ layers. 1) Mesoderm: immature cartilage (left of image). 2) Endoderm: gastrointestinal lining cells/glands (center-bottom of image). 3) Ectoderm: epidermis with keratin (right of image). (Reproduced courtesy of Dr. Michael Bonert.)

What are the three types of this condition?

- **Mature (benign dermoid cysts)** tumors compose 95% of all ovarian teratomata and are typically lined by epidermis and contain hair, bone, or teeth. These lesions can also be bilateral. Most teratomata are benign in women, but teratomas containing nervous tissue are at increased risk of being malignant.
- **Immature (malignant)** tumors are usually large, rapidly growing tumors with tissue resembling the fetus or embryo rather than the adult. Due to their rapid growth, these tumors also show necrosis and hemorrhage and present in younger women.
- **Monodermal/highly specialized** tumors are a rare subset that consist of a predominantly mature histologic cell type, the most common of which are struma ovarii and carcinoid.

What are the typical imaging findings in this condition?

Ultrasound is the most common modality for pelvic imaging, especially for suspected teratomata. Mixed cystic and solid lesions with fat-fluid and hair-fluid levels are commonly found.

What factors impact prognosis?

Prognosis depends on the grade and stage of the tumor. Only malignant teratomata are graded, and grading is based on maturity of the tissue present and the presence of neuroepithelium. The less mature the tissue is, the greater the grade. Staging depends on local or distant invasion of the cancer. More distant and widespread metastases receive higher staging with worse prognosis.

What is the treatment for this condition?

Complete surgical excision is the standard of care. Higher-grade malignant teratomata are additionally managed with chemotherapy such as methotrexate, with a high rate of cure.

CASE 35

A 36-year-old sexually active man goes to his doctor after noticing that his left testicle has been swollen for the past few weeks. The patient has noticed a dull, achy sensation in this testicle but no acute pain. On physical examination, the left testicle is larger than the right, and a nontender, round, firm, rubbery mass is palpated. Transillumination with a penlight reveals an opaque mass. Laboratory tests reveal a normal chemistry panel, normal complete blood count, elevated lactate dehydrogenase (LDH) level, normal serum human chorionic gonadotropin (hCG) level, and normal α-fetoprotein (AFP) level.

What is the most likely diagnosis?

Testicular tumor, as suggested by the presence of a painless, nontransilluminating testicular mass. In a young man, the most likely diagnosis is a seminoma, which has a peak incidence of age 35 years and accounts for approximately 35% of testicular tumors. This diagnosis is further supported by the elevated LDH level, normal hCG level (elevated in 20% of seminomas), and normal AFP level.

What is the differential diagnosis of a scrotal mass?

Conditions to consider in the differential of a scrotal mass include the following:

- Orchitis
- Epididymitis
- Hydrocele
- Spermatocele
- Varicocele
- Hernia
- Cancer (nonseminomatous and nongerminal)

Epididymitis and orchitis are accompanied by a painful testicle and an elevated WBC count, differentiating them from seminoma. Elevated AFP levels suggest a nonseminomatous germ cell cancer. Fluid collections, like a hydrocele, transilluminate. A hernia may be reducible or irreducible; if it is irreducible, the patient will likely be in significant pain from the presence of incarcerated bowel.

What is the analogous condition in women?

The analogous ovarian tumor is the **dysgerminoma**, the most common germ cell tumor in women. It is usually malignant and is more common in younger patients. Like seminomas, it can produce LDH. It can also produce alkaline phosphatase.

What is the lymphatic drainage of this tumor?

Understanding the lymphatic drainage of the testicles is important in considering metastases. Because the testicles descend from the abdomen during development, the lymph vessels ascend to the lumbar and para-aortic lymph nodes. This contrasts with the lymph drainage of the scrotum, which is an outpouching of skin. The lymph vessels of the scrotum drain to the superficial inguinal nodes.

What other conditions are characterized by an elevated hCG level?

Only 10%–20% of seminomas present with elevated hCG levels. Tumors in women that are likely to present with an elevated hCG level include hydatidiform moles, choriocarcinomas, and gestational trophoblastic tumors.

CASE 36

A 7-month-old Greek boy is brought to his pediatrician by his parents who have noticed that the baby has been jaundiced and dyspneic for about 2 weeks. The mother denies any previous health problems with her son. Physical examination reveals tachycardia. Laboratory tests reveal a mean corpuscular volume of 60 fL and a reticulocyte count of 0.3%. The serum iron concentration is within normal limits.

What is the most likely diagnosis?

β-Thalassemia major is the homozygous form of the genetically transmitted disease β-thalassemia, where the β-globin gene of hemoglobin is mutated, resulting in microcytic anemia. It is especially prevalent in Mediterranean populations.

By contrast, in α-thalassemia, α-globin genes in hemoglobin are deleted; this condition is most commonly present in Southeast Asians and African Americans.

What mutations are present in thalassemias?

Humans have two α-globin genes on chromosome 16, resulting in four total α alleles. α-Thalassemia can thus manifest as four types of thalassemia, depending on the number of α allele deletions that occur due to unequal meiotic crossover between adjacent α genes. Increasing severity results from increasing numbers of deletions, ranging from a clinically silent picture with one deleted allele to hydrops fetalis in utero with four deleted alleles.

Humans have one β-globin gene on chromosome 11, resulting in two total β alleles. In β-thalassemia, mutations, rather than deletions, occur. These mutations can occur in the promoter, exon, intron, or polyadenylation sites. Some mutations may produce no β-globin (thalassemia major, homozygous), whereas others may produce a small amount (thalassemia minor, heterozygous).

What are the symptoms and signs of this condition?

For the first 6 months of life, infants with β-thalassemia are asymptomatic because of the normal fetal hemoglobin that is present. After that, however, there is a decline in γ-globin production without a rise in β-hemoglobin production. The resultant initially presents as pallor, growth retardation, or jaundice. Left untreated, severe anemia triggers marrow expansion, which manifests as skeletal deformities (ie, "crew cut" on x-ray of the skull), as well as extramedullary hematopoiesis, manifesting as hepatosplenomegaly.

How is this condition diagnosed?

Peripheral blood smears showing target cells (see Figure 9-30) and a complete blood count showing severe microcytosis (mean corpuscular volume 60–65) may suggest the diagnosis, but definitive laboratory testing using gel electrophoresis is needed, as it can identify the presence of mutated and normal forms of hemoglobin.

In β-thalassemia minor, the anemia is not as severe, so there is an increase in HbA_2, an adult form of hemoglobin normally present in small amounts. In β-thalassemia major, however, the anemia is so severe that there is a marked increase in HbF, which normally declines steadily after birth.

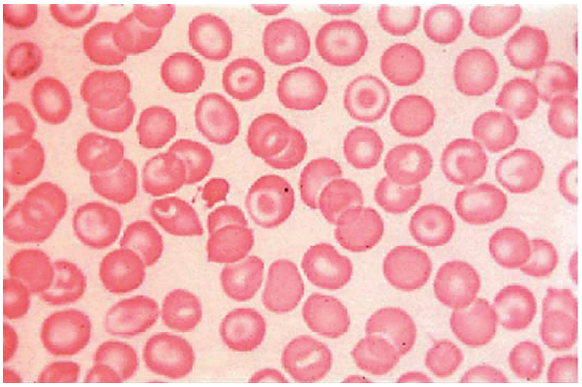

FIGURE 9-30. Target cells on a peripheral blood smear. (Reproduced with permission from USMLE-Rx.com.)

What is the treatment for this condition?

β-Thalassemia major causes severe anemia. While HbF induction (promoting the production of fetal hemoglobin with agents such as hydroxyurea) may be used, treatment with repeated blood transfusions may also be required. Subsequently, iron chelation for overload is important. Splenectomy may be necessary to treat the resulting hypersplenism. Stem cell transplantation may also be used in select cases. β-Thalassemia minor is usually asymptomatic; management typically only requires the avoidance of oxidative stressors of RBCs rather than any specific treatment.

CASE 37

A 10-year-old girl presents to the ED with confusion, severe headaches, and blurred vision. These symptoms have been progressive over the past week. The patient's mother shares that the girl has also had bloody diarrhea during the past week. On physical examination, she is febrile and disoriented with diffuse petechial hemorrhages throughout her body. Relevant laboratory results are as follows:

Serum BUN: 42 mg/dL	MCV: 90 fL
Serum creatinine: 4.0 mg/dL	WBC count: 7800/mm^3 with a normal differential
Hemoglobin: 9.6 g/dL	Platelet count: 36,000/mm^3
Hematocrit: 29%	Peripheral blood smear shows schistocytes and reticulocytes

What is the most likely diagnosis?

Thrombotic thrombocytopenic purpura/hemolytic-uremic syndrome (TTP/HUS).

What are the five cardinal symptoms of this condition?

- Transient neurological problems
- Fever
- Thrombocytopenia
- Microangiopathic hemolytic anemia
- Acute renal insufficiency

What is the pathogenesis of these symptoms?

TTP/HUS involves the widespread development of hyaline thrombi composed of platelet aggregates in the microcirculation. This consumption of platelets leads to thrombocytopenia and microangiopathic hemolytic anemia, which can cause widespread organ dysfunction. As RBCs pass by these platelet aggregates in the microcirculation, they are sheared, forming schistocytes, which are visible on microscopy of the blood.

What would this patient's coagulation studies show?

Coagulation studies will be within normal limits. This is predominantly a thrombocytopenic disease with no coagulation cascade abnormalities.

What is a common cause of this condition in children?

Typically, TTP/HUS is preceded by severe bloody diarrhea most often due to enterohemorrhagic *Escherichia coli* O157:H7 infection and less commonly *Shigella* infection. This is thought to be due to systemic absorption of a Shiga-like toxin that binds to and damages endothelial cells, inciting platelet activation and thrombosis.

Which inherited risk factor predisposes patients to this condition?

A deficiency of the **von Willebrand metalloproteinase** (ADAMTS-13) is an inherited factor that causes very large von Willebrand factor multimers to accumulate in the plasma and promote clot formation.

What is the management for this condition?

Plasma exchange reverses the platelet consumption that is responsible for the thrombus formation. Severe cases may also require adjunctive **immunosuppressive treatment** with prednisone. Platelet transfusion is contraindicated because it may lead to new or worsening thrombosis and subsequent neurologic symptoms. Prompt initiation of treatment is essential to avoid irreversible renal failure and possibly death.

CASE 38

A 2-year-old boy is brought to his family physician by his parents who are concerned about the multiple bruises on the boy's shins and hands. They report that the child seems to get large bruises with minimal injury and bleeds profusely when his teeth are brushed. They also report that a month ago he fell and hit his head on a coffee table, and they could not stop the bleeding for hours. On questioning, they reveal that the child has a grandmother with a bleeding disorder. The physician is concerned about child abuse but orders laboratory tests. Relevant findings are as follows:

Bleeding time: 14 minutes
PT: 12 seconds
PTT: 41 seconds

What is the most likely diagnosis?

Von Willebrand disease (vWD) is the most common inherited bleeding disorder. It is the result of a quantitative (type 1 or 3) or qualitative (type 2) defect in **von Willebrand factor** (vWF). vWF is a large protein made by endothelial cells and megakaryocytes. It is a carrier for factor VIII and is a cofactor for platelet adhesion. There are now more specific tests that measure vWF antigen levels and activity (ristocetin cofactor assay) directly.

What clinical findings are commonly associated with this condition?

vWD disturbs both primary and secondary hemostasis. Its role in adhesion of platelets to exposed subendothelium leads to **increased bleeding time** and an overall clinical picture of platelet dysfunction (mucous membrane bleeding, petechiae, and purpura) with vWF defects. The role of vWF as a carrier protein for factor VIII means that severe vWF deficiency leads to a clinical picture similar to a coagulation factor deficit ("pseudo-hemophilia"): "deep bleeds" such as hemarthroses (bleeding into joints), easy bruising. Patients often have a positive family history.

What do the PT and PTT values reflect?

The PT reflects changes in factor II, V, VII, IX, or X. The PTT reflects changes in any of the coagulation factors except factors VII and XIII, and it can be elevated in vWD.

How would the PT and PTT values differ with the administration of warfarin versus heparin?

Heparin affects the intrinsic pathway, causing increased PTT. **Warfarin** affects the extrinsic pathway, increasing PTT and PT. PT should always be monitored with patients taking warfarin (mnemonic: **WEPT** = **W**arfarin affects the **E**xtrinsic pathway, increasing **PT**.

Which coagulation factors require vitamin K for synthesis?

Factors II, VII, IX, and X and proteins C and S require vitamin K for synthesis. Warfarin interferes with vitamin K, leading to a clinical picture that is similar to vitamin K deficiency. The liver is important in the synthesis and metabolism of vitamin K and the coagulation factors (except VIII). Therefore, liver disease can also produce a similar clinical picture.

What are the treatments for this condition?

Treatment for mild bleeding in type 1 vWD involves the use of desmopressin, which causes release of vWF from endothelial stores. Severe disease may be treated with factor VIII concentrates that contain high vWF antigen. Cryoprecipitate is no longer used as viruses cannot be inactivated (high infection risk).

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10
Musculoskeletal, Skin, and Connective Tissue

CASE 1

A 17-year-old boy is brought to the ED by ambulance with a gunshot wound to the left flank. He seems to be breathing fine, but his abdomen is tense. He is in a lot of pain, but he is alert and oriented. While assessing the patient, you notice that there is an entrance wound on the left flank, but you cannot find where the bullet exits. You perform an ultrasound of the abdomen to look for blood in the abdomen. You see pooling of free blood in the abdomen. You quickly perform an x-ray of the abdomen to look for the bullet, and you see it lodged in the spleen. During your assessment, the patient's mental status deteriorates rapidly, and his blood pressure drops to 60/35 mmHg. The patient is going into shock. He is rushed to the operating room (OR) for an emergent laparotomy. Relevant laboratory findings are as follows:

Hematocrit: 22%
White blood cell (WBC) count: 17,000/mm^3
Blood pressure: 60/35 mm Hg

What retroperitoneal structures of the abdomen could the bullet have hit?

A useful mnemonic for abdominal retroperitoneal viscera is **SAD PUCKER**:

- **S**uprarenal gland (adrenal gland)
- **A**orta/IVC
- **D**uodenum (second and fourth segments)
- **P**ancreas (tail is associated with the intraperitoneal spleen)
- **U**reters
- **C**olon (ascending and descending)
- **K**idneys
- **E**sophagus
- **R**ectum

What layers of the lateral and anterior abdominal wall would the bullet have to penetrate to reach the peritoneum?

The **lateral** abdominal wall layers are:

Skin → Camper fascia → Scarpa fascia → deep fascia → external oblique muscle → internal oblique muscle → transversus abdominis muscle → fascia → extraperitoneal fat → peritoneum

The **anterior** abdominal wall layers superior to the arcuate line (the horizontal line inferior to the umbilicus demarcating the lower limit of the posterior layer of the rectus sheath and the point at which the inferior epigastric vessels perforate the rectus abdominis) are:

Skin → Camper fascia → Scarpa fascia → deep fascia → external oblique*→ anterior internal oblique* → rectus abdominis → posterior internal oblique* → abdominis* → transversalis fascia → extra-parietal fat → parietal peritoneum

(*Aponeurosis of these muscles forms the rectus sheath)

What is the blood supply to the kidney?

Renal artery → segmental artery → lobar artery → arcuate artery → afferent arteriole → glomerulus → efferent arteriole → vasa recta → segmental vein → renal vein

What is the blood supply to the spleen?

The main blood supply is from the splenic artery, which is a branch of the celiac trunk (the other two branches are the left gastric and common hepatic arteries). The left gastro-omental and short gastric arteries are branches off the splenic artery. The short gastrics supply the fundus of the stomach.

What is the venous drainage of the spleen?

The splenic vein starts at the hilus of the spleen and receives blood from the stomach, pancreas, and inferior mesenteric vein. The splenic vein joins with the superior mesenteric vein to form the hepatic portal vein.

CASE 2

A 16-year-old boy is brought to the ED via ambulance after a motor vehicle accident. During the accident, he rear-ended the car in front of him at a high rate of speed. He was not wearing a seat belt, so he has a large contusion on his head, and his chest is indented as well. He is responsive only to sternal rub, and he is unable to comply with directions. His gaze is not deviated, and he is struggling to breathe on his own. His right leg is flexed, adducted, and internally rotated on the stretcher, and the orthopedic team is being consulted. His abdomen is firm, as well, with significant bruising. Physical examination reveals bruising to the chest, and ribs look "caved in"; the patient is becoming increasingly tachypneic and hypotensive. X-ray of the chest shows a fluid in the thorax without tracheal deviation, and a chest tube is placed on the right.

What conditions should be considered in a patient with trauma to the chest?

Direct injury can cause pulmonary or myocardial contusion, rib or sternal fractures, diaphragmatic injury, vessel laceration, and aortic damage, which is often fatal. Conditions associated with chest trauma include pneumothorax, flail chest, hemothorax, and cardiac tamponade.

What important nerves are at risk in stab wounds to the thorax?

- Cardiac plexus
- Recurrent laryngeal nerve
- Phrenic nerve
- Pulmonary plexus (contiguous with the cardiac plexus)
- Vagus nerve

What are the major arteries and veins of the thorax?

Arterial Supply
Aortic arch
Brachiocephalic trunk
Common carotid
Internal thoracic
Internal thoracic
Subclavian
Left bronchial

Venous Supply
Azygos
Brachiocephalic
Internal thoracic
Jugular

Which side of the chest uses the thoracic duct for lymphatic drainage?

The thoracic duct drains the entire lower body, left arm, left side of the head and neck, and the left side of the thorax. The right arm, right side of the head and neck, and right side of the thorax, however, use the right lymphatic duct. The thoracic duct drains into the venous system at the junction of the left jugular and subclavian veins.

What is the difference between the left and right mainstem bronchi?

The mainstem bronchus passes inferolaterally from the bifurcation of the trachea at the sternal angle to the hilum. The **right main bronchus** is shorter and wider and runs more vertically, allowing for passage of aspirates more easily than the left bronchus. The **left main bronchus** is longer and travels anterior to the esophagus between the thoracic aorta and the left pulmonary artery.

What are the clinical features in a patient with pneumothorax post trauma?

Fractured ribs from trauma or trauma itself can lead to a pneumothorax. Patients will often be tachypneic, hypoxic, and/or have decreased/absent breath sounds on the side of the pneumothorax. Imaging can confirm a pneumothorax. A chest tube is usually used to manage a pneumothorax from trauma. If there is a pneumohemothorax, separate chest tubes should be used to remove the blood and the air. Tension pneumothorax can occur if a patient with a simple pneumothorax is intubated. The trachea deviates toward the side of the injury. A chest tube should be inserted very quickly to resolve the issue.

CASE 3

A 62-year-old woman presents to the ED with a 2-day history of right-sided chest pain. The pain started after she helped her daughter move into college. She points to an area on the front of her chest when asked to localize the pain. She describes the pain as sharp and nagging, but it does not radiate to other areas of her body. She is very worried that she is having a heart attack because her dad died from one 2 years ago. Physical examination reveals point tenderness over the chest wall. The pain is exacerbated by deep inspiration, but there is no swelling or erythema. When asked about family history of heart disease, she says that both sides have "heart issues." When asked about medical history, she says she has a history of generalized anxiety disorder and panic attacks for the last 40 years that are usually controlled with venlafaxine and therapy, but she forgot to bring her medicines with her on her daughter's move. Echocardiogram, electrocardiogram, and chest radiograph are all normal. Further workup reveals that her first troponin is 0.001.

What is the pathophysiology of this condition?

Costochondritis, inflammation of the costochondral or costosternal joints, causes localized pain and tenderness. Often, more than one of the seven costochondral joints are affected, especially between the second and fifth costosternal junctions. Repetitive minor trauma or repetitive activities are the likely causes, but bacterial and fungal infections (not likely here given the lack of swelling, erythema) and thoracic surgery may also be implicated.

What is the innervation of the intercostal space?

The intercostal nerves (thoracic spinal and ventral rami) supply general sensory innervation to the skin of the thoracic and anterior abdominal walls. The dermatomes follow a girdle-like distribution. The sensory nerves also supply the parietal pleura and parietal peritoneum. The intercostal nerves also have motor innervation through the ventral rami of T1–T12. Intercostal nerve 1 participates in the brachial plexus, nerves 2–6 innervate the thorax, and nerves 7–12 innervate the anterior abdominal wall.

What other conditions should be considered in the differential diagnosis?

Although the localized areas of tenderness suggest a musculoskeletal cause, serious conditions such as myocardial infarction and pericarditis (which has an abnormal echocardiogram, pain that changes with position, and frictional rub on auscultation) need to be ruled out (see Table 10-1). Other considerations include pleuritic pain, which could be a manifestation of pneumonia, pulmonary embolism, pneumothorax, or pleuritis. Pleuritis can be seen in inflammatory conditions such as systemic lupus erythematosus (abnormal serology), fibromyalgia (tender points), and gastroesophageal reflux disorder.

Table 10-1. Differential Diagnosis of Chest Pain

Conditions	Differentiating symptoms
Costochondritis	Painful in one specific point on exam
Pericarditis	Pleural friction rub, hard to lay flat, echocardiogram changes, and ECG changes
Myocardial infarction	ECG changes, echocardiogram changes, and sudden onset
Panic attack	History of anxiety, significant stressor in life, no ECG or echocardiographic changes

What is the blood supply of the intercostal space?

At each space, there is a posterior artery and anterior set of arteries (see Figure 10-1). The bottom nine posterior arteries originate from the descending thoracic aorta, whereas the anterior artery originates from the internal thoracic. The posterior intercostal vein, artery, and nerve run together as a neurovascular bundle along the lower border of each rib. Therefore, during thoracentesis the needle must be inserted just above the lower rib in the intercostal space to avoid injury to the vessels and nerve.

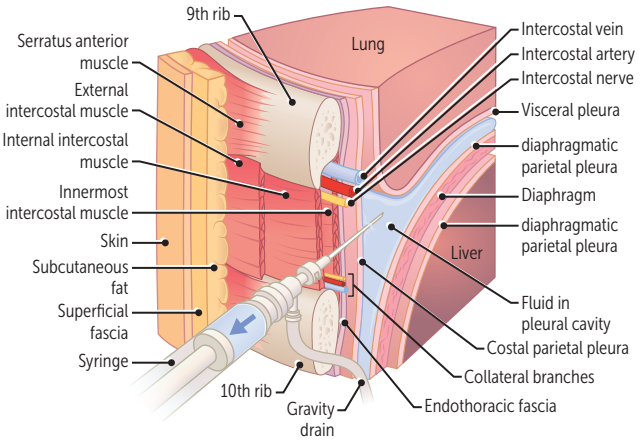

FIGURE 10-1. Blood supply to the intercostal space. (Reproduced with permission from USMLE-Rx.com.)

CASE 4

A 12-year-old boy is brought to the office by his mother because of leg pain. You notice that he is walking with a limp. The mother says that this has been going on for 6 weeks. She has given him aspirin, but it does not seem to help the pain and swelling. When you ask the boy about it, he points to a spot on his mid-thigh that he says hurts, and he states that he has been less active in soccer practice because he feels tired all the time. He denies any trauma or recent illness, but he went to the pediatrician last week because he keeps waking up covered in sweat. Physical examination reveals a firmly attached soft tissue mass of the right leg with overlying tenderness and warmth. X-ray of the leg shows a large, poorly demarcated lytic lesion with periosteal reaction in the right femoral diaphysis with extension to the soft tissue (see Figure 10-2). A biopsy of the mass reveals sheets of primitive round cells with small uniform nuclei, scant cytoplasm, and positive periodic acid–Schiff (PAS) staining.

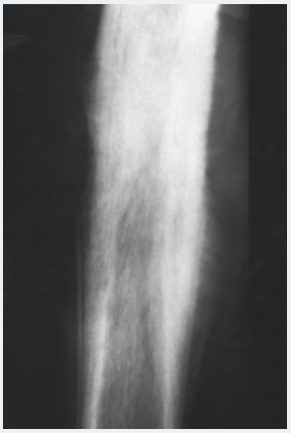

FIGURE 10-2. (Reproduced with permission from Skinner HB. *Current Diagnosis & Treatment in Orthopedics,* 4th ed. New York: McGraw-Hill, 2006.)

What is the most likely diagnosis?

The young age at clinical presentation, along with the tenderness, warmth, and swelling around the mass without systemic signs of infection suggests Ewing sarcoma (see Figure 10-2). This diagnosis is supported by the location of the lesion and the histologic appearance (small, round, blue neuroectodermal cells), which are characteristic of this neoplasm. The image shows the classic onion-skin appearance on x-ray.

What conditions should be considered in the differential diagnosis?

- Infectious causes to consider include acute osteomyelitis.
- Benign lesions, such as eosinophilic granuloma and giant cell tumor of bone, should also be considered.
- Other common solid tumors of childhood, such as osteosarcoma, primary lymphoma, spindle cell sarcoma, acute leukemia, and metastasis from a neuroblastoma, must also be ruled out.

What are the other small cell tumors?

Other small cell tumors include neuroblastoma, Wilms tumor, medulloblastoma, and rhabdomyosarcoma.

What is the most likely chromosomal aberration leading to this condition?

In total, 85% of Ewing sarcoma cases demonstrate a **t(11;22) translocation**. This translocation leads to an overexpression of the *EWSR1* gene (encodes RNA binding proteins) on chromosome 22, which is translocated next to the *FLI1* gene on chromosome 11 (encodes transcription factors). Ewing sarcoma and osteosarcoma most often develop in teenage years. Osteosarcoma and chondrosarcoma are more common in middle age. Osteosarcoma has a bimodal time of onset.

What is the treatment for this condition?

Ewing sarcoma is known to be a systemic disease due to the high relapse rate (80%–90%) of patients who undergo only local therapy. Therefore, most patients likely have subclinical microscopic metastatic disease at the time of diagnosis, which is treated with chemotherapy and radiation therapy.

What percentage of patients have metastatic disease at the time of diagnosis?

Only 25% of patients have overt metastases at the time of diagnosis.

CASE 5

A 40-year-old man presents to the clinic complaining of pain in his left big toe. The pain began suddenly this morning and woke him from sleep. He couldn't even stand to feel the bed sheet on his toe. He mentions that the night before, he and his fiancée had a dinner of liver pâté, cheese, and wine. Physical examination reveals a warm, erythematous, and exquisitely tender left metatarsophalangeal joint. Histological analysis of the affected toe is shown in Figure 10-3. Laboratory studies are significant for a serum uric acid level of 9 mg/dL.

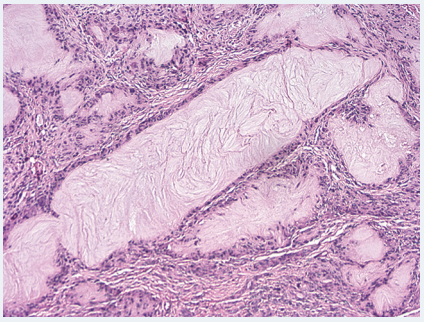

FIGURE 10-3. (Reproduced with permission from USMLE-Rx.com.)

What is the differential diagnosis for acute joint pain?

The causes of acute joint pain can be categorized as follows:

- Infection: Septic arthritis can present with joint warmth, swelling, and pain. Patients may also complain of fever and a history of trauma.
- Autoimmune disease: Joint inflammation secondary to rheumatoid arthritis may lead to erythema, swelling, pain, and stiffness of one or many joints.
- Osteoarthritis: Joint pain increases with use. In this case, however, the patient's relatively young age and the presence of redness and joint swelling are not consistent with osteoarthritis.
- Crystal arthropathy: Deposition of crystals in joint spaces (see Figure 10-3) leads to pain and inflammation.

What is the most likely diagnosis?

Gout, secondary to hyperuricemia. Gout characteristically causes monoarticular arthritis, often of the first metatarsophalangeal joint (**podagra**).

What are common causes of this condition?

Uric acid overproduction, which can be due to:

- Excessive cell turnover (such as lymphoproliferative disease, hemolytic anemia, cytotoxic drugs, or severe muscle exertion).
- Excessive dietary alcohol or purine intake.
- Inherited enzyme defects such as Lesch-Nyhan syndrome (hypoxanthine guanine phosphoribosyltransferase deficiency.
- Phosphoribosylpyrophosphate (**PRPP**) synthetase overactivity.

Uric acid underexcretion, which can be due to:

- Dehydration.
- Impaired renal function.
- Lactic acidosis.
- Use of certain drugs (thiazide diuretics, salicylates, cyclosporine A).

What are the most likely findings of arthrocentesis?

Needle-shaped **negatively birefringent crystals** are diagnostic for gout. By contrast, findings of pseudogout include basophilic rhomboid crystals of calcium pyrophosphate composition.

What are the treatments for this condition?

For acute attacks:

- Nonsteroidal anti-inflammatory drugs (NSAIDs) to reduce inflammation
- Colchicine, which depolymerizes microtubules, thus impairing leukocyte chemotaxis, which is first line
- In severe disease, NSAIDs and colchicine can be given at the same time for better control of symptoms.

For prevention of future attacks:

- Probenecid to inhibit renal reabsorption of uric acid
- Allopurinol to inhibit conversion of xanthine to uric acid by xanthine oxidase
- Diet control, including reduced intake of purine-rich foods (eg, meat, beans, and spinach) and alcohol

For patients with chronic kidney disease:

- NSAIDs should not be used in patients with chronic kidney disease, so for acute attacks, glucocorticoids should be first-line treatment.
- Allopurinol can also be used for chronic management.

CASE 6

A 72-year-old woman presents to the ED after slipping and falling on the sidewalk a few hours prior. She thought she would be able to walk after the fall, but she has been unable to walk because of severe pain in her left hip. Her son had to help her to the ED. Physical exam reveals normal vital signs and extreme pain with internal and external rotation of the hip with tenderness over the anterolateral portion of the hip. When sitting on the table, she has the leg externally rotated and shortened. She says she is in good health, but her primary care physician told her to take calcium and vitamin D. However, she has not been taking them because she doesn't like taking medicine.

What is the most likely diagnosis?

The most common causes of lateral hip pain in elderly patients include osteoarthritis, bursitis, metastases, and femoral fracture. In this patient, the sudden onset of pain after the fall and inability to walk strongly suggest a fracture of the neck of the femur (see Figure 10-4). Femoral neck fractures can be incomplete or complete with no, partial, or total displacement. Classically, the patient will present with an externally rotated and shortened leg. This is differentiated from a pathologic fracture from metastasis, which would present as a new fracture after no acute injury.

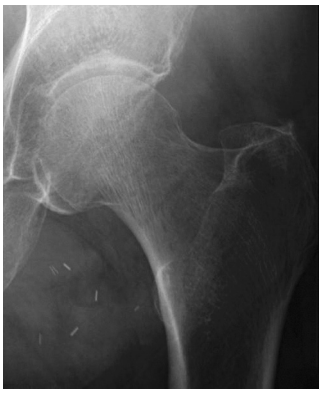

FIGURE 10-4. X-ray showing hip fracture. (Reproduced with permission from USMLE-Rx.com.)

What is a potential complication of this condition?

Fracture of the neck of the femur may disrupt blood supply to the head of the femur. The major arterial supply to the head of the femur is the medial and lateral circumflex femoral arteries (branches of the deep femoral artery) and the artery of the ligament of the head of the femur (branch of the obturator artery). The circumflex arteries may be disrupted by a fracture of the femoral neck, leaving only the artery of the ligament (a branch of the obturator) as a supply. Disruption of the blood supply may cause **avascular necrosis** of the femoral head.

What bones form the hip joint?

The hip joint consists of the head of the femur articulating with the acetabulum. The acetabulum is formed by the ilium, ischium, and pubis. The fibrocartilaginous rim, the acetabular labrum, attaches to the acetabular margin and deepens the acetabular cup.

Six weeks later, repeat x-ray shows a callus. What does the callus indicate about the patient's stage of healing?

Bone healing is often divided into three stages:

- **Inflammatory phase:** A hematoma forms at the site of fracture to help deliver the building blocks of new bone formation. Reabsorption occurs at the edges of bone, which is why fractures are more likely to be seen on x-ray several days after the injury.
- **Reparative phase**: New blood vessels that supply nutrients to the cartilage begin to form at the fracture site, followed by callus formation. The osteoprogenitor cells that form the callus derive from the inner surface of the periosteum, not from the marrow or the epiphyseal plate. The patient is in this stage of healing.
- **Remodeling phase**: The endochondral callus becomes ossified and bone undergoes structural remodeling (a process that is much slower in elderly people than in children).

CASE 7

A 2-week-old term boy is brought to his pediatrician for a well-child exam. The pediatrician noticed that the child had a large, full right scrotum. The left scrotum and testicle are normal. On physical examination, the right scrotum appears to be filled with a volume of fluid that is reduced by applying pressure. A small reducible bulging mass is also seen in the inguinal area on the right. The testicle is palpable in the scrotum on the right as well. There are no signs of trauma to the area.

What is the most likely diagnosis?

In a newborn, a painless collection of fluid in the scrotum is almost certainly a hydrocele. It should resolve on its own by 1 year. The fact that the fluid in the scrotum is reducible indicates that the hydrocele was caused by a communication with the intraperitoneal fluid via a hernia.

What would the differential diagnosis be if the patient were a child instead of a neonate?

In a child with a painless scrotal mass, tumor and varicocele must be considered. On palpation, a tumor is firm. The next test would be to illuminate the testicle. If the testicle transilluminates, it is a hydrocele. A tumor and varicocele would not transilluminate.

What structures define the Hesselbach triangle?

The Hesselbach triangle is formed by the lateral border of the rectus abdominis muscle, the inguinal ligament, and the inferior epigastric vessels.

What distinguishes the two major types of hernias?

Direct hernias protrude through a weakness in the floor of the inguinal canal within the Hesselbach triangle (directly through the triangle) medial to the inferior epigastric vessels to enter the external ring into the scrotal sac. **Indirect hernias** enter the inguinal canal lateral to the Hesselbach triangle (lateral to the inferior epigastric vessels) indirectly through the internal inguinal ring (located in the fascia transversalis), then via the inguinal canal to the external inguinal ring located above and lateral to the pubic tubercle, and finally into the scrotal sac (see Figure 10-5).

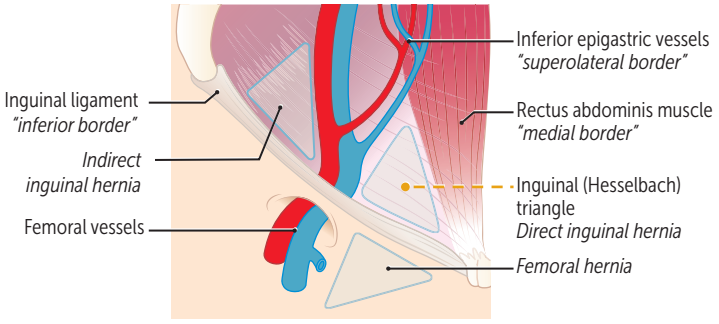

FIGURE 10-5. Direct and indirect inguinal hernia. (Reproduced with permission from USMLE-Rx.com.)

Which type of this condition is more common in infants and children?

Indirect inguinal hernias are more common in children, as they result from a congenital failure of the processus vaginalis to close. These can incarcerate, leading to bowel necrosis.

What are the contents of the normal spermatic cord?

The spermatic cord in the inguinal canal contains the testicular artery and veins, lymphatic vessels, and the vas deferens. The sheath of the cord is formed by the internal spermatic fascia, the cremasteric muscle, and the external spermatic fascia. The ilioinguinal nerve is in the sheath and exits at the external ring; it is vulnerable to injury in surgical repairs of hernias. The genital branch of the genitofemoral nerve supplies the cremaster muscle. The processus vaginalis is an extension of peritoneum that normally obliterates spontaneously between the upper pole of the testes and the internal inguinal ring. In some cases, however, it remains patent, increasing the risk of hydrocele and indirect hernia.

CASE 8

A gravid mother appears to the labor and delivery triage, and she has had no prenatal care. On exam, the baby is breech and needs to be delivered very quickly. During the delivery, the baby's arm is pinned above her head. The neonatologist quickly assesses the baby for any breathing or airway issues. Physical examination reveals that the newborn's right hand is slightly contracted, with the fingers curled toward the palm. The infant seems unable to extend the fingers on the right hand.

What is the most likely diagnosis?

Klumpke palsy results from birth injury to the lower trunk of the brachial plexus (C8 and T1 nerve roots). It is a proximal brachial plexus neuropathy. This injury frequently occurs with macrosomic babies that have the complication of shoulder dystocia. With physical therapy, most children have full return of function of the limb.

What motor deficits are likely to result from this condition?

The C8 and T1 nerve roots contribute to the ulnar and median nerves. The muscles affected are the medial part of the flexor digitorum profundus and the flexor carpi ulnaris (the only extrinsic muscles of the forearm supplied by the ulnar nerve), and all intrinsic muscles of the hand, including those innervated by the ulnar nerve (interosseous muscles, the second and third lumbrical muscles, and the adductor pollicis brevis muscles), and those innervated by the median nerve (thenar muscles and the first two lumbrical muscles). Over time, wasting of the thenar and hypothenar eminences occurs. Marked wasting between the metacarpals on both palmar and dorsal surfaces of the hand results from paralysis of the lumbricals and interossei.

What sensory deficits are involved in this condition?

The lower trunk from C8 and T1 contributes to the medial cutaneous nerves of the arm, forearm, and the ulnar and median nerves. Thus, in this patient, loss of sensation will occur on the medial side of the arm; the forearm; the dorsal and palmar surface of the fifth finger and half of the fourth finger; the palmar surface of the first, second, and third fingers and lateral half of the fourth finger extending onto the nail beds on the dorsal surface as far as the distal interphalangeal joints; and the palmar surface of the hand.

What other injuries can cause this condition?

- **Thoracic outlet syndrome**: This is a congenital defect in which a cervical rib or a scalenus minimus muscle compresses the lower trunk at C8 and T1.
- **Trauma**: Injuries to the inferior brachial plexus are much less common than injuries to the superior brachial plexus; traumatic injury can occur when a person grabs something to break a fall, or a baby's upper limb is pulled too hard during delivery.
- **Tumor infiltration**: Tumor infiltration from the apex of the lung (**Pancoast tumor**) can be associated with compression of the stellate ganglion, resulting in **Horner syndrome**.

What is another nerve lesion that can cause claw hand?

An ulnar nerve injury will also present with claw hand. However, with ulnar nerve injury, only the little finger and the ring finger are clawed because the median nerve is spared (resulting in normal thenar muscles). Also, the sensory deficit involves only the ulnar nerve distribution: the palm and dorsal surfaces of the medial part of the hand and the dorsal and palmar surfaces of the fifth finger and half of the fourth finger.

CASE 9

A 19-year-old woman athlete comes to the ED with her coach after injuring her left knee during soccer practice. She made a quick turn while running, and she heard a pop and fell down. She has not been able to walk without the assistance of her coach. Her MRI results are below (see Figure 10-6). On physical exam, the knee exam is limited by pain and swelling. When performing the anterior drawer test, the knee slides forward more than normal, which is considered a positive physical exam finding.

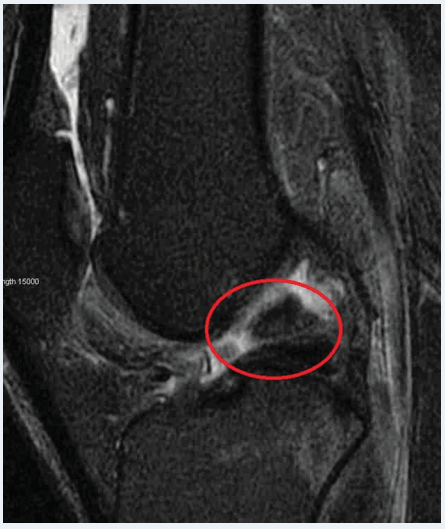

FIGURE 10-6. (Reproduced with permission from USMLE-Rx.com.)

What is the diagnosis?

Anterior cruciate ligament (ACL) tear (indicated by the red circle on Figure 10-6).

What are the two main intracapsular ligaments in the knee?

The ACL extends from the anterior intercondylar area of the tibial plateau and traverses superior and lateral to the medial surface of the lateral femoral condyle. The **posterior cruciate ligament** (PCL) extends from the posterior intercondylar area of the tibial plateau and traverses superior and medial to the lateral surface of the medial condyle of the femur (see Figure 10-7).

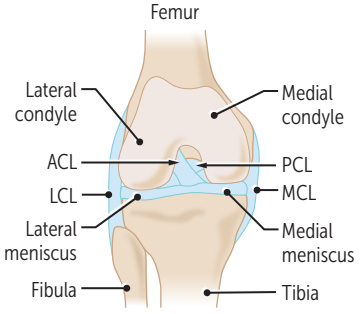

FIGURE 10-7. Anatomy of the knee. (Reproduced with permission from USMLE-Rx.com.)

What is the artery most commonly injured during ACL injuries and what can that cause?

The genicular artery can be injured, which can cause hemarthrosis.

What is the role of the meniscus?

The half-moon–shaped **meniscus** is cartilage that is found between the femur and tibia. The meniscus absorbs the impact load of the joint and is involved in stability. The meniscus is mostly avascular and is divided into the anterior horn, body, and posterior horn. The transverse ligament connects the medial and lateral meniscus. If torn, the knee hurts while standing and straightening or locking the knee. The McMurray test is the best for determining whether the meniscus is injured. The knee can also hurt while going from sitting to standing. See Table 10-2 for presentation of injuries to various ligaments.

Table 10-2. Injuries of Knee Ligaments

Ligament injured	Presentation
ACL	Lachman and anterior drawer tests positive; instability; knee "gives way"; injury from a sudden stop, change of direction, or jumping
MCL	Injury from blow to the lateral portion of the knee, knee feels like it's catching and locking when moving
LCL	Injury from force directed at the inside part of the knee, often seen with knee dislocations, pain and tenderness along the lateral aspect of the knee
PCL	Striking knee on dashboard or falling on knee when bent, posterior drawer test positive, trouble walking, and wobbly sensation in the knee
Meniscus	Can be from sports injury with sudden or degenerative changes in older patients, pain with straightening or bending the knee

How do the collateral and cruciate ligaments differ in function?

The cruciate ligaments remain tight in flexion and extension and relax at 30 degrees of flexion. The collateral ligaments are tight in extension and relaxed in flexion. Also, the cruciate ligaments prevent anterior and posterior displacement of the tibia. The collateral ligaments prevent abduction/adduction of the knee. The anterior and posterior drawer tests are common tests of the anterior and posterior cruciate ligaments. If the knee slides forward when pulled toward the physician, the anterior drawer test is considered positive. If the knee is pushed back towards the patient and slides, the posterior drawer test Is considered positive, and the posterior cruciate ligament is torn. The Lachman test is another ACL test that can be mentioned.

Which ligament of the knee is most often injured?

The medial collateral ligament is weaker than the anterior or the posterior cruciate ligaments, so medial collateral ligament injuries are more common. Anterior cruciate ligament tears are much more common than posterior cruciate ligament tears. The medial collateral ligament is tested with a valgus test. The patient lies flat, and lateral pressure is applied to the knee. The lateral collateral ligament can be tested in the same way, but it is a varus strength test, so medial pressure is applied to the knee. Table 10-2 describes the presentation of each knee ligament injury.

What is the terrible or unhappy triad?

This is a common contact-sport injury to the knee that occurs when lateral trauma is applied to the knee joint while the foot is fixed to the ground. Subsequently, the medial collateral ligament, medial meniscus, and anterior cruciate ligament are damaged.

CASE 10

A 47-year-old man presents to his primary care physician because he is concerned about a suspicious lesion on his chest that has increased in size over the past 2 years. He used to be a professional surfer and has never "bothered with sunscreen." He had a squamous cell carcinoma removed from his lower lip a few years ago. Physical examination reveals a 4-cm asymmetric, irregularly colored lesion with notched borders. It is slightly tender to palpation. Several other nevi are noted to be scattered over his chest and back. He has a few matted axillary lymph nodes on the same side as the chest lesion. He reports no other symptoms, but his wife has noticed the lesion has been growing larger more quickly.

What is the differential diagnosis and what is the most likely diagnosis?

Benign causes of an irregularly colored lesion include hemangioma, seborrheic keratosis, compound or junctional nevus, and pigmented dermatofibroma. But given the characteristics of this lesion, the most likely diagnosis is a malignant melanoma. The **ABCDE** rules help distinguish melanoma from other lesions (see Figure 10-8):

- **A**symmetry: Malignant lesions are usually asymmetric.
- **B**order irregularity: Most melanomas lack smooth, round, uniform boundaries.
- **C**olor variations: Malignant lesions usually have variations in pigmentation and occasionally lose pigmentation.
- **D**iameter: A diameter > 6 mm greatly increases the chances of malignancy, and most lesions are > 10 mm.
- **E**volution: change over time

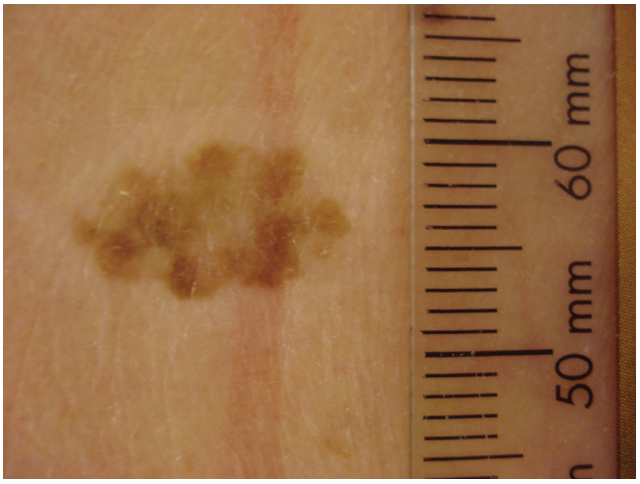

FIGURE 10-8. (Reproduced with permission from USMLE-Rx.com.)

Which cells are responsible for this lesion and what is their embryonic origin?

Melanomas originate from melanocytes, which are derived from neural crest tissue and reside in the epidermis or, less frequently, in the dermis.

What is the etiology of this lesion?

Malignant melanomas are more likely to appear on areas that receive **sun exposure**. Other risk factors include atypical/dysplastic nevi and family history.

What is the most important prognostic factor for this condition?

The most concerning factor is vertical invasion, as deeper lesions have a worse prognosis. This is classified as the Breslow depth. Detection of melanoma at early stages is crucial, and prognosis is excellent if treated early. However, after the tumor has penetrated the basement membrane and entered the subcutaneous fat, 5-year survival is only 49%. The S-100 protein can help determine prognosis; elevated S-100 serum levels correlate with a worse prognosis. BRAF mutations in melanoma have become a new target for drug therapy. If the patient has the mutation, they can be treated with vemurafenib, which is a BRAF kinase inhibitor. The BRAF mutation leads to a greatly increased activation of signaling pathways for growth and proliferation.

How and where does this lesion tend to spread?

Initial lesions usually spread superficially and horizontally across the skin and then enter a vertical growth phase into the deeper layers of the skin. Melanomas may then spread either hematogenously or through the lymphatics; earliest detectable metastases occur in regional lymph nodes. Classic sites of hematogenous spread include brain, lung, liver, and bone; however, melanomas are notorious for metastasizing to odd locations such as the heart.

What is the treatment for this condition?

Surgical excision with optional regional node dissection for more advanced disease remains the first-line treatment.

CASE 11

A 3-year-old boy is brought to the pediatrician by his parents who noticed that he has been stumbling recently and uses his hands to stand up. They are very worried because it seems to be getting worse. His developmental history is notable for delayed motor skills; he began to walk at 18 months. The boy has a waddling gait and when sitting uses his arms to push himself into the upright position (see Figure 10-9). Physical examination shows marked muscle weakness of the extremities, particularly of the proximal muscle groups, and hypertrophy of his calf muscles. The patient's maternal uncle, who died at 16 years of age, suffered from similar symptoms when he was younger, so the mother is very concerned that the same thing will happen to her child. She is also very worried that her current pregnancy will have the same condition.

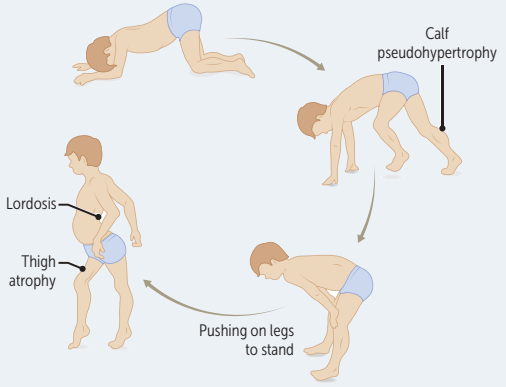

FIGURE 10-9. (Reproduced with permission from USMLR-Rx.com.)

What is the likely diagnosis and what is the pathogenesis of the disorder?

Duchenne muscular dystrophy (DMD) is an X-linked recessive (Xp21) disorder marked by a deficiency of functional **dystrophin**, a 23,000-kB protein that helps stabilize muscle fibers. Approximately one-third of cases are sporadic and due to spontaneous mutations (noninherited) that arise from a misalignment of chromosomes during a recombination event. Figure 10-8 describes the Gower sign: because of muscle weakness, children with DMD often used their hands and arms to "walk up" their body from a squatting or supine position..

What is the prognosis for patients with this condition?

Patients with DMD are usually unable to walk by the end of the first decade and are confined to a wheelchair by 12 years of age. Most patients die by the end of the second decade; respiratory failure is the leading cause of death. Dilated cardiomyopathy and/or conduction abnormalities are common and can be fatal.

What tests are used to diagnose this condition?

If DMD is clinically suspected, serum creatine kinase levels are markedly elevated, and electromyography shows myopathic changes; genetic testing or a muscle biopsy can confirm the diagnosis. Muscle biopsy shows atrophic muscle fibers of various sizes in disarray, degeneration, and necrosis of individual muscle fibers with fibrous replacement.

The patient's parents have a second son who is 6 months of age. What is the chance that he, too, will develop this condition?

The chances are 50% (assuming that the first case was not sporadic). Because the mother is a carrier of this disorder, each son has a 50% chance of inheriting the X chromosome with the mutated allele from her.

Which band in a sarcomere stays constant in length during muscle contraction?

The A band, which corresponds to the length of the thick myosin filaments (see Figure 10-10).

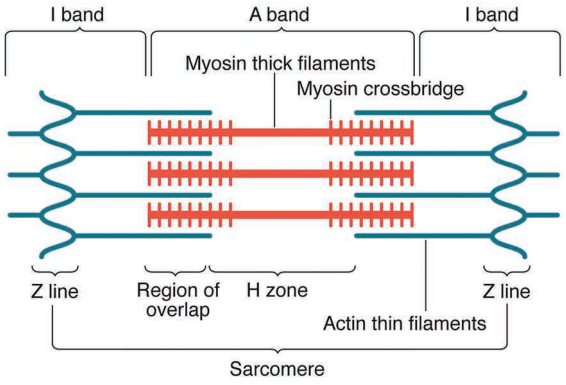

FIGURE 10-10. Muscle contraction. (Reproduced with permission from USMLE-Rx.com.)

How would the presentation of a patient with Becker muscular dystrophy (BMD) differ from that of this patient?

The most obvious difference is the age of onset of symptoms and degree of clinical involvement. BMD patients typically remain ambulatory until at least 15 years of age and commonly into adulthood. Intellectual disability and contractures are more common in BMD. BMD is milder than Duchenne muscular dystrophy. BMD has a later onset than DMD and does not start to show up symptomatically until teenage years, so the patients have a long life expectancy. This is because there is partial activity of the protein instead of its complete absence, as in DMD. In DMD, the patient is likely to be wheelchair-bound by the age of 13. With BMD, the neck flexor is preserved, which leads to better outcomes. BMD most often presents with cardiomyopathy as a more prevalent feature, but both BMD and DMD can have cardiomyopathy.

CASE 12

A 65-year-old man presents to his primary care physician for a well-care visit. His only complaint is increasing hip stiffness and dull pain in his lower back and left hip. This started 10 years ago, and he takes occasional ibuprofen to relieve it. He is an avid marathon runner, but the pain is starting to decrease his activities. The pain is typically exacerbated by activity and relieved by rest. He is worried that he will have to stop running altogether. Physical examination reveals limited range of motion in the affected joints and tenderness on palpation without warmth or erythema. X-ray of the pelvis and lower spine shows joint space narrowing, incomplete articular surface, and swelling joint capsule (see arrows in Figure 10-11).

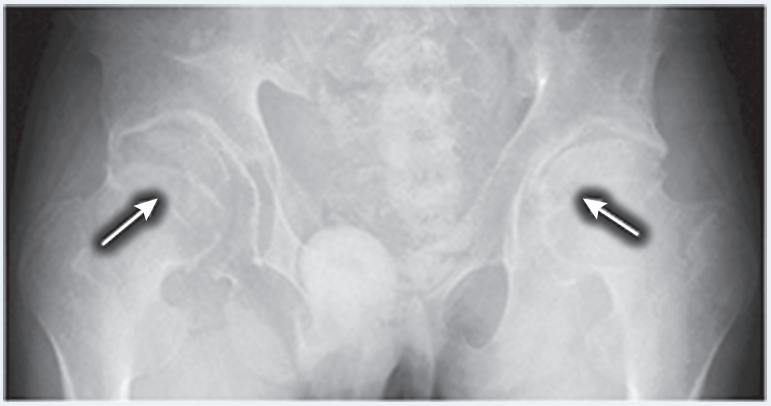

FIGURE 10-11. (Reproduced with permission from Yu H, et al. Clinical features and outcome in patients with osseomuscular type of Wilson's disease. *BMC Neurol*. 2017;17:34.)

What is the likely diagnosis?

The asymmetric, gradually progressive joint pain and stiffness in this case point to osteoarthritis (x-ray findings in Figure 10-11 confirm). Physical examination findings in osteoarthritis include tenderness to palpation without signs of inflammation, joint effusions, crepitus, and bony enlargement of affected joints.

What are the radiographic features of this condition?

Radiographic findings in osteoarthritis can be summarized by the mnemonic **LOSS**: **L**oss of joint space, **O**steophytes, and **S**ubchondral **S**clerosis.

What conditions should be considered in the differential diagnosis?

In an elderly patient with joint disease, the other conditions to consider are rheumatoid arthritis (RA), gout, pseudogout, and infectious monoarticular disease.

- RA joint stiffness (causing morning stiffness usually lasting $>$ 30 minutes) increases with rest and improves with activity. Affected joints are soft, warm, and tender. Neither of these factors is the case in this patient.
- Infectious monoarticular disease is unlikely in this case given the lack of warmth or erythema. It also is a rapid presentation, unlike the current case, which is insidious over 10 years.
- Gout is unlikely because the initial attack of acute gout is usually in the foot (first metatarsophalangeal joint) or knee, and the pain is acute, not dull.
- Pseudogout can also be ruled out as it would likely present acutely in the hips and/or wrists with different radiographic findings, such as ossification of cartilaginous structures.

What is the characteristic distribution of this condition?

Osteoarthritis most often affects large weight-bearing joints including the knees, hip, and spine, as well as the distal interphalangeal joint. In contrast, RA commonly affects the proximal interphalangeal and metacarpophalangeal joints. Osteoarthritis only rarely affects the elbows, wrists, and ankles. Heberden and Bouchard nodules are common presentations, and they are both nodules on the fingers. Heberden nodules are on the distal interphalangeal joint, and the Bouchard nodules are on the proximal interphalangeal joint.

What is the pathophysiology of this condition?

Osteoarthritis is characterized by degenerative noninflammatory changes in articular cartilage secondary to chondrocyte dysfunction. These changes may be caused by a complex interaction between metabolic, biochemical, and biomechanical factors with secondary components of inflammation. The result is progressive mechanical damage to the joint and bone eburnation, particularly in weight-bearing joints. This degeneration also causes reactive bone formation subchondrally and at the margins of affected joints.

What would arthrocentesis (aspiration of the joint fluid) likely show?

Arthrocentesis is mostly normal, with perhaps mild pleocytosis and modestly elevated protein.

What is the treatment for this condition?

Acetaminophen and nonsteroidal anti-inflammatory drugs remain the mainstays for analgesia. In a patient with a history of gastroduodenal disease, a gastroprotective agent, ebrotidine, could also be given. Occasionally, intra-articular glucocorticoids are used when symptoms persist in a few joints. Surgery may be required for refractory cases (joint replacement or fusion).

What risk factors are associated with this condition?

Risk factors for osteoarthritis include increased age, obesity, female gender, lack of osteoporosis, physically demanding occupations, previous injury, or genetic disorder such as Wilson disease and hemochromatosis.

CASE 13

A young couple seeks genetic counseling before conceiving their first child. The husband had bilateral tumors removed from his head, but he cannot remember the exact tumor. He had dizziness and vertigo as a child, but he has not had these symptoms since the tumors were removed. His mother had similar tumors "in her ears," which were removed before he was born. The wife has multiple axillary freckles and light brown patches covering her torso. Many of her siblings have these freckles as well, so she always thought they were normal. She has spots around her iris, as well, that do not affect her vision. She has an odd lesion over the sphenoid bone on her hand on examination. She has been told before that she has tumors that will happen under her skin, which her father and sister also had. She has been told before that they are benign and do not need to be removed.

What genetic syndromes do this man and woman have?

The woman has neurofibromatosis type 1 (NF1, or von Recklinghausen neurofibromatosis), and the man has neurofibromatosis type 2 (NF2). NF1 is characterized by café-au-lait spots, meningiomas, **neurofibromas** (subcutaneous nodules), and axillary freckling. NF2 presents with bilateral acoustic neuromas (vestibular schwannomas).

What is the probability that the couple will have an asymptomatic child?

NF1 and *NF2* are both autosomal dominant genes. Based on their family histories, the man and woman must be heterozygous for NF2 and NF1, respectively. Thus, each mutant gene has a 50% chance of being inherited by the child. *NF1* is on chromosome 17, and *NF2* is on chromosome 22; therefore, the inheritance of each mutant gene occurs independently of the other. The probability of two independent events occurring at once is the product of the probability of each event: $50\% \times 50\% = 25\%$.

Which cell line is implicated in the formation of the woman's lesions?

Neural crest cells are involved. Most clinical signs of NF1 are related to abnormal descendants of neural crest cells.

What is the mechanism of tumor formation for the woman?

The *NF1* gene is a tumor suppressor gene belonging to a family of guanosine triphosphatase–activating proteins. Multiple loss-of-function mutations in this gene lead to tumor growth.

What is the path of the eighth cranial nerve (CN VIII) from the periphery to its site of entry into the central nervous system?

From the cochlea and vestibular canals in the petrous bone, CN VIII enters the cranial vault through the internal acoustic meatus to enter the brain stem at the junction of the pons and the medulla. The most common presentation of this is acoustic neuroma. If the patient has bilateral acoustic neuromas, this is indicative of NF2. The patient will present with dizziness and nausea, with increase of these symptoms over time, as well as headaches. This can also have symptoms of cranial mass effect.

What other clinical features could a patient with the woman's condition have?

NF1 patients may have iris hamartomas (Lisch nodules), optic gliomas, distinctive bony lesions such as sphenoid dysplasia, and thinning of a long bone cortex with or without pseudarthrosis.

CASE 14

An 8-year-old girl is brought to the pediatrician for evaluation of recurrent fractures. Most recently, she broke her femur walking down the bleachers at the gym. She avoids contact sports, but she has sustained fractures to her femur, tibia, and elbow following seemingly minor trauma. Her mother has been investigated for abuse because of the fracture history, but she was found not responsible. At birth, the girl had multiple bilateral rib fractures. The pediatrician notes the girl is short for her age and has mild scoliosis and blue sclerae.

What is the differential diagnosis for recurrent fractures in children?

- Accidental injury
- Birth trauma
- Bone fragility (including osteogenesis imperfecta and rickets)
- Child abuse (which accounts for the vast majority of cases)

What is the most likely diagnosis?

Osteogenesis imperfecta (OI), an inherited disorder involving defects in type I collagen, usually due to mutations in the *COL1A1* or *COL1A2* gene. It is also known as **brittle bone disease**, and its most common form has autosomal dominant inheritance.

What pathologic findings are associated with this condition?

OI is associated with cardiac insufficiency, mitral valve prolapse, hearing loss, basilar skull deformities (causing nerve compression and other neurological sequelae), and kyphoscoliosis. Death due to multiple fractures or pulmonary failure is common in utero or soon after birth in severe forms, which are recessively inherited.

What are the four major types and locations of collagen?

- **Type I** collagen is found in bone, skin, tendon.
- **Type II** collagen is found in cartilage.
- **Type III** collagen is found in reticular tissue, arterial walls, and uterus.
- **Type IV** collagen is found in the basement membrane.

What steps are involved in collagen synthesis?

Procollagen strands containing a repeating Gly-Pro-X sequence are synthesized in the ribosome, hydrolyzed by prolyl hydrolase, and glycosylated in the rough endoplasmic reticulum and Golgi complex. Three procollagen strands associate in a triple helix and are secreted into the extracellular space, where the propeptides are cleaved, allowing for polymerization with other collagen molecules to form collagen fibrils.

What enzymes in collagen synthesis depend on ascorbic acid?

Proline hydroxylase (which hydroxylates prolyl and lysyl residues) cross-links collagen and depends on ascorbic acid. Vitamin C deficiency can lead to **scurvy**, which causes ulceration of the gums, bruising, anemia, poor wound healing, and hemorrhage due to deficient collagen synthesis.

CASE 15

A 65-year-old woman presents to the ED with sharp pain in her lower back after lifting some heavy objects while moving into a new home. The pain radiates to the anterior abdomen and is exacerbated by sitting and moving. She said she has had trouble with depression after the death of her husband, so she has not been very active recently. She normally eats frozen meals for every meal because her husband used to cook for her. She states that she used to take some sort of vitamins for her bones a few years ago, but she currently doesn't take any medicine. On physical examination, she appears kyphotic with a "dowager hump." A plain film radiograph reveals multiple vertebral compression fractures. Her lab values for calcium and PTH are all normal.

What underlying condition contributed to these fractures?

Osteoporosis. This disease is characterized by reduced bone mass with microarchitectural disruption, porosity, and skeletal fragility. Osteoporosis is difficult to diagnose, as a fracture is often the first clinical manifestation.

What two factors contribute most to this condition?

Most postmenopausal women with osteoporosis have bone loss related to **age** and/or **estrogen deficiency**. Estrogen naturally suppresses cytokines (such as interleukin-1 and -6) and receptor activator of nuclear κ-B ligand (RANKL) which both increase osteoclast activity. RANKL interacts with RANK to promote development and function of osteoclasts. Denosumab is the first osteoporosis treatment that acts by blocking RANK-RANKL binding.

What secondary factors increase the risk of this condition?

- Physical inactivity
- Calcium and vitamin D deficiency
- Prolonged glucocorticoid therapy
- Hyperparathyroidism
- Hyperthyroidism.

What sites of fracture are most common in this condition?

Vertebral compression fractures are the most common clinical manifestation of osteoporosis. Most fractures are asymptomatic and are usually an incidental finding on x-ray of the chest or abdomen. However, they may manifest as spinal deformity and shortened stature. **Hip** and **distal radius (Colles) fractures** are also common.

What tests and/or imaging tools can be used to test bone density?

DEXA scans are used to compare bone density to an age-matched reference population. Density more than 2.5 standard deviations below the expected range confirms the diagnosis.

What are the treatments for this condition?

- The mainstay of treatment and prevention of osteoporosis is **bisphosphonates** such as alendronate and risedronate. This is in addition to continuation of both calcium and vitamin D supplementation. These agents act by decreasing osteoclastic bone resorption. One of the adverse effects of bisphosphonates is esophagitis; thus, patients are instructed to take it with water and while standing or sitting upright (and remain so for at least 30 minutes). Osteonecrosis of the jaw can also occur with bisphosphonates.
- Raloxifene, a **selective estrogen receptor modulator** is also used in refractory cases.
- Intermittent administration of recombinant parathyroid hormone has also shown to be effective.

CASE 16

A 62-year-old woman presents to her clinician with joint pain and morning stiffness for the past few years. It has been getting worse, but it tends to get better as she moves them throughout the day. The joint pain is present in both hands and feet bilaterally and has caused significant deformity and weakness. She now struggles to make breakfast in the morning until "her joints loosen up." When asked about previous health issues, she states that she had something wrong with her thyroid many years ago, and she has been taking levothyroxine ever since. On physical examination, these joints are tender to palpation, warm, and swollen with no erythema. Her metacarpal joints display ulnar deviation bilaterally, and subcutaneous nodules can be palpated at the elbow.

What is the most likely diagnosis?

Rheumatoid arthritis (RA). Clinical features of RA include the following:

- Morning stiffness for more than 1 hour that is present for more than 6 weeks
- Arthritis in three joints or more for more than 6 weeks
- Arthritis of hand joints for more than 6 weeks
- Symmetric joint swelling and involvement
- Rheumatoid subcutaneous nodules
- Positive serum rheumatoid factor and/or anticyclic citrullinated protein antibodies (anti-CCP)
- Abnormal C-reactive protein (CRP) and/or erythrocyte sedimentation rate (ESR)
- Typical radiographic changes (shown in Figure 10-12)

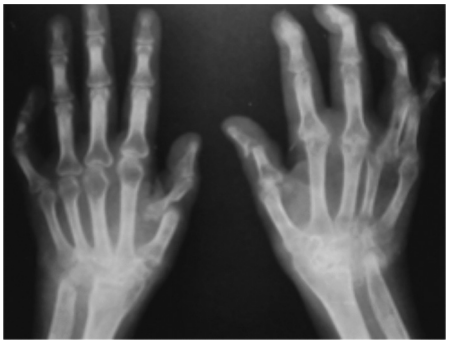

FIGURE 10-12. Radiographic changes in rheumatoid arthritis. Severe destruction of radiocarpal articulation with subluxation and ulnar deviation at the wrist; loss of ulnar styloid bilaterally; dislocation of the proximal interphalangeal joint of the left thumb and dislocation of the right fourth and fifth finger metacarpophalangeal joints and left metacarpophalangeal joint; diffuse joint space narrowing of many interphalangeal joints. (Reproduced, with permission, from Brunicardi FC, et al. *Schwartz's Principles of Surgery*, 8th ed. New York: McGraw-Hill, 2005: 1679.)

What is the pathophysiology of this condition?

RA is a chronic **systemic autoimmune inflammatory disorder** that destroys articular cartilage. While the etiology is unclear, the autoimmune reaction is mediated by CD4+ T cells, macrophages, and cytokines (tumor necrosis factor and interleukin-1), which promote the inflammatory response. Together these elements form a pannus that gradually erodes and disfigures joints. This process is mediated by type 3 and type 4 hypersensitivity reactions.

What test can help diagnose this condition?

Although no specific laboratory test is diagnostic of RA, most patients have a **positive serum rheumatoid factor (RF; not perfectly sensitive nor specific)** and anti-CCP (similar sensitivity and better specificity than RF).

What joints are typically affected in this condition?

Symptoms usually develop symmetrically in the small joints of the hands and feet (metacarpophalangeal, proximal interphalangeal, metatarsophalangeal joints), as well as wrist, elbows, knees, and ankles. The cervical spine may also be involved, which is important to know when the patient is being intubated. Patients with RA can have serious spinal cord injury if they are intubated emergently, which puts more traction on the neck than a normal intubation.

What are the characteristic joint deformities in this condition?

Ulnar deviation/drift, swan-neck, and Boutonniere deformities of the fingers and the "bow-string" sign (prominence of the tendons in the extensor compartment of the hand) are all characteristic of RA. Occasionally patients present with synovial cysts from increased intra-articular pressure and eventual tendon rupture.

What are the primary pharmacologic therapies for this condition?

- Analgesics including acetaminophen
- Nonsteroidal anti-inflammatory drugs
- Glucocorticoids
- Disease-modifying antirheumatic drugs such as methotrexate, hydroxychloroquine, or sulfasalazine
- Anticytokine therapies such as etanercept, infliximab, and adalimumab
- Other biologic agents such as abatacept and rituximab

What are some nonarticular manifestations of this condition?

- Musculoskeletal manifestations include osteopenia, osteoporosis, muscle weakness, vasculitis, and skin symptoms such as rheumatoid nodules.
- Pulmonary manifestations include pleuritis, pleural effusion, and interstitial fibrosis.
- Cardiac manifestations include coronary artery disease and heart failure.
- Other manifestations include scleritis, anemia, and Felty syndrome (RA with splenomegaly and neutropenia).
- Baker cyst behind the knee

CASE 17

A 63-year-old woman complains that since falling on her outstretched hands 3 weeks ago, she can no longer use her right arm to remove books from the overhead shelves in her office. Further questioning reveals that she has pain in her right shoulder at night that wakes her up and that she can no longer sleep on her right side. Physical examination reveals tenderness to palpation below the right acromion. She has pain with the empty can test.

Among the conditions that can cause shoulder pain in elderly patients, what is the most likely diagnosis in this case?

A rotator cuff tear, which presents with both pain and weakness and is consistent with the physical examination findings. The subacromial bursa may also be involved, in which case pain is also felt at the insertion of the deltoid muscle in the middle of the upper arm.

Other common causes of shoulder pain include rotator cuff tendinitis, adhesive capsulitis (frozen shoulder), and subscapular bursitis.

- Rotator cuff tendinitis is unlikely in this case because it presents with pain but not weakness.
- Adhesive capsulitis is unlikely because it is characterized by an absolute loss of range of motion.
- Subscapular bursitis would localize pain to the upper back and have an audible popping sound with shrugging.
- In a lidocaine injection test (in which the subacromial space is injected with lidocaine), rotator cuff tears show decreased pain but persistent weakness; rotator cuff tendinitis has normal strength; and frozen shoulder shows persistent loss of range of motion.

What events commonly precipitate this condition?

Rotator cuff tears are rare in patients younger than 40 years of age but common in patients older than 50 years of age with shoulder pain. However, sports injuries with rotator cuff tears are seen in young athletes. Other common causes of rotator cuff tears include the following:

- Direct blow to the affected shoulder
- Falling onto an outstretched hand (as this patient did)
- History of recurrent rotator cuff tendinitis
- Lifting a heavy object
- Shoulder dislocation

What other tendons are likely involved in this condition and what is their distal attachment?

The rotator cuff is made up of the tendons of the "**SITS**" muscles: **S**upraspinatus (the most commonly affected tendon with rotator cuff tears), **I**nfraspinatus, **T**eres minor insert on the greater tuberosity, and the **S**ubscapularis inserts on the lesser tuberosity (see Figure 10-13).

What are the innervations and actions of these muscles?

- Supraspinatus: Suprascapular nerve (C4–C6); abduction of the arm for the initial 20 degrees (the deltoid abducts the arm beyond the initial 20 degrees)
- Infraspinatus: Suprascapular nerve (C4–C6); external rotation of the arm
- Teres minor: Axillary nerve (C5–C6); aids in external rotation of the arm
- Subscapularis: Upper and lower subscapular nerves (C5–C7); help with median rotation and adduction of the arm

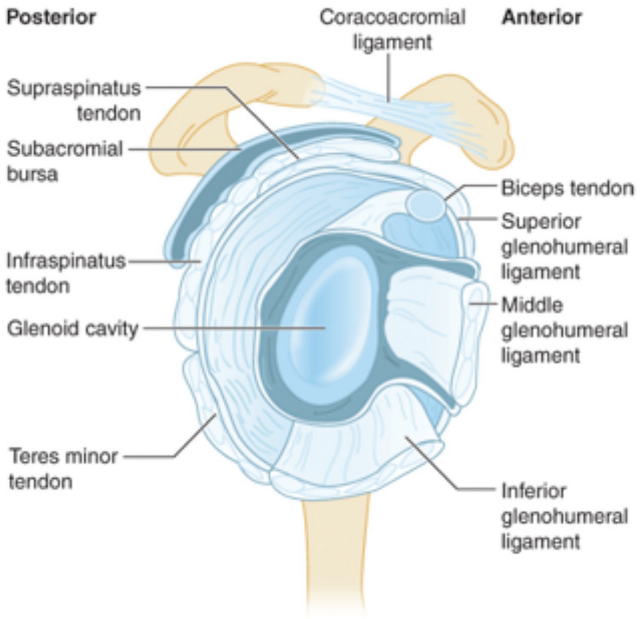

FIGURE 10-13. Lateral view of shoulder illustrating coracoacromial arch with rotator cuff and subacromial bursa. (Reproduced with permission from Tintinalli JE, et al. eds. *Tintinalli's Emergency Medicine: A Comprehensive Study Guide*, 8th ed. New York, NY: McGraw-Hill; 2016.)

CASE 18

A 63-year-old farmer came to see you today for a yearly health maintenance exam. He seems in good health, but you notice a discoloration on his lip. You ask how long it has been there and if there have been any changes. He has noticed that it has been enlarging more recently. He refuses to wear sunscreen and is very tan from working in the sun for many years. It has been on his lower lip for many years. On further questioning, he reveals that he burned his face with grease in the same area when he was younger. There was always a scar there, but recently it seems to bleed when touched, and there is an ulcer over the old scar. On physical examination, there is a well-demarcated 1.5 cm rough, scaly, erythematous patch. Biopsy of the lesion reveals hyperkeratosis and keratin pearls.

What is the most likely diagnosis?

The patient's biopsy shows atypical keratinocytes that have invaded the basement membrane; therefore, malignancy is present. Although basal cell carcinoma (BCC) is the most common type of skin cancer, the description of the lesion suggests squamous cell carcinoma (SCC). BCC typically arises on the upper lip, and SCC typically arises on the lower lip. Cutaneous SCC is the second most common tumor of the skin. It arises from the malignant proliferation of epidermal keratinocytes. The condition typically presents as a firm, well-demarcated lesion that is scaling, crusting, or ulcerated. Histologic examination is necessary for a diagnosis. Keratin pearls are seen on exam for SCC.

What precursor lesion can lead to this condition?

Actinic keratosis (AK), a dysplastic lesion of the epidermis, can lead to SCC. These lesions occur only on sun-exposed skin and consist of hyperkeratotic papules that have a coarse sandpaper feel; some may present as a "cutaneous horn."

What risk factors are associated with this condition?

The most important risk factor for SCC is **sunlight exposure** in which ultraviolet (UV) rays cause DNA damage. Other exogenous factors include ionizing radiation, immunosuppression, chronic inflammation (from burns, scars, or ulcers), and arsenic exposure. The ulcers that arise in old burns are called Marjolin ulcers and are indicated by an ulcer that does not heal in an old burn scar.

What inherited disorders predispose patients to this condition?

Xeroderma pigmentosum is a rare autosomal recessive disorder that displays a defect in DNA excision repair, which impairs the ability to repair UV-induced DNA damage. **Albinism** is also associated with SCC because of the generalized pigment loss due to dysfunction and deficiency of melanocytes.

What is the prognosis for patients with this condition?

Even though cutaneous SCC can be locally invasive, it rarely metastasizes (1%–5% of cases). Therefore, more than 90% of patients can be cured with local excision.

CASE 19

A 24-year-old woman presents to the clinic complaining of fatigue and muscle and joint aches over 2 months. She said she has noticed that she has been having intermittent fevers. She also believes her face has been getting sunburned more easily. She currently has a rash over her cheeks. Two years ago, she was diagnosed with Graves disease and had to have her thyroid removed. She also has had type 1 diabetes since the age of 13. She is currently well maintained on medications for both, but she is worried these adverse effects are from her medications to control these conditions. Upon examination, she has a friction rub on cardiac auscultation. Laboratory tests show the following:

Hemoglobin: 10.8 g/dL
Hematocrit: 32.8%
Platelet count: 145,000/mm^3
WBC count: 4350/mm^3
Urinalysis: 3+ proteinuria

What is the most likely diagnosis?

Systemic lupus erythematosus (SLE). SLE is a multisystem autoimmune connective tissue disease with a variable clinical presentation that most commonly affects young women in their 20s and 30s. Most manifestations of SLE are secondary to immune complex deposition.

What explains the friction rub on auscultation?

SLE patients can develop pericarditis leading to friction rub. People with SLE can also have Libman-Sachs endocarditis, which can lead to murmurs on auscultation. When the valve is examined, it will have small vegetations along both sides of the valve.

What laboratory tests can be used to confirm the diagnosis?

Antibody testing, including antinuclear antibodies (ANA), antiphospholipid antibodies, antibodies to double-stranded DNA (dsDNA), and anti-Smith (Sm) antibodies are used to diagnose SLE. Positive anti-dsDNA and anti-Sm test results are the most specific for SLE. A positive ANA test is sensitive but not specific. High-yield fact: antiphospholipid antibodies also bind the cardiolipin antigen used in syphilis testing; therefore, lupus patients have a false-positive syphilis test.

What would a positive anti-histone antibody suggest?

It would suggest **drug-induced lupus**, but the reason for this correlation is unknown. Common medications that can cause drug-induced lupus include hydralazine, procainamide, minocycline, penicillamine, and isoniazid.

What are the 11 classification criteria for this diagnosis?

For SLE, remember the mnemonic **SOAP BRAIN MD**: **S**erositis, **O**ral ulcers, **A**rthritis, **P**hotosensitivity, **B**lood changes (SLE patients often have leukopenia, a mild anemia, and clinically insignificant thrombocytopenia), **R**enal involvement (proteinuria or casts), **A**NA, **I**mmunologic changes, **N**eurologic signs (seizures, frank psychosis), **M**alar rash, and **D**iscoid rash.

For the diagnosis of SLE, a patient must display a minimum of four of 11 characteristics.

What are the typical renal findings in this condition?

Most SLE patients have an abnormal urinalysis. There are six classes of renal disease in SLE, which are usually differentiated with a renal biopsy. Immune complex (anti-ds-DNA)–mediated glomerular diseases are most common. SLE nephropathy most commonly displays a nephrotic syndrome pattern with a histologic subtype of diffuse lupus nephritis (class IV). The pathologic finding on histology that is almost pathognomonic for SLE is "**wire loop**" lesions (tubuloreticular structures in the glomerular endothelial cells, which may also be seen in HIV nephropathy). Other findings include subepithelial or subendothelial deposits with inflammation. Lupus nephritis is a type III hypersensitivity reaction.

CASE 20

A 54-year-old woman presents to the clinic with fatigue, difficulty swallowing, a nonproductive cough, stiffness in the joints of her hands, and tightness in her fingers. Additionally, she says when her fingers get cold they turn blue, so she often wears gloves, but this has happened for many years. In regard to her swallowing, she states that it feels like her food gets "stuck in her chest" when she swallows. She has lost significant amounts of weight because of these swallow issues over the last 6 months. On physical examination, her skin is taut and thickened over her hands and face. Her hands appear claw-like and have decreased motion at all the small joints symmetrically.

What is the most likely diagnosis and what are the two forms of this condition?

Systemic sclerosis (scleroderma), an autoimmune connective tissue disorder, exists in two forms, **limited** and **diffuse**, both of which occur in the setting of Raynaud phenomenon (exaggerated vasoconstriction in response to cold or stress leading to sharply demarcated color changes of the fingertips). This patient displays the limited form in which the skin of the fingers, forearms, and face are often affected with distinctive thickening (see Figure 10-14).

Diffuse systemic sclerosis eventually involves visceral organs as well as the gastrointestinal tract (particularly the esophagus), heart (myocardial fibrosis), muscles, lungs (interstitial lung disease is seen in most patients, causing dyspnea on exertion and cough), and kidneys. This results in dysphagia, respiratory difficulty, arrhythmias, and mild proteinuria. The most concerning manifestation of this disease is malignant hypertension and pulmonary failure.

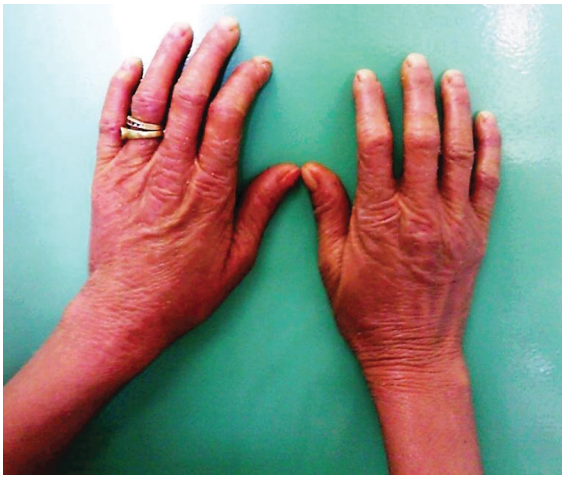

FIGURE 10-14. Flexion deformities of the fingers and sclerodactyly. The skin over the fingers and hands is taut and indurated. There is shortening and bony resorption of distal phalanges of the second and third fingers. Ulcers may develop over the distal phalanges and dorsal surfaces of the metacarpophalangeal and proximal interphalangeal joints. (Reproduced with permission from Faten F, et al. Systemic sclerosis in a patient with pityriasis rubra pilaris. *Pan Afr Med J*. 2010;6:6.).

What serologic marker is used to test for this condition?

Anti-DNA topoisomerase I (**Anti-Scl-70**) antibody is highly specific for systemic sclerosis. Anticentromere antibodies are more characteristic of limited scleroderma (CREST syndrome).

What is the pathogenesis of this condition?

The etiology of this condition is unknown; however, symptoms begin with vascular damage and are due to excessive synthesis of extracellular matrix, increased deposition of collagen in normal tissue, fibrosis, immune activation, and vascular damage.

What is CREST syndrome?

CREST is an acronym for the five findings in individuals with limited systemic sclerosis: **C**alcinosis, **R**aynaud phenomenon, **E**sophageal dysmotility, **S**clerodactyly, and **T**elangiectasia.

What is the treatment for this condition?

Most therapies are supportive; skin-softening agents and gloves are used to help skin sclerosis and Raynaud phenomenon. Bosentan and prostacyclin analogs might also be useful in pulmonary hypertension. Cytotoxics have a role in treating inflammatory lung disease. The mechanism of action of Bosentan is high-yield, which is endothelin-1 antagonist.

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11
Neurology and Special Senses

CASE 1

A 73-year-old well-educated woman is brought to the physician by her daughter, who has become concerned about her mother's behavior. The mother used to volunteer at the local library shelving books but began to forget where the books went on the shelf. Recently, the mother was found wandering in the grocery store parking lot. In addition, she often forgets to turn the stove off after cooking her family's long-time favorite dishes.

What is the most likely diagnosis?

This history is consistent with Alzheimer disease, which is characterized by loss of short-term memory and general preservation of long-term memory. There is an insidious progression from forgetfulness to having visuospatial defects and decline in executive functioning.

How are the causes of dementia classified?

Dementia is often classified into reversible and irreversible causes. Reversible causes include major depression, hypothyroidism, vitamin B_{12} deficiency, normal pressure hydrocephalus, and chronic subdural hematoma. Irreversible causes are vascular dementia, Creutzfeldt-Jacob disease, Pick disease, and Lewy body dementia.

What are the likely gross pathology findings in this condition?

Neurofibrillary **tangles** (see Figure 11-1) and amyloid **plaques** are commonly seen on autopsy. A high degree of cerebral atrophy in the frontal, temporal, and parietal regions is also present.

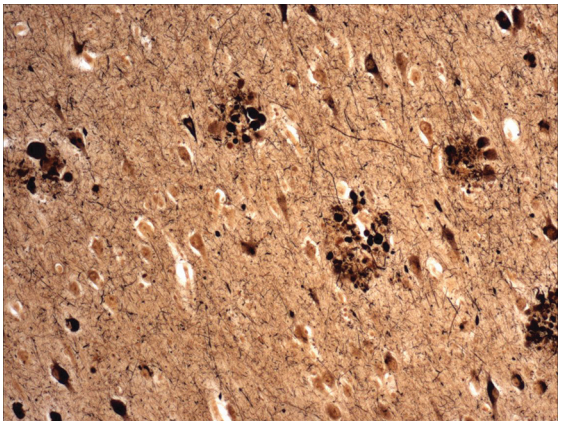

FIGURE 11-1. Alzheimer disease. Brain neurofibrillary tangles highlighted by silver stain in the brain of a patient with advanced dementia (Reproduced with permission from USMLE-Rx.com.)

What risk factors are associated with this condition?

Advancing age and a family history of Alzheimer disease are two well-known risk factors. Additionally, because the amyloid precursor protein (APP) is located on chromosome 21, patients with Down syndrome (trisomy 21) have increased APP levels; these patients often develop Alzheimer disease at 30–40 years of age. Presenilin-1 is located on chromosome 14 and is noteworthy for its association with early-onset Alzheimer disease. Abnormalities in this gene result in increased β-amyloid accumulation. For familial cases, there is an association with alteration in the ApoE4 and increased risk in developing Alzheimer disease. ApoE are proteins found on the surface of the chylomicrons that are generated by endoplasmic reticulum of the enterocytes found on the small intestine.

What biochemical mechanism is likely involved in the pathogenesis of this condition?

A preferential loss of acetylcholine and choline acetyltransferase in the cerebral cortex may play a role in the development of clinical disease.

What is the treatment for this condition?

The acetylcholinesterase inhibitor class of medications, including tacrine, donepezil, rivastigmine, and galantamine, have been shown to slow the progress of memory loss. Memantine, an *N*-methyl-D-aspartate receptor antagonist, may protect from Alzheimer disease by blocking the excitotoxic effects of glutamate, independently of the effects of acetylcholinesterase inhibitors.

What is the prognosis for the patient's daughter?

Onset of the familial form of Alzheimer disease, which affects approximately 10% of patients with the disease, is usually 30–60 years of age. Because this patient was older than 70 years of age at onset, she likely does not have the familial form, and the daughter is unlikely to have an increased risk based on family history alone.

CASE 2

A 38-year-old man presents to his primary care physician with a complaint of progressive weakness in his hands and feet. The patient states that these symptoms have slowly progressed over the past few months. Initially, he was unable to manipulate small objects, such as picking up a coin or buttoning his shirt. Now he complains of difficulty grasping a gallon of milk and notices the muscles in his hands twitching. He often trips while walking because he feels he cannot lift his toes up and lacks coordination. In addition, he says that the muscles in his leg occasionally cramp or spasm.

What is the most likely diagnosis?

Amyotrophic lateral sclerosis (ALS), or Lou Gehrig disease, is a neurodegenerative disorder that causes progressive muscle weakness. It is associated with progressive destruction of the upper motor neurons in the cerebral cortex and lower motor neurons in the spinal cord and brainstem.

Where are the lesions located and how does this explain the hallmark findings?

The hallmark of this disorder is the presence of **both upper motor neuron (UMN)** and **lower motor neuron (LMN)** lesions. ALS affects anterior horn motor neurons in the spinal cord (LMN) and the lateral corticospinal tracts carrying UMNs from the cortex. Sensory and cognitive functions are generally preserved.

How is this condition distinguished from the ascending paralysis syndromes?

ALS has both UMN and LMN findings, whereas Guillain-Barré syndrome (or acute inflammatory demyelinating polyradiculoneuropathy) and chronic inflammatory demyelinating polyradiculoneuropathy are solely LMN diseases and present with characteristic decreased reflex response.

What distinguishes UMN signs from LMN signs?

UMN signs result from lesions that disrupts neurons or their pathways in the brain or spinal cord. UMN signs include weakness, hyperreflexia, increased tone, positive Babinski sign, positive clasp knife spasticity, and no fasciculations.

LMN signs result from lesions that disrupt LMN neurons in the spinal cord, ventral horn, or their peripheral axons. LMN signs include weakness, muscle atrophy, decreased tone, hyporeflexia, muscle fasciculations, negative Babinski sign, negative clasp knife spasticity.

What is the Babinski sign?

The Babinski sign is obtained by taking the end of a Taylor reflex hammer or the finger nail and stroking the plantar surface of the foot. A positive sign is when the big toe extends upward (also called "extensor response"). Babinski sign is shown in Figure 11-2. A negative sign is when the big toe does not extend upward. It is normal for infants to have a positive Babinski sign until the age of 12 months due to incomplete myelination of the corticospinal tract.

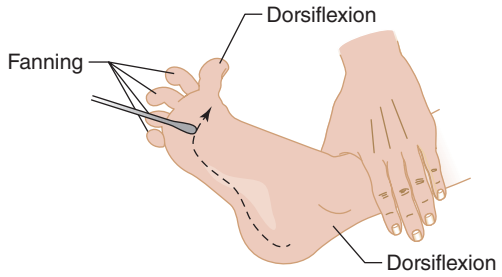

FIGURE 11-2. Babinski sign. (Modified with permission from LeBlond RF, et al. *DeGowin's Diagnostic Examination*. 9th ed. New York: McGraw-Hill; 2009.)

What is clasp knife spasticity?

Clasp knife spasticity is expressed by taking the patient's arm and passively flexing at the elbow joint. A positive result is when there is initial resistance by the extensor muscle to the passive flexion. As the arm is continued to be flexed, the extensor resistance gives way abruptly (the arm "collapses"), allowing the flexion of the limb to become easier.

What is the course of this disease?

ALS is currently an untreatable disease with progressive neurodegeneration and muscle weakness, resulting in death within 3–5 years of diagnosis. Riluzole can prolong survival by 2–3 months, likely by blocking glutaminergic transmission in the central nervous system (CNS). Supportive care, including dietary modification, respiratory assistance, and palliative care, is an important part of management. Neuromuscular respiratory failure is the primary cause of death.

CASE 3

A 10-year-old boy is brought to his pediatrician because of a painful ear. The pain began 1 week earlier with a runny nose and sinus pressure that progressed to ear pain and dizziness. Otoscopic examination reveals the findings in Figure 11-3. He has a low-grade fever of 37.8°C (100.0°F) but no other physical findings.

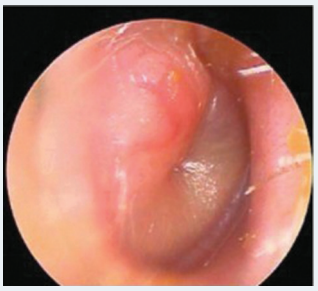

FIGURE 11-3. (Reproduced with permission from Kuruvilla A, et al. *Int J Biomed Imaging*. 2013:327515.)

What is the most likely diagnosis?

Acute otitis media. The bulging, red tympanic membrane is a sign of middle ear infection. The clinical course suggests a viral upper respiratory infection leading to secondary involvement of the middle ear due to inflammation and congestion of the eustachian tube. The eustachian tube connects the middle ear to the nasopharynx.

From what embryologic structure is the tympanic membrane derived?

The tympanic membrane derives from the first pharyngeal membrane. The **pharyngeal membranes** constitute the tissue between the pharyngeal groove, or cleft, and the pharyngeal pouch. Only the first pharyngeal membrane is retained in the adult; the rest are obliterated during development.

What three bones are located in the middle ear?

The three bones located in the middle ear (auditory ossicles) are the malleus, incus, and stapes (see Figure 11-4); together, they transmit sound from the tympanic membrane to the inner ear. The **malleus**, which is attached to the tympanic membrane, derives from the first branchial arch. The **incus**, which lies between the malleus and the stapes, derives from the first branchial arch. The **stapes**, which is anchored to the oval window of the inner ear, derives from the second branchial arch.

What two muscles control the movement of the bones of the middle ear?

The tensor tympani inserts on the malleus and dampens the amplitude of the tympanic membrane oscillations, which prevents damage to the inner ear from loud sounds. Innervation is by the mandibular nerve (CN V3). The stapedius inserts onto the neck of the stapes and dampens movement of this ossicle. It is innervated by the facial nerve (CN VII). A lesion denervating the stapedius causes hypersensitivity to sound (hyperacusis).

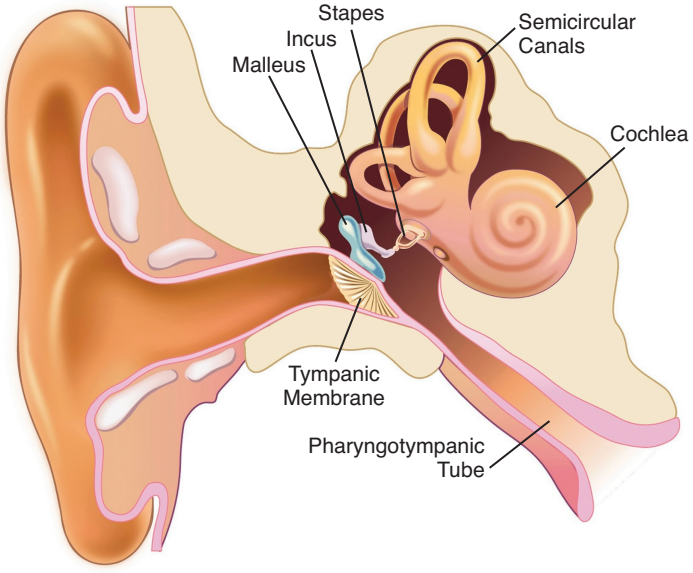

FIGURE 11-4. Anatomy of the ear. (Reproduced with permission from USMLE-Rx.com.)

What organisms commonly cause pediatric ear infections?

In order of prevalence, common bacteria that cause middle ear infection are *Streptococcus pneumoniae*, *Haemophilus influenzae* (although rarely type B since the introduction of the conjugated vaccine), and *Moraxella catarrhalis.* Appropriate antibiotic coverage involves a β-lactam such as amoxicillin. Less common organisms are group A streptococci, *Staphylococcus aureus*, *Pseudomonas*, and in newborns, gram-negative bacilli. Approximately 15%–20% of middle ear infections are due to viruses, including respiratory syncytial virus, rhinovirus, influenza viruses, and adenovirus.

CASE 4

A 35-year-old construction worker is taken to the ED after an accident in which a piece of metal became lodged in his back. The patient has excruciating pain at the site of his injury and is unable to move his right leg. In the ED, neurologic examination reveals paralysis of the right leg, ipsilateral hyperactive patellar reflex, and a positive Babinski sign. The patient can move his left leg without difficulty and has a normal patellar reflex and no Babinski sign. However, sensory testing reveals loss of temperature and pinprick sensation on the left leg up to the navel and loss of vibration sensation on the left leg up to the navel.

What is the most likely diagnosis?

Brown-Séquard syndrome due to a hemisection of the spinal cord. Using Figure 11-5, the characteristics of Brown-Séquard can be exemplified as follows: Labels 1 and 2 show the region where the injury occurred in the patient. At the level of injury, the patient will have ipsilateral segmental loss of all sensation (due to destruction of the dorsal horn of the spinal cord) and lower motor neuron signs such as flaccid paralysis (due to destruction of the anterior horn of the spinal cord). Labels 3 and 4 show the distribution of ipsilateral region to injury; the patient will have upper motor neuron lesion signs, such as spastic paralysis (due to damaged corticospinal tract) below the level of the injury. Label 5 shows the distribution of contralateral region where the patient will have loss of pain and temperature sensation (due to damaged spinothalamic tract).

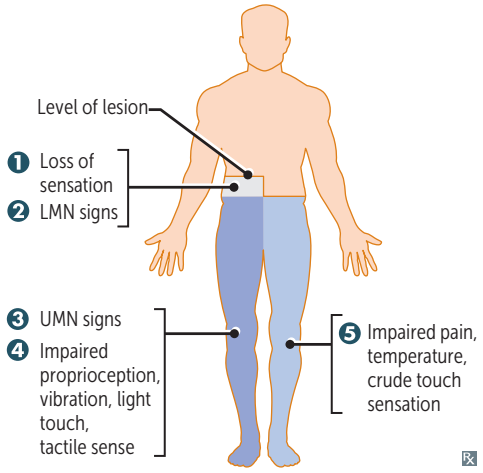

FIGURE 11-5. Brown-Séquard syndrome. (Reproduced with permission from USMLE-Rx.com.)

Why are there contralateral and ipsilateral deficits when the tracts are damaged in this case?

The upper motor neuron deficits are due to damage to the **lateral corticospinal tract** (see Figure 11-6), which carries motor fibers from the cortex that have decussated in the pyramids. The loss of vibration and position sense is due to damage to the **dorsal columns**, which carry information from sensory nerves that enter through the dorsal root and ascend in the ipsilateral spinal cord to the caudal medulla (where the primary neurons synapse). These deficits are ipsilateral because the tracts cross the midline above the level of the spinal cord.

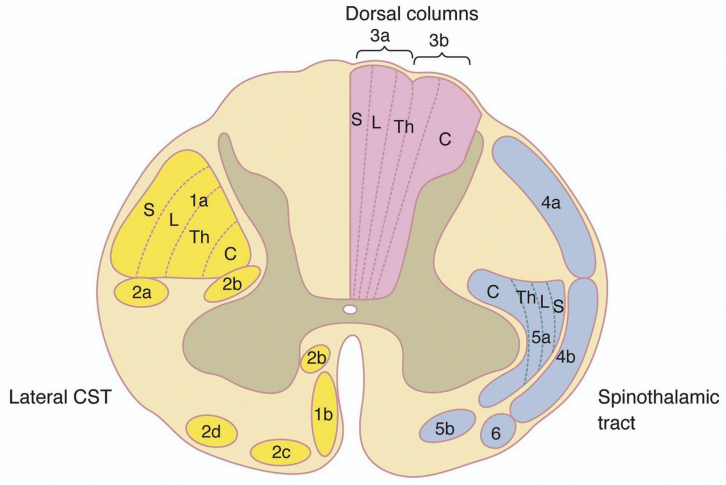

FIGURE 11-6. Spinal cord cross section showing locations of the ascending dorsal column (3a/3b), and spinothalamic tracts (5a), and the descending lateral corticospinal tract (1a). (Reproduced with permission from USMLE-Rx.com.)

The loss of pain and temperature sensation is due to damage to the spinothalamic tract (see Figure 11-6). The sensory fibers that carry pain and temperature enter the spinal cord through the dorsal root and synapse in the dorsal horn. The fibers then cross midline (within one or two levels) via the anterior commissure to ascend in the spinothalamic tract to the ventral posterolateral (VPL) nucleus of the thalamus and ultimtely to the primary sensory cortex.

At what level is the lesion located?

The loss of sensation up to the navel suggests that the lesion is near T10 because the dermatome that includes the navel is supplied by T10. Other dermatomes that involve a landmark on the body include T4 for the nipple, T7 for xiphoid process, and L1 for inguinal ligament.

If the lesion were above T1, how would the presentation differ?

If the spinal cord were damaged at T1 or above, the oculosympathetic pathway would be damaged and would present as Brown-Séquard plus Horner syndrome, the latter consisting of ptosis, miosis, and anhidrosis (droopy eyelid, constricted pupil, and decreased sweating).

CASE 5

A 70-year-old man with a history of rheumatoid arthritis comes to his physician complaining of weakness 1 day after a motor vehicle accident. Physical examination reveals intact sensation and strength in the lower extremities but weakness in the upper extremities bilaterally. The patient is able to move his arms parallel to the ground but is unable to lift his arms, forearms, or hands upward against gravity. Muscle strength is 2/5 throughout, bilaterally. CT scan of the cervical spine rules out cervical spine fracture, and MRI demonstrates traumatic C6 disk herniation, buckling of the ligamentum flavum, and edema within the cervical cord in that area.

What is the most likely diagnosis?

Central cord syndrome. This syndrome is characterized by upper extremity weakness that exceeds lower extremity weakness and varying degrees of sensory loss below the level of the lesion.

What is the arterial supply to the cervical spinal cord?

The spinal cord is supplied by a single midline anterior spinal artery (derived from the vertebral arteries) that supplies the anterior two-thirds of the cord and by two posterior spinal arteries (which originate from either the vertebral or the posterior inferior cerebellar arteries) that supply the dorsal columns and part of the posterior horns.

What is a vascular watershed zone?

A **watershed zone** is an area between two major arteries in which small distal branches of the arteries form anastomoses. Important watershed zones lie between the anterior, middle, and posterior cerebral arteries and in the central spinal cord. These areas are susceptible to infarction during hypotension or hypoperfusion. In this case, edema and trauma impaired blood flow to the cervical enlargement, and the predominant symptoms resulted from damage within the central cord watershed zone.

What is supplied by the long tracts in the areas labeled "Region A" in Figure 11-7?

Region A in Figure 11-7 indicates the most medial portions of the somatotopically organized corticospinal tracts. These fibers control LMNs that supply the muscles of the upper extremity. Because of their medial location, motor impairment of the upper extremities can occur after a smaller central cord lesion. The red oval over the axial view of the spinal cord in Figure 11-7 indicates the area of impairment that is associated with a central cord lesion. Figure 11-8 presents the axial view of the spinal cord, illustrating the location and the direction of the spinal tracts.

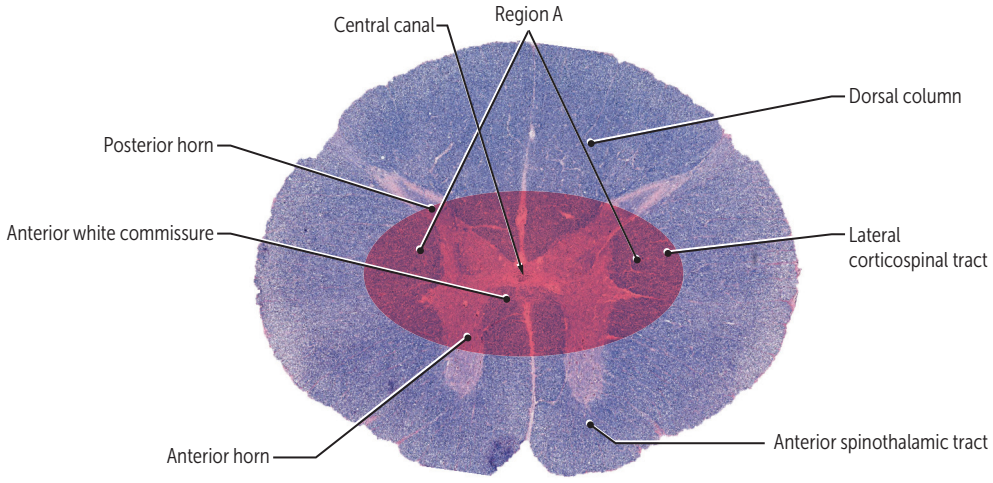

FIGURE 11-7. Axial view of the spinal cord. (Reproduced courtesy of Regents of University of Michigan Medical School.)

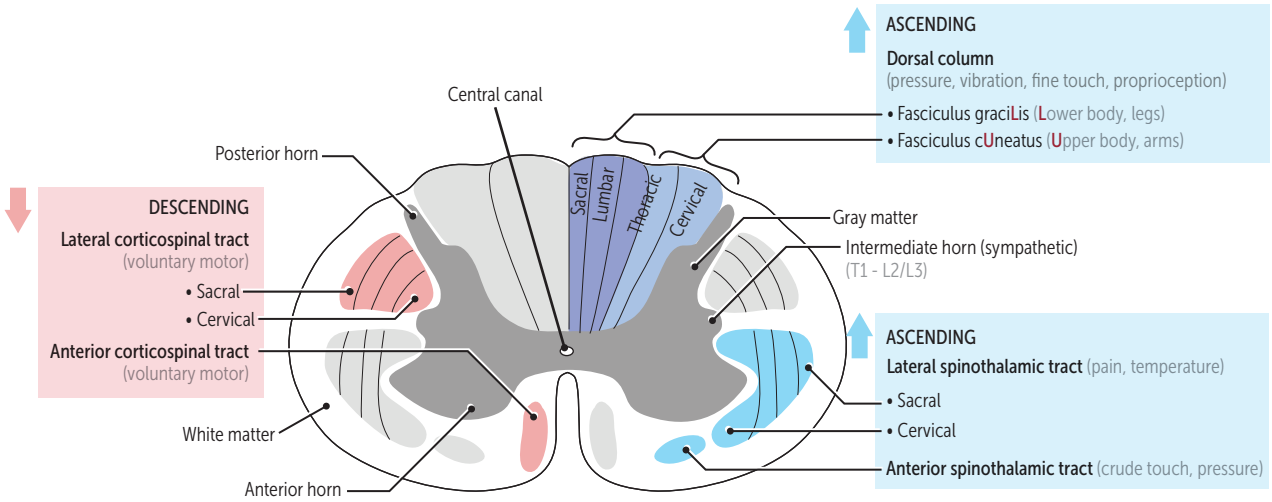

FIGURE 11-8. Axial view of the spinal cord illustrating the location and the direction of spinal tracts. (Reproduced with permission from USMLE-Rx.com.)

What changes in the biceps, triceps, and brachioradialis reflexes are expected after damage to the anterior horn cells supplying the C6 nerve root?

The biceps reflex, which is regulated by fibers from C5 and C6, will be moderately diminished secondary to diminished C6 lower motor neuron output. The triceps reflex is regulated primarily by C7 and should thus be unaffected by a pure C6 lesion. The brachioradialis reflex is primarily regulated by C6 and will thus be markedly diminished after a C6 lesion.

What is the relationship between spinal nerves and herniated discs at specific levels?

At cervical levels, spinal nerves exit **above** their corresponding vertebrae (except for spinal nerve C8 because there is no C8 vertebra). Herniated cervical discs typically affect the nerve root exiting at the level of the disc. Thus, a herniated C5-C6 disc will usually compress the C6 spinal nerve. At thoracic and lumbar levels, spinal nerves exit **below** their corresponding vertebrae. Herniated discs at these levels typically affect the nerve root exiting one level **below** the disc. Thus, a herniated L1-L2 disc will damage spinal nerve L2.

CASE 6

A 16-year-old high school student goes to see the school nurse because of severe eye pain and a feeling that there is something "stuck" in his right eye. He does not wear contact lenses. He reports that he was recently working with machines in shop class without wearing protective goggles. Ophthalmologic examination reveals no visible foreign body in the eye; visual acuity is slightly decreased at 20/30; pupils are equal, round, and reactive to light bilaterally; corneal reflex is intact; and extraocular muscles are intact, although the student says his right eye hurts when he moves it.

What is the most likely diagnosis and what are other causes of acute unilateral vision impairment?

The student has a corneal abrasion, which typically presents with significant eye pain and a foreign body sensation. The patient will also have photophobia. This patient's history suggests the source for his eye injury: working with machinery without wearing protective eyewear. Other etiologies of acute unilateral vision impairment are optic neuritis, retinal detachment or tear, giant cell arteritis, and amaurosis fugax.

What are the layers of the cornea?

The outermost layer of the cornea is the corneal epithelium, which is fast growing and undergoes constant physiologic renewal. The next layer is the Bowman layer, an acellular layer composed of collagen. Next is the corneal stroma, followed by Descemet membrane, and finally the corneal endothelium.

What is the pathway of the corneal blink reflex?

The excruciating pain experienced by this patient is due to the rich innervation of the cornea by the ophthalmic branch of trigeminal nerve (CN V). This nerve constitutes the afferent portion of the corneal blink reflex. After synapsing in the sensory nucleus of CN V, there is bilateral projection to the nucleus of CN VII. From there, motor fibers project to the orbicularis oculi muscles, causing a direct (ipsilateral) and consensual (contralateral) blink response.

What space lies between the cornea and the lens?

The space between the cornea and the lens is the anterior compartment, which is subdivided by the iris into the anterior chamber and the posterior chamber (see Figure 11-9). The entire anterior compartment is filled with aqueous humor, which is secreted by the ciliary body.

From what embryologic structures do the cornea, iris, ciliary body, lens, optic nerve, and retina develop?

The optic cup is an embryologic structure derived from neuroectoderm (diencephalon) that gives rise to the retina, iris, and ciliary body. The optic stalk (also derived from the neuroectoderm) creates the optic nerve. The lens is derived from surface ectoderm. The inner layers of the cornea are derived from mesoderm, and the outer layer derives from the surface ectoderm.

What are the types of refractory errors?

The cornea is responsible for most of the refractory power of the eye, and the lens is responsible for the rest. The lens and cornea work together to project an image perfectly on to the retina. A mismatch in cornea and lens refractory power results in refractory errors. A farsighted person will have hyperopia. Hyperopia means the image created by the cornea and lens is projected behind the retina. A nearsighted person will have the image projected too far ahead of the retina.

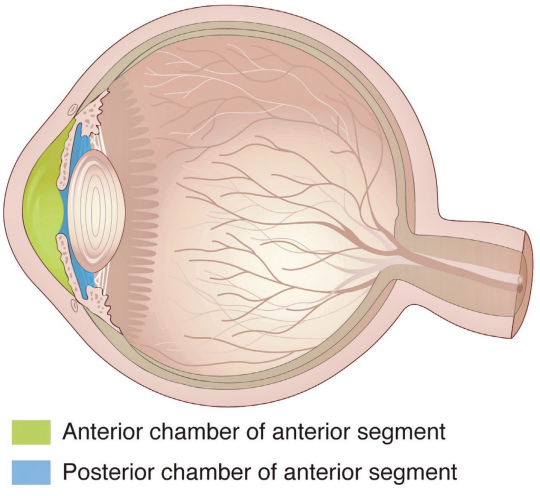

FIGURE 11-9. Diagram of the eye emphasizing the anterior chamber of the anterior segment and the posterior chamber of the anterior segment. (Reproduced with permission from USMLE-Rx.com.)

CASE 7

A 10-year-old boy is brought to the pediatrician by his parents for evaluation of short stature. The child is below the 10th percentile for height. Both parents are of average height and state they were average height among their peers at age 10. Thyroid-stimulating hormone (TSH) levels are at 0.01 mIU/L. On physical exam, the patient has difficulty with peripheral vision. Cornea reflex is intact. MRI of the head reveals a suprasellar cystic, calcified mass (see Figure 11-10).

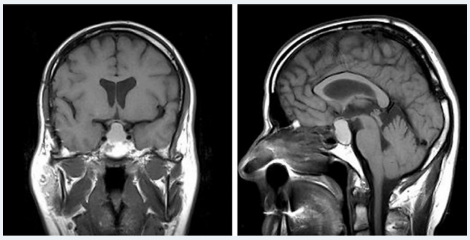

FIGURE 11-10. (Reproduced with permission from Lewandowski KC, et al. New onset Graves' disease as a cause of an adrenal crisis in an individual with panhypopituitarism: brief report. *Thyroid Research*. 2008;1:7.)

What is the most likely diagnosis?

The hallmark lesion for craniopharyngioma is a **suprasellar**, **cystic**, **calcified mass** (as seen in Figure 11-10). The differential diagnosis for a suprasellar mass includes optic gliomas, meningiomas, pituitary adenomas, and metastases.

What are other causes of short stature?

Other causes of short stature can arise from endocrine disorders including Cushing syndrome, growth hormone deficiency, hypothyroidism, and gastrointestinal disorders including malabsorption syndromes such as celiac disease, lactase deficiency, or inflammatory bowel disease.

Dwarfism is a condition that can be diagnosed even in the prenatal stages. Achondroplasia is due to an autosomal dominant gain of function mutation in the fibroblast growth factor receptor 3 gene.

From what tissue does the tumor in this condition derive?

Craniopharyngiomas are rare tumors derived from the pituitary gland's embryonic tissue. The adenohypophysis (anterior lobe of the pituitary gland) derives from Rathke pouch, an invagination of **ectoderm** lining the roof of the primitive oral cavity. The remnants of Rathke pouch can give rise to craniopharyngiomas. The posterior lobe of the pituitary (neurohypophysis) develops from the infundibulum of the hypothalamus.

What tests or imaging tools may be used to confirm the diagnosis?

CT scan or MRI of the head can visualize the cystic calcified suprasellar mass characteristic of craniopharyngioma. Plain radiographs of the skull can detect advanced cases. Testing of the pituitary axis and optic pathways can determine whether the tumor has affected these structures.

What is the epidemiology of this condition?

Craniopharyngiomas exhibit a bimodal distribution, with one peak among children and the second among patients 55–65 years of age. It is the third most common intracranial tumor in children.

What are the clinical manifestations of this condition?

Craniopharyngiomas are slow-growing tumors with a highly variable clinical presentation. Symptoms occur because the tumor involves the pituitary gland or the optic chiasm. Patients may present with growth hormone deficiency, hypothyroidism, or central diabetes insipidus. These hormonal deficiencies are due to mass effect from the tumor on the normal tissue. Visual disturbances (eg, bitemporal hemianopsia, or tunnel vision) and headaches are common due to compression of the optic chiasm. Patients may complain of difficulty with peripheral vision.

What neurological structures would be affected due to clot forming in the venous sinus above the pituitary gland?

Cavernous sinus thrombosis is a condition where a thrombosis develops within the cavernous sinus. This can lead to occlusion of the dural sinus and elevation of intracranial pressure (ICP). Clinically this condition manifests as headaches (due to increased ICP) and may be accompanied by vomiting, periorbital edema, fever, facial pain, papilledema and reduced visual acuity, and ocular motility disturbances. Cranial nerve palsies (III, IV, VI, V1, and V2) are common. The most common cranial nerve that is affected is cranial nerve VI.

CASE 8

A 72-year-old woman falls while at home and lands face down. She is unable to get up and remains prone on the floor overnight until a neighbor notices her and calls 911. She is taken to the ED where she is noted to have several hematomas on her face and a large hematoma on her right upper thigh. On physical examination, the patient is unable to flex her right hip or extend her right lower leg. Patellar reflex cannot be elicited on the right. Patellar reflex is normal on the left side. Leg adduction and abduction are intact bilaterally.

What is the most likely diagnosis?

Weakness of the quadriceps muscles and hip flexors (which are innervated by the femoral nerve) and lack of patellar reflex suggest femoral neuropathy (L2–L4). The cause of the neuropathy in this case is a hematoma (secondary to trauma) compressing the nerve. Because both the hip flexors (L2–L3) and the quadriceps muscles (L3–L4) are involved, the nerve is affected above the inguinal ligament. If the compression had affected the nerve distal to the inguinal ligament where the nerve branches into anterior and posterior divisions, a deficiency in either the hip flexors (anterior) or the quadriceps muscles (posterior), but not both, would be expected.

What sensory defects are expected in this patient?

The femoral nerve innervates the skin of the anterior and medial thigh; thus, light touch sensation is decreased in these areas. The lateral aspect of the thigh is innervated by the lateral femoral cutaneous nerve (L2–L3) and is spared in an isolated femoral neuropathy. The **saphenous nerve** is a cutaneous branch of the femoral nerve that arises from the femoral nerve in the femoral triangle. It innervates the skin of the anteromedial knee, leg, and foot to the medial side of the big toe. Because this lesion is above the femoral ligament, the saphenous nerve distribution is also involved.

What other structures are found in the femoral triangle?

The femoral nerve is the largest branch of the lumbar plexus and, after forming in the abdomen, runs posterolaterally to the inguinal ligament. It crosses under the inguinal ligament lateral to the psoas muscle and enters the femoral triangle. In the **femoral triangle** (bounded by the sartorius muscle, inguinal ligament, and adductor longus), it runs lateral to the femoral artery, which is lateral to the femoral vein. The vessels are enclosed within the femoral sheath and the nerve is outside it (see Figure 11-11).

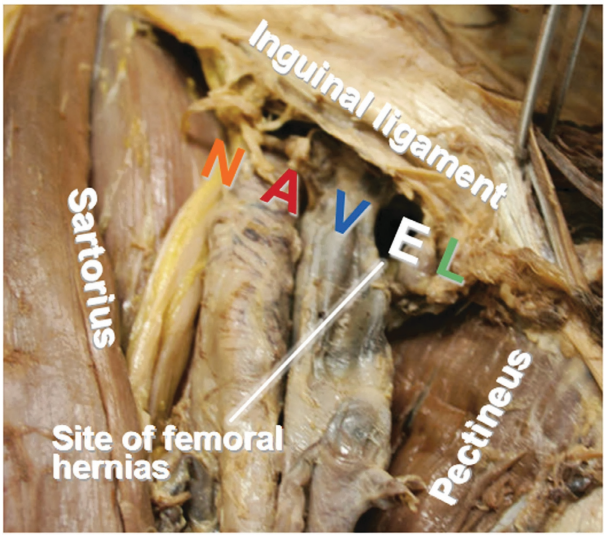

FIGURE 11-11. Femoral triangle dissection specimen. N: Nerve (Femoral nerve), **A**: Artery (Femoral artery), **V**: Vein (Femoral vein), **E**: Empty (site of possible femoral hernias), **L**: Lymphatics. (Reproduced with permission from USMLE-Rx.com. Photo contributor: Dr. Craig Goodmurphy.)

Why is thigh adduction spared in this patient?

The major muscles responsible for thigh adduction are the adductor longus, adductor brevis, adductor magnus, and the gracilis, which are innervated by the obturator nerve (L2–L4). Because this is a peripheral neuropathy, not pathology of the nerve root, the obturator nerve is spared and so is thigh adduction.

What other clinical scenarios can be associated with this condition?

- Diabetic vasculitic damage
- Direct penetrating trauma
- Hip fracture
- Iliac aneurysms
- Incorrect placement of the femoral line
- Prolonged hip flexion during gynecologic or urologic procedures
- Tumor

CASE 9

A 52-year-old man is brought to the ED after sustaining a witnessed tonic-clonic seizure. The patient states he has had a bitemporal dull, constant headache for the last 2 weeks. CT of the head is shown in Figure 11-12.

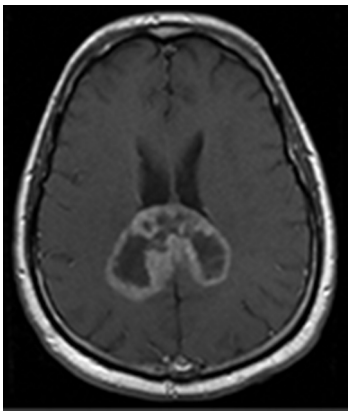

FIGURE 11-12. (Reproduced with permission from USMLE-Rx.com.)

What is the most likely diagnosis?

Glioblastoma multiforme (GBM), the most common primary brain tumor. GBM represents almost 20% of all primary intracranial tumors. Other brain tumors that can occur in adults are hemangioblastomas, Schwannomas, oligodendrogliomas, and meningiomas.

Where are these lesions typically located?

Glioblastomas are found supratentorially in the cerebral hemispheres and often cross hemispheres via the corpus callosum ("butterfly glioma") (see Figure 11-12). The CT shows a large, lobulated mass that enhances with contrast and crosses the midline. The center of the mass does not enhance, which suggests central necrosis.

What are the histologic findings in this condition?

Glioblastomas are composed of highly malignant astrocytes that are visualized by immunohistochemical staining with antisera against glial fibrillary acidic protein (GFAP). Histology of glioblastomas shows pseudopalisading tumor cells surrounding focal areas of necrosis and hemorrhage (see Figure 11-13).

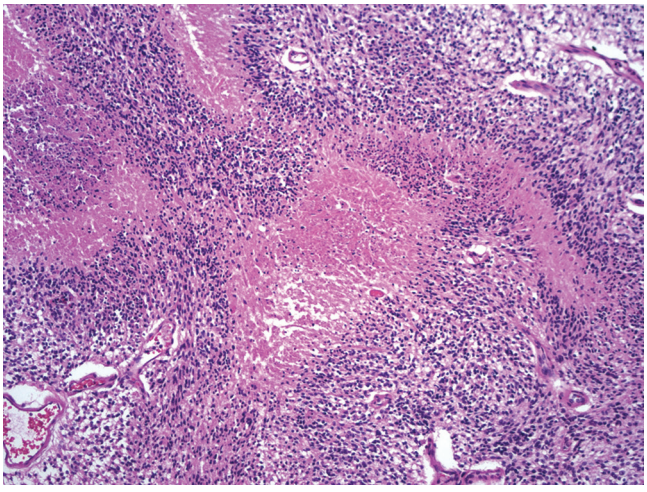

FIGURE 11-13. Glioblastoma multiforme. Histology shows necrosis with surrounding pseudopalisading of malignant tumor cells. (Reproduced with permission from USMLE-Rx.com.)

What is the treatment for this condition?

Treatment is largely palliative and only moderately increases survival time. Treatment may include surgical resection, radiation, and chemotherapy.

What are some other adult brain tumors?

Oligodendroglioma is a primary tumor that develops from oligodendrocytes and occurs often in the frontal lobes. A benign tumor that arises from arachnoid cells is called a meningioma. The latter often are asymptomatic or cause focal neurological symptoms. Histologically, meningiomas contain spindle cells that are arranged into a specific pattern called psammoma bodies.

What is the natural history of this condition?

Glioblastoma is an aggressive tumor. Without treatment, most patients die within 3 months of diagnosis. With treatment, the median survival time is 1 year, and $<$ 10% of patients survive 5 years.

CASE 10

A 27-year-old man comes to his physician complaining of a tingling sensation in his toes and progressive weakness in both legs. On questioning, he says that he had bloody diarrhea, nausea, vomiting, and cramps 3 weeks ago that lasted for a few days. He also complains of back pain. He has not traveled recently and has not eaten anything out of the ordinary. Physical examination reveals markedly decreased patellar and Achilles tendon reflexes bilaterally.

What is the most likely diagnosis?

Guillain-Barré syndrome (GBS), or acute inflammatory demyelinating polyradiculoneuropathy, is characterized by symmetric ascending muscle weakness or paralysis that begins in the lower extremities. Hyporeflexia or areflexia is invariable but may not be present early in the course of disease.

What physical findings are commonly associated with this condition?

Findings in GBS include ascending paresthesias, cranial nerve deficits leading to dysphagia, dysarthria, facial weakness, papilledema, autonomic dysfunction, and respiratory muscle paralysis in extreme cases. Figure 11-14 shows papilledema of the optic nerve head in GBS, along with the vascular congestion, elevation of the nerve head, and blurred disc margins often seen in papilledema, papillitis, and compressive lesions of the optic nerve. Hyporeflexia is commonly seen.

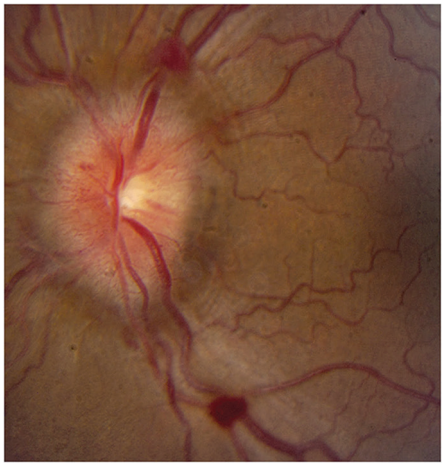

FIGURE 11-14. Papilledema seen on fundoscopic exam. (Reproduced with permission from USMLE-Rx.com. Photo contributor: Dr. Nicholas Mahoney.)

In what settings does this condition usually occur?

GBS often occurs 1–3 weeks after a gastrointestinal or upper respiratory tract infection, vaccination, or allergic reaction. Common associated infections include *Campylobacter jejuni* and herpesvirus. Although a preceding event is present in most patients, approximately one-third of patients with GBS report no such events during the preceding 1–4 weeks.

What is the etiology of this condition?

GBS is thought to be an autoimmune reaction that develops in response to a previous infection or other medical condition. This process results in aberrant demyelination of peripheral nerves and ventral motor nerve roots. Cranial nerve roots can also be affected. One may also see autonomic dysregulation such as arrhythmias, hypotension, or hypertension.

What laboratory finding is likely in this condition?

Cerebrospinal fluid (CSF) reveals a markedly elevated protein concentration with a normal cell count, commonly referred to as **albuminocytologic dissociation**. This contrasts to the increased cell counts typical of CNS infection. Increased CSF protein can lead to papilledema and increased intracranial pressure.

What is the treatment for this condition?

The first element of GBS management is supportive care and treatment of the underlying condition with either IV immunoglobulin or plasmapheresis. Pulmonary function should be monitored with peak flow studies to assess for respiratory failure. Rehabilitation may be required to restore function.

If this patient's symptoms worsen over the next few months with no signs of improvement, what alternative diagnosis should be considered?

Chronic inflammatory demyelinating polyradiculopathy is a chronic progressive counterpart of GBS that often presents with similar symptoms.

CASE 11

A 45-year-old woman visits her primary care physician because she noticed a sudden loss of hearing in her right ear. She says it started just a few days ago, but she does not recall any trauma or inciting event. She does not take any medications but says she was hospitalized 1 month ago for a serious urinary tract infection requiring some "powerful antibiotics." On further questioning, she also notes an increased sensation of ringing in her right ear. Otologic examination reveals a translucent, pink-gray tympanic membrane on the right. When a vibrating tuning fork is placed at the center of the patient's forehead, she hears the sound better in the left ear. She also hears the tuning fork better on both sides when it is outside the ear compared to when it is placed on the mastoid process.

What is the most likely diagnosis?

This patient has sensorineural hearing loss. The recent hospital course suggests antibiotics, most commonly aminoglycosides, as the likely culprit. Sensorineural hearing loss is often associated with tinnitus. The otologic examination reveals a normal external ear canal and visualizes a normal tympanic membrane on the affected side. Weber testing lateralizes to the opposite ear, whereas Rinne testing in the affected ear is normal.

What is the mechanism underlying the findings on Weber and Rinne testing?

In sensorineural hearing loss, the cochlea or CN VIII is damaged. This means that sound signal does not transmit appropriately into the CNS; the result is hearing loss on the affected side. **Weber testing** is conducted by placing a vibrating tuning fork in the center of the patient's forehead and asking whether the volume is different between the two ears. In sensorineural hearing loss, Weber testing lateralizes to the opposite side because of normal sound signal to CNS transmission contralaterally (see Figure 11-15A).

Rinne testing compares air conduction with mastoid bone conduction of sound. The vibrating tuning fork is placed just outside the external ear canal and then on the mastoid bone, and the patient is asked to identify which location produces a louder perception of sound (see Figure 11-15B). There is no obstruction of air conduction in sensorineural hearing loss, so Rinne test results in a louder perception of sound through air conduction (as is the case in normal hearing function).

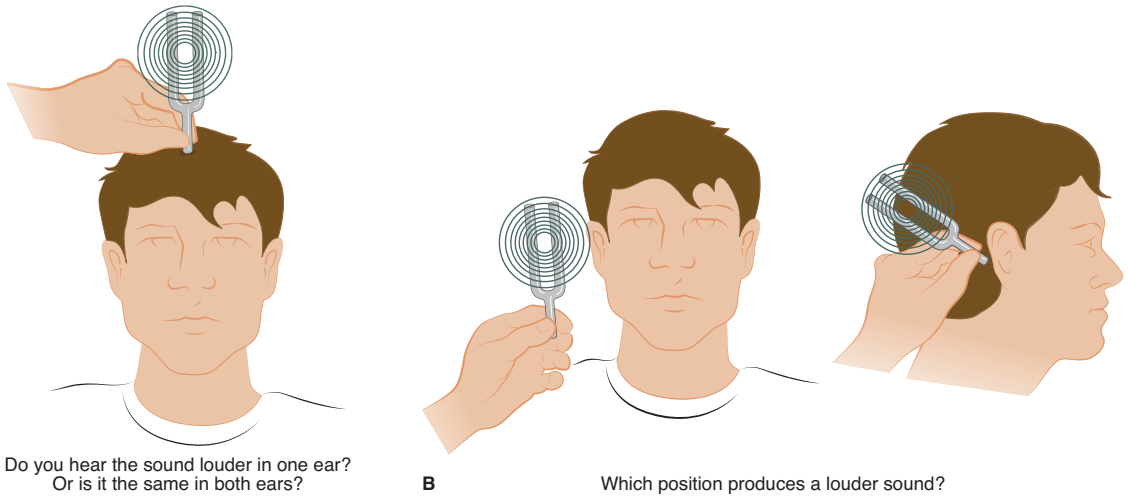

FIGURE 11-15. (A) Weber and (B) Rinne hearing testing. (Reproduced with permission from USMLE-Rx.com.)

What is the primary differential diagnosis of this patient's hearing loss?

Hearing loss can also be conductive in nature. This occurs when there is an obstruction of the ear canal (cerumen impaction) or mechanical dysfunction of the middle ear apparatus (due to an inflammatory process such as otitis media or otitis externa) that helps transmit sound waves to the cochlea.

What would the Weber and Rinne tests find in conductive hearing loss?

In conductive hearing loss, the Weber test lateralizes to the affected ear. This is due to the reverberation and accentuation of sound caused by entrapment of sound waves behind the occlusion or site of dysfunction. The Rinne test results in greater bone conduction of sound in the affected ear because air conduction is obstructed.

CASE 12

A 67-year-old man with a history of hypertension and coronary artery disease presents to the ophthalmologist complaining that, for the past month, he has noticed decreased vision on his right side two or three times a week. Each episode lasts about 20 minutes and is accompanied by a severe retro-orbital headache. During the episodes, he is unable to read and bumps into objects on his right. Yesterday, he experienced the same visual loss, which has not resolved. Automated perimetry visual field testing reveals the pattern shown in Figure 11-16, with areas of visual loss in black.

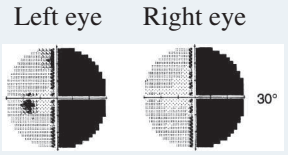

FIGURE 11-16. (Reproduced with permission from Kasper D, et al. eds. *Harrison's Principles of Internal Medicine*, 19th ed. New York: McGraw-Hill; 2014.)

What is this visual field defect?

The defect is a right homonymous hemianopia likely caused by a stroke. The patient's symptoms suggest that he has experienced a number of transient ischemic attacks (TIAs). The classical definition of a TIA is a vascular event that causes neurologic deficits that last $<$ 24 hours. Clinically, it is defined as a neurologic deficit that lasts $<$ 1 hour in the absence of abnormal imaging findings.

What is the pathway from retinal photoreceptors in the retina to the visual cortex?

Photoreceptors (rods and cones) synapse on **bipolar cells** that synapse on **ganglion cells** in the retina. Axons of ganglion cells form the **optic nerve**.

The optic nerves travel posteriorly and merge to form the **optic chiasm**. In the chiasm, nasal (medial) retinal fibers from both eyes cross, while temporal (lateral) retinal fibers remain uncrossed. Nasal hemiretina fibers carry information from the temporal halves of the visual fields, while temporal hemiretina fibers convey information from the nasal halves of the visual fields. As a result of this partial decussation, the entire left half of the visual world is projected to the right side of the brain, and vice versa. Once past the chiasm, the retinal axons enter the **optic tract** and synapse on the lateral geniculate nucleus (**LGN**) of the thalamus.

Axons exiting the LGN fan out posteriorly through the cerebral white matter as the optic radiations. The inferior part of the optic radiation carries information from the **inferior retina** or **superior visual field**, travels briefly through the posterior temporal lobe as Meyer loop, then continues through the parietal lobe to the occipital lobe. The superior radiations carry information from the superior retina or inferior visual field and travel directly through the parietal lobe to the occipital lobe.

The **optic radiations** synapse in the **visual cortex** of the occipital lobe near the calcarine fissure. The superior radiations synapse superior to the calcarine fissure, and the inferior radiations synapse inferior to the fissure (see Figure 11-17).

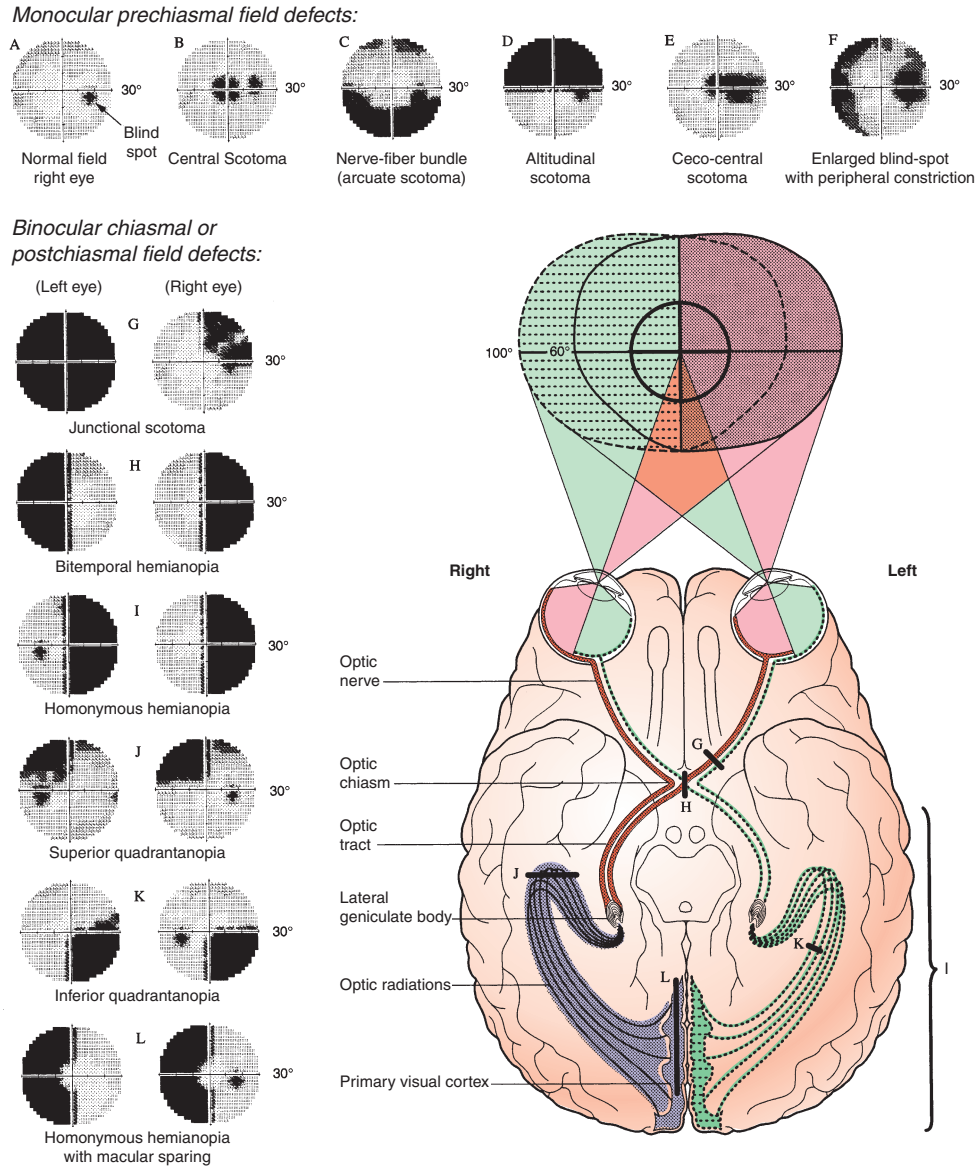

FIGURE 11-17. Visual field defects caused by lesions of the visual system pathway. Lesion I illustrates the visual field defect observed in this patient with lesions possible in the left optic tract, the optic radiations, or the primary visual cortex. (Reproduced with permission from Kasper D, et al. eds. *Harrison's Principles of Internal Medicine*, 19th ed. New York: McGraw-Hill; 2014.)

Where along the optic pathway may a lesion be located to give this visual field defect?

A lesion in the left optic tract or lateral geniculate nucleus can cause this defect, as may a large lesion of the optic radiations or a lesion in the left visual cortex. An ischemic stroke involving the posterior cerebral artery (PCA) can cause homonymous hemianopia. The PCA supplies the occipital lobe.

What visual field defect would a lesion in the right temporal lobe cause?

The inferior optic radiations (Meyer loop) travel through the temporal lobe. A lesion to this area shows a left upper quadrantic anopia ("pie in the sky") as indicated by lesion **J** in Figure 11-17.

CASE 13

A 45-year-old woman comes to the physician for a routine visit. On physical examination, her left eye appears abnormal (see Figure 11-18). In addition, her left pupil is constricted but reacts normally to light and accommodation. The left side of the patient's face is dry and flushed. On questioning, she states the left side of her face has become abnormally dry.

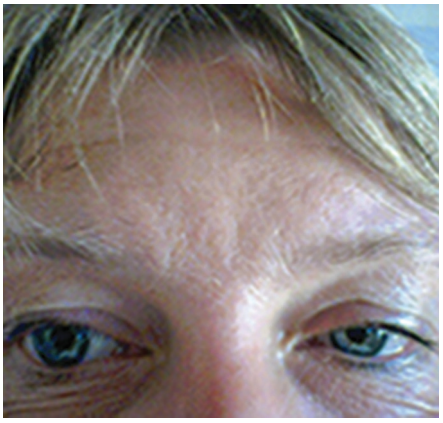

FIGURE 11-18. (Reproduced with permission from Nautiyal A, et al. *PLoS Med*. 2005; 2(1): e19.)

What is the most likely diagnosis?

Horner syndrome.

What is the pathophysiology of this condition?

Horner syndrome results from a disruption in the sympathetic innervation of the face and eye and subsequent unopposed parasympathetic activity, which produces the classic symptoms: ipsilateral **P**tosis (slight drooping of the eyelid, as in Figure 11-18), **A**nhidrosis (absence of sweating), and **M**iosis (pupillary constriction) (mnemonic: **PAM**).

What nerve pathway is disrupted in this condition?

The first neuron of the sympathetic pathway begins in the hypothalamus and synapses in the intermediolateral column of the spinal cord near T1 (see Figure 11-19). The second, preganglionic neuron sends fibers to the superior cervical ganglion. The third and final neuron of the pathway innervates the pupillary dilator muscle, the sweat glands of the face, and the smooth muscle of the upper eyelid.

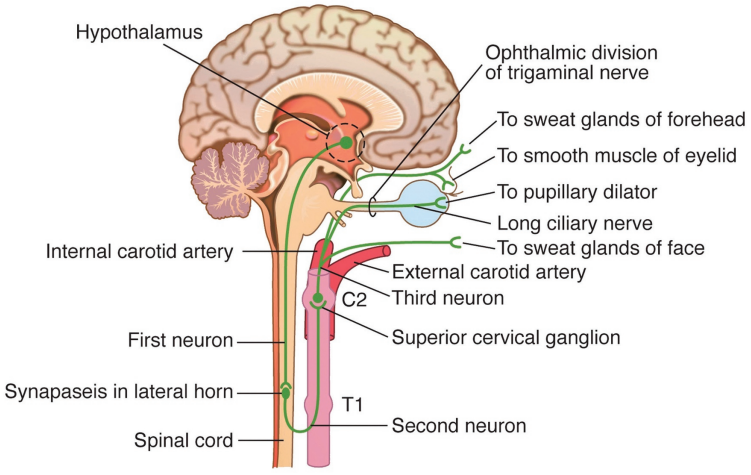

FIGURE 11-19. Nerve pathways disrupted in Horner syndrome. (Reproduced with permission from USMLE-Rx.com.)

If this patient presented with nystagmus to the left side and frequent falling, what acute condition should be considered?

Wallenberg syndrome results from a stroke in the lateral medullary region supplied by the posterior inferior cerebellar artery. It can present with ipsilateral Horner syndrome, nystagmus to the opposite side of the lesion, ipsilateral limb ataxia, and vertigo. Another distinguishing feature is impaired pain and temperature sensation in the ipsilateral face and contralateral body.

What are other common causes of this patient's condition?

Any pathology that interrupts the described pathway can cause Horner syndrome. A number of etiologies can occur such as Pancoast tumor, Brown-Séquard syndrome (spinal cord lesion above T1), syringomyelia, and chest wall trauma.

What is Pancoast tumor?

Pancoast tumor is a carcinoma that usually occurs in the apex of the lung. It can cause Horner syndrome by compression of the superior cervical ganglion and ulnar nerve pain.

CASE 14

A 39-year-old man is concerned about his health because his father died at 45 years of age after several years of dementia, uncontrollable twitching, and dance-like movements in his extremities. On further questioning, the patient reports that many members of his family have had similar symptoms. The patient's knowledge of his family history allows the physician to construct a detailed family tree (see Figure 11-20; the asterisk represents the patient).

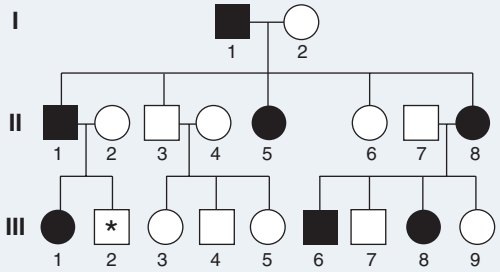

FIGURE 11-20.

What condition is the patient at risk for developing?

Huntington disease is characterized by dementia, choreoathetoid movements of the face and extremities, and early death. Huntington disease has an autosomal dominant inheritance. Other causes of early-onset dementia include early-onset Alzheimer disease, multiple sclerosis, HIV infection, or Creutzfeldt-Jakob disease.

What is the genetic basis of this condition?

Huntington disease is a genetic disease that results from increased trinucleotide repeats on chromosome 4. The trinucleotide that repeats is CAG, which codes for glutamine. The gene specifically encodes the huntingtin (*HTT*) gene. The exact function of *HTT* is not exactly known. However, when the huntingtin protein is broken down, toxic fragments are created due to the mutant gene.

What neuronal pathology in patients with this condition makes CT imaging useful?

Patients with Huntington disease have marked atrophy of the striatum, including the caudate and putamen. Neuronal death in the striatum leads to a decrease in GABAergic inputs from the putamen to the thalamus. Removal of these inhibitory inputs results in increased activity of thalamocortical projections to the motor cortices and causes the choreiform movements that are classically seen in Huntington patients.

What other conditions often present with similar movement abnormalities?

Sydenham chorea in rheumatic fever, tardive dyskinesia, and Wilson disease are among other diseases associated with choreoathetoid movements.

What is the prognosis for this patient?

Expansion of trinucleotide repeats over successive generations leads to earlier manifestations of disease in offspring; this is called **anticipation**. The patient's father died at age 45 years and likely developed Huntington disease many years earlier. If this patient has the genetic mutation, he might already be expected to show symptoms.

What other conditions are associated with trinucleotide repeats?

Fragile X syndrome, myotonic dystrophy, and Friedreich ataxia are also associated with trinucleotide repeats. In Fragile X, there is a repeat of CGG on the FMR1 gene on the X chromosome. Myotonic dystrophy has CTG trinucleotide repeat on chromosome 19. Friedreich ataxia is a trinucleotide repeat of GAA on the FXN gene that codes for frataxin. There is a reduction in frataxin causing iron buildup in the mitochondria.

CASE 15

The parents of a term, 1-year-old girl are concerned because the child's head seems abnormally large. Their pediatrician notes that the child's head circumference has accelerated beyond her established growth curve in the past month. Axial CT of the head (see Figure 11-21) demonstrates dilated atria of the lateral ventricles, a rounded third ventricle and a normal-sized fourth ventricle.

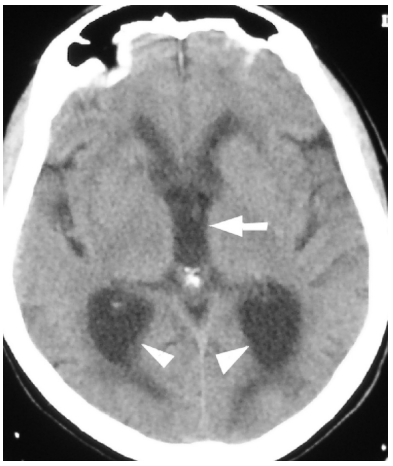

FIGURE 11-21. (Reproduced, with permission, from Brunicardi FC, et al. *Schwartz's Principles of Surgery*, 8th ed. New York: McGraw-Hill; 2005: 1650.)

What is the most likely diagnosis?

Hydrocephalus is defined as an excessive volume of cerebrospinal fluid (CSF) within one or more ventricles of the brain. Because CSF cannot flow freely through the ventricles to enter the subarachnoid space, this case is an example of an **obstructive hydrocephalus**. CT scan of the head in this patient shows a dilated ventricular system (see Figure 11-21) with dilated atria of the lateral ventricles (arrowheads) and rounded third ventricle (arrow). Cerebral aqueductal stenosis, a common congenital malformation, is the most common cause of obstructive hydrocephalus. In contrast, in cases of **communicating hydrocephalus** there is normal flow of CSF but an imbalance between CSF production (rare) and reabsorption (much more common).

Other causes of disproportionally large head size or growth include trauma, Canavan disease, and Hurler syndrome.

Where is CSF produced?

CSF is produced by the choroid plexus epithelium in the ventricle, especially within the cerebral ventricles (see Figure 11-22). The lateral ventricle communicates with the third ventricle via the foramen of Monro. The third ventricle communicates with the fourth ventricle via the cerebral aqueduct (of Sylvius). The fourth ventricle communicates with the subarachnoid space via the foramina of Luschka (laterally) and the foramen of Magendie (midline).

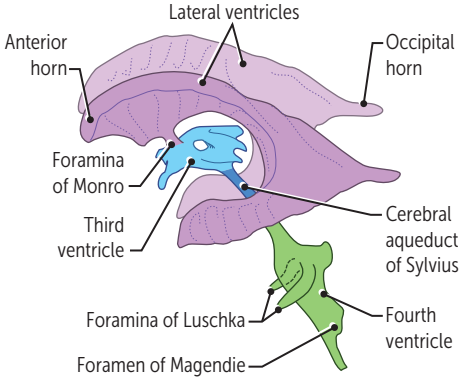

FIGURE 11-22. Anatomy of the ventricular system. (Reproduced, with permission, from Le T, et al. *First Aid for the USMLE Step 1: 2019.* New York: McGraw-Hill, 2019.)

How is CSF reabsorbed?

Arachnoid granulations (composed of arachnoid villus cells) are located in the superior sagittal sinus and connecting venous lacunae. The villus cells return CSF to the bloodstream within vacuoles (through a process called pinocytosis).

What forms the blood-brain barrier?

In the CNS, tight junctions between capillary endothelial cells form the **blood-brain barrier** (BBB) and regulate the passage of water and solutes into the brain and spinal cord. In contrast, capillaries in the choroid plexus are are fenestrated and lack a BBB. In the choroid plexus, tight junctions between the choroid epithelial cells regulate the transport of water and solutes into the ventricles.

What is the pathophysiology of this condition?

Hydrocephalus results from either a blockage of CSF flow or a mismatch of CSF production and reabsorption in which the rate of production exceeds reabsorption. Causes of hydrocephalus include the following:

- Excess CSF production (eg, choroid plexus papilloma; rare)
- Impaired CSF reabsorption (due to obstruction or disruption of arachnoid villi)
- Blockage of the flow of CSF (eg, brain tumor)

What is the treatment for this condition?

Treatment is surgical and involves a ventriculoperitoneal shunt, which allows for reabsorption of fluid in the peritoneum.

CASE 16

A 75-year-old woman visits an ophthalmologist because she has noticed a gradual decline in both her distance and near vision during the past 2 years. In particular, she has difficulty reading, focusing on objects in front of her, and adjusting her vision to the dark. She denies pain in her eye or any associated trauma. Funduscopic examination reveals deposits in the macula (see Figure 11-23) and abnormal vision as assessed by the Amsler grid (see Figure 11-24). Her peripheral vision and extraocular movements are intact.

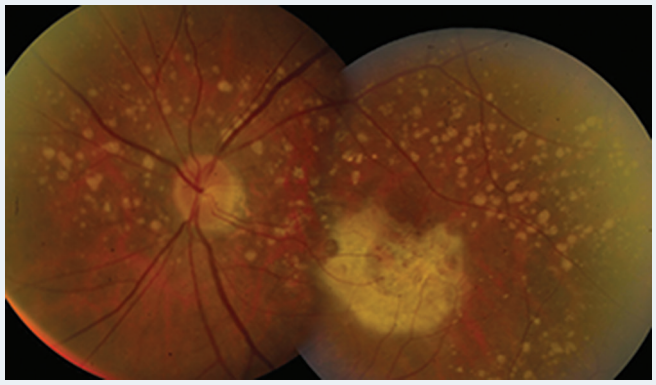

FIGURE 11-23. (Reproduced with permission from USMLE-Rx.com.)

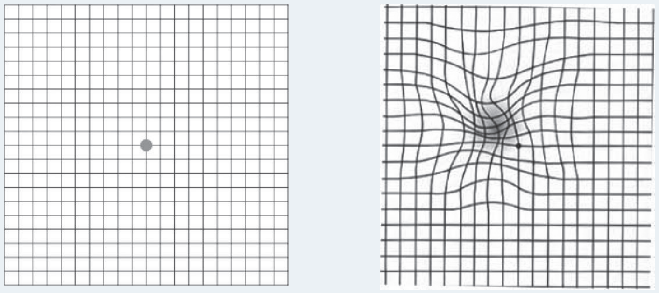

FIGURE 11-24. Amsler grid. (A) Normal grid. (B) Patient's view.

What is the abnormality in this patient's vision as assessed by the Amsler grid?

The **Amsler grid** assesses the degree of central vision loss (see Figure 11-24A). In this assessment, the patient covers one eye and, with the open eye, focuses on the dot at the center of the grid. Patients with vision deficits in their macula will exhibit metamorphopsia, meaning the patient will see a distortion of the grid (see Figure 11-24B).

What is the macula?

The **macula**, located temporal to the optic disc, is the area of the retina that is specialized for central and fine-detail vision. The center of the macula is the **fovea**, which has the highest density of cone photoreceptor cells in the retina and the smallest amount of convergence to bipolar cells. This provides for exquisite detail in visual perception.

What is the most likely diagnosis?

Age-related macular degeneration (ARMD), in which central vision is blurred, is a significant cause of vision loss in the elderly. By contrast, glaucoma typically affects peripheral vision while sparing central vision. Central vision loss can also be caused by optic neuritis and cataracts.

What are the two variants of this condition?

There are dry and wet forms of macular degeneration. The **dry form** (85% of cases) typically progresses more slowly and occurs earlier in the disease process. The **wet form**, although less frequent (15% of cases), can cause significant blindness in patients. The wet form is due to abnormal blood vessel growth within the eye.

What are the histologic features of the retina in this condition?

Drusen are extracellular protein and lipid deposits in the retina, which appear on funduscopic examination as yellow or white spots in the eye (see Figure 11-23). Irregularity and, in later stages, atrophy of the retinal pigmented epithelium also occur. In wet ARMD, new blood vessels from the choroid may grow into the subretinal space, causing **metamorphopsia** (a wavy distortion of vision), hemorrhage, and scarring.

CASE 17

A 5-year-old boy is brought to the pediatrician by his mother for a follow-up appointment. Two months ago, the boy was seen for a chief complaint of morning headaches, vomiting, and decreased energy. A gastrointestinal illness was suspected. At this visit, the mother reports that her son's symptoms have worsened and that he now is falling and has a stumbling gait.

What is the likely diagnosis?

The history suggests medulloblastoma, a highly malignant tumor most often found in the cerebellum. The majority of patients are 4–8 years of age, and males are affected more than females. In children, 70% of intracranial tumors are infratentorial, whereas in adults 70% are supratentorial. Although medulloblastoma is the most common pediatric brain tumor, astrocytomas, brain stem gliomas, and ependymomas are also common. Astrocytomas can occur anywhere in the hemispheres or in the brain stem. In children, ependymomas typically occur in the fourth ventricle and are characterized by pseudorosettes, in which cells are arranged around vessels with ependymal processes directed toward the vessel wall (see Figure 11-25).

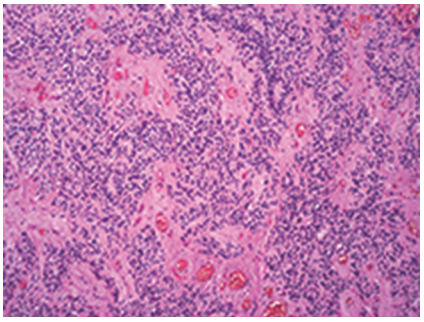

FIGURE 11-25. Ependymoma. Ependymomas arise adjacent to the ependyma-lined ventricular system. In children they most commonly occur near the fourth ventricle, while in adults they are often seen in the spinal cord. The tumor is composed of cells with regular, round to oval nuclei, and long, delicate processes arranged around vessels forming the characteristic perivascular pseudorosettes. (Reproduced with permission from USMLE-Rx.com.)

How do cerebellar lesions present?

Cerebellar lesions can occur in either the vermis or the hemispheres. Lesions in the hemispheres cause ipsilateral limb ataxia, intention tremor, and loss of muscle tone. Superior vermis lesions are characteristic of Wernicke encephalopathy and alcoholic cerebellar degeneration. Wernicke encephalopathy presents with the classic triad of gait or truncal ataxia, ophthalmoplegia, and confusion.

What imaging technique is used to visualize this condition?

On MRI of the head, medulloblastomas are heterogeneous enhancements located in the cerebellum, often extending into the fourth ventricle (see Figure 11-26).

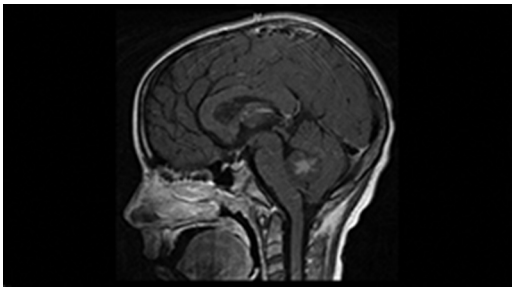

FIGURE 11-26. Medulloblastoma. Post-contrast sagittal T1-weighted MRI shows lobulated mass centered in the fourth ventricle with central contrast enhancement. Scan revealed posterior fossa mass and pathology following resection showed medulloblastoma. (Reproduced with permission from USMLE-Rx.com.)

This condition may present with what other syndrome?

The association of inherited colonic syndromes with brain tumors is named Turcot syndrome. Patients with autosomal dominant familial adenomatous polyposis are at risk for medulloblastomas and gliomas. Patients with hereditary nonpolyposis colorectal cancer are at risk for gliomas only.

What is the morphologic appearance of this condition?

Medulloblastomas are rapidly growing, well-circumscribed friable tumors found exclusively in the cerebellum, more frequently in the midline adjacent to the roof of the fourth ventricle. Microscopically, **Horner-Wright rosettes**, described as circular patterns of tumor cells surrounding a center of neuropil, can be seen.

What is the treatment for this condition?

Treatment consists of complete or near-complete surgical excision followed by radiation and chemotherapy. Current treatment protocols are designed to minimize damage to adjacent structures and prolong survival.

CASE 18

A 46-year-old woman is brought to the physician because she complains of vision changes that have been slowly progressing for several months. Other than changes in her vision, the patient has no complaints of nausea, vomiting, or headaches. Physical exam shows changes in visual acuity. Fundoscopic exam is normal. The patient has a CT scan of the head, which reveals a homogeneous mass on the left aspect of the sagittal sinus (see Figure 11-27).

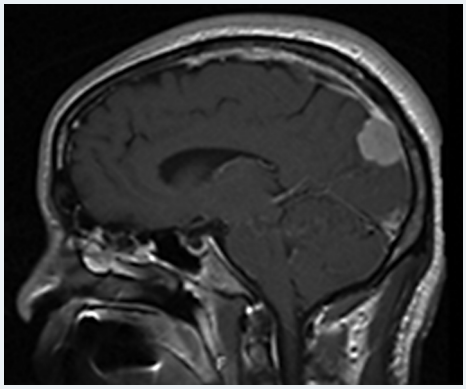

FIGURE 11-27. (Reproduced with permission from USMLE-Rx.com.)

What is the most likely diagnosis?

The location of the lesion on MRI scan is typical of a meningioma. Meningiomas are usually benign, slow-growing tumors arising from the arachnoid cells of the meninges. They are the second most common primary brain tumor.

Where are the lesions associated with this condition typically located?

Meningiomas may be found anywhere along the dura but most often in the superior parasagittal (falx) region, cerebral convexity, sphenoid wing, olfactory groove, and posterior fossa. Other diseases that commonly involve the dura include lymphoma, metastatic carcinoma, and tuberculosis.

What are the histologic findings of this condition?

Meningiomas display psammoma bodies and elongated spindle cells arranged concentrically in a whorled pattern. Psammoma bodies are laminated, concentric calcified concretions formed by meningiomas (**head**), papillary adenocarcinomas of the thyroid (**neck**), malignant mesothelioma (**thorax**), and serous papillary cystadenocarcinoma of the ovary (**pelvis**).

What is the treatment for this condition?

For small, slow-growing, and asymptomatic tumors, careful observation is appropriate. Surgical resection is indicated for symptomatic tumors or quickly growing tumors. Complete resection is often curative; however, tumors can recur if incompletely resected.

What other symptoms are common in patients with this condition?

Because of their slow growth, many meningiomas are detected incidentally after neuroimaging for other reasons. However, large tumors may displace normal brain tissue and cause focal neurologic deficits such as visual disturbances, hearing loss, mental status changes, extremity weakness, obstructive hydrocephalus, and/or seizures.

CASE 19

A 54-year-old woman was successfully treated for small cell lung cancer 3 years ago. She received chemotherapy and radiation therapy and was declared disease free via CT scan of the chest 1 year ago. She now comes to her primary care physician with a complaint of nausea, vomiting, and right-sided headaches of a few weeks' duration. A CT scan of the head is shown in Figure 11-28.

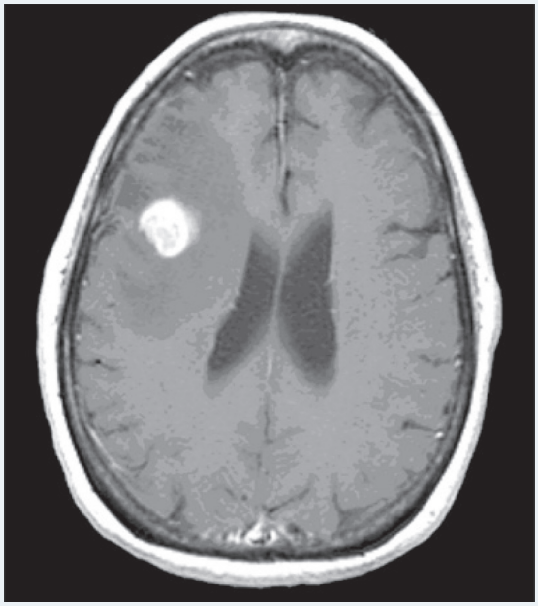

FIGURE 11-28. (Reproduced, with permission, from Kantarjian HM, et al. *MD Anderson Manual of Medical Oncology*. New York: McGraw-Hill; 2006: 797.)

What is the most likely diagnosis?

Metastatic brain tumor from her small cell lung cancer. Brain metastases are more prevalent than primary central nervous system tumors.

What is the differential diagnosis for this condition?

The differential diagnosis includes a primary brain tumor, metastatic tumor from a second primary brain tumor, infection, cerebral infarct, or radiation necrosis.

What types of cancer most often metastasize to the brain?

Lung, **B**reast, **S**kin (melanoma), **K**idney (renal cell carcinoma), and **G**astrointestinal (mnemonic: **Lots of Bad Stuff Kills Glia**) tumors can spread hematogenously to the brain.

Where are these lesions usually located in the brain?

Metastases are most often supratentorial, located at the **gray-white matter junction**, where the arterial vessels narrow sufficiently for tumor cells to lodge (see Figure 11-28). They are also found at **watershed areas** (vascular territories situated between two supplying arteries; eg, middle cerebral artery and anterior cerebral artery).

What are the common symptoms of this condition?

Symptoms include headaches, seizures, stroke, nausea, vomiting, cognitive dysfunction such as personality changes, and focal neurologic deficits such as aphasia or weakness.

What tests and/or imaging tools can help confirm the diagnosis?

MRI is the imaging modality of choice because of its superior sensitivity for soft tissue. Biopsy of the lesion is often indicated to confirm the diagnosis before a definitive treatment plan is chosen.

What paraneoplastic syndromes are associated with small cell lung carcinoma?

The most common paraneoplastic syndromes are the syndrome of inappropriate antidiuretic hormone secretion and the syndrome of ectopic adrenocorticotropic hormone; however, small cell lung cancer can also cause variable nonspecific neurologic symptoms.

CASE 20

An 18-year-old woman presents to her family physician for an evaluation of severe headaches. She describes her headaches as unilateral, beginning with a dull and steady ache and increasing in severity to a throbbing, debilitating pain after a few hours. No aura is associated with the headaches, but they are exacerbated by physical activity and light. Consequently, the patient prefers to remain in a dark room when her headaches occur. She also states this is the fifth episode she has had; the first episode dissipated within 2 days, but the three others lasted 4-8 hours and resolved with sleep.

What is the most likely diagnosis?

Migraine headache.

What signs and symptoms are commonly associated with this condition?

Migraines are unilateral in 60%–70% of cases; the remaining cases are typically bifrontal or, less frequently, bioccipital. The pain often begins with the gradual onset of a deep, steady ache that reaches a pulsatile, severe pain within several hours. Migraines can last from 4 hours to several days. They are typically worsened by movement and are made worse by routine activity. There may also be sensitivity to loud noises and bright lights, or they may be accompanied by nausea and vomiting. Although auras (temporary neurologic symptoms such as light flashes and zigzag lines or numbness and tingling in the arms and face) are commonly associated with migraine headaches, they are seen in only 20% of cases.

How is this condition differentiated from other, more serious pathologic conditions of the head?

The following warning signs indicate that a headache may be serious:

- Absence of similar episodes in the past
- Association with vigorous exercise or trauma (suggesting carotid dissection)
- Change in mental status
- Concurrent infection
- Sudden onset within seconds to minutes (suggesting subarachnoid hemorrhage)
- Sudden change is the severity or frequency of a prior headache
- Worse with changes in position or with Valsalva maneuver (suggesting a brain tumor)

Physical findings pointing to potentially serious pathology include nuchal rigidity (meningitis), poor general appearance, or papilledema (elevated intracranial pressure).

How can this woman's headache be differentiated from pseudotumor cerebri, cluster headaches, or tension headaches?

Tension headaches are typically bilateral and are often described as a bandlike tightness or pressure (as if the patient were wearing a tight hat). They are typically not debilitating, and the pressure waxes and wanes over an unpredictable time course. Tension headaches are closely associated with stress.

Idiopathic intracranial hypertension, also called **pseudotumor cerebri**, is a cause of headache that occurs most often in obese women and can be associated with use of retinoids and tetracyclines. These headaches are commonly accompanied by nausea, vomiting, tinnitus, and vision changes, especially cranial nerve VI palsies. They characteristically have positional symptoms; they will worsen with lying down and improve upon standing. Papilledema is typically present on examination, and the diagnosis is confirmed by the presence of elevated lumbar puncture opening pressure. Idiopathic intracranial hypertension can be treated with acetazolamide or topiramate, both of which decrease CSF production through inhibition of carbonic anhydrase. Serial lumbar puncture, optic nerve sheath fenestration, and CSF shunting are all options in refractory cases.

Cluster headaches typically occur in males and are always unilateral. The pain often begins around the eye or temple, is sudden in onset (and could thus be mistaken for subarachnoid hemorrhage) and is described as deep and persistent. Cluster headaches are typically accompanied by autonomic symptoms, such as miosis, lacrimation, or rhinorrhea. They are relatively short lasting (15–180 minutes) and are treated with oxygen or triptans.

What are the treatments for this condition?

- **Preventative agents** include β-blockers, calcium channel blockers, antidepressants (amitriptyline or venlafaxine), and anticonvulsants (valproate or topiramate).
- **Abortive agents** include nonsteroidal anti-inflammatory drugs, acetaminophen, triptans, and ergotamine agents.
- **Antiemetics** are often used for control of associated nausea and vomiting.

CASE 21

A 28-year-old previously healthy woman comes to the physician after suffering loss of vision in her right eye that resolved within a few hours. She also complains of weakness in her legs, urinary incontinence, and difficulty speaking. She has noticed a tremor in her right hand when writing and eating that has worsened over the past few weeks. Although she has had occasional tremors and troubled speech, her problems have never lasted this long and have never been accompanied by urinary incontinence or loss of vision. Upon questioning, she recalls a 2-week long episode of left arm numbness that resolved and that her mother had similar transient symptoms when she was young. Physical examination reveals left-sided facial droop, left tongue deviation, and lateral gaze weakness. An MRI is shown in Figure 11-29. Relevant laboratory findings are as follows:

White blood cell (WBC) count: 9100/mm^3
Hemoglobin: 13.3 g/dL
Hematocrit: 37.1%
Platelet count: 287,000/mm^3
CSF IgG index: 0.89

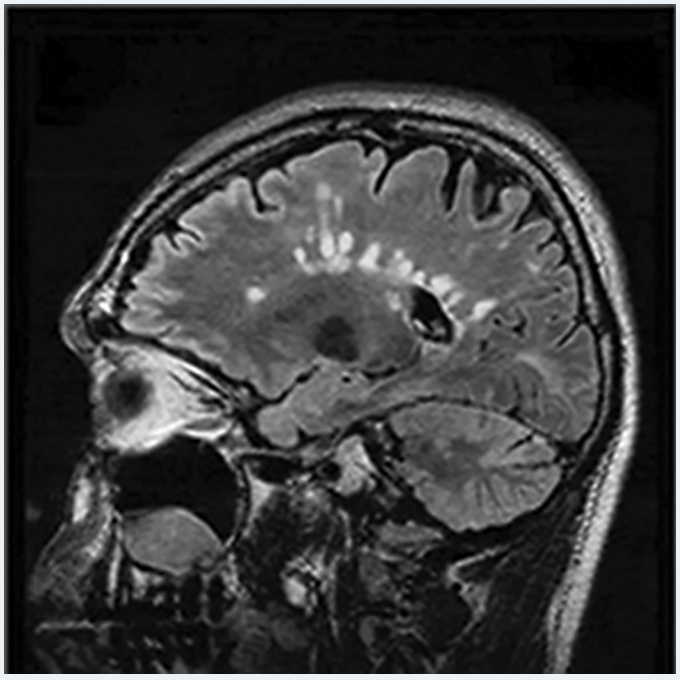

FIGURE 11-29. (Reproduced with permission from USMLE-Rx.com. Photo contributor: Dr. Vanja Douglas.)

What is the most likely diagnosis?

Multiple sclerosis (MS). Figure 11-29 shows periventricular white matter hyperintensities, which are classic lesions of MS.

What risk factors are associated with this condition?

Risk factors for MS include the following:

- Age 20–50 years (mean age of onset is 30 years)
- Female gender (female/male ratio is 1.77:1.00)
- Having grown up in higher latitudes, perhaps because sunlight exposure and vitamin D may be protective against MS
- Family history of MS

What anatomic feature could explain the findings on physical examination?

A **medial brain stem lesion** involving cranial nerves VI, VII, and XII (see Figure 11-30) leads to the constellation of facial droop, tongue deviation, and lateral gaze weakness. The intention tremor indicates cerebellar involvement.

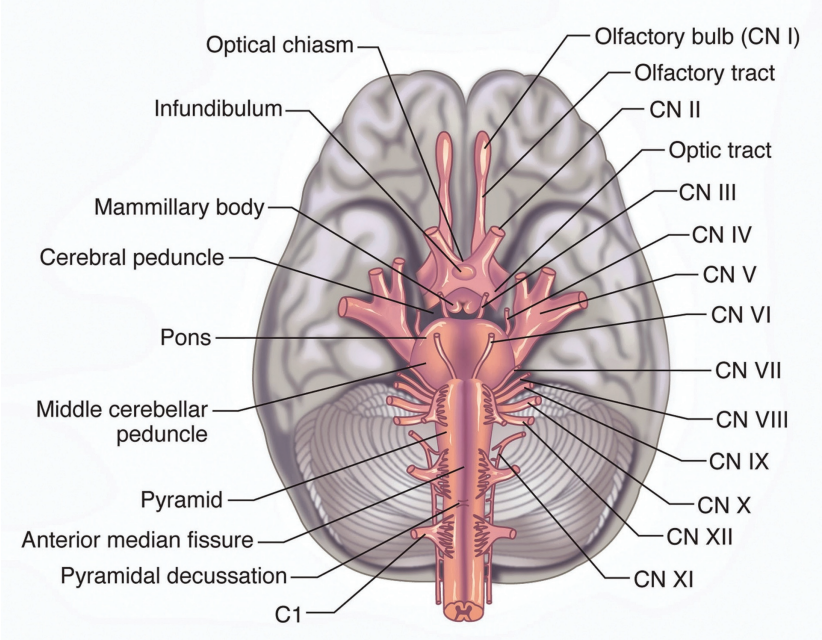

FIGURE 11-30. Brain stem anatomy. (Reproduced with permission from USMLE-Rx.com.)

What are the typical CSF findings in this condition?

Oligoclonal bands are seen in 85%–95% of cases. The presence of these immunoglobulins reflects the autoimmune nature of the disease. Oligoclonal bands are sensitive but not specific for MS and can be elevated in Lyme disease, lupus, syphilis, Sjögren syndrome, and neurosarcoidosis. Similarly, the **IgG index** is elevated in $>$ 90% of patients with definite MS. The total CSF WBC count is normal in most patients, but an elevated WBC count is nonspecific.

What is the likely finding on imaging of the brain?

Multiple **demyelinating plaques** are usually present in the brains of patients with MS, especially in the periventricular region, corpus callosum, and centrum semiovale.

What are the treatments for this condition?

Acute attacks are treated with high-dose corticosteroids; however, these drugs do not change the course of the disease. Common disease-modifying treatments include interferon-β1b, natalizumab, and glatiramer. Other newer oral therapies include dimethyl fumarate, teriflunomide, and fingolimod. Interferon-β binds a receptor and induces a transcriptional response that reduces T-cell proliferation and antigen presentation and alters cytokine levels. Natalizumab is a monoclonal antibody against α-4 integrins that blocks the adhesion and migration of T-cells out of the vasculature and into the CNS. Notably, natalizumab increases the risk of developing progressive multifocal leukoencephalopathy (PML), a demyelinating disease caused by reactivation of JC virus. The risk of PML is highest in immunocompromised patients, such as those with HIV, and natalizumab should be avoided in such patients.

What similar condition should be first excluded?

Neuromyelitis optica (NMO) is another autoimmune disease that has a similar presentation to MS. NMO has characteristic findings of optic neuritis and long spinal cord lesions on MRI and is caused by antibodies to aquaporin 4. It is important to rule out, as standard treatments for MS may actually worsen this disease.

CASE 22

A 25-year-old woman presents to her physician with difficulty chewing and swallowing food. She also complains of occasional double vision and ptosis of her right eye. She states her symptoms are often absent in the morning and appear to worsen as the day progresses but can improve with a nap.

What is the most likely diagnosis?

Myasthenia gravis. Differential diagnosis includes Lambert-Eaton syndrome, which is a paraneoplastic syndrome associated with small cell lung cancer involving muscle weakness; however, strength improves if a contraction is maintained. In myasthenia gravis, symptoms worsen as activity progresses. Lambert-Eaton syndrome also typically spares the extraocular muscles.

What patient characteristics are typically associated with this diagnosis?

The age of onset of myasthenia gravis follows a bimodal distribution, with females most commonly diagnosed in their 20s and with male incidence peaking later in life, after age 50.

What signs and symptoms are commonly associated with this condition?

Patients may present with a variety of findings, including ptosis, diplopia, dysarthria, difficulty chewing, and difficulty swallowing. Proximal muscle weakness is usually greater than distal muscle weakness. Weakness increases with use of the muscles, making symptoms more prominent later in the day. In myasthenic crisis, the weakness can become so severe that it results in respiratory failure.

What is the pathophysiology of this condition?

The majority of patients have autoantibodies against the **acetylcholine** receptor (AChR), found on the muscle membrane at the neuromuscular junction (see Figure 11-31). The binding of these autoantibodies initiates an immune reaction that results in decreased numbers of AChRs. When acetylcholine (ACh) is released from the motor nerve terminal, there are fewer AChRs available to bind. Therefore, muscle stimulation is decreased, resulting in weakness. Some patients instead express antibodies against the muscle-specific receptor tyrosine kinase (MuSK). MuSK is a protein that mediates the clustering of AChRs at the muscle cell membrane.

What tumor is commonly associated with this condition?

Myasthenia gravis has been associated with an increased frequency of **thymomas**. It is thought that the thymus is the site of production of autoantibodies against acetylcholine receptors.

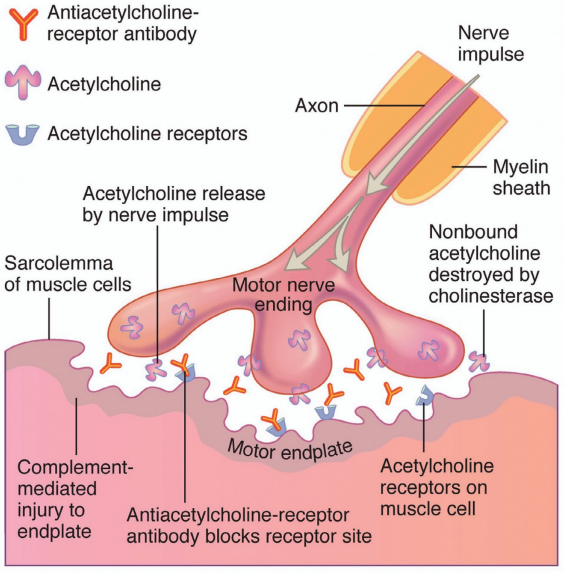

FIGURE 11-31. The pathogenesis of myasthenia gravis at the neuromuscular junction. (Reproduced with permission from USMLE-Rx.com.)

How does the Tensilon test help to diagnose this condition?

Edrophonium (Tensilon) is a rapidly acting acetylcholinesterase inhibitor that has short duration. It inhibits the breakdown of ACh at the neuromuscular junction, thereby increasing the amount of ACh available to stimulate muscle contraction. Thus, increased muscle strength immediately after injection of edrophonium is suggestive of myasthenia gravis.

What is the treatment for this condition?

Acetylcholinesterase inhibitors, especially pyridostigmine, treat the underlying symptoms and may be enough on their own. Immunomodulating agents such as glucocorticoids or azathioprine are often used with frequent exacerbations or poor control. In myasthenic crisis, plasmapheresis and intravenous immunoglobulin (IVIG) can provide rapid relief, and it is also important to closely monitor patients' respiratory status with frequent pulmonary function testing. **Thymectomy** is considered for all younger (< 60 years) patients with thymoma and has even been shown to be of some benefit in patients without thymoma.

CASE 23

A 12-year-old boy is brought by mother to the dermatologist for numerous skin lesions. Physical examination reveals 10 uniformly hyperpigmented macules, 15–25 mm in diameter, scattered over the patient's trunk and limbs. Freckling is present in both armpits, and dozens of soft, skin-colored, domed nodules have recently appeared on the patient's back. The dermatologist notes kyphosis and refers the patient to an ophthalmologist for further evaluation.

What is the most likely diagnosis?

Neurofibromatosis type 1 (NF1), or von Recklinghausen disease, is a common neurocutaneous disorder. NF1 has complete penetrance with variable expression. Diagnosis is made on clinical criteria. Although neurofibromatosis type 2 (NF2) can present with skin lesions, NF2 most commonly causes bilateral vestibular schwannomas and eye lesions, especially childhood cataracts; tumors of the spinal cord, cranial nerves, and meninges are also common in NF2.

What are the genetics of this condition?

NF1 is an autosomal dominant disorder caused by mutation in the *NF1* gene found on chromosome **17**. Approximately 50% of NF1 cases are familial, and the rest represent new mutations. *NF1* codes for the protein neurofibromin, a GTPase activating protein that enhances the inactivation of the protein Ras. Because Ras normally promotes cell growth, neurofibromin functions as a tumor suppressor by downregulating Ras.

What are the typical dermatologic findings of this condition?

The hallmark finding is six or more hyperpigmented macules called **café-au-lait** spots. In addition, **neurofibromas**, multiple soft fleshy tumors, usually develop during adolescence (see Figure 11-32). **Freckling** is also present in the axilla and groin. Although NF2 often demonstrates neurofibromas, café-au-lait spots are rare in this condition.

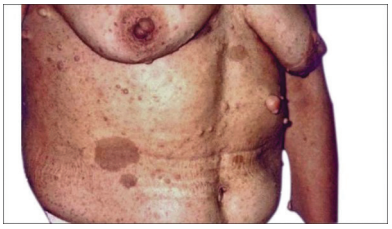

FIGURE 11-32. The multiple small skin-colored papules seen here are neurofibromas. The large hyperpigmented macule is a café-au-lait spot. (Reproduced with permission from Antônio JR, et al. Neurofibromatosis: chronological history and current issues. *An Bras Dermatol*. 2013;88(3):329-343.)

What are the typical ophthalmologic findings in this condition?

Lisch nodules, which are raised, pigmented, hamartomas, are found on the iris (see Figure 11-33).

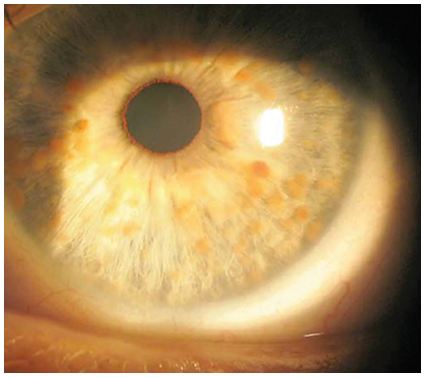

FIGURE 11-33. Multiple hamartomas (Lisch nodules) on the iris of this patient with neurofibromatosis type 1. (Reproduced with permission from USMLE-Rx.com.)

Patients with this condition are predisposed to what tumors?

Optic gliomas may arise anywhere along the optic tract, particularly in the optic nerve or chiasm. Patients are also at increased risk for other central nervous system tumors such as astrocytomas and other gliomas. Peripheral neurofibromas can undergo malignant transformation into neurofibrosarcomas.

What are other signs of this condition?

Skeletal abnormalities such as sphenoid bone dysplasia, dural ectasia, or, more commonly, focal kyphosis or scoliosis can be seen. Weakness and reduced skeletal muscle fiber size can also be observed. Patients can also have behavioral and cognitive effects, including attention-deficit hyperactivity disorder (ADHD), speech delays, and math deficits.

CASE 24

A 16-year-old boy presents to his pediatrician with a few months' history of progressive hearing loss in both ears. His deteriorating hearing has been accompanied by ringing in his ears (tinnitus). The pediatrician notices hyperpigmented macules on the patient's arms and legs. MRI of the head is shown in Figure 11-34.

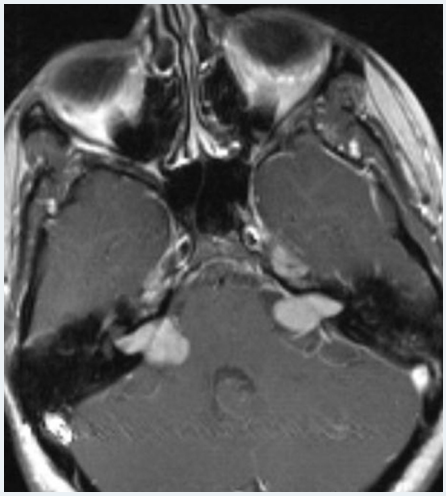

FIGURE 11-34. (Reproduced with permission from USMLE-Rx.com.)

What is the most likely diagnosis?

Neurofibromatosis type 2 (NF2) is an autosomal dominant disorder whose hallmark is bilateral acoustic neuromas, as seen in this man's MRI. Perforation of the eardrum, ototoxic medication, otosclerosis, or Ménière disease can also cause acquired hearing loss in children.

What is the pathogenesis of this condition?

Mutation of the gene *merlin* found on chromosome **22** (mnemonic: **type 2 = 22**). **Merlin** codes for a protein involved in cytoskeleton components responsible for contact inhibition of tumor progression.

What other signs and symptoms are common in patients with this condition?

Blurry or cloudy vision due to juvenile cataracts is also seen in NF2. Patients may also present with skin findings similar to those seen in neurofibromatosis type 1, such as café-au-lait spots.

What are the two forms of hearing loss?

- **Conductive hearing loss** involves the ear canal, tympanic membrane, middle ear, and ossicles.
- **Sensorineural hearing loss** involves the inner ear (cochlea), vestibulocochlear nerve, or central processing centers in the brain.

How do the Weber and Rinne tests distinguish between the two forms of hearing loss?

In the **Weber** test, a vibrating tuning fork is placed at the center of the patient's cranium, allowing sound to be transmitted directly through the bone to the inner ear. A patient with **unilateral sensorineural** hearing loss will have lateralization to the unaffected ear (ie, the tone will be louder in the unaffected ear). However, in a patient with **unilateral conductive** hearing loss, the inner ear attempts to compensate for the conductive losses. As a result, the sound that is transmitted through the bone (bypassing the conduction problem) will be perceived as louder on the affected side.

In the **Rinne** test, a vibrating tuning fork is placed on the mastoid process behind the ear (bone conduction; BC) and then next to the external auditory canal (air conduction; AC). Normally AC is greater than BC. A patient with **conductive** hearing loss will "hear" the vibration louder when the tuning fork is on the mastoid process than when it is near the external auditory canal (**BC > AC**). In a patient with sensorineural hearing loss, the normal relationship (**AC > BC**) will be preserved. This patient has **bilateral** sensorineural hearing loss and tests normal in both examinations.

CASE 25

A 70-year-old man with a history of hypertension goes to his ophthalmologist for a routine eye examination. He has needed to wear eyeglasses while driving since he was 18 years of age. Ocular examination reveals increased intraocular pressure in both eyes. On visual field testing, there is significant loss of peripheral vision and funduscopic examination reveals cupping in both eyes.

What is the most likely diagnosis?

Open-angle glaucoma is the most common form of glaucoma in the United States (90%) and presents as progressive, painless visual loss. Closed-angle glaucoma is painful, has acute onset, and can cause additional symptoms such as seeing halos around lights and red eye.

What is the pathophysiology of this condition?

Open-angle glaucoma is caused by elevated intraocular pressure resulting from obstruction of flow of aqueous humor through the normal outflow channels (see Figure 11-35).

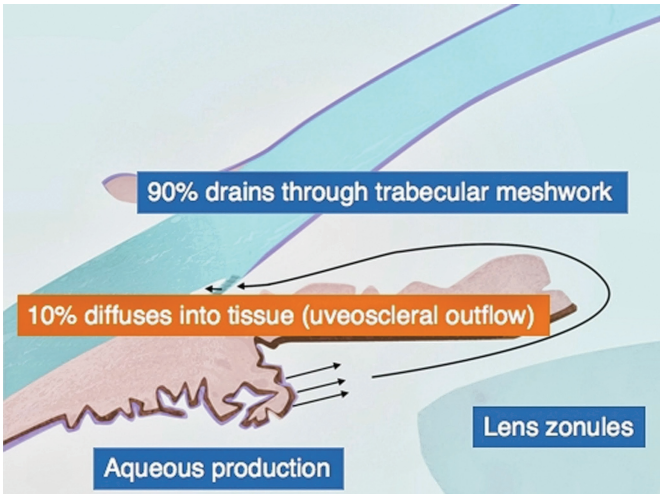

FIGURE 11-35. Aqueous flow in the angle of the eye. (Reproduced with permission from USMLE-Rx.com. Photo contributor: Dr. Nicholas Mahoney.)

Causes of open-angle glaucoma can be divided into primary and secondary causes. Primary cause is idiopathic, where the exact cause cannot be determined. Secondary causes do have a reason. Increased intraocular pressure can be due to blocked trabecular meshwork due to white blood cells (from infection of the eye), erythrocytes (from vitreous hemorrhage), and retinal debris (from retinal detachments).

What are the treatments for this condition?

The direct cholinergic agonists pilocarpine and carbachol are used to treat open-angle glaucoma. These agents act by stimulating ciliary muscle contraction, thereby relieving tension in the suspensory ligament. Cholinomimetics also stimulate the sphincter pupillae of the iris, which widens the canal of Schlemm and constricts the pupil (miosis). Adverse effects include nausea, vomiting, diarrhea, salivation, sweating, vasodilation, and bronchoconstriction.

What effect does pilocarpine have on cardiac muscle?

Pilocarpine is an M_3/M_2 muscarinic receptor agonist. Cardiac cells have M_2 receptors that, when activated, stimulate a G protein that inhibits adenyl cyclase and increases potassium conductance. Pilocarpine stimulation decreases the heart rate and the force of contraction (**negative inotrope**).

What additional classes of drugs are useful in treating this condition?

Other drug classes used to treat open-angle glaucoma include the following:

- Adrenergic agonists such as epinephrine
- β-Blockers and acetazolamide (a carbonic anhydrase inhibitor), which decrease aqueous humor secretion
- Prostaglandins, which increase the outflow of aqueous humor

CASE 26

A 66-year-old man presents to his physician with difficulty walking, describing a shuffling pattern, and his friends note that he has not been able to keep up with them when walking. He has a history of tremor in his right hand that worsens when he is sitting down watching television. His wife has noticed that he does not seem to get excited about anything.

What is the most likely diagnosis?

Parkinson disease typically presents with the following symptoms: **T**remor that is worse at rest, **R**igidity, **A**kinesia or bradykinesia, and **P**ostural instability (mnemonic: **TRAP**).

What are the Parkinson-plus syndromes?

The Parkinson-plus syndromes and their associated symptoms are as follows:

- Dementia with Lewy bodies: Fluctuating cognition and visual hallucinations
- Multiple system atrophy: Ataxia and autonomic instability (especially urinary and erectile dysfunction and hypotension)
- Progressive supranuclear palsy: Early postural instability, loss of voluntary eye movements, and dysarthria
- Corticobasal degeneration: sensory loss, apraxia, aphasia, myoclonus, dementia

What neuropathologic findings are associated with this condition?

Parkinson disease is marked by significant neuronal loss in the **substantia nigra**, which decreases dopaminergic input into the basal ganglia. Characteristic findings include depigmentation of neurons in the substantia nigra and **Lewy bodies**, which are eosinophilic cytoplasmic inclusions composed of alpha-synuclein protein (see Figure 11-36).

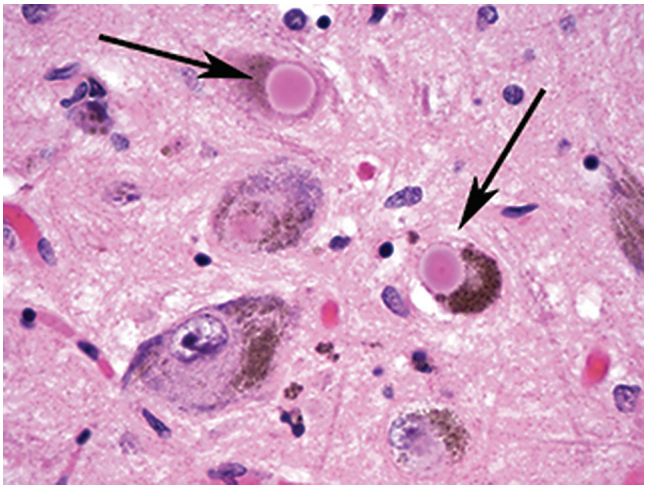

FIGURE 11-36. Lewy bodies in Parkinson disease. (Reproduced with permission from USMLE-Rx.com.)

How does a loss of dopamine release from the substantia nigra decrease movement?

Dopamine produced by the substantia nigra activates the direct pathway and inactivates the indirect pathway in the basal ganglia. Normally, the direct pathway is prokinetic and the indirect is akinetic. In the direct pathway, dopamine activates the D1 receptors in the caudate nucleus; these inhibit the globus pallidus internus, which in turn inhibits the ventral lateral thalamus nucleus, resulting in frontal motor stimulation. In the indirect pathway, dopamine inhibits the caudate via D2 receptors, which inhibits the globus pallidus externus, which in turn inhibits the subthalamic nucleus, resulting in stimulation of the globus pallidus internus (the opposite end result as the direct pathway) (see Figure 11-37). The loss of dopamine results in a decrease of the prokinetic pathway and an increase of the akinetic one, resulting in a decrease in frontal motor stimulation, causing bradykinesia.

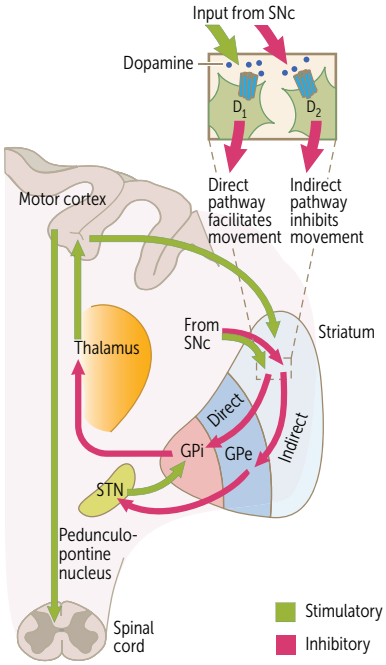

FIGURE 11-37. The direct and indirect pathways through the basal ganglia. SNc, substantia nigra pars compacta; GPe, globus palidus externus; GPi, globus palidus internus; STN, subthalamic nucleus. (Reproduced with permission from USMLE-Rx.com.)

What symptoms are likely to develop over time in this patient?

As the disease progresses, shuffling or freezing gait, masked facies, autonomic dysfunction, and dementia are likely to occur.

What are the treatments for this condition?

Many of the drugs available for treating Parkinson disease act by increasing dopaminergic input into the basal ganglia. Levodopa is a metabolic precursor of dopamine that is converted to dopamine by the enzyme DOPA-decarboxylase. However, when dopamine is formed peripherally, it results in adverse effects of nausea, vomiting, and orthostatic hypotension. To avoid this, levodopa is combined with the peripheral decarboxylase inhibitor carbidopa so that conversion of levodopa to dopamine will occur only in the central nervous system. Both catechol-O-methyltransferase inhibitor (entacapone and tolcapone) and monoamine oxidase-B inhibitors (selegiline) act by preventing the metabolism of dopamine. Pramipexole and bromocriptine, which are direct dopaminergic agonists, can also be used to augment dopamine signaling. Anticholinergic drugs (benztropine) and amantadine are also used in Parkinson disease.

What other etiologies might result in a similar presentation?

Typical antipsychotic agents have antidopaminergic activity. Thus, patients taking these medications for schizophrenia can exhibit Parkinson-like symptoms. 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine and antiemetic agents can also induce Parkinson-like symptoms.

CASE 27

A 36-year-old woman presents to her primary care physician with a 6-month history of occasional milky discharge from her breasts, chronic headaches, and decreased libido. Her medical history reveals long-standing amenorrhea and infertility. The patient denies any visual disturbances. Laboratory tests reveal a negative urine pregnancy test, a normal thyroid-stimulating hormone level, and a prolactin level of 88 μg/L (normal 5–20 μg/L).

What is the most likely diagnosis?

Hyperprolactinemia from a prolactin-secreting anterior pituitary adenoma. Classic symptoms in females are amenorrhea, infertility, and galactorrhea.

What class of drugs can cause this condition?

Hyperprolactinemia also occurs in patients on antipsychotic medication. Because dopamine inhibits prolactin production, the dopamine inhibitors cause hyperprolactinemia.

What is the differential diagnosis of a mass in the sella turcica?

The differential diagnosis includes pituitary adenoma, pituitary hyperplasia, craniopharyngioma, meningioma, germ cell tumor, chordoma, primary lymphoma, cyst, abscess, or arteriovenous fistula of the cavernous sinus.

What is the pathogenesis of elevated prolactin levels in this condition?

Dopamine secreted from the hypothalamus travels to the anterior pituitary where it inhibits prolactin secretion. A mass in the pituitary may compress the infundibulum, causing a "stalk effect," in which dopamine cannot reach its target. Thus, prolactin is continuously secreted. Physiologic hyperprolactinemia may occur during **pregnancy**. Pregnancy must always be ruled out in any female who presents with amenorrhea.

What other hormones are secreted from the anterior pituitary?

The anterior pituitary hormones are given by the mnemonic **FLAT PiG**: **F**ollicle-stimulating hormone, **L**uteinizing hormone, **A**drenocorticotropic hormone, **T**hyroid-stimulating hormone, **P**rolactin, and **G**rowth hormone. Although prolactinomas are the most common hyperfunctioning tumor, a pituitary adenoma may secrete any of the above hormones.

What is the treatment for this condition?

Reduction in tumor size, suppression of prolactin secretion, and return of menses are usually accomplished with a dopamine agonist such as **bromocriptine** or cabergoline. Both are ergot derivatives that act directly on dopamine receptors in the hypothalamus to decrease prolactin secretion. When medical management is no longer effective, or the mass is very large, transsphenoidal surgery with resection of a large hyperfunctioning sellar mass is typically indicated.

What visual disturbance is classically seen with this condition?

Because the pituitary gland sits immediately above the optic chiasm, a pituitary tumor can compress the center of the chiasm. The central aspect of the optic chiasm is where fibers carried via the optic nerve from the nasal hemiretina cross. Since the nasal hemiretina is responsible for vision from the temporal fields, compression of the optic chiasm by a pituitary tumor causes vision loss of the temporal fields, called **bitemporal hemianopsia** (see Figure 11-38).

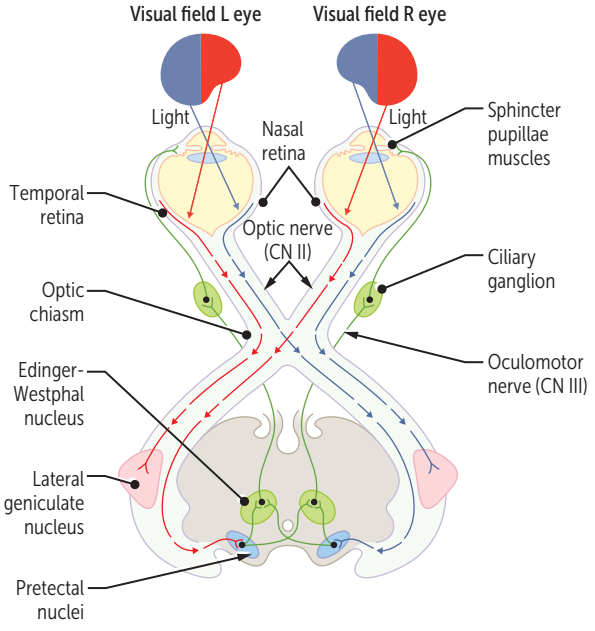

FIGURE 11-38. Optic nerve fibers from the nasal retina, carrying visual information from the temporal field cross at the optic chiasm. A lesion at the optic chiasm will result in loss of the temporal fields. (Reproduced with permission from USMLE-Rx.com.)

CASE 28

A 45-year-old woman presents to her physician with a 3-month history of anxiety, tremor, hyperreflexia, hair thinning, and an unintentional weight loss of 4.5 kg (10 lb). On physical examination, she has a palpable thyroid. TSH is measured to be 0.01 mU/mL. She is treated with a thyroidectomy. After surgery, her symptoms have resolved, but the patient now complains of hoarseness. The patient denies difficulty swallowing and breathing.

What is the cause of the patient's hoarseness?

This patient underwent surgery for hyperthyroidism. Damage to the left recurrent laryngeal nerve (a branch of the vagus nerve) may occur as the surgeon is ligating the inferior thyroid artery, which is adjacent to the nerve. The left recurrent laryngeal nerve descends down to the aortic arch and wraps around and ascends upwards. The right recurrent laryngeal nerve simply branches off the vagus nerve (CN X) with a more direct course.

What is the course of the nerve that is damaged in this patient?

The left recurrent laryngeal nerve branches off the vagus nerve at the level of the aortic arch, wraps posteriorly around the aorta, and ascends superiorly to the larynx (see Figure 11-39). The right recurrent laryngeal nerve branches off the vagus at the level of the right subclavian artery and vein and wraps around the artery to ascend posteriorly to the larynx. Because the left recurrent laryngeal nerve has a long course arising from the vagus in the superior mediastinum, it is prone to injury from abnormal structures, such as enlarged lymph nodes, aneurysm of the arch of the aorta, a retrosternal goiter, or a thymoma.

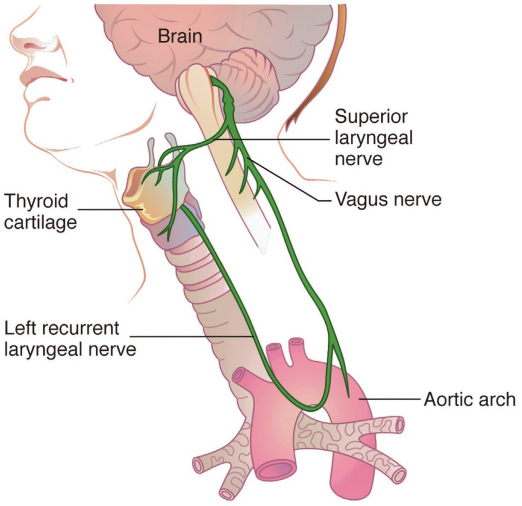

FIGURE 11-39. The course of the recurrent laryngeal nerve as it passes under the aortic arch and travels upward. (Reproduced with permission from USMLE-Rx.com.)

What other structures can be damaged during this surgery?

The parathyroid glands are located behind the thyroid and can often be damaged during surgery. Current surgical technique focuses on preservation of the parathyroid glands; however, hypoparathyroidism can occur after surgery. For this reason, surgeons often remove the parathyroid gland and reimplant it elsewhere in the neck.

What are other scenarios in which this nerve may be injured?

Left atrial enlargement (eg, from mitral regurgitation) and tumor in the apex of the right upper lobe of the lung (Pancoast tumor) can impinge on and injure the recurrent laryngeal nerve. Injury of the left recurrent laryngeal nerve may also result in compression by abnormal structures in the superior mediastinum, as described above.

How do you test a damaged vagus nerve?

The vagus nerve innervates a wide variety of organs and muscles in addition to the larynx. One physical test you can do is have the patient open her mouth and say "Ahhh." This allows you to visualize the uvula and see if it deviates. The uvula deviates away from the side of the lesion.

A patient will also have an impaired gag reflex due to paralysis of the ipsilateral pharyngeal constrictor muscles. A person will exhibit "gagging" or coughing if a tongue depressor is pressed gently against the posterior aspect of the tongue or posterior wall of the pharynx. The vagus nerve is the efferent pathway for the gag reflex while CN IX (glossopharyngeal) constitutes the afferent limb.

CASE 29

An emergency medical team is called to help a 60-year-old woman with small cell lung cancer who is unconscious at work. Her coworkers state that for about 10 seconds before she lost consciousness, she pointed to her right hand as it began twitching rhythmically, then stiffened every muscle, groaned, and fell down. After about 15 seconds, she became incontinent and her arms and legs began jerking rhythmically. She then was still, unresponsive, and unconscious for about 3 minutes. The medical team notes she is now breathing deeply but remains unresponsive.

What is the most likely diagnosis?

Seizure. Involvement of the left motor cortex is implicated because the seizure started with right-handed motor activity. In this patient a metastasis is the likely culprit. Seizures can also be caused by infection, ischemia, drug exposure or withdrawal, certain ion imbalances including hypoglycemia and hyponatremia, and trauma.

How is this condition classified?

This is a simple partial (focal) seizure with motor signs secondarily generalizing into a tonic-clonic seizure. During the first 10 seconds, the patient maintained consciousness, pointing to a **simple seizure** (complex seizures require a loss of consciousness). After the first 10 seconds, her simple partial seizure evolved into a generalized tonic-clonic seizure. The **tonic phase** is characterized by the immobile contraction of all muscles, and the **clonic phase** is characterized by the bilateral rhythmic jerking of the extremities.

Why is the patient breathing deeply after her incident?

The patient is likely responding to acidosis. A **respiratory acidosis** can develop from the loss of coordinated respirations during the seizure, and a **metabolic acidosis** can develop as muscles contract under anaerobic conditions and produce lactic acid.

What is the treatment for this condition?

Older antiseizure medications include valproic acid, phenytoin, phenobarbital, primidone, and carbamazepine. Newer medications such as topiramate, levetiracetam, and lamotrigine have become more prevalent. Many antiseizure medications work by enhancing γ-aminobutyric acid (GABA) binding on chloride channels. GABA binding allows chloride ions to flow into neurons, thereby inhibiting neuronal firing. Barbiturates act on the same chloride channels and enhance GABA signaling by increasing the duration of chloride channel opening. Benzodiazepines act on the same channels and enhance GABA signaling, but they do so by increasing the **frequency** of chloride channel opening. Other antiseizure medications, such as carbamazepine, phenytoin, and lamotrigine work by inhibiting voltage-dependent sodium channels. Valproate both inhibits sodium channels and increases presynaptic GABA levels. Topiramate blocks sodium channels, enhances GABA activity, and has some carbonic anhydrase inhibition.

What are the most common adverse effects of treatment?

Adverse effects of seizure treatments are as follows:

- Valproate: Hepatotoxicity, neutropenia, thrombocytopenia, teratogenicity (neural tube defects in the fetus, cognitive effects)
- Carbamazepine: Hepatotoxicity (check liver function), aplastic anemia, agranulocytosis
- Phenytoin: Gingival hyperplasia, teratogenicity
- Ethosuximide and lamotrigine: Stevens-Johnson syndrome (a bullous form of erythema multiforme that involves mucous membranes and large areas of the body)
- Carbamazepine and phenobarbital: Induction of cytochrome P-450, resulting in drug interactions
- Topiramate: weight loss, nephrolithiasis, paresthesias
- Levetiracetam: agitation and aggression and worsening of depression

What is status epilepticus and how should it be treated?

Status epilepticus is when a seizure occurs continuously for at least 5 minutes, or when two or more seizures occur without complete recover of consciousness in between. It is a neurologic emergency. Initial treatment involves the use of benzodiazepines, usually lorazepam, in attempt to break the seizure. Fosphenytoin or phenytoin can be used to prevent recurrence of seizures.

CASE 30

A 35-year-old woman presents to the ED complaining of back pain. Six years ago, she was diagnosed with a 2.5-cm primary breast tumor with metastases to one axillary lymph node. At that time, she underwent a mastectomy and adjuvant chemotherapy. She had been feeling well until 3 months ago, when she began to develop back pain. The pain has become progressively worse, particularly when she lies down. She also notes some weakness in both legs but no leg pain. She denies fever, night sweats, weight loss, or headache. Physical examination reveals no cervical lymphadenopathy; 4/5 muscle strength in the lower extremities bilaterally; normal pain, vibration, and position sensation; 3+ patellar reflexes bilaterally; a positive Babinski reflex on the right; and normal anal sphincter tone.

What are common causes of back pain?

Common causes of back pain include the following:

- Musculoskeletal conditions (eg, muscle strain, osteoarthritis, compression fracture, or ankylosing spondylitis)
- Disk herniation
- Multiple myeloma
- Metastases
- Osteomyelitis
- Referred pain from visceral disease (eg, gallstones or kidney stones, pancreatitis, or aortic aneurysm)

What is the most likely cause of this patient's back pain?

The patient's history of breast cancer raises concern for the development of metastases resulting in epidural spinal cord compression. Her leg weakness, hyperreflexia, and positive Babinski signs indicate upper motor neuron lesions, which are likely the cause of her weakness as well. Her pain at rest and lack of sciatica argue against disk herniation.

How do signs of upper motor neuron lesions contrast with those of lower motor neuron lesions?

As in this patient, upper motor neuron lesions are characterized by spastic paralysis, hyperreflexia, and a positive Babinski sign. By contrast, lower motor neuron lesions are associated with flaccid paralysis, muscle atrophy, muscle fasciculations and fibrillations, and hyporeflexia.

What are the most common metastases to bone?

The most common sources of bone metastases are cancers of the breast, prostate, lung, and kidney (renal cell carcinoma). Most bone metastases are osteolytic, meaning they cause destruction of normal bone. Prostate cancer is notable in that it causes osteoblastic lesions, characterized by the deposition of new bone.

What are the treatments for this condition?

Treatment options include steroids such as dexamethasone, radiation therapy, and surgical decompression. Spinal cord compression is an oncologic emergency because neurologic dysfunction, if present, may become permanent if it is not immediately addressed.

CASE 31

A 72-year-old woman is at home with her husband when he notices she sounds confused even though she had been speaking clearly just moments before. He brings her into the ED, where she is unable to follow commands. Her speech is fluent but does not make any sense. CT scan of the head 24 hours later is shown in Figure 11-40.

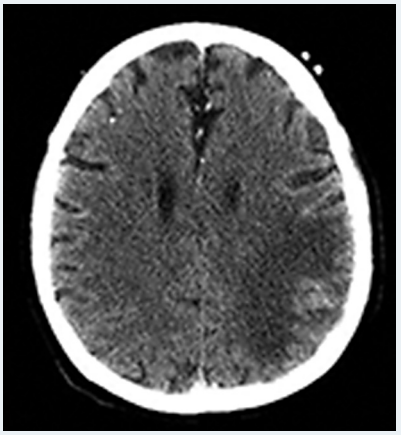

FIGURE 11-40. (Reproduced with permission from USMLE-Rx.com.)

What is the most likely diagnosis?

Stroke.

What risk factors are associated with this condition?

- Advanced age
- Cardiovascular disease
- Carotid disease
- Diabetes mellitus
- Dyslipidemia
- Family or personal history of transient ischemic attack or stroke
- Hypertension
- Smoking

What type of aphasia does the patient exhibit?

The combination of fluent but nonsensical speech and poor comprehension is characteristic of **Wernicke aphasia** (sensory aphasia). These patients also display poor repetition and naming ability. Other findings commonly associated with Wernicke aphasia include contralateral visual field cut (due to ischemia of optic radiation) and anosognosia (unawareness of one's deficit).

A lesion in what anatomic area causes these findings?

Wernicke aphasia is usually the result of ischemia in the superior temporal gyrus (see Figure 11-41), which is supplied by the inferior division of the left middle cerebral artery.

What speech pattern results when this condition affects the inferior frontal gyrus?

The inferior frontal gyrus controls motor aspects of speech (see Figure 11-41). A stroke in this area causes **Broca aphasia** (motor aphasia), which is characterized by nonfluent, agrammatic speech. Because of the proximity of the primary motor cortex for the face and arm, **dysarthria** (difficulty in articulating words) and right face and arm weakness are often associated with Broca aphasia. Comprehension is intact in these patients.

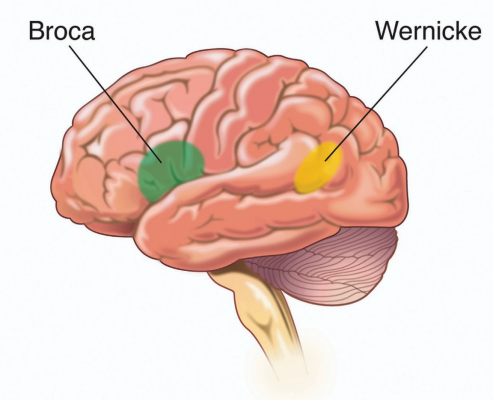

FIGURE 11-41. Diagram of the cerebral cortex showing Broca and Wernicke areas. (Reproduced with permission from USMLE-Rx.com.)

If the patient had nail-bed hemorrhages, nodules on her fingers and toes, and retinal hemorrhages, what diagnosis should be considered?

This constellation of symptoms suggests **infective endocarditis**, which is characterized by splinter hemorrhages, Osler nodes on the pads of the fingers and toes, and Roth spots on the retina. Infective endocarditis can lead to the release of thrombi from the valvular vegetations, resulting in embolic events that could cause an ischemic stroke. Ischemic strokes, however, appear as hypodense regions on CT, as opposed to hemorrhagic strokes, which are hyperdense relative to the brain parenchyma.

CASE 32

A mother brings a 14-month-old girl to the neurologist for evaluation of new-onset seizures and right-sided hemiparesis. The infant has a purple-red superficial skin lesion distributed on the right forehead and upper eyelid. The infant has also failed to meet developmental milestones for her age.

What is the most likely diagnosis?

Sturge-Weber syndrome is a rare neurocutaneous congenital disorder with unknown etiology. The disorder manifests vascular malformations of the skin (**port-wine stain**; see Figure 11-42) and leptomeninges (leptomeningeal angiomatosis).

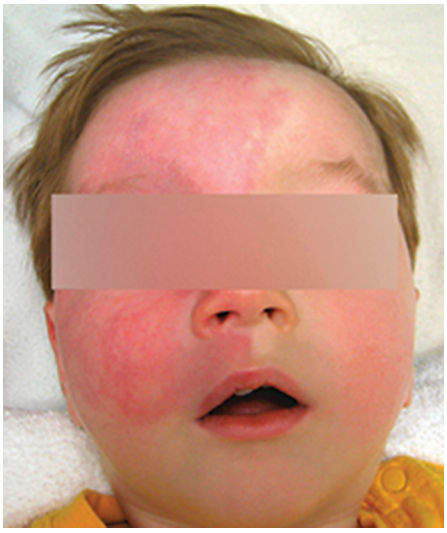

FIGURE 11-42. A child with a port-wine stain in the distribution of the first and second branch of the trigeminal nerve. (Reproduced with permission from USMLE-Rx.com.)

What are the genetics of this disorder?

Sturge-Weber syndrome results from somatic mutations in the *GNAQ* gene that occur during early embryonic development. It is not due to a germline mutation and is therefore not a heritable disorder.

What other tests or imaging tools can be used to confirm the diagnosis?

MRI is most useful for identifying a leptomeningeal angioma. Often, these tumors are ipsilateral to the port-wine stain. These lesions are responsible for the seizures, hemiparesis, and intellectual disability in Sturge-Weber syndrome. Leptomeningeal angiomas can result in cortical calcifications that appear as parallel opacities on x-rays, referred to as the "tram-track sign."

What ocular features may be present in this condition?

Many patients may also have **glaucoma** due to vascular malformations obstructing the flow of aqueous humor out of the anterior chamber of the eye. **Heterochromia** of the iris (different-colored irises), visual field defects, and vascular malformations of the choroid may also be present.

What is the treatment for this condition?

Treatment is aimed at alleviating symptoms. Port-wine stains may be treated with laser therapy. Seizures can be managed with anticonvulsants. Patients with seizures refractory to pharmacotherapy may undergo surgical resection of the lesion, sometimes requiring a hemispherectomy of the affected side.

CASE 33

A tall, thin 44-year-old woman with a history of hypertension presents to her physician with a severe headache. She says it is the most painful headache she has ever experienced. The headache began suddenly this morning while she was eating breakfast. Since then she has had two episodes of vomiting but denies abdominal pain or nausea. She denies any traumatic events. Cardiac examination reveals a midsystolic click with a late systolic murmur at the apex. CT scan of the head is shown in Figure 11-43.

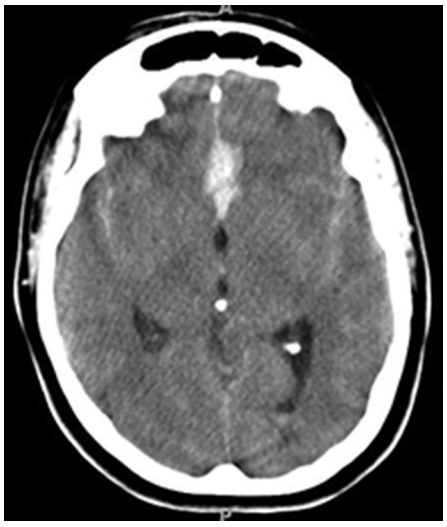

FIGURE 11-43. (Reproduced with permission from USMLE-Rx.com.)

What is the most likely diagnosis?

Subarachnoid hemorrhage. Figure 11-43 shows a hyperdense collection of blood in the subarachnoid space within the interhemispheric fissure. The classic presentation is a complaint of "the worst headache in my life" after a "thunderclap" sensation marking the onset of severe pain. Hypertension is the most common risk factor.

What are some common etiologies of this condition?

Most spontaneous subarachnoid hemorrhages occur as the result of the rupture of a **berry aneurysm** in the **circle of Willis**. Other causes are trauma or an arteriovenous malformation. The risk is increased by a history of hypertension. The most common location of a berry aneurysm is the anterior communicating artery, followed by the posterior communicating artery and then the middle cerebral artery.

Given this patient's symptoms, what is the pathophysiology of this condition?

The murmur on cardiac examination is characteristic of mitral valve prolapse, which is commonly seen in **Marfan syndrome**. Berry aneurysms have been associated with Marfan syndrome, Ehlers-Danlos syndrome, adult polycystic kidney disease, and coarctation of the aorta.

What are the typical findings from CT scan of the head and CSF analysis?

After a subarachnoid hemorrhage (SAH), CT scan of the head will show blood in the subarachnoid space if the scan is performed within 24 hours of the bleed. CSF analysis will show elevated RBC count. However, RBCs can also be found in the CSF sample if a blood vessel is broken by the needle during the lumbar puncture, called a traumatic tap. One way to distinguish SAH from a traumatic tap is to compare the RBC count in the first tube of collected CSF with subsequent tubes. In a traumatic tap the RBC count should diminish sequentially with each tube collected, while in SAH the RBC count will remain relatively constant between CSF samples. Another distinguishing feature of SAH is the presence of xanthochromia, a yellow supernatant caused by bilirubin release from the breakdown of hemoglobin, a process that occurs when RBCs are in the CSF for several hours. In a traumatic tap, there will have been insufficient time for hemoglobin breakdown, so xanthochromia will not be present.

What caused the patient to vomit?

Vomiting is a common sign of increased intracerebral pressure, which, in this patient, is secondary to the mass effect caused by the hemorrhage.

What is an important short-term sequela for patients with this condition?

Patients who have recently suffered a subarachnoid hemorrhage are prone to cerebral vasospasm, as a result of substances released from lysed RBCs irritating vessels in the subarachnoid space. If vasospasm occurs, most often several days after SAH, it can cause ischemia and infarction that may present with new neurologic deficits. Prophylaxis is typically achieved with nimodipine, a calcium channel blocker that improves outcomes in SAH. Other important complications of SAH are seizures and hydrocephalus. Hydrocephalus occurs as a result of blood contents obstructing CSF flow.

CASE 34

A 73-year-old man falls while climbing the stairs to his apartment. He temporarily loses consciousness and awakens with a mild headache. His relatives do not notice any problems until 3 days later, when they begin to see a change in his mental status. Typically a pleasant man, he starts to yell at his family members for no reason. He does not recognize people he knows well. He is brought to the ED where a CT scan of the head is obtained (see Figure 11-44).

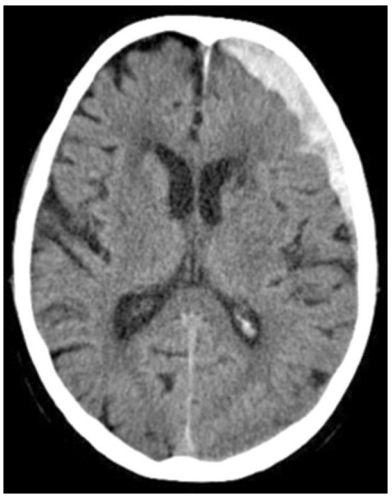

FIGURE 11-44. (Reproduced with permission from Rasmussen M, et al. *BMC Cardiovas Disord.* 2014;14:13.)

What is the most likely diagnosis?

The temporary loss of consciousness followed by gradual mental status change over the course of days or even weeks is the classic history of a subdural hematoma. The diagnosis is confirmed by CT scan, which shows a crescent-shaped area of hemorrhage that **crosses** cranial suture lines (Figure 11-44).

What is the source of bleeding in this type of injury?

Subdural hematomas result from head trauma that causes venous bleeding, most commonly from rupture of bridging veins within the dura, which then bleed into the space between the arachnoid and dura mater. The elderly and alcoholics are more prone to subdural hemorrhage due to cortical atrophy and subsequent increased tension on the bridging veins.

What explains the delayed onset of symptoms?

Venous bleeding results in a slowly expanding blood accumulation and gradual compression of the cerebrum. Symptoms result from the compression of cortical and subcortical structures and therefore are variably delayed depending on when specific intracranial areas are affected by the compression.

What is a CT scan likely to show if the patient experienced no loss of consciousness, followed shortly thereafter by mental status changes?

An immediate "lucid interval," or temporary conscious state, after a head trauma, followed by rapid decline in function is more consistent with an **epidural hematoma**. Unlike subdural hematomas, epidural hematomas are due to arterial bleeding and thus cause a dramatic decline in mental status after an initial period of intact function. The CT scan of an epidural hematoma (see Figure 11-45) shows a subosteal blood accumulation in the shape of a biconcave disk. It **does not** cross suture lines because the dura is tightly adhered to the skull bone at the suture lines.

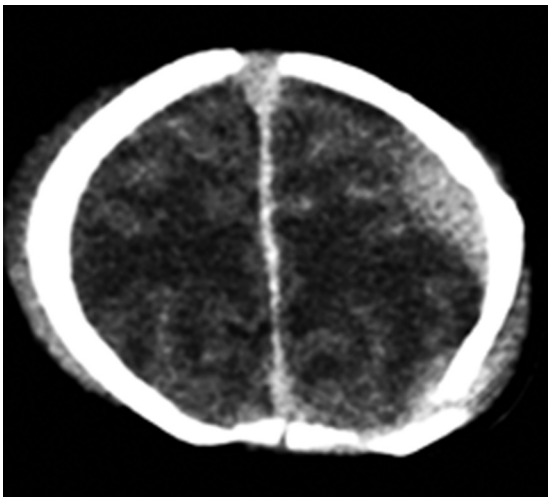

FIGURE 11-45. Epidural hematoma of the left parietal region. (Reproduced with permission from USMLE-Rx.com.)

What is the treatment for this condition?

Treatment for both acute subdural and epidural hematomas is decompression and evacuation of the blood via a craniotomy. If the lesion is small enough, conservative monitoring can be considered.

CASE 35

A 57-year-old obese, right-handed man with a history of atrial fibrillation and mitral valve repair is brought to the ED by a coworker, who noticed a sudden onset of slurred speech and right-hand clumsiness. The coworker denied seeing any seizure-like activity or loss of consciousness. The patient can converse appropriately and denies any recent head trauma. Physical examination reveals an irregularly irregular heartbeat and a left carotid bruit. Neurologic examination reveals grossly intact cranial nerves with the exception of mildly decreased facial sensation on the right. He has 4/5 muscle strength and diminished sensation in the right arm. CT scan of the head is negative for bleeding or mass lesion. The patient's symptoms resolve spontaneously within 1 hour of onset, and diffusion-weighted MRI is negative for signs of acute infarction.

What is the most likely diagnosis?

Transient ischemic attack (TIA). Classically, TIA has been defined as stroke-like symptoms that resolve within 24 hours. However, increasingly sensitive imaging techniques have helped refine the definition of TIA; it is now defined as focal neurologic symptoms due to ischemia with no evidence of infarction on radiologic or pathologic studies. Diffusion-weighted MRI is the most sensitive imaging method for detecting early infarction.

What is the most likely cause of this patient's condition?

This TIA is most likely caused by an **embolic stroke**, as the patient has several risk factors for emboli:

- Carotid stenosis, usually from atherosclerosis, which can be a source of emboli
- History of atrial fibrillation, which can predispose to embolus formation
- Mitral valve repair, which can harbor vegetations that may embolize

What findings on CT scan of the head suggest the presence of cerebral edema?

Signs of cerebral edema include loss of the gray matter–white matter junction; loss of prominence of sulci; and evidence of a mass effect, such as midline shift, decreased size of the lateral ventricle on the affected side, and uncal herniation.

How are motor and sensory functions represented on the cerebral cortex?

Motor and sensory functions are predominantly represented by the primary motor cortex and primary sensory cortex, respectively. The primary motor cortex is located along the posterior aspect of the frontal lobe. This region is called the precentral gyrus because it lies just anterior to the central sulcus, the fold in the cerebral cortex that separates the frontal and parietal lobes. Just posterior to the central sulcus, at the anterior-most aspect of the parietal lobe, is the postcentral gyrus, which is where the primary sensory cortex is found.

The distribution of motor and sensory function across the primary motor and sensory cortices is represented by the homunculus (see Figure 11-46). The medial-most portions of the motor and sensory cortices supply the inferior portions of the body (ie, the lower extremity). The upper extremity and face are represented progressively more laterally along the cortex.

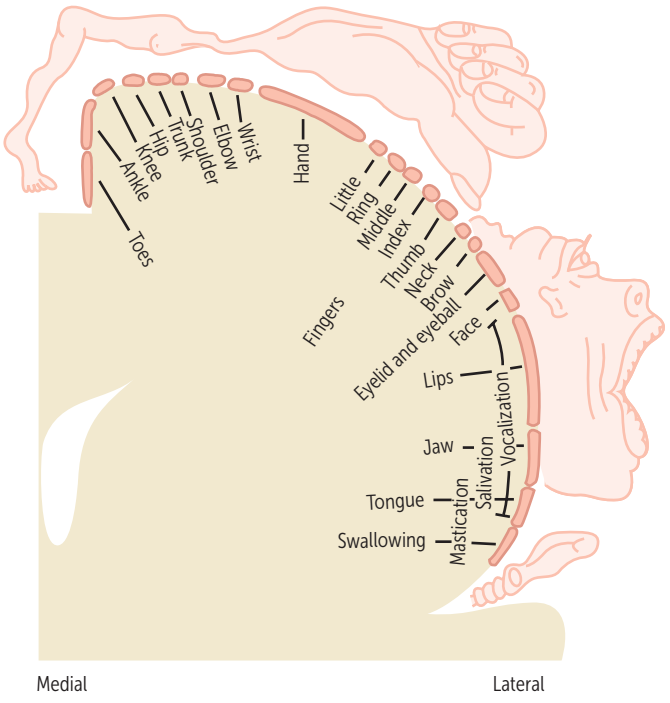

FIGURE 11-46. The cortical homunculus depicts the sensory and visual representation of the human body onto the cerebral cortex. (Reproduced with permission from USMLE-Rx.com.)

What is the vascular distribution of the three major vessels supplying the cerebral cortex, and what are the clinical features of stroke due to occlusions of each of the three vessels?

The anterior cerebral, middle cerebral, and posterior cerebral arteries are the three major vessels supplying the cortex. The anterior cerebral artery branches off the internal carotid artery and supplies the medial portion of motor cortex, the sensory cortex, and the majority of the frontal lobe. A stroke of this artery will therefore result in lower extremity deficits. The middle cerebral artery also stems from the internal carotid artery and supplies the lateral portion of the motor cortex, temporal lobe, and the somatosensory cortex. A stroke of this artery will result in deficits of the face and upper extremity, as well as aphasia. The posterior cerebral artery stems from the basilar artery and supplies the visual cortex as well as a large portion of the thalamus. A stroke in the posterior artery typically causes visual deficits (see Figure 11-47).

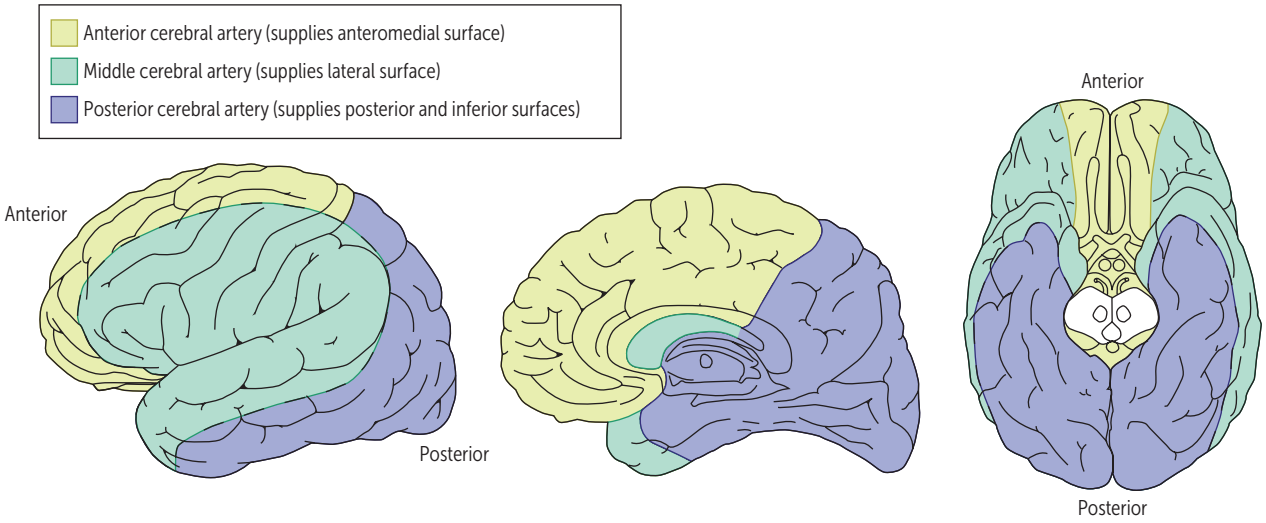

FIGURE 11-47. Cerebral vascular distribution. The arterial distribution of the three main vessels supplying the cortex. (Reproduced with permission from USMLE-Rx.com.)

CASE 36

A 61-year-old man with a history of chronic diarrhea presents to the ED after fainting. He reports that he suddenly collapsed after getting up to go to the bathroom. He did not note any prodromal symptoms or vertigo. The patient has spent the past few days recovering from the flu, during which time he has had a poor appetite. He denies a history of seizures and has no known cardiac or valvular abnormalities. On admission, his blood pressure is 115/80 mm Hg supine and 90/70 mm Hg standing. His pulse is 88/min supine and 106/min standing. His respiratory rate is 20/min.

What is the most likely diagnosis, and how is it distinguished from other causes of transient loss of consciousness?

This patient has most likely experienced an episode of syncope, which is a transient loss of consciousness and postural tone due to hypoperfusion of the brain. Syncope is most commonly confused with seizure. Features suggestive of syncope are a prodrome of lightheadedness, associated symptoms of diaphoresis and pallor with little motor activity, and a rapid recovery. In contrast, seizures may be characterized by auras of olfactory hallucinations or déjà vu, associated symptoms of tongue biting and convulsions, and a prolonged postictal state of confusion and lethargy.

What are the most common causes of this condition?

The primary differential for syncope is divided into cardiogenic and noncardiogenic causes. Cardiogenic causes include arrhythmias, aortic stenosis, tamponade, and aortic dissection. Noncardiogenic causes include orthostatic hypotension and vasovagal, or neurogenic, syncope, which is a reflex drop in blood pressure caused by activation of the vagus nerve.

What is the most likely cause of this condition in this patient?

The most likely cause of syncope in this patient is orthostatic hypotension. Orthostatic hypotension is defined as a 20 mm Hg drop in systolic blood pressure or a 10 mm Hg drop in diastolic blood pressure from supine to standing position. When it is due to volume depletion, the postural hypotension is often accompanied by an increase in pulse rate $>$ 20/min. Orthostatic hypotension in this patient is secondary to poor food and water intake and chronic diarrhea leading to volume depletion.

What signs of volume depletion are evident on physical examination?

Orthostatic hypotension, tachycardia, tachypnea, dry mucous membranes, and decreased skin turgor are signs of volume depletion evident on physical examination.

What common chronic disease can be associated with this condition?

Late-stage diabetes mellitus can be associated with orthostatic hypotension. This is due to autonomic neuropathy and is one of the microvascular complications of diabetes mellitus. The autonomic nervous system dysfunction causes a diminished compensatory response to decreased blood pressure.

How does the vascular system normally compensate for the decrease in venous return following an orthostatic change?

Mechanoreceptors in the heart react to the decrease in blood pressure and compensate by increasing sympathetic tone, decreasing vagal tone and causing release of antidiuretic hormone. This results in increased peripheral vascular resistance (increasing venous return) and an increase in cardiac output, thereby minimizing the drop in blood pressure.

CASE 37

A 6-year-old boy with a history of intellectual disability and seizures is brought by his mother to the pediatrician for an evaluation of skin lesions. The pediatrician notes firm, discrete, brown papules in the nasolabial folds and on the cheeks. Further examination reveals an elliptical, hypopigmented macule on the patient's abdomen and a pink-brown plaque with a cobblestone appearance on his lower back. Funduscopic examination reveals a flat, translucent lesion on the left retina.

What is the most likely diagnosis?

Tuberous sclerosis, an autosomal dominant syndrome manifested by numerous benign neoplasms and hamartomas of the brain, skin, heart, and kidney. Hamartomas are benign masses composed of cells that are normally found in the area of the body where the mass is located but are growing in a disorganized manner. Tuberous sclerosis demonstrates complete genetic penetrance but highly variable expressivity. Most cases arise from a sporadic mutation, but offspring of an affected individual will inherit the mutation in an autosomal dominant pattern.

What dermatologic and ophthalmic abnormalities are common in this condition?

- **Ash-leaf spots**, which are elliptical hypopigmented macules, may develop. In fair-skinned individuals, they can be visualized with a Wood lamp (see Figure 11-48).
- **Adenoma sebaceum**, which are small angiofibromas typically distributed in a malar fashion on the face, are also seen (see Figure 11-49).
- **Shagreen patches**, which are firm, reddish, raised lesions with a leathery texture, are commonly found on the lumbar area of the back.
- **Retinal hamartomas**, which appear as gray or yellow lesions on funduscopic examination, may also be present.

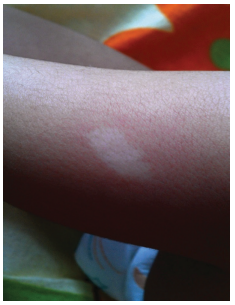

FIGURE 11-48. Hypopigmented macules, or ash-leaf spots. (Reproduced with permission from Tonekaboni SH, et al. Clinical and para clinical manifestations of tuberous sclerosis: A cross sectional study on 81 pediatric patients. *Iran J Child Neurol*. 2012;6(3):25-31.)

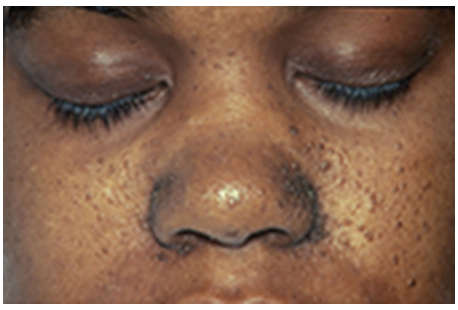

FIGURE 11-49. Small angiofibromas in a malar pattern known as adenoma sebaceum. (Reproduced courtesy of Dr. James Heilman.)

What are the cardiac and renal manifestations of the condition?

Patients classically present with **cardiac rhabdomyomas** that often regress spontaneously in the first few years of life. Renal manifestations include bilateral **angiomyolipomas** and cysts.

What brain lesions are typically seen in people with this condition?

Cortical tubers and subependymal nodules are common, and both are considered **hamartomas**. Subependymal nodules can undergo malignant transformation to subependymal giant cell **astrocytomas**. Consequences of cortical hamartomas are seizures and intellectual disability. Seizures, especially infantile spasms, are the most common presentation of tuberous sclerosis.

What are two other neurocutaneous disorders with autosomal dominant inheritance?

- **Neurofibromatosis I** is characterized by café-au-lait spots, neurofibromas on the skin, Lisch nodules, and optic gliomas. This condition is associated with astrocytomas and pheochromocytomas.
- **Von Hippel–Lindau syndrome** is characterized by hemangiomas of the skin and retina, hemangioblastomas in the central nervous system, and bilateral renal cell carcinoma.

CASE 38

A 14-year-old boy is brought to his family physician complaining of weakness of his left hand and wrist for 2 days. He is a varsity tennis player and has been having difficulty playing and complains of a burning sensation in the fourth and fifth fingers of his left hand. He says he woke up 2 days ago with the change in sensation and strength after falling asleep with his left arm over the side of his bed. Physical examination reveals no evidence of fracture, but there is significant edema of his elbow and weakness of the medial digits of the left hand.

What is the most likely diagnosis?

Ulnar neuropathy due to nerve compression. Ulnar nerve injuries often present with acute onset of numbness/tingling in the fourth and fifth digits and weakness of wrist and fourth/fifth finger flexion.

What is the characteristic hand sign associated with this condition?

In severe cases, ulnar injury can present as a partial claw-like deformity known as the "ulnar claw" where the metacarpophalangeal (MCP) joint of the fourth and fifth fingers is in extension while the distal interphalangeal (DIP) and proximal interphalangeal (PIP) joints are in flexion (see Figure 11-50). It occurs when the hand is at rest and when attempting to extend the fingers. This sign is mainly the result of loss of the third and fourth lumbrical muscles, which are normally responsible for flexion at the MCP joint and extension of the DIP and PIP joints. This sign must be distinguished from the "Pope's blessing" that occurs in patients with median nerve injuries when attempting to make a fist. It is due to the inability to flex the second and third fingers.

FIGURE 11-50. Ulnar claw. (Reproduced with permission from USMLE-Rx.com. Photo contributor: Dr. Lauren Shapiro.)

What are the most common causes of this condition?

Injuries that cause ulnar neuropathy include direct trauma or prolonged pressure on the nerve. Symptoms occur when there is destruction of the myelin sheath or damage to axons sufficient to hinder nerve conduction. The most common site of ulnar nerve injury is at the elbow because the nerve lies superficially in the groove between the medial epicondyle and the olecranon. A blow to the medial epicondyle often hits the nerve, causing tingling in the territory of the ulnar nerve and the so-called "funny bone" sensation.

Another important but less common site of injury is the wrist, where the ulnar nerve passes between the hook of hamate and the pisiform bone, a space called Guyon canal. Injury here is common in cyclists due to compression of the canal against the bicycle handlebar. Fracture of the hook of hamate can also cause an ulnar neuropathy.

What is the primary diagnosis to consider in the differential diagnosis?

Medial epicondylitis, or "golfer's elbow," is an overuse injury affecting the muscle origins at the medial epicondyle, often due to repetitive swinging motions at the elbow joint. It causes medial elbow pain and pain with wrist flexion. It can result in irritation of the ulnar nerve. In contrast, lateral epicondylitis, or "tennis elbow," presents with lateral elbow pain and pain with wrist extension.

What treatment is used to reduce the swelling at the elbow?

Anti-inflammatory agents such as corticosteroids and nonsteroidal anti-inflammatory drugs are used to treat ulnar neuropathy due to nerve compression and medial epicondylitis. Patients can also benefit from braces or casts that reduce movement at the elbow joint to decrease chronic inflammation.

CASE 39

A 72-year-old man with a history of coronary artery disease, diabetes, and hypertension is brought to the primary care physician by his wife. She began noticing lapses in his memory around a year ago. Three months later, he had an episode of dizziness, after which she noticed changes in his personality where he began making inappropriate comments in public, something she says he would never have done in the past. One month ago, he had a fall and has since then had difficulty talking. MRI scan of the head is shown in Figure 11-51.

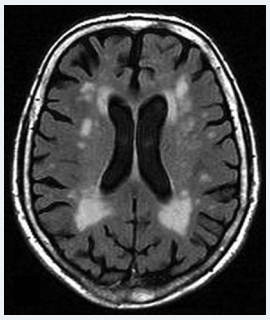

FIGURE 11-51. (Reproduced with permission from Jellinger KA. *Front Aging Neurosci.* 2013;5:17.)

What is the most likely diagnosis?

Multi-infarct dementia, also known as vascular dementia. Vascular dementia is the second most common cause of dementia after Alzheimer disease. It can be broadly categorized as either large vessel or small vessel in origin. Large-vessel disease results from recurrent infarctions or hemorrhage in the vessels that supply the cortical territories and is usually due to chronic atherosclerotic disease. It is characterized by a stepwise decline in cognitive, executive, and motor or language function. By contrast, small-vessel disease results from recurrent infarctions in subcortical and white-matter regions of the brain and is usually due to poorly controlled hypertension. The stepwise decline in these patients can be subtle and may lack major defining events.

What are the risk factors for this condition?

History of stroke, advanced age, hypertension, vascular disease, diabetes, smoking, and dyslipidemia are all risk factors for vascular dementia. Treatment is aimed at any of these underlying causes. Antiplatelet therapy may be used to prevent further cerebrovascular accidents.

What imaging tools can be used to confirm the diagnosis?

MRI is the best imaging choice to diagnose vascular dementia. The T2-weighted MRI shown in Figure 11-51 of a patient with diffuse white-matter disease demonstrates numerous periventricular and corona radiata lesions.

What are the causes of dementia?

The etiologies of dementia can be broadly categorized as reversible or irreversible. The irreversible causes constitute the majority of cases; however, reversible causes should be sought out since treating them can significantly improve the patient's quality of life (see Figure 11-52).

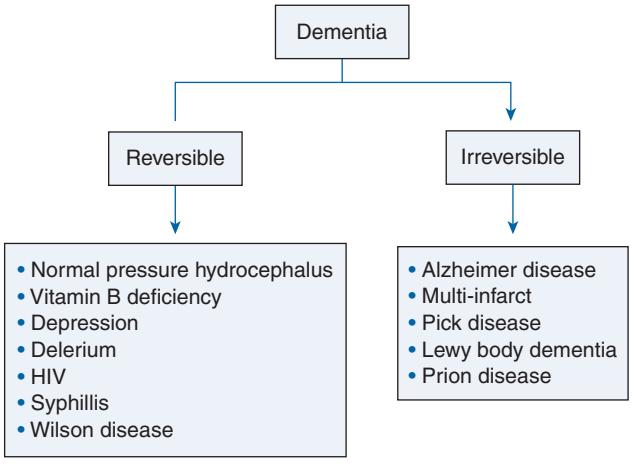

FIGURE 11-52. Causes of dementia categorized by potentially reversible and irreversible etiologies.

What characteristics differentiate delirium from dementia?

Delirium is characterized by an acute, rapid decrease in attention span with a waxing and waning level of consciousness. The patient may be difficult to arouse and classically has changes in mental status with visual hallucinations. The EEG in delirium shows nonspecific slowing. By contrast, dementia is more gradual in onset with **no changes in level of consciousness**. The EEG is usually normal in dementia.

CASE 40

A 14-year-old boy is sent to the ED by the nurse at his summer camp after he experienced a 1-minute seizure earlier that day. The boy has no previous history of seizure activity. In the ED, the boy complains of lethargy, vomiting, myalgia, severe headache, and neck stiffness. On further questioning, he reveals that he has had many of these symptoms for the past few days. A lumbar puncture is performed, and a Gram stain of the CSF is negative. CSF analysis gives the following results: WBC 435 with predominance of mononuclear cells, glucose 53 mg/dL, protein 98 mg/dL.

What is the most likely diagnosis?

This presentation likely represents a viral meningitis.

What organisms are most likely to cause this condition?

The most common causative organism of viral meningitis is **echovirus**, which is part of the Enterovirus subgroup of the Picornaviridae family. Enterovirus outbreaks tend to occur during the summer and are often associated with summer camps. Other causative organisms include coxsackievirus (another enterovirus), adenovirus, HIV, cytomegalovirus, Epstein-Barr virus, and herpes simplex virus.

Detecting enteroviruses with polymerase chain reaction (PCR) assay requires modifying the standard PCR strategy. What type of enzyme is essential to this modification?

Reverse transcriptase is essential in this modified PCR. Because enteroviruses are RNA viruses, detection proceeds with reverse transcription PCR (RT-PCR). Normal transcription is the synthesis of RNA from DNA; this process is the **reverse**. Viral RNA is reverse transcribed into the complementary DNA (cDNA), and that cDNA can then be amplified using the standard PCR DNA amplification strategy.

What changes in this patient's CSF glucose and protein levels are most likely to be seen?

As with most cases of viral meningitis, CSF glucose concentration is typically normal (two-thirds of plasma glucose level) and CSF protein concentration is typically normal to slightly increased. CSF cell count reveals a lymphocytosis. This is in contrast to CSF findings in bacterial meningitis, in which protein is increased, glucose is decreased, and CSF cell count reveals a predominance of polymorphonuclear leukocytes. In a traumatic tap, WBCs may be introduced to the CSF via blood contamination, resulting in a falsely elevated WBC count. In normal serum, the ratio of RBC to WBC is roughly 500 to 1. Therefore, in a traumatic tap, the WBC count can be corrected for by subtracting 1 from the number of WBCs for every 500 RBCs in the specimen.

Some viruses capable of causing this patient's symptoms are sensitive to acyclovir. What is the mechanism of action of this drug?

Acyclovir is a nucleoside analog that is converted to acyclovir monophosphate by the viral enzyme thymidine kinase. Subsequent phosphorylations by host enzymes then form acyclovir triphosphate, which is incorporated into viral DNA by DNA polymerase. However, because acyclovir lacks a 3′ hydroxyl group, no additional nucleosides can be attached to the growing DNA chain, resulting in premature chain termination. Acyclovir is active against most of the herpesviruses, with the exception of cytomegalovirus, which does not produce the necessary thymidine kinase needed for drug activation. RNA viruses, like the picornaviruses, do not contain DNA polymerase, and therefore they are not sensitive to acyclovir.

CASE 41

A 26-year-old man is evaluated by a neurologist for recurrent headaches and changes in vision. A careful ophthalmologic examination reveals multiple groups of dilated blood vessels on both retinas, and an MRI of the brain demonstrates three hemangioblastomas of the cerebellum.

What is the most likely diagnosis?

Von Hippel–Lindau (VHL) disease is characterized by diffuse hemangioma formation, commonly in the retina and central nervous system, as well as by an increased incidence of renal cell carcinoma (RCC).

What is the pattern of inheritance for this condition?

VHL disease is inherited in an autosomal dominant fashion in 75% of cases. It is associated with deletion of the *VHL* gene, a tumor suppressor gene on the short arm of chromosome 3. Approximately 25% of cases occur sporadically. In the United States, the incidence of VHL disease is approximately 1:36,000.

What is the pathophysiology underlying the formation of hemangiomas in this condition?

One of the main functions of VHL protein is to regulate the activity of a transcription factor known as hypoxia-induced factor 1a (HIF1a). HIF1a activation induces the transcription of vascular endothelial growth factor (VEGF), which is responsible for the process of neovascularization. As its name suggests, HIF1a activation occurs under hypoxic conditions to facilitate the growth of new blood vessels in response to low oxygen levels. In the presence of oxygen, HIF1a is hydroxylated, which allows for binding of HIF1a to the VHL protein (see Figure 11-53). The binding of VHL facilitates degradation of HIF1a in the presence of oxygen to restrict unnecessary neovascularization. However, the mutations in VHL disease cause HIF1a to be constitutively active. This causes the overproduction of VEGF and the formation of hemangiomas.

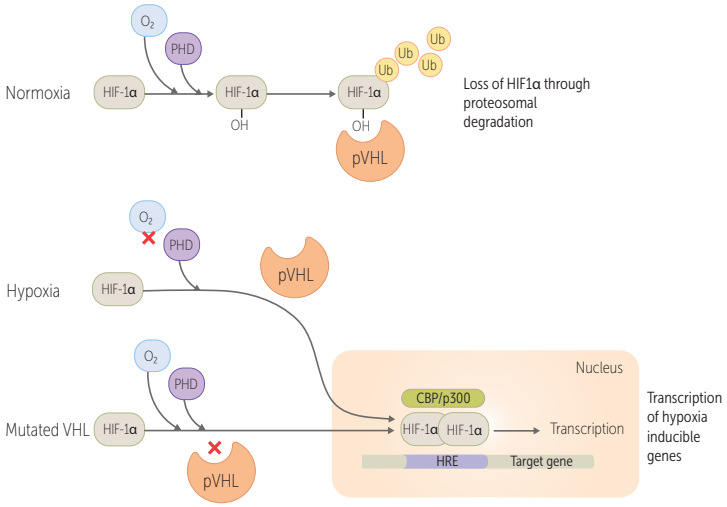

FIGURE 11-53. Pathway for VHL regulation of HIF1a. (Reproduced with permission from USMLE-Rx.com.)

What is the leading cause of death in patients with this condition?

RCC, predominantly the clear cell type, is the leading cause of death in patients with VHL; some case series report prevalence rates as high as 40%–75% at autopsy. In patients with VHL, RCC develops from malignant degeneration of renal cysts and is usually bilateral. The average age for development of RCC in patients with VHL is 44 years. Because of the high incidence of renal cysts and RCC in patients with VHL, periodic imaging of the kidneys is indicated in patients and at-risk relatives.

What other tumors or lesions are associated with this condition?

Patients with VHL disease are at risk for developing multiple cysts in the liver, epididymis, pancreas, and kidneys. Pheochromocytomas, rare pancreatic carcinomas, and endolymphatic sac tumors are also within the spectrum of VHL. Hemangioblastomas are typically in the cerebellum or medulla but may also occur in the spinal cord. In a significant number of patients, the hemangioblastomas release erythropoietin; these patients can present with polycythemia. Hemangiomas of the skin, mucous membranes, and retina are common.

How is this disease managed, and what pharmacologic treatments attempt to target the pathogenesis of this disease?

The management of VHL disease primarily involves surveillance to detect early tumors, followed by surgical removal of these lesions. Several drugs have been designed to specifically inhibit overactivity of VEGF. Bevacizumab and ranibizumab are monoclonal antibodies against VEGF, while sunitinib is a small-molecule receptor tyrosine kinase inhibitor that inhibits the VEGF receptor. While these drugs have had little utility in treating VHL disease, they have been successfully used in the treatment of a number of cancers, especially renal cell carcinoma. In addition, they have been used for the treatment of other diseases that occur due to excessive growth of vasculature, such as diabetic retinopathy and wet age-related macular degeneration.

CASE 42

A 55-year-old man is brought to the ED by a friend who has noticed that the patient has had memory lapses and difficulty with walking and balance. The patient has a 26-year history of excessive alcohol use. On further questioning, the patient is unable to provide a consistent history. When asked about his location, the patient states he is at home. Physical examination reveals nystagmus in the left eye and an ataxic gait.

What is the most likely diagnosis?

This patient has Wernicke encephalopathy, which presents as the triad of **nystagmus**, **ataxia**, and **confusion**. This may progress to Korsakoff syndrome, which consists of irreversible memory loss, confabulation, and personality changes. Excessive alcohol abuse is the primary culprit of Wernicke-Korsakoff syndrome.

What type of memory deficit is likely to be seen in this condition?

Patients with Wernicke-Korsakoff syndrome usually suffer from **anterograde amnesia**, which is characterized by an inability to form new memories but a general preservation of long-term memories. This is in contrast to **retrograde amnesia**, in which only long-term memories that precede the precipitating event are lost.

What is the pathophysiology of this condition?

This disease is seen in alcoholics with thiamine deficiency due to poor nutrition and absorption. Thiamine deficiency results in degeneration in a symmetric pattern in multiple cerebral areas, including the cerebellum, brain stem, and bilateral mammillary bodies (see Figure 11-54; red circles highlight abnormal enhancement of the mammillary bodies).

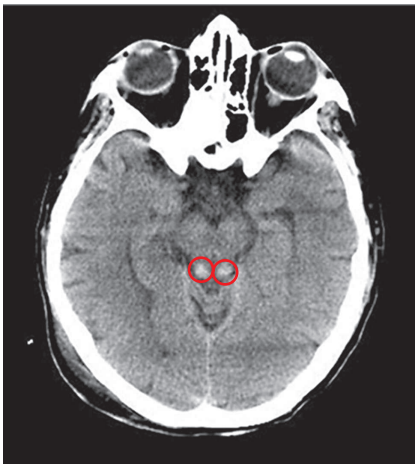

FIGURE 11-54. MRI of mammillary bodies in Wernicke encephalopathy. (Reproduced with permission from Busani S, et al. Wernicke's encephalopathy in a malnourished surgical patient: a difficult diagnosis. *BMC Res Notes*. 2014;7:718.)

For which essential biochemical pathways is thiamine required?

Thiamine (vitamin B_1) is needed in glycolysis as a cofactor for pyruvate dehydrogenase; in the tricarboxylic acid cycle as a cofactor for α-ketoglutarate dehydrogenase; in the hexose monophosphate shunt as a cofactor for transketolase; and in the breakdown of amino acids as a cofactor for branched-chain amino acid dehydrogenase.

How is thiamine deficiency most reliably detected in the laboratory?

While most laboratories can now directly measure blood thiamine concentration, thiamine deficiency in Wernicke-Korsakoff syndrome was classically assessed by measuring the activity of erythrocyte transketolase before and after the addition of thiamine, which is a cofactor for the enzyme. A low erythrocyte transketolase activity that increases with the addition of thiamine is diagnostic for thiamine deficiency.

What complication must be prevented when treating an alcoholic patient who is severely hypoglycemic and confabulating?

Glucose repletion in an alcoholic patient must always be accompanied by thiamine administration. Since thiamine is a cofactor for the enzyme pyruvate dehydrogenase in glycolysis, administration of glucose further depletes thiamine stores. This can lead to worsening of the Wernicke-Korsakoff syndrome.

Besides transketolase and pyruvate dehydrogenase, what other enzymes require thiamine?

Thiamine is also a cofactor for α-ketoglutarate dehydrogenase, an enzyme in the Krebs cycle, and the branched-chain α-ketoacid dehydrogenase complex.

What other disease can result from thiamine deficiency?

Beriberi is also caused by a deficiency of thiamine secondary to malnutrition. There are two forms of beriberi: dry and wet. Dry beriberi is characterized by peripheral neuropathy and symmetrical muscle wasting due to axonal loss. Wet beriberi is characterized by edema and high-output cardiac failure due to dilated cardiomyopathy.

12
Psychiatry

CASE 1

A mother brings her 8-year-old son to the pediatrician because she is concerned about his behavior. She states that her son is unable to finish activities at home and is easily distracted. He is unable to sit still long enough to complete his homework and is constantly "bouncing off the walls." The mother has received complaints from school about her son talking back to teachers and interacting poorly with peers. He may have to repeat the third grade.

What is the most likely diagnosis?

Attention-deficit hyperactivity disorder (ADHD). ADHD may affect up to 8% of U.S. school-age children. Males are more often affected, as are North American children.

What are the typical manifestations of this condition?

ADHD can be characterized by hyperactivity, impulsivity, and/or inattention that lead to significant academic, social, or occupational impairment. **Hyperactivity** manifests as fidgetiness and an inability to remain seated or play quietly. It is more commonly seen in boys. **Impulsivity** may present as talking at inappropriate moments, constantly interrupting, or being unable to wait for one's turn. **Inattention** is characterized by forgetfulness, poor concentration, an inability to finish tasks, and a lack of attention to detail. It is more commonly seen in girls.

What are the subtypes of this condition, and what are the diagnostic criteria for each of them?

Symptoms must occur often, present in more than one setting, persist for at least 6 months, manifest before age 12, and, for children, be excessive relative to level of development.

- **Predominantly inattentive:**
  - For children under age 17: 6+ symptoms of inattention
  - For patients age 17+: 5+ symptoms of inattention
- **Predominantly hyperactive-impulsive:**
  - For children under age 17: 6+ symptoms of hyperactivity and impulsivity
  - For patients age 17+: 5+ symptoms of hyperactivity and impulsivity
- **Combined:**
  - For children under age 17: 6+ symptoms of inattention and 6+ symptoms of hyperactivity and impulsivity
  - For patients age 17+: 5+ symptoms of inattention and 5+ symptoms of hyperactivity and impulsivity

What are the known risk factors for this condition?

Pregnant women who smoke or use illicit drugs are at increased risk of having children with ADHD. Genetics also plays an important role, as one in four children with ADHD has at least one relative with the condition.

What is the treatment for this condition?

Treatment includes behavioral intervention before the age of 6, pharmacologic therapy (the preferred option at age 6+), or both. It may seem counterintuitive, but stimulants are effective by increasing the patient's ability to attend to tasks. Stimulants, such as methylphenidate and dextroamphetamine, act by increasing catecholamine release.

What is the natural course of this condition?

Many patients with ADHD find that they outgrow it during adolescence. In approximately one-third of patients, however, the disorder continues into adulthood; these patients benefit from pharmacotherapy with stimulants. Adverse effects of stimulants include weight loss, anxiety, loss of appetite, and insomnia. Children may experience reduction in adult height.

CASE 2

A 22-year-old woman presents to the clinic with an 8-day history of insomnia and boundless energy. Her father is concerned because she has been talking rapidly and loudly. The patient has been going on shopping sprees, acting in an uncharacteristically seductive manner, and drawing attention to herself by falsely claiming to be a pop star. She denies substance abuse, and her urine toxicology screen is negative.

This patient displays symptoms of what category of psychiatric disorders?

This patient's symptoms are within the spectrum of mood disorders; specifically, she manifests symptoms of a manic episode of bipolar disorder. Other disorders in this class include major depressive disorder and persistent depressive disorder (formerly known as dysthymic disorder).

What signs and symptoms are commonly associated with this disorder?

Bipolar disorder is characterized by periods of major depression alternating with mania or hypomania. Symptoms of mania may include:

- Increased goal-directed activity or goalless psychomotor agitation
- Decreased need for sleep
- Elevated, expansive, or irritable mood
- Pressured speech
- Flight of ideas or subjective experience of racing thoughts
- Distractibility
- Excessive involvement in pleasurable activities that may have unwanted consequences (eg, shopping, gambling, or sex)

How is this disorder classified into its different forms?

As per the *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition *(DSM-5)*, three or more of the above symptoms must persist for **at least 1 week** to be classified as a manic episode; if the patient's mood is irritable as opposed to expansive, four or more of these symptoms must persist for at least a week. In addition, the symptoms must be severe enough to cause impairment in daily functioning, to necessitate hospitalization for safety, or to include psychotic features. In contrast, **hypomanic episodes** are milder (but still include three or more manic symptoms or four or more if the mood is merely irritable), **do not cause gross functional impairment**, and last at least four consecutive days for most of the day.

- **Bipolar I**: Distinct manic and/or depressive syndromes. A manic episode like our patient's, in the absence of substance abuse or a general medical condition, is sufficient for this diagnosis to be made.
- **Bipolar II**: Distinct hypomanic and depressive syndromes.
- **Mixed**: Both manic and depressive symptoms concurrently over a period of time (often described as dysphoric mania or agitated depression).
- **Cyclothymic**: Both hypomania and mild, non-major depression (dysthymia). In essence, a very mild and very uncommon form of bipolar disorder.

Important: the diagnosis of bipolar disorder in any of its forms cannot be made if the disorder can be attributed to substance use or to a general medical condition.

What are the treatments for this disorder?

The underlying disorder should be addressed with mood stabilizers (lithium, valproate, or carbamazepine). Mania usually also needs an antipsychotic agent (olanzapine, haloperidol, or risperidone) to return to baseline mood. Hospitalization may be necessary to ensure patient safety.

Which treatments can be given during pregnancy and which should not?

Treatment of bipolar disorder during pregnancy requires recognition that there are significant risks of not treating; periods of severe depression or mania can be damaging to the developing fetus. There is some evidence that lamotrigine is relatively safe as a mood stabilizer, and lurasidone as an antipsychotic during pregnancy.

- Lithium should not be given to pregnant bipolar patients. It classically causes Ebstein anomaly, a defect of the right ventricle in which the septal and posterior leaflets of the tricuspid valve are apically displaced.
- Carbamazepine is another mood stabilizer that should not be given in pregnancy. It is known to increase the risk of neural tube defects and vitamin K deficiency in the fetus.
- Valproic acid is yet another teratogen to be avoided in pregnancy; it can cause neural tube defects.
- If all else fails, ECT can be used over the short term for depressive or manic episodes.

CASE 3

A 51-year-old woman presents to her primary care physician because she is anxious about everything. She is unable to identify a precipitating event or a particular concern. She worries about her family, health, and finances. She has little respite and is frequently irritable, tired, and unable to concentrate. She has always been a worrier, but the symptoms have become so intense in the past 6 months that she thinks she may have to stop working.

What is the most likely diagnosis?

Generalized anxiety disorder (GAD).

What signs and symptoms are commonly associated with this condition?

The *DSM-5* defines the major diagnostic criteria for GAD as excessive and uncontrollable anxiety occurring more days than not for **at least 6 months**. In addition, the anxiety is not the result of substance abuse and causes clinically significant impairment in social, occupational, or other areas of function. GAD may also be associated with the following symptoms:

- Difficulty concentrating
- Fatigue
- Insomnia
- Irritability
- Restlessness

What other conditions should be considered in the differential diagnosis?

Normal worry/anxiety and adjustment disorder should also be considered. Unlike individuals with normal anxiety, patients with GAD have evidence of social dysfunction secondary to the disorder. Adjustment disorder is characterized by emotional symptoms within 3 months of the onset of an identifiable stressor (eg, divorce or loss of a job) and lasts $<$ 6 months. The symptoms are excessive and impair the patient's functioning. In contrast, symptoms in GAD persist for 6$+$ months.

If there were an identifiable precipitating event (traumatic incident), post-traumatic stress disorder (PTSD) would be among the differential diagnoses. Symptoms would last for at least 1 month and would interfere with relationships or work. They would include reliving the event, avoiding thoughts related to it, and being easily startled or on edge. Cognition and mood disturbances, such as loss of interest in previously enjoyable activities, would also be seen.

What are the treatments for this condition?

- Antidepressants (SSRIs)
- Buspirone (a serotonin receptor partial agonist)
- Benzodiazepines (fast-acting sedatives) **for short-term use**
- Cognitive-behavioral therapy

What is the danger of using benzodiazepines to treat this condition?

While benzodiazepines show beneficial effects in the short term, they must be used with caution and are not recommended for long-term use, as they are associated with the development of tolerance, physical dependence, addiction, and withdrawal. Benzodiazepines should not be mixed with alcohol or taken with opioids; these combinations can cause significant respiratory depression.

CASE 4

A 37-year-old pianist visits her physician because of difficulty sleeping over the past 3 weeks. She wakes up early in the morning, well before the usual time, and cannot get back to sleep. She says she does not enjoy playing the piano as much as she used to and finds it hard to concentrate when she tries to play. She has noticed a decrease in appetite, and she has lost 4.5 kg (10 lb) in the past month. Upon questioning, she reveals she had a similar episode about 1 year ago.

What is the most likely diagnosis?

Major depressive disorder.

What symptoms are commonly associated with this condition?

The diagnosis of major depressive disorder requires two or more episodes of five of the following symptoms, present for at least 2 weeks: **S**leep disturbances, decreased **I**nterest, **G**uilt, decreased **E**nergy, decreased **C**oncentration, change in **A**ppetite (usually decreased), **P**sychomotor retardation, and **S**uicidal ideations (mnemonic: **SIG E CAPS**) in addition to depressed mood. This patient cannot be diagnosed until additional symptoms are determined.

What other conditions can present with similar symptoms?

Bereavement can present with depressive symptoms within 1 year of the loss of a loved one, but symptoms are related to that loss. Grief is characterized by shock, denial, guilt, and somatic symptoms. Depressive symptoms can also suggest **dysthymia**, a milder form of depression with less intense symptoms that lasts at least 2 years. **Adjustment disorder** with depressed mood also presents as a milder form of depression, but symptoms are usually in response to a significant psychological stressor (eg, marital or financial problems) and usually last less than 6 months.

What is the epidemiology of this condition?

Women are diagnosed with major depression at approximately twice the rate of men. Studies show that living in urban areas, being of lower socioeconomic status, and being married (for women only) are independent risk factors for major depression.

What neurotransmitter disturbances are common in this condition?

Patients with major depressive disorder commonly have decreased levels of serotonin and norepinephrine. Dopamine may also be decreased in major depression.

What are the treatments for this condition?

Psychotherapy, antidepressants (including selective serotonin reuptake inhibitors [SSRIs], monoamine oxidase inhibitors [MAOIs], and tricyclic antidepressants [TCAs]), or both may be appropriate. Trazodone is a unique antidepressant that can cause priapism. Bupropion is another unique antidepressant; it lowers the seizure threshold and is thus contraindicated in patients with a history of seizures.

ECT can be used for major depressive disorder that is refractory to other treatments.

CASE 5

A 29-year-old well-groomed man with no medical or psychiatric history is being evaluated by a psychiatrist. He has noticed that, over the past 6 months, he has been preoccupied with counting items such as bricks in his driveway, raisins in his cereal, and tiles in the ceiling. He says he feels compelled to count to the number 30 particularly; for example, he does 30 push-ups in the morning, jogs for 30 minutes, and chews his food 30 times. He has not told anyone about his recent bothersome habit and does not believe it is interfering with his work. However, he is troubled by his own behavior and feels unable to stop. During the medical history, the patient reveals his 30th birthday is the following week.

What is the most likely diagnosis?

The patient's obsessions (recurrent thoughts) and compulsions (recurrent acts) suggest obsessive-compulsive disorder (OCD). The diagnosis requires obsessions, compulsions, or both. In other words, an OCD patient may have only obsessions or only compulsions.

The *DSM-5* defines the symptoms of OCD as follows:

- Obsessions are recurrent and persistent thoughts, impulses, or images that cause marked distress above and beyond real-life worries. The patient attempts to ignore or suppress them and recognizes that they are a product of the mind.
- Compulsions are repetitive behaviors (washing, ordering, checking) or mental acts (praying, counting) that a person is driven to perform in response to an obsession.

What is the epidemiology of this condition?

OCD occurs in approximately 3% of the general population. Males are much more frequently affected than females. The disorder often runs in families and may be associated with tic disorders (eg, Tourette syndrome). ADHD is also commonly associated with Tourette syndrome.

What are the treatments for this condition?

SSRIs and clomipramine, a TCA, are common pharmacologic treatments. Cognitive-behavioral therapy is also used with or without pharmacologic therapy.

What is cognitive behavioral therapy?

Cognitive behavioral therapy aims to modify a patient's emotions by identifying and adjusting maladaptive thought patterns and beliefs. In this patient, for example, turning 30 may represent the beginning of adulthood and the end of the impulsiveness of youth. The maladaptive thought may be, "If I count to 30, I am in control and an adult." Therapy consists of identifying problematic thought patterns and consciously replacing them with more reasonable ways of thinking. "I feel a need to count, I must be worried about whether I am in control; I am in good enough control, and counting does not really help anyway." Repeatedly forcing oneself to think the alternative thoughts helps break the patterns.

What comorbidities are associated with this condition?

The prevalence of **major depressive disorder** among individuals with OCD is as high as 30%. Panic disorders and social phobia also commonly coexist with OCD.

CASE 6

A 48-year-old lawyer visits his physician for a routine physical examination. During the interview, he mentions difficulty at work and takes copious notes as the psychiatrist speaks. He has frequent arguments with his assistant because she cannot carry out tasks, and he constantly has to check on everything she does. He says his coworkers "don't do things the way I tell them to," and he feels he cannot delegate tasks because "they don't do things right." He also admits to frequent arguments with his wife, who does not put things where they are supposed to go. He cannot tolerate her lack of organization.

What is the most likely diagnosis?

This patient exhibits traits consistent with obsessive-compulsive personality disorder (OCPD). Personality **traits** are patterns of relating to or thinking about the world that are exhibited in various social and personal contexts. A personality trait becomes a **personality disorder** when the traits are extreme and/or exclude other traits, causing problems functioning, and an adverse impact on the social environment. People often aren't aware of their maladaptive personality traits.

How are these conditions classified?

The *DSM-5* divides the ten major personality disorders into three clusters, A through C. An easy way to remember them is the phrase "weird, wild, or worried" (see Table 12-1).

Table 12-1. Major Personality Disorder Clusters

Cluster A ("weird"): odd or eccentric	Cluster B ("wild"): dramatic, emotional, erratic	Cluster C ("worried"): anxious or fearful
Paranoid	Antisocial	Avoidant
Schizoid	Borderline	Dependent
Schizotypal	Histrionic	Obsessive-compulsive
	Narcissistic	

This patient, who has obsessive-compulsive personality disorder, falls into cluster C.

How is this condition differentiated from OCD?

OCD is a disorder involving obsessions and compulsions, both of which are irresistible and unpleasant to the patient **(egodystonic)**. In OCPD, patients have a rigid preoccupation with order and control. However, they view their beliefs and behaviors simply as part of who they are **(egosyntonic)**. Compulsive behaviors cause stress and anguish to the OCD patient but don't trouble the OCPD patient.

What is the first-line treatment for this condition?

Both cognitive behavioral therapy and psychodynamic psychotherapy can be useful in patients with OCPD. Medications can be used to treat comorbid conditions such as anxiety and depression.

CASE 7

A 20-year-old college student complains to her physician of sudden episodes of overwhelming anxiety. The episodes include palpitations, nausea, sweating, breathlessness, and an intense fear of dying. The episodes started about 8 months ago but are increasing in frequency. They begin suddenly at variable times during the day, and she must take deep breaths to calm herself down. The patient is confused and frustrated, and she goes to class only if she can sit in the back, so she can leave if an attack occurs.

What is the most likely diagnosis?

Panic disorder.

How are panic attacks related to this condition?

Panic disorder requires repeated **panic attacks** followed by at least 1 month of fear of not being able to control future panic attacks. Patients tend to avoid situations where panic attacks occur and arrange their lives around fear of having an attack. This can lead to agoraphobia (ie, fear of having a panic attack in a place with no place to hide and no easy means of escape). However, the *DSM-5* makes it clear that agoraphobia is a separate diagnosis and can exist apart from panic disorder.

A panic attack requires the presence of at least four of the following symptoms:

- Palpitations
- Sweating
- Trembling
- Chest pain or discomfort
- Fear of losing control
- Fear of dying
- Chills or hot flashes

What other conditions must be ruled out before a diagnosis can be made?

Organic causes of symptoms (including tachycardia, hyperthyroidism, hyperparathyroidism, pheochromocytoma, hypoglycemia, seizure, and drug use) must be ruled out before the diagnosis of panic disorder can be made.

What are the treatments for this condition?

Panic disorder is often treated with SSRIs, TCAs, and MAOIs. Benzodiazepines are also useful in the short term, but they come with higher risks of abuse and relapse upon discontinuation.

These different drugs influence levels of norepinephrine, serotonin, and gamma-aminobutyric acid in the central nervous system and seem to be of similar efficacy in treating panic disorder, though with differing adverse effect profiles. TCAs have significant anticholinergic and antiadrenergic effects. MAOIs require that the patient follow a diet low in tyrosine and avoid medications that rely on MAO for metabolism, such as ephedrine.

Physical symptoms of panic attacks (eg, rapid heart rate) can be treated with β-blockers.

What syndrome can develop when SSRIs are used with MAOIs?

Serotonin syndrome may result from the use of drugs that enhance serotonin signaling. MAOIs and SSRIs enhance serotonin signaling through different mechanisms, so the risk of serotonin syndrome is higher when these drugs are taken together. Serotonin syndrome is more likely to occur with this combination of drugs because most MAOIs irreversibly inhibit MAO.

Symptoms of serotonin syndrome fit into three main categories:

- Autonomic dysfunction (eg, hyperthermia, tachycardia, unstable blood pressure, diarrhea, and sweating)
- Cognitive and behavioral changes (eg, agitation, confusion, and coma)
- Neuromuscular abnormalities (eg, hyperreflexia, shivering, myoclonus, and ataxia)

CASE 8

A 20-year-old man who returned from military service in Iraq a year ago visits his primary care physician complaining of a year's history of difficulty sleeping. He states that he gets only 4 hours of sleep per night. When he does fall asleep, he has recurring nightmares about a roadside bomb attack he suffered while driving a Humvee. The bomb killed his passenger and severely injured the patient. The patient states that he has difficulty driving because being in a car sometimes makes him "relive" the experience, and he avoids parking lots and busy freeways. He has no interest in returning to college and recently broke up with his girlfriend because she could not deal with his outbursts of anger and "numbness" to her feelings.

What is the most likely diagnosis?

Post-traumatic stress disorder (PTSD). PTSD is a complex and heterogeneous disorder characterized by reliving an extremely traumatic event with symptoms of increased arousal, dissociation, and avoidance. The disturbance(s) must **last more than 1 month** and cause significant social and occupational distress.

If these symptoms occur in the first month following a traumatic event, the diagnosis is **acute stress disorder**. PTSD is diagnosed once these symptoms have lasted for over a month.

What causes this condition?

PTSD is caused by any event that exposes an individual to real or threatened death or injury. The individual's response to the event must involve intense fear and horror. Examples include military combat, sexual or physical assault, accidents, and natural disasters.

How do patients with this condition relive the traumatic event?

Recurring distressing dreams or intrusive thoughts of the event are common. Patients may also describe flashbacks in which they feel as if the event is recurring. Flashbacks are often triggered by stimuli that pertain to the traumatic event such as sights, smells, or sounds.

In what ways do patients cope with this condition?

Patients with PTSD often avoid thoughts, feelings, stimuli, and conversations that are associated with the trauma. Because of this, it is often difficult for patients to talk about their experience. They also display a restricted range of affect, often described as numbness or detachment.

What symptoms may be present in this condition?

PTSD is characterized by hyperarousal that may manifest as insomnia, bouts of rage, hypervigilance, being easily startled, or having poor concentration.

What treatment options are available for this condition?

SSRIs are usually the first line of treatment for PTSD. TCAs and MAOIs can be used to decrease symptoms of hyperarousal. Effective psychotherapy includes cognitive behavior therapy, exposure therapy, and anxiety management.

CASE 9

The parents of a 22-year-old man bring him to the family physician because they have noticed a distinct change in their son's behavior over the past 4 months. The young man appears unkempt, does not have any friends at school, and has let his grades drop. He believes that a family neighbor has been sent to spy on him, and his parents hear him having conversations with imaginary partners. He denies any history of substance use, and his urine toxicology is negative.

What is the most likely diagnosis?

The constellation of symptoms suggests schizophreniform disorder, which is the presence of psychotic symptoms for **> 2 weeks but < 6 months**. This contrasts with a diagnosis of schizophrenia, which requires the presence of symptoms for at least 6 months. The majority of patients with schizophreniform disorder ultimately develop schizophrenia.

As of *DSM-5*, schizophrenia is no longer categorized into subtypes.

What symptoms are associated with this condition?

Patients with psychosis can present with positive and negative symptoms. **Positive symptoms** include formal thought disorder (disorganized speech and loosening of associations), delusions (often persecutory in nature), hallucinations (most commonly hearing voices), and ideas of reference (beliefs or perceptions that irrelevant, unrelated, or innocuous things are referring to a person directly or have a special significance for that person). **Negative symptoms** include flat affect, social withdrawal, and avolition (inability to initiate and maintain goal-directed activities).

The prognosis is generally better for females, when onset is in adulthood rather than in childhood, and if symptoms are positive rather than negative (positive symptoms respond better to medication).

What other conditions should be considered in the differential diagnosis?

- **Brief psychotic disorder**: The symptom criteria are the same as for schizophrenia, but the duration of symptoms is greater than 1 day yet less than 1 month. The prognosis is generally good.
- **Schizoaffective disorder**: The symptom criteria are the same as for schizophrenia, but the patient must also have at least one concurrent major mood episode (ie, major depressive disorder or mania). There must be at least 2 weeks of psychosis without mood symptoms.
- **Mood disorder (eg, bipolar disorder) with psychotic features**: Psychotic symptoms occur during mood episodes, and the criteria for schizoaffective disorder are not met.

What are the pharmacologic treatments for this condition?

- **Typical antipsychotics** (such as thioridazine, haloperidol, fluphenazine, and chlorpromazine) block dopamine-2 receptors. This class of drugs carries a higher rate of extrapyramidal adverse effects, including muscle rigidity, body posturing, akathisia (feeling of restlessness), and Parkinson-like tremors.
- **Atypical antipsychotics** (such as quetiapine, olanzapine, and risperidone) block serotonin receptors and multiple subtypes of dopamine receptors. They are also known as second-generation antipsychotics.
- Clozapine is a second-generation/atypical antipsychotic, and it is the most effective treatment for schizophrenia. It can be highly toxic, however, and can only be prescribed by physicians familiar with its adverse effect profile (significantly, agranulocytosis, seizures, sedation, postural hypotension, drooling, and eosinophilic myocarditis).

CASE 10

A 28-year-old woman presents to her physician with abdominal pain that has persisted intermittently for a decade. The pain has been particularly intense for the past several weeks. She is unable to sleep at night and has "tried everything for the pain but it won't go away." She reports nausea and diarrhea. She also has longstanding complaints of chronic headaches, muscle spasms, and dyspareunia (painful sexual intercourse). Her chart shows multiple visits over the years for similar symptoms with only vague physical examination findings and no laboratory findings. She has had several investigative surgeries and procedures without results. She asks if she should have another surgery to find out what is wrong.

What is the most likely diagnosis?

Somatic symptom disorder.

What are common symptoms of this condition?

Patients must have at least one somatic symptom causing distress or psychosocial impairment (persistent thoughts or anxiety, resulting in excessive time and energy spent on the symptom[s] and related health concerns). The specific symptom(s) may change, but the overall disorder must persist for at least 6 months.

What are some conditions that may present similarly?

- **Body dysmorphic disorder**: Patients are excessively concerned with an imagined or slight physical defect, to the extent that social, occupational, and/or academic functioning is adversely affected.
- **Conversion disorder**: Patients present with a neurologic complaint (eg, numbness, blindness, or paralysis) that cannot be explained by any physiologic process. Patients may be completely unconcerned about their symptoms.
- **Illness anxiety disorder**: Patients persistently believe they have a particular disease, despite evidence to the contrary.
- **Pain disorder**: Patients complain of pain, but psychological factors contribute to the onset, severity, maintenance, and exacerbation of these complaints.

These were formerly known as the somatoform disorders, a term no longer used as of *DSM-5*.

What other conditions must be distinguished from this condition?

In the above disorders, patients **unconsciously** mimic medical symptoms; in the following disorders, patients **deliberately** induce symptoms for personal gain:

- **Factitious disorder**: A condition in which patients consciously induce or mimic medical disorders (eg, by contaminating urine specimens or surreptitiously injecting insulin) in order to play the sick role: to be taken care of, to feel superior to the treatment team, to take advantage of the medical system. This was formerly known as Munchausen syndrome. Munchausen syndrome by proxy is now called factitious disorder imposed on another.
- **Malingering**: A condition in which patients consciously feign medical disorders for secondary gain (eg, to get out of work or collect disability).

CASE 11

A 38-year-old man having a severe asthma attack is brought to the ED and given IV steroids, which help to resolve his breathing. He is sent home on a steroid taper and seen in follow-up 2 days later when he reports insomnia and appears agitated. His speech is rapid and pressured, he has grandiose plans for the future, and he appears to have a euphoric affect. He is also tachycardic. When asked about his mood, he says he feels "sunny."

What is the most likely diagnosis?

Steroid-induced mania.

What drugs are most commonly associated with these symptoms?

Drug-induced mania can be secondary to ingestion of cocaine or amphetamines. Corticosteroids are a common iatrogenic cause of mood symptoms.

What signs and symptoms are commonly associated with this condition?

- Dilated pupils
- Hypertension
- Mood elevation, general activation
- Tachycardia

What laboratory tests are useful in confirming the diagnosis?

Urine or serum toxicology screening can identify specific drugs the patient may have ingested. Medications should be reviewed for possible iatrogenic cause.

What are the treatments for this condition?

The use of steroids should be tapered; it should not be halted abruptly. If agitation or psychotic symptoms are present, low-dose antipsychotic medications such as haloperidol or quetiapine may be useful, sometimes with lorazepam. Calcium channel blockers can be used for acute autonomic symptoms.

These symptoms could also be seen in which other psychiatric disorders?

These symptoms could also be evidence of delirium or a manic phase of bipolar disorder.

CASE 12

A 40-year-old woman is brought to the ED by her brother, who is worried about her "twitching of lips and tongue." The brother knows his sister was diagnosed with schizophrenia about a decade ago but has not seen her in years and is worried about these movements. The patient has achieved fairly good control of her psychotic symptoms with both oral and intramuscular depot antipsychotic agents. She recalls one prior visit shortly after she was diagnosed with schizophrenia to evaluate a neck spasm that was painful and "locked my neck to the left."

What is the most likely diagnosis?

Tardive dyskinesia, a long-term side effect of antipsychotic medication. The patient's experience with a "locked neck" is suggestive of torticollis, one form of acute dystonic reaction. Other extrapyramidal symptoms, such as stereotypic oral, buccal, or lingual movements and choreiform or athetoid movements, can also occur after several months or years of therapy with antipsychotic agents. These symptoms are often irreversible.

The estimated time at which extrapyramidal symptoms can appear is as follows:

- 4 hours: acute dystonia
- 4 days: akinesia/Parkinsonism
- 4 months: tardive dyskinesia
- Akathisia can occur at any time.

What is the pathophysiology of this condition?

It is hypothesized that long-term blockade of dopamine-2 receptors leads to supersensitivity.

What risk factors are associated with this condition?

- Diabetes mellitus
- History of movement disorders
- Tobacco use
- Typical antipsychotic agents (strong risk factor, especially at higher doses for longer periods)

What other movement abnormalities are associated with the use of antipsychotic agents?

- **Acute dystonia** is the earliest symptom to present (within hours) and is characterized by sustained muscle spasms of the face, neck (spasmodic torticollis), and eye (oculogyric crisis).
- **Akathisia**, characterized by extreme restlessness and an inability to sit still, is a common extrapyramidal disorder.

What can be done to minimize the risk of these symptoms continuing?

Lowering the dose of typical antipsychotic agents can help resolve symptoms. However, this may produce a transient worsening of dyskinesia as supersensitive receptors are less tightly blocked. Switching patients to atypical antipsychotic agents is advised, as they are associated with fewer extrapyramidal symptoms. Clozapine is the least likely of all antipsychotic drugs to cause tardive dyskinesia and is also the only medication to treat it. However, clozapine can cause agranulocytosis, so patients receiving clozapine require routine blood monitoring for neutropenia. This need for monitoring, along with clozapine's availability only as an oral preparation, limits its use.

CASE 13

A mother brings her 6-year-old son to see the pediatrician because she is concerned about his facial movements. The mother states that her son has always "blinked too much," but recently he started jerking his head to the right and sticking out his tongue. She describes these as very quick movements that happen multiple times a day. She also reports that the child makes grunting noises. The boy says he does not know why he does these things but feels a sense of relief once he does them.

What is the most likely diagnosis?

This patient displays criteria for Tourette syndrome, which is characterized by multiple motor **and** one or more vocal tics present since childhood but not necessarily concurrently. (**A tic is a sudden, stereotypical, repetitive movement or vocalization**.) The tics in Tourette syndrome occur many times a day for at least 1 year.

What is the epidemiology of this condition?

- Since the tics of Tourette syndrome are believed to begin in childhood and diminish with age, the prevalence is much higher among children than adults.
- Current data suggest that 1–10 children per 1,000 have Tourette syndrome, which is believed to be three to four times more common in males than females.
- Tourette syndrome is frequently associated with other conditions, including OCD and ADHD.

What motor abnormalities are seen in this condition?

Motor tics can be simple or complex and can affect any part of the body. Often, patients will initially have simple tics such as blinking, shoulder shrugging, head jerking, or grimacing. Complex tics may involve jumping, squatting, turning, or obscene gestures (copropraxia).

What vocal abnormalities are seen in this condition?

The classic vocal tic is coprolalia, or involuntary vocalization of obscene words. Other vocal tics include echolalia (repetition of others), and sounds such as barking, coughing, sniffing, grunting, or snorting.

Are the tics of this condition involuntary?

Yes, the tics are involuntary, but for brief periods patients may be able to consciously suppress them. Patients often describe a sense of relief once the tic is over.

What is the natural history of this condition?

Onset is usually during childhood and must occur before 18 years of age. The disorder may be lifelong, but many patients find that the severity of the tics decreases with age.

What is the treatment for this condition?

In many cases, education and reassurance may be sufficient. If the tics significantly interfere with the patient's social interactions, a dopamine antagonist (such as haloperidol) can be effective.

What is the difference between Tourette syndrome and chronic tic disorder?

Chronic (persistent) tic disorder involves only one type of tic (ie, there is chronic motor tic disorder and there is chronic vocal tic disorder). Single or multiple motor or vocal tics present at some time during the illness. In contrast, the diagnosis of Tourette syndrome requires multiple motor tics and one or more vocal tics to have presented at some time during the illness, though not necessarily at once.

13
Renal

CASE 1

A 70-year-old woman presents to her physician complaining of a 3-day history of nausea and malaise. She states that she is essentially in good health, although she recently started taking omeprazole for her gastroesophageal reflux disease. The patient denies use of any other medications. Her physical examination reveals a temperature of 38.5°C (101.4°F), but it is otherwise unremarkable. Laboratory blood testing demonstrates eosinophilia and elevated serum creatinine. Urinalysis shows mild proteinuria. Urine microscopy is pending.

What is the most likely diagnosis?

There is a high clinical suspicion for drug-induced acute interstitial nephritis (AIN) because of the patient's recent initiation of a medication. Drug therapy is responsible for 71% of reported AIN cases, with infections (eg, Legionella, leptospirosis, cytomegalovirus, streptococci) and autoimmune disorders (eg, systemic lupus erythematosus, Sjögren syndrome, sarcoidosis) responsible for the rest. The time of onset of medication-induced AIN is variable and can range from just days to many months following a drug exposure.

What drugs are associated with this condition?

Many medications have been associated with AIN, although methicillin remains the classic drug.

- Antibiotics commonly associated with a high risk of causing AIN include penicillin, cephalosporins, rifampin, quinolones, and sulfonamides.
- Nonsteroidal anti-inflammatory drugs (NSAIDs), including COX-2 inhibitors, are known to lead to AIN.
- Proton pump inhibitors and H2-blockers are increasingly reported as causes of AIN.

How do drugs induce this patient's condition?

Drug-induced AIN occurs as a result of hypersensitivity reactions. Drugs that cause AIN likely function as haptens, which are small molecules that stimulate an immune reaction only after binding a larger carrier molecule, like a protein. In the case of AIN, the drug binds a plasma membrane protein of a tubular cell and then induces an IgE or cell-mediated immune reaction.

What other symptoms are common in patients with this condition?

Other nonspecific complaints, such as weakness, fatigue, and anorexia, are common. Rash can sometimes accompany fever and eosinophilia to complete the classic triad of a drug-induced hypersensitivity reaction. However, only 10% of cases of drug-induced AIN manifest with all three signs.

What are the typical urinalysis findings?

Urinalysis often reveals sterile pyuria and microscopic hematuria. WBC casts in the absence of a urinary infection is highly suggestive of AIN. Urine eosinophils and mild proteinuria increase the suspicion but are not always present.

What kidney biopsy findings are common in this condition?

Kidney biopsy is the gold standard to confirm this condition. Renal tissue histopathology often shows interstitial edema with diffuse cellular infiltration of the interstitium by inflammatory cells including lymphocytes, monocytes, and eosinophils (see Figure 13-1). The presence of granulomas may suggest an autoimmune cause, such as sarcoidosis.

What is the treatment for this condition?

Withdrawal of the offending agent is paramount. The effectiveness of corticosteroid treatment has not been proven by a prospective, randomized controlled trial, but prednisone is often used empirically, especially in cases of failure to induce remission in 3-7 days despite withdrawal of the offending drug or in cases of advanced renal failure.

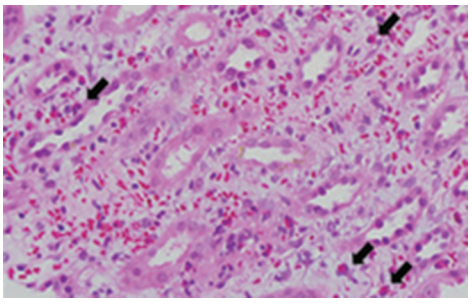

FIGURE 13-1. Numerous eosinophils (arrows) in the interstitium and mild tubular cell flattening, consistent with AIN. (Reproduced with permission from Ha Yeon Kim, et al. Acute interstitial nephritis induced by *Dioscorea quinqueloba*. *BMC Nephrol* 2014, 15:143.)

CASE 2

A 16-year-old previously healthy girl visits her doctor with recent-onset flank pain. She is given ibuprofen and sent home. A day later, she develops a fever accompanied by nausea, emesis, and worsening flank pain. Upon questioning, she recalls episodes of urgency as well as decreased urine output. Physical examination is notable for a temperature of 38.9°C (102.0°F) and costovertebral angle tenderness. Laboratory findings are as follows:

WBC count: 13,900/mm^3
Neutrophils: 74%
Hematocrit: 33%
Blood urea nitrogen (BUN): 10 mg/dL
Serum creatinine: 1.1 mg/dL
Urinalysis: 2+ protein, small leukocyte esterase, many WBCs, 2–5 RBCs/hpf, few bacteria, and WBC casts

What is the most likely diagnosis?

The presence of flank pain, emesis, high fever, and costovertebral angle tenderness indicate acute pyelonephritis. Pyelonephritis is a urinary tract infection (UTI) that has progressed from the lower urinary tract (bladder/urethra) to the upper urinary tract. It is most common in young children and sexually active women. Men are less likely to develop pyelonephritis or acute cystitis because of their longer, less exposed urethras as well as the antibacterial properties of prostatic fluid. Other predisposing factors include vesicoureteric reflux (congenital), flow obstruction, catheterization, gynecologic abnormalities, diabetes, and pregnancy.

What are the most likely pathogens that cause UTIs?

Escherichia coli is the most common cause of UTIs (50%–80% of cases). *Staphylococcus saprophyticus* is the second most common cause of UTIs in young, sexually active women. Other common causative organisms include *Proteus mirabilis*, *Klebsiella* (second most common cause overall), *Serratia*, *Enterobacter*, and *Pseudomonas*. Group B β-hemolytic streptococcal infection can cause UTIs in infants as part of the sepsis they develop.

How can this patient's symptoms be distinguished from those associated with cystitis, urethritis, or vaginitis?

The classic primary complaint in cystitis is dysuria accompanied by frequency, urgency, suprapubic pain, and hematuria. Pyelonephritis may include similar symptoms but is differentiated by the presence of additional features such as flank pain, costovertebral angle tenderness, nausea, and vomiting with high fever. Urethritis and vaginitis present with dysuria, discharge, pruritus, dyspareunia, and an **absence** of frequency or urgency.

What are the characteristic laboratory findings in this condition?

Pyuria is an essential finding in UTIs. Urinalysis typically shows > 10 WBCs/hpf. Hematuria is also common in women with UTI but not with urethritis or vaginitis. In a patient with UTI, white blood cell casts indicate the infection is of the upper urinary tract (ie, pyelonephritis rather than cystitis). Additionally, serum tests show leukocytosis, an elevated erythrocyte sedimentation rate, and an elevated C-reactive protein level.

What are the treatments for this condition?

The goal of empiric therapy is to use drugs that achieve high concentrations in the renal medulla. Oral medications include the fluoroquinolones (especially ciprofloxacin) and trimethoprim-sulfamethoxazole. Intravenous options include ceftriaxone, ciprofloxacin, ampicillin and gentamicin, and piperacillin/tazobactam.

CASE 3

A 29-year-old woman who was involved in a motor vehicle accident is brought to the ED, where she is found to be hypotensive with severe internal bleeding. She is given several units of blood by transfusion and sent to the intensive care unit for monitoring. Within 36 hours, a slight decrease in urine output and an increase in blood urea nitrogen (BUN) are noted, and by 72 hours, there is a dramatic drop in urine output. Laboratory studies at 72 hours are as follows:

Serum potassium: 5.1 mEq/L
BUN: 25 mg/dL
Serum creatinine: 2.5 mg/dL
Urinalysis: Mild hematuria, mild proteinuria, granular casts, and renal tubular epithelial cells in sediment
Fractional excretion of sodium (Fe_{Na}): 2.2%

What is the most likely diagnosis?

The patient most likely has acute tubular necrosis (ATN) secondary to renal ischemia as a consequence of shock due to the accident. ATN is the most common cause of acute kidney injury and is a result of direct injury to the renal tubular epithelia.

What are common causes of this condition?

Ischemia, infections, and nephrotoxins are three major causes of ATN. Hypotension and other prerenal diseases can cause renal ischemia. Common nephrotoxins include antibiotics (eg, aminoglycosides, amphotericin, foscarnet), radiocontrast, immunosuppressants (eg, cyclosporine, tacrolimus), chemotherapy agents (eg, cisplatin), myoglobin (eg, in rhabdomyolysis), and hemoglobin (eg, hemolysis).

What is the cause of the patient's azotemia?

ATN involves direct damage to renal tubular epithelial cells. The proximal tubule and thick ascending limb are particularly vulnerable to ischemic injury because they are highly metabolically active. In addition, the sloughing of intact tubular cells and necrotic cellular debris into the tubular lumen blocks the tubule. This leads to a back leak of the filtrate and, consequently, a decrease in the glomerular filtration rate (GFR). As a result, substances such as creatinine and BUN that are normally filtered by the kidney will begin to accumulate, which is called azotemia.

How do the laboratory findings help distinguish this condition from prerenal disease?

The BUN/serum creatinine ratio, FENa, and urine sodium concentration can help distinguish prerenal disease from ATN and other causes of intrarenal disease, as summarized in Table 13-1. Note that results for postrenal disease can be highly variable depending on the degree and time-course of obstruction.

Table 13-1 Prerenal versus Intrarenal

	BUN/Serum Cr	FENa (%)	Urine Na (mEq/L)
Prerenal	> 20:1	< 1%	< 20
Intrarenal	< 15:1	> 2%	> 40

Microscopic examination of sediment from the urinalysis can also help in distinguishing prerenal and intrarenal disease. In prerenal disease, hyaline casts can be observed, but this can also be a normal finding. In contrast, depending on the cause of intrarenal disease, various types of sediment may be seen. ATN is characterized by muddy brown granular casts.

Why is FENa < 1% in prerenal states but > 1% in this patient's condition?

In prerenal states, the kidney actively reabsorbs sodium from the tubular fluid in an attempt to compensate for volume depletion. This decreases the fractional excretion of sodium. In ATN, however, the tubular epithelium becomes dysfunctional and is no longer able to effectively reabsorb sodium. Instead, the fractional excretion of sodium increases as sodium is lost in the urine. Notably, high FENa is not diagnostically useful in patients taking diuretics since sodium reabsorption is altered by the diuretic. In these patients, the FEUrea can be used instead. However, a low FENa in a patient taking a diuretic still favors a prerenal cause.

Why is the BUN/creatinine ratio elevated in prerenal disease but not in intrinsic renal disease?

Urea is a water-soluble molecule that is passively reabsorbed in the proximal tubule where volume depletion increases reabsorption of sodium and water in parallel with an increase in BUN.

Creatinine, however, is not reabsorbed in the proximal tubule; hence, when there is volume depletion, there is not a commensurate rise in serum creatinine. Creatinine is freely filtered, and then gets secreted in the tubules.

Thus, in cases of renal hypoperfusion, BUN is elevated but creatinine may be normal. Other causes of isolated elevation in BUN include gastrointestinal bleed, steroids, and high-protein diet.

In contrast, in intrinsic renal disease, the kidney itself is damaged and BUN can no longer be actively reabsorbed. Instead, both BUN and creatinine levels rise equally as the GFR declines, resulting in a normal BUN/creatinine ratio.

What is the natural course of this condition?

Within 36 hours of injury, ATN undergoes an initiatory phase, during which time urine output decreases and BUN increases. Within 2–6 days, a maintenance phase begins, where urine output falls dramatically and there is a significant risk of death without treatment. Finally, the recovery phase typically occurs within 2–3 weeks, in which urine output increases.

How do the results of a fluid challenge test differ between this patient's condition and prerenal disease?

A fluid challenge (the use of IV fluids to restore intravascular fluids) usually restores normal renal function in patients with prerenal disease (ie, hypoperfused kidneys). However, in patients with ATN, renal dysfunction often persists **despite fluid challenge**. A fluid challenge is contraindicated in patients with volume overload (eg, heart failure).

CASE 4

A 37-year-old man visits his physician because he has noticed blood in his urine over the past week. He denies increased frequency or dysuria. He admits intermittent aching back pain over the past few months, which he attributes to sitting at his desk for long periods of time each day at work. Ultrasound shows massively enlarged kidneys bilaterally. The surface of the right kidney is studded with several well-circumscribed cysts, and the left kidney demonstrates similar lesions. His blood pressure is 148/84 mm Hg.

What is the most likely diagnosis?

Autosomal dominant polycystic kidney disease (ADPKD). ADPKD has a prevalence of approximately 1:1000 and is the leading genetic cause of chronic renal failure. It is diagnosed with imaging.

How is this condition inherited?

The disease is inherited in an autosomal dominant fashion. Approximately 78% of cases of ADPKD are due to a mutation in the *PKD1* gene on chromosome 16; the remainder of the cases are caused by mutations in the *PKD2* gene on chromosome 4.

What is the presentation of this condition?

ADPKD may present at any age but is most frequently diagnosed in the third to fifth decades (although ADPKD due to mutation in *PKD2* has a later onset). Because ADPKD is dominantly inherited, patients may be aware of a family history of the disease. Patients can present with hypertension or chronic flank pain due to calculi, urinary tract infection, or massively enlarged kidneys (see Figure 13-2). Patients may also present with gross hematuria, and nocturia may be present if renal concentrating ability is impaired. Microscopic hematuria, proteinuria, or renal insufficiency may prompt abdominal imaging, resulting in diagnosis of ADPKD.

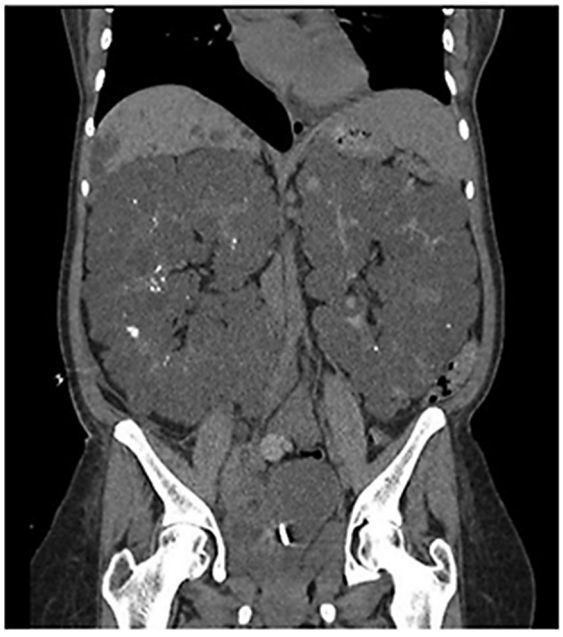

FIGURE 13-2. Bilateral kidney cysts in polycystic kidney disease. (Reproduced with permission from USMLE-Rx.com.)

What are the extrarenal manifestations of this condition?

Hepatic cysts are present in 50%–70% of patients and are generally asymptomatic with little effect on liver function. Colonic diverticula are also seen with increased frequency in ADPKD. There is also an association between ADPKD and saccular (berry) aneurysms of the circle of Willis, which show familial clustering. Rupture of such aneurysms results in subarachnoid hemorrhage and increased mortality and morbidity. Mitral valve prolapse is found in 25% of patients with this disease. Most patients with APDKD die from cardiac causes, mainly cardiac hypertrophy and coronary artery disease.

What is the prognosis for patients with this condition?

Progression to chronic renal failure is common, with 50% of patients developing end-stage renal disease by 60 years of age (ADPKD accounts for approximately 5% of patients who initiate dialysis annually). There is great variability in the progression of the disease even within families. Early age at diagnosis, male gender, recurrent infection, proteinuria, and hypertension are all associated with an early onset of renal failure. *PKD1* carriers tend to have a more severe course. At present, there is no proven treatment for ADPKD; management generally consists of controlling any associated hypertension and/or proteinuria to preserve the glomerular filtration rate, but renal replacement therapy is eventually indicated.

How do the clinical features of autosomal recessive polycystic kidney disease (ARPKD) differ from ADPKD?

ARPKD is generally more severe than ADPKD and typically presents in neonates or in early childhood. Renal failure during gestation decreases fetal urination, thus leading to a decreased volume of amniotic fluid, termed oligohydramnios. In neonates with ARPKD, oligohydramnios can result in a constellation of findings known as Potter syndrome, including pulmonary hypoplasia and limb and facial deformities. In children, ARPKD may result in progressive renal failure. In addition, the liver is predominantly affected in ARPKD and can manifest as portal hypertension from hepatic fibrosis.

CASE 5

A 70-year-old African-American man returns to his physician for his annual follow-up visit after prior diagnosis of monoclonal gammopathy of undetermined significance (MGUS). He reports he continues to have mild lower back pain and proximal extremity weakness and notes that he has had polydipsia and polyuria in the past several months. Physical examination is unremarkable. Urinalysis is notable for aminoaciduria, glucosuria, and phosphaturia. Relevant laboratory results are as follows:

Sodium: 133 mEq/L
Potassium: 3.3 mEq/L
Chloride: 110 mEq/L
Bicarbonate: 18 mEq/L
Glucose: 85 mg/dL
Calcium: 8.3 mg/dL
Phosphate: 2.1 mg/dL
Uric acid: 2.0 mg/dL

What is the most likely diagnosis?

This patient has likely developed Fanconi syndrome (FS), which is characterized by a generalized transport defect in the **proximal tubules** leading to wasting of compounds normally reabsorbed in proximal tubules, thus representing a form of proximal (type II) renal tubular acidosis (RTA). FS is either acquired or inherited. It can be acquired as a rare complication of plasma cell dyscrasias, including multiple myeloma, MGUS, Waldenström macroglobulinemia, and primary amyloidosis. FS may also result from Sjögren syndrome, heavy metal poisoning, and drug reactions (eg, tenofovir or ifosfamide). Autosomal recessive disorders such as Wilson syndrome, cystinosis, or tyrosinemia are the most common causes of Fanconi syndrome in children. Fanconi syndrome caused by these inherited disorders most commonly presents in children as failure to thrive, although the diagnosis is often overlooked.

Although all of the urinalysis and laboratory findings support the diagnosis of FS, in a patient with MGUS and back pain, multiple myeloma should be on the differential. MGUS progresses to multiple myeloma at a rate of about 1% per year, and back pain is often a presenting feature of multiple myeloma since plasma cells may infiltrate the bone and cause lytic lesions.

What are the functions of the proximal convoluted tubules?

The proximal convoluted tubules are the "workhorses of the nephron" and reabsorb all glucose and amino acids and the majority of filtered sodium, potassium, phosphate, bicarbonate, and water. Ammonia is also secreted to buffer distally secreted H^+. The energy needed for the reabsorption of filtered solute is provided by the Na^+-K^+-ATPase pump, which is found on the basolateral membrane of proximal tubular cells. It actively reabsorbs sodium, thereby creating an electrochemical gradient that promotes the passive transport of sodium from the proximal tubular lumen into the cell across the luminal membrane. Sodium movement across the luminal membrane occurs via cotransporters, which couple sodium transport to the transport of other solutes such as glucose, phosphate, uric acid, and amino acids (see Figure 13-3).

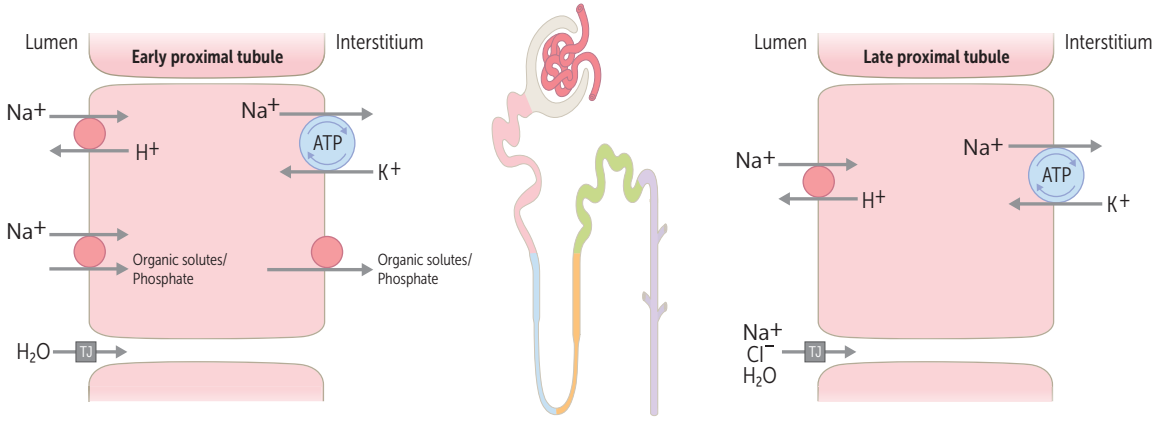

FIGURE 13-3. Physiology of electrolyte transport of a cell of the proximal tubule. (Reproduced with permission from USMLE-Rx.com.)

What is the pathogenesis of this condition?

FS is characterized by generalized **proximal tubular dysfunction**. The exact mechanism varies with the etiology of FS. In FS associated with monoclonal gammopathies, filtered light chains accumulate in proximal tubular cells and are resistant to degradation by lysosomes in tubular cells. This results in intracellular crystal formation which may eventually compromise tubular function.

What medication can mimic the presentation of this condition?

Acetazolamide works by inhibiting carbonic anhydrase in the proximal tubule, an enzyme needed for bicarbonate reabsorption. Thus, like Fanconi syndrome, it can cause proximal RTA. Fanconi syndrome differs in that it is not an isolated proximal RTA, but rather a generalized dysfunction of the proximal tubule with failed reabsorption of multiple solutes besides bicarbonate.

What is glomerular filtration rate (GFR)?

The glomerulus filters plasma predominantly by molecular size and net charge. GFR measures the amount of plasma that is filtered into the Bowman capsule from the glomerular capillaries within the glomeruli per unit time (milliliters per minute) and is a marker of renal function. Infusion of inulin is necessary for an accurate assessment of GFR because it is fully filtered but is not reabsorbed, secreted, metabolized, or produced endogenously. GFR, however, is more conveniently approximated by creatinine clearance (C_{Cr}), as represented by the formula:

$$GFR = U_{Cr} \times V/P_{Cr} = C_{Cr}$$

(P_{Cr}, plasma concentration of creatine; U_{Cr}, urine concentration of creatine; V, volume of urine per unit time)

Since creatinine, unlike inulin, is secreted in the kidney, a creatinine-based GFR results in an overestimate of the true GFR. In FS, GFR is normal.

What is the mechanism of the observed hypokalemia?

The primary function of the kidneys is to preserve volume though the reabsorption of sodium and free water. In FS, there is an increased distal delivery of sodium due to the incompetent proximal tubules. The principal cells within the collecting ducts will compensate by increasing sodium reabsorption through an exchange for potassium. This results in potassium clearance rates that may be more than twice the GFR, indicating net tubular secretion. **Metabolic acidosis** secondary to defective proximal tubule bicarbonate reabsorption may also contribute to potassium loss, as cells tend to remove H^+ from circulation through an exchange for potassium, thereby increasing the filtered load of potassium.

CASE 6

A 42-year-old woman presents to her physician after coughing up blood several times in the past week. She reports she has been coughing more frequently and experiencing difficulty finishing her daily walks despite the fact that she recently stopped smoking. She has not noticed any significant changes in her urinary habits. Physical examination is notable for a blood pressure of 144/82 mm Hg and an absence of fever and tachypnea. X-ray of the chest demonstrates fluffy infiltrates bilaterally. Urinalysis reveals proteinuria, hematuria, and RBC casts. A spot protein/creatinine ratio shows significant but subnephrotic-range proteinuria.

What conditions should be considered in the differential diagnosis?

Rapidly progressive glomerulonephritis and alveolar hemorrhage suggest Goodpasture syndrome (GP) or an antineutrophil cytoplasmic antibody (ANCA) vasculitis, such as Wegener granulomatosis or microscopic polyangiitis. While vasculitis is more common, it usually also presents with constitutional symptoms. Pulmonary hemorrhage can also be seen in other forms of acute glomerulonephritis due to pulmonary edema or to lung involvement in other forms of systemic vasculitis and lupus.

To aid in the diagnosis, which antibodies should be tested for by serology?

- Anti–glomerular basement membrane (anti-GBM) antibody (Goodpasture syndrome)
- Anti–neutrophilic cytoplasmic antibody (vasculitides)
- Anti-Smith antibody and anti–double-stranded DNA (lupus)

Only anti-GBM antibodies are subsequently isolated from the patient's serum. What is the epidemiology of the associated condition?

Isolation of anti-GBM antibodies suggests GP, which is a form of anti-GBM disease characterized by rapidly progressive glomerulonephritis and alveolar hemorrhage, as a result of autoantibodies to type IV collagen. GP has a prevalence of 1:1 million. GP occurs with alveolar hemorrhage in 40%–60% of cases. Males 5–40 years of age are most commonly affected. Both genders are affected equally in older adults. Patients younger than 30 years of age are more likely to be severely affected. Untreated, GP has a fatality rate of 50%.

What is the pathogenesis of this condition?

IgG (rarely IgA or IgM) **autoantibodies against type IV collagen** are the distinguishing feature of GP, and they also correlate with the severity of disease. The expression of α_3 chains of type IV collagen is highest in glomerular and alveolar basement membrane and several other organs. The antigen targets of GP autoantibodies are normally inaccessible because of the presence of endothelial cells. The exposure of these antigens to circulating antibodies is more likely in the kidneys and lungs because of the fenestrated nature of the endothelial lining of glomerular capillaries and the increased susceptibility of the lungs to injury. For instance, patients with GP who have lung infections, are smokers, or have other toxic inhalations are more likely to have pulmonary involvement in their disease due to the endothelial damage and exposure of the basement membrane antigens.

What type of hypersensitivity reaction is responsible for this patient's disease process?

A **type II hypersensitivity** reaction is responsible. Fixation of complement to the anti-GBM antibodies activates the classic complement pathway that results in the recruitment of neutrophils and monocytes. Type II hypersensitivity is also seen in myasthenia gravis, pernicious anemia, Graves disease, pemphigus vulgaris, and other conditions.

What are the typical kidney biopsy microscopy findings in this condition?

Light microscopy (LM) typically shows **crescentic glomerulonephritis** (see Figure 13-12 in Case 19). Immunofluorescence microscopy (see Figure 13-4) demonstrates the nearly pathognomonic finding of a smooth linear deposition of IgG along the glomerular capillaries.

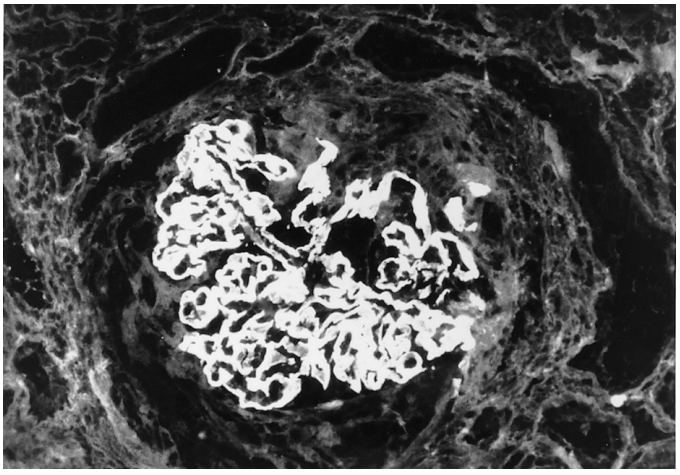

FIGURE 13-4. Immunofluorescence microscopy of a kidney biopsy specimen from a patient with Goodpasture syndrome. Note the linear ribbon-like pattern when stained for immunoglobulin. (Reproduced with permission from Toy EC, et al. *Case Files: Pathology*. 2nd ed. New York: McGraw-Hill; 2015.)

Which other renal disease occurs due to pathology involving type IV collagen?

Alport syndrome is also a disease of the glomerular basement membrane that involves type IV collagen. However, it is due to an inherited mutation in type IV collagen, rather than an autoimmune response against type IV collagen, as occurs in GP.

CASE 7

A 4-year-old boy presents with a 2-day history of rash that has spread from his legs to his buttocks. He is afebrile and has no sick contacts or other pertinent exposures. The rash consists of nonclustering, nonblanching, raised spots > 2 mm in size spread over his buttocks and posterior surfaces of his lower extremities. The boy also complains of knee and ankle stiffness and acute abdominal pain. His vital signs are stable, and urinalysis reveals microscopic hematuria and mild proteinuria. His laboratory findings are as follows:

- Hematocrit: 35%
- International normalized ratio (INR): 1.0
- WBC count: 7000/mm^3
- Prothrombin time: 12 sec
- Platelet count: 200,000/mm^3
- Partial thromboplastin time: 25.2 sec

What is the most likely diagnosis?

In children, the classic tetrad of palpable purpura with lower limb predominance, arthralgias, abdominal pain, and renal disease is pathognomonic for Henoch-Schönlein purpura (HSP). However, only 63% of patients with HSP actually present with abdominal pain and only 40% with renal disease. An additional 33% of patients also have evidence of gastrointestinal bleeding. Less common symptoms include testicular torsion, intussusception, pancreatitis, cholecystitis, and protein-losing enteropathy. Approximately 1% of children with HSP progress to end-stage renal disease, and approximately 10% of HSP cases are seen in adults.

What are the dermatologic findings for this condition?

Both **purpura and petechiae** may be seen in HSP. Purpura is characterized by nonblanching, flat lesions measuring > 2 mm in diameter. Petechiae are non-blanching, flat lesions measuring < 2 mm in diameter. Both are signs of bleeding occurring in the skin. In contrast, a blanching rash results from dilation of blood vessels rather than vascular destruction and applying pressure to the lesion reduces blood flow to the skin, causing it to lose its red color.

What is the pathophysiology of this condition?

HSP is a small-vessel vasculitis. Although the precipitating factor is unknown, anecdotal evidence suggests upper respiratory infection for children. With HSP, IgA deposition in blood vessels causes leaking, which leads to purpura and petechiae. This is pathophysiologically similar to IgA nephropathy, and they have identical renal histologic findings. However, patients with IgA nephropathy lack the extrarenal clinical findings seen in HSP.

Which conditions should be considered in the differential diagnosis of this patient's rash?

The main concerns, in addition to HSP, are clotting disorders and sepsis; as a result, coagulation studies should be performed. A similar rash can be caused by rickettsial infections, although this patient is afebrile. It is important to distinguish HSP from **hemolytic-uremic syndrome** (HUS), as the two conditions present similarly and can both cause extensive renal disease. However, HUS is not likely in this patient, as there are no signs of hemolytic anemia such as schistocytes on blood smear. In adults, HSP must be distinguished from systemic diseases such as hypersensitivity vasculitis and systemic lupus erythematosus.

What are the treatments for this condition?

Treatment is based on the severity of symptoms, as the disease is typically self-limiting. An asymptomatic patient requires no treatment. However, severe symptoms, including signs of renal involvement, may require renal biopsy and steroids. Regardless of the severity of symptoms, all patients with HSP require blood pressure monitoring and urinalysis biweekly for 1-2 months and then every other month for up to 1 year, as HSP has a high rate of recurrence. Recurrence or flares typically occur within 4 months of the initial diagnosis.

CASE 8

A 10-year-old boy is brought to his pediatrician for evaluation of bloody urine. A urine sample is positive for hemoglobin and RBC casts. The boy's maternal grandfather suffered from deafness and died of renal failure. The boy also has a 25-year-old male maternal cousin who uses a hearing aid and requires dialysis for end-stage renal disease. The family pedigree is shown in Figure 13-5; the boy is indicated by the arrow, his maternal grandfather by the number 1, and his maternal cousin by the number 2. Darkened symbols represent people with known renal disease.

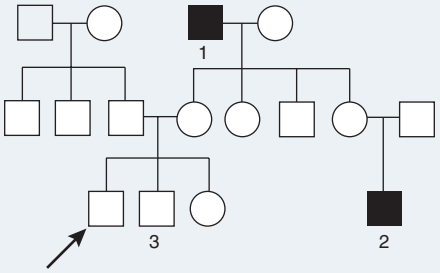

FIGURE 13-5. (Reproduced with permission from USMLE-Rx.com.)

What is the most likely diagnosis?

The most common causes of gross hematuria in a child are urinary tract infection and trauma. The most likely diagnosis in this case, however, is hereditary nephritis, or Alport syndrome, which consists of glomerular disease, sensorineural deafness, and ocular abnormalities, such as anterior lenticonus, a conical projection of the lens surface. These patients often progress to end-stage renal disease by the second to third decade of life.

This condition is due to a mutation in a gene that codes for which protein?

Alport syndrome is due to a defect in the gene that encodes for any of several subunits of type IV collagen. **Type IV collagen** is a crucial component of the glomerular basement membrane (GBM), the lens of the eye, and the cochlear basement membrane in the inner ear.

What electron microscopic changes are typical of the renal pathology of this patient's condition?

In Alport syndrome, the GBM exhibits alternating thickening and thinning. In addition, there is splitting of the lamina densa (the central zone of the GBM) into interlacing strands, giving it a characteristic "basket-weave" appearance.

Because of this mutation, the glomerulus loses the ability to selectively filter on the basis of what property?

The glomerular basement membrane is both a size-selective and charge-selective filter; In Alport syndrome, the altered basement membrane leads primarily to loss of size selectivity.

What is the probability that this patient's brother (person 3 in Figure 13-5) has the same disease?

The probability is 50%. The pedigree represents X-linked inheritance. Since the boy's mother is a carrier, each son has a 50% chance (one of two X chromosomes in the mother) of inheriting the mutation. Though less common, there are also autosomal recessive and autosomal dominant variants of Alport syndrome.

What other screening tests, in addition to urinalysis, can be used to confirm the diagnosis?

Alport syndrome is associated with ocular abnormalities and deafness; therefore, an ophthalmological examination and a formal audiogram should be performed, as deficits may be subtle. Skin biopsies, from which the absence of specific subunits of type IV collagen can be detected, can also be useful in diagnosing Alport syndrome.

CASE 9

A 45-year-old man is brought to the ED by his mother after 2 days of worsening confusion. She mentions that he has not had a bowel movement in several days, although he has been urinating frequently. His medical history is significant only for chronic osteomyelitis of the right arm secondary to a burn injury sustained in a house fire 5 years ago. Physical examination is unremarkable except for uniformly depressed deep tendon reflexes. The patient is also visibly uncomfortable and disoriented and is uncooperative during much of the examination. Electrocardiogram (ECG) reveals a QTc interval of 390 msec. Relevant laboratory findings are as follows:

- Serum calcium: 11.88 mEq/L
- Serum albumin: 1.45 mEq/L
- BUN: 21mg/dL
- Serum creatinine: 1.4 mg/dL
- Parathyroid hormone (PTH): 12 pg/mL
- Alkaline phosphatase: 980 U/L

What is the most likely diagnosis?

Hypercalcemia. Symptoms include lethargy, hyporeflexia, confusion, depression, headaches, psychosis, bradycardia, a shortened QT interval, nausea, vomiting, constipation, muscle weakness, polyuria, polydipsia, and gastroduodenal ulcer disease (secondary to calcium-induced gastrin release).

How are ionized calcium and albumin used in the diagnosis of this condition?

Ionized calcium is the primary determinant of cellular and membrane activity. However, routine reporting of serum calcium levels includes calcium that is bound to proteins. Approximately 45% of calcium circulates in the free or ionized form, and another 40% is bound to albumin (the remainder is bound to various anions). Accurate assessment of calcium levels therefore requires the simultaneous measurement of albumin and serum calcium levels.

How do hypoalbuminemia and pH changes affect this condition?

Hypoalbuminemia can decrease measured serum calcium levels independently of any net change in ionized calcium levels. For each decrease of 1.0 g/dL in serum albumin below the laboratory's reference normal value, 0.8 mg/dL should be added to the total calcium measured (the opposite is done in cases of hyperalbuminemia). Given the patient's hypoalbuminemia, the actual total serum calcium level is even greater than the already elevated total calcium observed.

Because calcium and hydrogen ions compete for negatively charged binding sites on albumin, changes in pH will impact the proportion of serum calcium that is in the ionized form (although the total calcium measured will not change). When the pH is low, more calcium will be displaced from albumin by $H+$, thereby increasing ionized calcium. Conversely, ionized calcium decreases with alkalemia.

What are the most common causes of this patient's condition?

Hyperparathyroidism and malignancy are the leading causes of hypercalcemia. Malignancy can cause hypercalcemia by multiple mechanisms. Tumor cells from bone metastases or multiple myeloma can directly induce bone resorption, resulting in osteolytic lesions. Other tumors (especially squamous cell carcinomas) secrete PTH-related protein. In sarcoidosis, macrophages produce calcitriol, which subsequently enhances intestinal absorption of calcium. Thiazide diuretics and excessive vitamin D intake are two other causes of hypercalcemia.

What are the treatments for this condition?

Symptomatic hypercalcemia, as seen in this patient, should first be treated with a saline infusion to expedite renal calcium excretion. Calcitonin is also administered for short-term control of symptomatic hypercalcemia, as it increases renal excretion of calcium and decreases bone resorption by osteoclasts. Bisphosphonates also inhibit osteoclast activity and can be used to manage hypercalcemia in the long-term. Although loop diuretics such as **furosemide** can promote calciuresis, their use is not recommended in the absence of renal failure or heart failure. Given this patient's history of chronic osteomyelitis, suppressed PTH, and dramatically elevated alkaline phosphatase levels, there is a high clinical suspicion for underlying malignancy.

What is the mechanism of action of furosemide, and how does it increase calcium excretion?

Loop diuretics such as furosemide act by inhibition of the Na-K-2Cl cotransporters in the thick ascending limb of the loop of Henle (see Figure 13-6). These cotransporters normally absorb sodium, potassium, and chloride from the tubular lumen, although some potassium leaks back into the lumen. This creates a lumen positive potential, which drives the reabsorption of other cations, such as calcium and magnesium. Furosemide inhibits this process, resulting in greater calcium excretion.

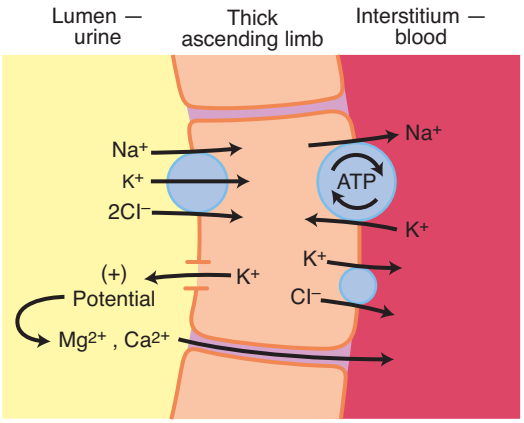

FIGURE 13-6. Ion transport in the thick ascending loop of Henle, the site of action of loop diuretics. (Reproduced with permission from USMLE-Rx.com.)

CASE 10

A 58-year-old man presents to the ED with a 1-week history of progressive weakness, fatigue, and shortness of breath on exertion. On physical examination, the man's heart rate is irregularly irregular, and his lung examination is notable for bilateral crackles that are most pronounced at the bases. X-ray of the chest demonstrates pulmonary edema. The patient is started on digoxin and furosemide. Three days later, he complains of light-headedness with progressive weakness. Laboratory values are significant for a serum sodium level of 142 mEq/L and a serum potassium level of 2.7 mEq/L. An ECG demonstrates torsades de pointes.

What is the most likely diagnosis?

Hypokalemia.

What two main factors predisposed the patient to torsades de pointes?

The patient was started on digoxin to increase cardiac output and to treat the atrial fibrillation; furosemide was added to treat the pulmonary edema. However, furosemide-induced diuresis can lead to severe hypokalemia (serum potassium level < 2.5 mEq/L). Hypokalemia has been shown to promote digoxin-induced arrhythmias, even when digoxin levels are in the therapeutic range. This is because digoxin competes with potassium for its bindings site to the Na^+-K^+-ATPase on cardiac myocytes. When potassium levels are low, digoxin will bind to a greater extent, resulting in digoxin toxicity, which can induce fatal arrhythmias.

In a patient without an arrhythmia, what ECG change is characteristic of this patient's condition?

Hypokalemia characteristically causes U waves on the ECG, which are small waves immediately following a T wave (see Figure 13-7).

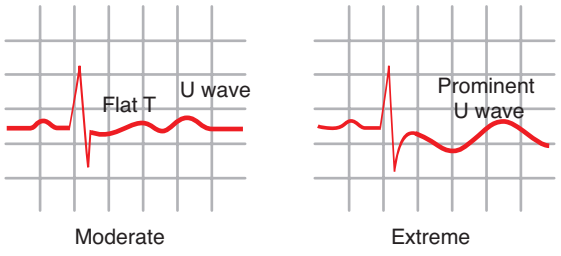

FIGURE 13-7. ECG showing U waves, which can be seen with hypokalemia. (Modified with permission from USMLE-Rx.com.)

What are the most common causes of this condition?

There are three broad etiologies of hypokalemia: decreased intake, increased losses, and increased translocation into cells.

- Decreased intake is a rare cause of hypokalemia.
- Increased losses can be:
  - gastrointestinal, from diarrhea, laxative abuse, VIPomas, nasogastric suctioning, and/or vomiting.
  - renal, as from diuretic use, hypomagnesemia, polyuria and other salt-wasting conditions, hyperaldosteronism, loss of gastric secretions, or metabolic acidosis.
  - due to excessive sweating.
- Increased translocation into cells occurs with hypothermia, alkalosis, increased insulin availability, and β-adrenergic activity.

How does alkalosis lead to this condition?

The Na^+-K^+-ATPase pump keeps intracellular potassium levels much higher than the serum/extracellular level. However, in the setting of alkalosis, hydrogen ions leave cells to minimize serum pH change. In the process, hydrogen ions function in an apparent exchange for potassium that can lead to hypokalemia.

How is metabolic acidosis associated with this condition?

Metabolic acidosis causes an exchange of hydrogen ions into the cells for potassium ions into the plasma, leading to **hyperkalemia**. However, in the setting of metabolic acidosis (notably diabetic ketoacidosis), urinary potassium excretion is also increased. This leads to a situation in which potassium is being moved from the cells and then excreted in the urine. As a result, although the serum potassium level is normal or even high in metabolic acidosis, the total body stores are actually low. The hypokalemia often reveals itself once the acidosis is corrected.

What are the treatments for this condition?

Potassium can be repleted either directly (ie, with potassium chloride) or through the use of a potassium-sparing diuretic such as amiloride, spironolactone, or triamterene. Amiloride is often the diuretic of choice, as it lacks the hormonal adverse effects of spironolactone (gynecomastia and amenorrhea).

CASE 11

An 86-year-old woman living in a nursing home is brought to the attention of the medical staff because of her lethargy. Relatives note that she has been unable to recognize family members in the past week. Her medical history is notable for Alzheimer disease, osteoporosis, and hypertension. Her medications include memantine, donepezil, alendronate, and hydrochlorothiazide, the dose of which was recently increased. Physical examination reveals a blood pressure of 139/80 mm Hg. The patient is sleepy and oriented only to person. CT scan of the head is unremarkable. Laboratory testing is notable for a sodium concentration of 122 mEq/L and normal glucose levels, renal function, and hematocrit.

What is the most likely diagnosis?

Hyponatremia, which is commonly defined as a serum sodium concentration **< 135 mEq/L**. Hyponatremia is more prevalent in the hospital setting or in nursing homes.

What are the common causes of this condition?

The causes of hyponatremia are often categorized clinically according to volume status:

- **Hypovolemia**: renal losses (diuretics, hypoaldosteronism) or gastrointestinal losses (diarrhea or vomiting)
- **Euvolemia**: syndrome of inappropriate [secretion of] antidiuretic hormone (SIADH), hypothyroidism, adrenal insufficiency, or primary polydipsia
- **Hypervolemia**: heart failure, cirrhosis, some cases of nephrotic syndrome

What symptoms are typically associated with this condition?

The decreased osmolarity (for most cases of hyponatremia) causes an osmotic water shift that increases intracellular fluid volume. Clinical manifestations are typically neurologic in nature secondary to cerebral edema within the confines of the cranial vault. Nonspecific symptoms, such as malaise or nausea, are common. Headache, lethargy, confusion, and obtundation may appear as sodium levels fall further. Stupor, seizures, and coma can occur if progression is rapid or concentrations fall **below 120 mEq/L**.

What is the pathogenesis of this condition in this particular patient?

This patient is likely suffering from diuretic-induced hyponatremia. Thiazides block sodium reabsorption in the distal tubule resulting in renal losses of sodium and water (which follows sodium). The resulting volume loss stimulates ADH release, which enhances water reabsorption in the collecting duct. Thus, while there is net volume loss with the diuretic, some water is retained, and sodium concentration decreases. It should be noted that loop diuretics are unlikely to cause hyponatremia, as the maximal urine concentrating ability, and thereby water retention, is reduced with the decrease in medullary interstitial tonicity. If hyponatremia develops over a period of days rather than acutely, the brain cells adapt by secreting salts and, over time, organic osmolyte to prevent excess water entry and swelling. This may explain why no significant swelling can be seen on CT scan of the head.

What other laboratory test will help identify the etiology of this condition in this patient?

Plasma osmolality, urine osmolality, fractional excretion of sodium, urine sodium concentration, and urine potassium concentration are helpful. If diuretics are responsible, as in this case, the plasma osmolality may be slightly low. Urine osmolality is elevated, as thiazides stimulate antidiuretic hormone (ADH). Urine sodium is elevated because of a thiazide-mediated decrease in reabsorption. However, some of the excess sodium delivered to the collecting duct is reabsorbed at the expense of potassium. Urine potassium therefore would also be elevated.

What is the treatment for this condition?

Treatment should include discontinuing the thiazide and, because the patient is symptomatic, sodium should be replenished with isotonic saline. In cases such as acute seizures, hypertonic saline should be used, but care must be taken not to correct the hyponatremia too quickly. Rapid correction of chronic hyponatremia can result in **central pontine myelinolysis**, a diffuse (not limited to the pons) demyelination syndrome. A rapid increase in serum osmolarity leads to brain cell shrinkage, and this is believed to result in demyelination. If hyponatremia occurs suddenly, over a few hours, then rapid correction is unlikely to cause demyelination as the brain will not have time to undergo compensatory measures as discussed above.

CASE 12

A 60-year-old man with a 30-year smoking history presents to his physician with complaints of cough, fatigue, and a recent 9.1-kg (20-lb) weight loss. X-ray of the chest reveals a 2-cm hilar mass that is identified on biopsy as small cell lung cancer. On physical examination, the patient has some cachexia but normal skin turgor, no edema or jugular venous distention, and no orthostatic hypotension. Relevant laboratory findings are as follows:

Serum:
- Sodium: 128 mEq/L
- Potassium: 4 mEq/L
- Blood urea nitrogen (BUN): 8 mg/dL
- Glucose: 90 mg/dL

Urine:
- Sodium: 110
- Osmolality: 610 mOsm/kg H_2O

What is the most likely diagnosis?

Hyponatremia, which is defined as serum sodium concentration below 135 mEq/L.

How is the etiology of this condition determined?

Volume status is assessed first. Although sodium loss can cause hyponatremia, excessive retention of water is usually the cause. A thorough history and physical examination can help correlate the patient's volume status to a cause of hyponatremia, and laboratory values can be used to confirm volume status. The cause of fluid loss can be determined by history (eg, vomiting, diuretics, diarrhea) and physical findings of low volume (eg, decreased skin turgor, low jugular venous pressure, orthostatic hypotension). Signs of excessive fluid retention include peripheral edema and increased JVP. In this case, the lack of such findings suggests that this patient is euvolemic.

What laboratory findings can help determine a patient's volume status?

Serum and urine osmolarity and **sodium concentration** can help confirm a patient's volume status. Most hyponatremic patients have a decreased serum osmolarity; however, intravenous mannitol or immunoglobulin therapy and hyperglycemia are causes of hyponatremia that accompany normal or increased serum osmolarity.

In patients with low plasma osmolarity, urine osmolarity can differentiate primary polydipsia (low/normal urine osmolarity) from impaired water excretion (high urine osmolarity, as in the majority of patients).

In patients with hypoosmolar serum and hyperosmolar urine, **urinary sodium** can then distinguish between hyponatremia caused by circulating volume depletion (eg, from heart failure, cirrhosis, or hypovolemia) leading to a decreased urinary sodium of less than 40 mEq/L, and euvolemic hyponatremia (eg, syndrome of inappropriate secretion of antidiuretic hormone [SIADH], hypothyroidism, or adrenal insufficiency), leading to urinary sodium of greater than 40 mEq/L.

In this case, what is the most likely etiology of the patient's volume status?

This patient's small cell lung tumor raises the likelihood of **SIADH (a paraneoplastic syndrome for small cell lung cancer)**. Physical findings and lab values are also consistent with SIADH.

What are the major causes of this condition?

- Ectopic ADH production by a tumor, particularly small cell (oat cell) carcinoma of the lung
- Intracranial pathology, such as trauma, stroke, tumors, or infection
- A wide range of drugs
- Major surgery, pain
- HIV infection
- SIADH may also be idiopathic.

What is the mechanism of action of ADH?

ADH is the main regulator of serum osmolality. ADH causes water channels (eg, aquaporin-2) of the principal cells of the kidney's collecting ducts to translocate to the cell membrane, thereby allowing more water to be reabsorbed. Its release from the posterior pituitary is stimulated by hyperosmolarity and by decreased effective circulating volume.

What are the treatments for this condition?

Treatment consists of tumor resection. If evidence of SIADH persists or resection is not possible, treatment involves restriction of free water intake, high salt diet, and loop diuretics. ADH receptor antagonists such as conivaptan, tolvaptan, and demeclocycline can also be used. Sometimes hypertonic saline may be needed for symptomatic hyponatremia.

CASE 13

The parents of a 5-year-old boy bring their son to a physician seeking a second opinion on his short stature and the bowing of his legs that has existed since he was 2 years of age. The family history is notable for bowed legs in the maternal grandfather and poor dentition in the mother. Physical examination is remarkable for frontal bossing, dental abnormalities, and tibia vara. Urine electrolyte analysis reveals elevated phosphate. Serum calcidiol is within normal limits, but calcitriol is low. Other relevant laboratory values are as follows:

Blood urea nitrogen: 16 mg/dL
Serum creatinine: 0.4 mg/dL (normal for age)
Parathyroid hormone (PTH): 54 pg/mL (normal: 10–55 pg/mL)
Serum albumin: 4.5 g/dL
Serum phosphate: 1.3 mg/dL
Alkaline phosphatase: 450 U/L
Total calcium: 8.7 mg/dL

What is the most likely diagnosis?

Hypophosphatemic (previously vitamin D–resistant) rickets is suggested by the patient's slow growth and skeletal findings as well as by his laboratory values: upper normal PTH, normal calcidiol and calcium levels with low calcitriol (which would normally be elevated in the setting of hypophosphatemia), and phosphaturia in the setting of normal renal function. Two inheritable forms exist. X-linked hypophosphatemic (XLH) rickets is more likely in this case, as it generally affects males and presents in childhood. The grandfather likely was similarly affected, whereas the heterozygous mother is only mildly affected with dentition problems. Less common autosomal dominant and recessive forms also exist, which affect both genders equally and present later in life.

What is the pathogenesis of this condition?

XLH is associated with a loss-of-function mutation in a gene named *PHEX* on the X chromosome responsible for the clearance of fibroblast growth factor-23 (FGF-23). Failure to clear this FGF-23 leads to phosphaturia and decreased 1α-hydroxylase activity in the kidney. This results in increased excretion of phosphate, decreased calcitriol production, and bone deformities.

What are the typical radiologic findings in this condition?

Figure 13-8 shows the widened diaphyses, funnel-like beaking of the metaphyses, and increased curvature of the femoral and tibial shafts. Enthesopathy (calcification of tendons, ligaments, and joint capsules) is also often seen. Lower-extremity deformities develop as the child begins to bear weight with ambulation.

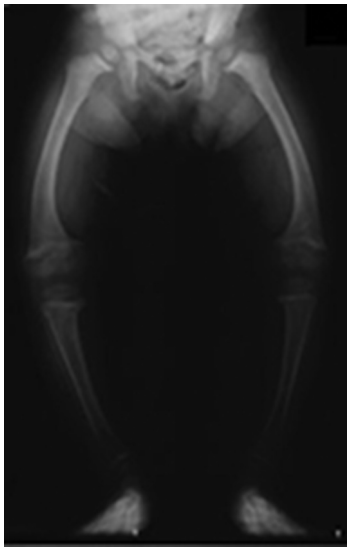

FIGURE 13-8. Bowed long bones and irregular, flared physes. (Reproduced courtesy of Dr. Michael Richardson.)

How is phosphate regulated in the body?

Calcium and phosphate regulation are linked. Phosphate is primarily reabsorbed in the proximal renal tubules. PTH and FGF-23 induce phosphaturia. PTH release is stimulated by low serum calcium, high phosphate, and low vitamin D. PTH decreases phosphate levels by inhibiting phosphate reabsorption in the proximal tubules. It also increases calcium levels by enhancing bone resorption and stimulating calcium reabsorption in the distal tubule. **Calcitriol** formation is stimulated by low serum calcium and phosphate levels and high PTH levels. It enhances gut absorption of both calcium and phosphate in order to promote bone mineralization. It also decreases PTH secretion.

What is the treatment for this condition?

A combination of phosphorus and calcitriol is required to restore age-appropriate growth velocity. Administration of either substance alone is insufficient. Phosphorus by itself binds calcium, thereby decreasing ionized calcium levels, which results in PTH release and secondary hyperparathyroidism. Serum phosphorus normalization also simultaneously decreases calcitriol formation. This removes the inhibitory effect of calcitriol on PTH synthesis and its stimulatory effect on intestinal reabsorption of calcium and calcium deposition in bone.

CASE 14

A 24-year-old woman presents to the ED with nausea, vomiting, tachypnea, sweating, and tinnitus. Her mother reports that she found an empty bottle of aspirin in the patient's bedroom. Physical examination reveals a temperature of 38.6°C (101.5°F), a heart rate of 100/min, a respiratory rate of 40/min, and altered mental status. Relevant laboratory values are as follows:

Arterial blood gas: pH 7.28
P_{CO_2}: 25 mm Hg
Bicarbonate: 17 mEq/L

Serum:
Sodium: 146 mEq/L
Potassium: 3.6 mEq/L
Chloride: 107 mEq/L
Salicylate: pending

Intravenous fluids are initiated, and charcoal and sodium bicarbonate are administered orally. The patient is transferred to the intensive care unit for further stabilization.

What is this patient's serum anion gap?

The equation $\mathbf{Na^+ - (Cl^- + HCO_3^-)}$ is typically used to calculate serum anion gap. K^+ is typically not included because of its small contribution as it is predominantly an intracellular cation. This patient's anion gap is $146 - (107 + 17) = 22$. A normal anion gap is 6–12 mEq/L, so this patient has an elevated anion gap.

What is the acid-base disturbance in this patient?

A mixed metabolic acidosis and respiratory alkalosis. The pH $<$ 7.35 indicates acidemia. Respiratory acidosis is unlikely given the below-normal P_{CO_2} and the high anion gap. In this setting the low bicarbonate indicates metabolic acidosis. Applying Winter's formula $\mathbf{(P_{CO_2} = (1.5 \times [HCO_3^-]) + 8 \pm 2)}$, the expected P_{CO_2} should be $P_{CO_2} = 1.5(17) + 8 = 33.5 \pm 2$. The "compensation" in this case is therefore excessive, suggesting an independent respiratory alkalotic process, which is consistent with a respiratory rate of 40/min.

What are the causes and two main types of acidosis in this patient's condition?

Metabolic acidosis derives from the loss of bicarbonate or the retention of acid, leading to a non–anion gap acidosis in the former, and an anion gap acidosis in the latter. A non–anion gap acidosis is always the result of conditions that result in hyperchloremia ($Cl^- > 109$ mEq/L). The major causes of normal anion gap metabolic acidosis can be remembered with the mnemonic **HARDASS** (**H**yperalimentation, **A**ddison disease, **R**enal tubular acidosis, **D**iarrhea, **A**cetazolamide, **S**pironolactone, and **S**aline infusion). The excess chloride suppresses bicarbonate reabsorption. Metabolic acidosis that is caused by retention of acid results in an anion gap metabolic acidosis because unmeasured acidic anions are retained. To recall the major causes of anion gap metabolic acidosis, the mnemonic **MUD PILES** is useful (**M**ethanol, **U**remia, **D**iabetic ketoacidosis, **P**araldehyde or **P**henformin, **I**ron tablets or **I**soniazid, **L**actic acidosis, **E**thylene glycol, **S**alicylates).

What are the causes of respiratory alkalosis?

Anything that stimulates the central respiratory drive and causes hyperventilation, such as cerebrovascular accidents or neurologic disease, can cause respiratory alkalosis. Hypoxia, such as that caused by anemia, high altitudes, and pulmonary disease, can likewise increase respiratory rate and thus cause respiratory alkalosis. Other hyperventilatory states such as mechanical overventilation or voluntary hyperventilation, such as in cases of anxiety, can also be causative.

What is the pathogenesis of this patient's condition?

Aspirin is hydrolyzed to salicylate once ingested. At toxic levels, salicylates cause a primary respiratory alkalosis by stimulating the medullary respiratory center to hyperventilate. Salicylates also stimulate skeletal muscle metabolism, increasing oxygen consumption and carbon dioxide production. This further stimulates hyperventilation. The metabolic acidosis component occurs because salicylates cause both lipolysis and uncoupling of oxidative phosphorylation, resulting in the production of organic acids, pyruvate, and ketones.

How is this condition treated?

Salicylate poisoning is primarily treated with sodium bicarbonate, which alkalinizes the serum and urine. Alkalinization promotes ionization of salicylic acid (HSal) to form the organic anion salicylate (Sal$-$) and H^+. Because salicylate is a charged species, it becomes trapped in the serum and urine and is unable to pass through hydrophobic lipid membranes and into cells. This inhibits diffusion of salicylate through the blood brain barrier and into the central nervous system (CNS), as well as promotes excretion through the urine.

CASE 15

A 19-year-old man on his first postoperative day after an appendectomy develops nausea and vomiting that is unresponsive to antiemetic therapy. He is unable to retain any fluids and has not consumed anything by mouth. Physical examination is notable for orthostatic hypotension. His arterial blood gas is notable for a pH of 7.48, partial pressure of carbon dioxide (P_{CO_2}) of 42 mm Hg, and bicarbonate of 28 mEq/L.

What acid-base disturbance is seen in this patient?

Metabolic alkalosis. The pH of the arterial blood is $>$ 7.45, which indicates alkalemia. Metabolic alkalosis can be distinguished from respiratory alkalosis by examining the P_{CO_2}. Normal or increased P_{CO_2} with increased bicarbonate indicates that the alkalosis is metabolic.

What does the body do to partially compensate for this condition?

A patient may **hypoventilate** to cause respiratory acidosis, which reduces pH as a compensatory measure. P_{CO_2} is increased by 0.7 mm Hg for every 1 mEq/L increase in bicarbonate. In this case, the bicarbonate is approximately 3 mEq/L above normal, which translates into an expected P_{CO_2} of $40 + 0.7(3) = 42.1$ mm Hg. Therefore, the metabolic alkalosis here is appropriately compensated.

How is this condition further classified?

Metabolic alkalosis usually reflects chloride losses. It can be caused by a number of conditions. Saline-responsive conditions are characterized by hypochloremia ($Cl^- < 95$ mEq/L) and low urinary chloride ($Cl^- < 10$ mEq/L). Saline-responsive metabolic alkalosis is caused by volume depletion (such as from persistent vomiting), cystic fibrosis, hypokalemia secondary to diuretic use, congenital familial chloridorrhea, and posthypercapnia.

Saline-unresponsive conditions are associated with low serum chloride and high urinary chloride ($Cl^- > 10$ mEq/L). Saline-unresponsive metabolic alkalosis can be caused by hyperaldosteronism, Cushing syndrome, alkali administration, and exogenous stimulation of mineralocorticoid production (eg, from licorice).

What is the pathogenesis of this patient's condition?

This patient is volume depleted because he stopped his intravenous fluids. In addition, he has been vomiting, which removes further fluid and chloride (from HCl). His alkalemia is therefore likely saline responsive. Hypovolemia stimulates the renin-angiotensin-aldosterone system. Elevated aldosterone causes reabsorption of Na^+ in exchange for K^+ and H^+. This further exacerbates the alkalemia and also leads to hypokalemia. Treatment involves restoration of volume status to prevent further exacerbation of the alkalemia and the complications of hypokalemia.

How does aciduria occur in this condition?

Aciduria is paradoxical in the setting of alkalemia. It can occur, however, in the setting of an extended period of volume depletion. The activated renin-angiotensin-aldosterone system exchanges Na^+ for K^+ and H^+. Over time, the pool of available intracellular K^+ becomes depleted, resulting in the exchange of only H^+. The subsequent aciduria is an indication of a metabolic emergency with severe hypokalemia.

CASE 16

A 64-year-old woman presents to her physician with sudden onset of nausea and severe back pain on her right side. The patient is in acute distress and is unable to find a comfortable position. She has no prior history of back pain. Her temperature is 36.9°C (98.4°F), her heart rate is 90/min, and her blood pressure is 130/80 mm Hg. Relevant laboratory findings are as follows:

Serum:
- Sodium: 140 mEq/L
- Chloride: 100 mEq/L
- Potassium: 4 mEq/L
- Phosphoric acid: 2.1 mEq/L
- Magnesium: 1.8 mg/dL
- Uric acid: 5.8
- Glucose: 100 mg/dL
- Calcium: 13 mg/dL
- Bicarbonate: 25 mEq/L
- BUN: 15 mg/dL
- Creatinine: 1 mg/dL

Urine:
- pH: 5.85
- RBCs: many

What is the most likely diagnosis?

Nephrolithiasis (kidney stones). Acute back/side pain (especially related to movement or that waxes and wanes) with gross or microscopic hematuria indicates kidney stones.

How is this condition classified?

Approximately 85% of renal calculi are **calcium oxalate** stones, which are strongly radiopaque. The second most common kidney stones are **struvite** (ammonium magnesium phosphate), which are radiopaque and associated with Proteus vulgaris or Klebsiella UTI (see Figure 13-9). Other, less common stones include **uric acid** stones (radiolucent) and **cystine stones** (moderately radiopaque). This patient most likely has calcium oxalate stones, given her hypercalcemia and normal urinary pH. Regardless of the type of stone, the diagnosis of nephrolithiasis is best confirmed with a noncontrast CT.

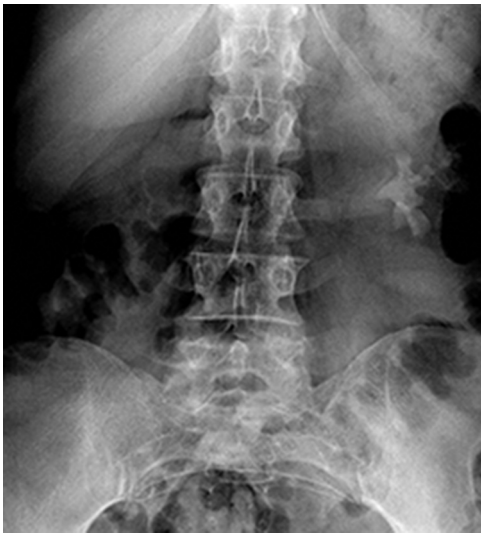

FIGURE 13-9. Plain radiograph showing a radiopaque struvite stone, which fills the renal pelvis and calyces and is commonly called a staghorn calculus. (Reproduced with permission from USMLE-Rx.com.)

What is the pathogenesis of this condition?

Calcium oxalate stones can be caused by hypercalciuria, hyperoxaluria, or hypocitraturia (citrate is a potent inhibitor of calcium precipitation/stone formation). Hyperoxaluria is often associated with malabsorption syndromes such as Crohn disease, in which fatty acids are poorly absorbed. These fatty acids then bind calcium in the intestinal lumen, which normally binds oxalate in the gut. As a result, oxalate absorption increases in these conditions.

What is the pathogenesis of the other three classifications of this condition?

Struvite stones form in the presence of increased ammonia in an alkaline urine. Such an environment is created by organisms such as *Proteus vulgaris*, *Klebsiella*, or *Staphylococcus aureus*, which produce urease, an enzyme that converts urea to ammonia and carbon dioxide. Uric acid stones are formed in acidic urine, which promotes uric acid precipitation. They are also associated with hyperuricemia, which is seen in gout and conditions with high cell turnover such as leukemia or myeloproliferative disease, where the metabolism of purine nucleic acids leads to uric acid production. Cystine stones are observed in congenital cystinuria.

What is the treatment for this patient's condition?

Treatment is conservative and consists of analgesics and hydration, and if obstructed or infected, antibiotics ± stenting. Extracorporeal shockwave lithotripsy may be necessary for stones that do not pass spontaneously as minimally invasive surgical intervention is usually indicated for stones $>$ 5 mm.

What hormonal imbalance can cause the electrolyte abnormalities seen in this condition?

Hyperparathyroidism should always be considered in a patient with calcium stones. The high calcium concentration and low phosphate concentration may be a result of excess parathyroid hormone (PTH). High PTH level increases renal reabsorption of calcium and decreases renal reabsorption of phosphate. It also stimulates renal activation of vitamin D, which increases calcium and phosphate absorption from the gastrointestinal tract.

CASE 17

A 7-year-old boy is sent to his school nurse after his gym teacher notes that he was unusually short of breath while playing basketball. After noticing that the boy's socks left deep indentations in his calves and shins bilaterally and that there is swelling around his eyes, the nurse obtains a urine sample that demonstrates proteinuria but not glucose, RBCs, or WBCs. The boy is then brought to the ED for further workup. Blood tests show:

Serum:
- Sodium: 129 mEq/L
- Potassium: 2.9 mEq/L
- Albumin: 2.3 g/dL
- Cholesterol levels: 276 mg/dL

What is the most likely diagnosis?

The boy's presentation suggests nephrotic syndrome, which is characterized by the triad of high urine protein losses, hypoalbuminemia, and hyperlipidemia. Patients often present with periorbital edema, peripheral edema, and/or ascites secondary to decreased plasma protein. This results in decreased plasma oncotic pressure, which, in turn, leads to sodium and free water retention.

What is the most likely cause of this patient's proteinuria?

The likely mechanism of action is loss of charge barrier at the glomerular membrane due to **effacement** of foot processes. The pathological changes would be evident only on electron microscopy; LM would appear normal.

What are the typical laboratory findings in this condition?

Serum albumin levels are low, and 24-hour urine protein excretion is high secondary to the massive loss of albumin at the glomerulus. Patients also often demonstrate severe hyperlipidemia. Less than one-half of patients have microscopic hematuria.

What are the treatments for this condition?

Nephrotic syndrome is treated with prednisone. Although the etiology of minimal change disease is unknown, it is thought to be due to an immune system abnormality. Therefore, corticosteroids (prednisone) and other immune suppressants are commonly used. Symptomatic treatment should also be initiated for edema, hypercoagulability, infection, decreased intravascular volume, and other clinical manifestations.

After 2 months of steroid treatment, the patient shows no decrease in his proteinuria, and a renal biopsy is obtained. What is the most likely diagnosis?

The boy likely has developed focal segmental glomerular sclerosis (FSGS), which can be resistant to steroid treatment. LM of the biopsy specimen may demonstrate focal areas of glomeruli with segmental sclerosis (see Figure 13-10). Electron microscopy demonstrates diffuse foot process derangement. FSGS can occur both as an idiopathic condition (primary FSGS) and as secondary to many predisposing factors including HIV infection, heroin use, severe obesity, and sickle cell disease.

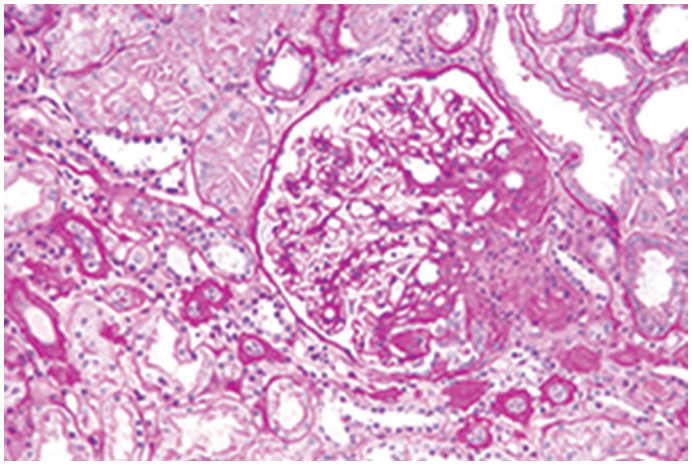

FIGURE 13-10. Periodic acid-Schiff (PAS) stain showing focal segmental glomerulosclerosis. Note the well-defined segmental increase in matrix and obliteration of capillary loops. (Reproduced courtesy of Dr. Michael Bonert.)

CASE 18

A 3-year-old boy is brought to his pediatrician after his mother notices that his limbs seem swollen and his stomach distended. She says the boy received an influenza shot 1 week ago. Physical examination reveals generalized pitting edema and shifting dullness of the abdomen suggestive of ascites. Urinalysis reveals 4+ proteinuria, and laboratory findings show decreased serum albumin, hypertriglyceridemia, and normal serum ionized calcium. Blood pressure, blood urea nitrogen (BUN), and serum creatinine values are within normal limits.

What is the most likely diagnosis?

The boy likely has nephrotic syndrome in the form of minimal change disease (lipoid nephrosis). It accounts for 90% of cases of nephrotic syndrome in children younger than 10 years of age. Age younger than 6 years, normal renal function, and absence of hypertension are strong indicators for this diagnosis.

What are the classic clinical features of this condition?

Nephrotic syndrome refers to the constellation of clinical and laboratory features of renal disease defined by the presence of proteinuria (greater than 3.5 g/day), hypoalbuminemia (less than 3 g/dL), edema, and hyperlipidemia (see Table 13-2). Besides albumin, other serum proteins, including immunoglobulins and antithrombin III, are also lost in the urine. As a result, patients with nephrotic syndrome are at increased risk for infection and thromboembolism.

Table 13-2. Findings in Nephrotic Versus Nephritic Syndrome

	Nephrotic syndrome	Nephritic syndrome
Clinical findings	Edema (often periorbital) Minimal hematuria	Hypertension Gross hematuria Decreased urine output
Laboratory findings	Hypoalbuminemia Hypercholesterolemia Proteinuria	Red cells/casts in urine Elevated creatinine Mild proteinuria

What pathologic changes at the glomerular level are associated with this condition?

The glomerular basement membrane contains heparan sulfate, which acts as a negative charge barrier that keeps small and negatively charged proteins such as albumin from crossing the membrane. Minimal change disease can be preceded by a recent infection or vaccination. It is believed that T cells release cytokines that injure glomerular epithelial cells. Consequently, the negative charge barrier is lost, whereas the size filter provided by the slit diaphragm proteins may remain intact during the initial course of disease. This leads to renal albumin wasting since albumin has a negative charge at neutral pH.

What are the likely histology findings?

Glomeruli appear normal on LM, leading to the name **minimal change**. However, when the glomeruli are viewed under electron microscopy, effacement or flattening of foot processes can be seen. The electron micrograph in Figure 13-11 shows effacement of the foot processes (arrows).

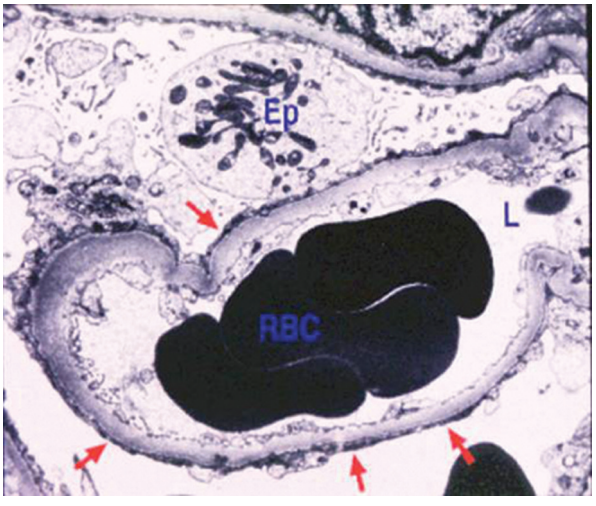

FIGURE 13-11. Electron micrograph showing effacement of the foot processes (arrows) in minimal change disease. (Reproduced with permission from USMLE-Rx.com.)

What is the treatment for this condition?

Given the high incidence of minimal change disease in children with nephrotic syndrome, this can be presumed to be the diagnosis until proven otherwise. Corticosteroids are given both as treatment and as a diagnostic tool because the majority of patients with minimal change disease respond promptly (thus avoiding biopsy).

CASE 19

A 37-year-old woman presents to her rheumatologist complaining of increased fatigue, periorbital edema, and swelling of her lower extremities of 3 days' duration. One month earlier she started on prednisone and hydroxychloroquine for her newly diagnosed lupus. Her previously normal urinalysis now reveals hematuria, proteinuria, dysmorphic RBCs, and RBC casts. Her serum creatinine is 2.5 mg/dL. Physical examination at this visit reveals a temperature of 38.3°C (100.9°F), a blood pressure of 150/90 mm Hg, and a weight increase of 5 kg (11 lb).

What classification of renal disorders do these symptoms represent?

Hematuria with RBC casts, dysmorphic RBCs, and variable degrees of proteinuria on urinalysis in the setting of new onset hypertension and edema indicate a nephritic syndrome. Causes of nephritic syndrome include membranoproliferative glomerulonephritis (GN), poststreptococcal GN, and vasculitis, which includes HSP/IgA nephropathy, lupus nephritis, ANCA vasculitis, and Goodpasture syndrome.

The next day, the patient is oligoanuric, and her serum creatinine rises to 3.2 mg/dL. What is the most likely diagnosis?

This patient most likely has rapidly progressive glomerulonephritis (RPGN), a clinical diagnosis characterized by features of glomerular disease in urine and by progressive loss of renal function over a short period of time. Any of the nephritic syndromes mentioned above can present as RPGN.

Kidney biopsy is performed the next day (see Figure 13-12). How does it aid in the diagnosis of this condition?

Kidney biopsy remains the gold standard for diagnosis. LM demonstrates the typical crescent formation of RPGN (see Figure 13-12). Immunofluorescence microscopy of a renal specimen distinguishes three major patterns of immunoglobulin deposition, representing three diagnostic categories:

- **Immune-complex glomerulonephritis** is categorized by scattered granular deposits of immune complexes. This is the typical "lumpy bumpy" pattern. It can be seen in Henoch-Schönlein purpura/IgA nephritis, postinfectious GN, and lupus, among others.
- **Anti–glomerular basement membrane disease** shows smooth, linear deposition of immunoglobulin as seen in Figure 13-4 in Case 6.
- **Pauci-immune glomerulonephritis** (the most common type) manifests sparse or absent immunoglobulins. It can be seen idiopathically or in the setting of anti–neutrophilic cytoplasmic antibody vasculitides.

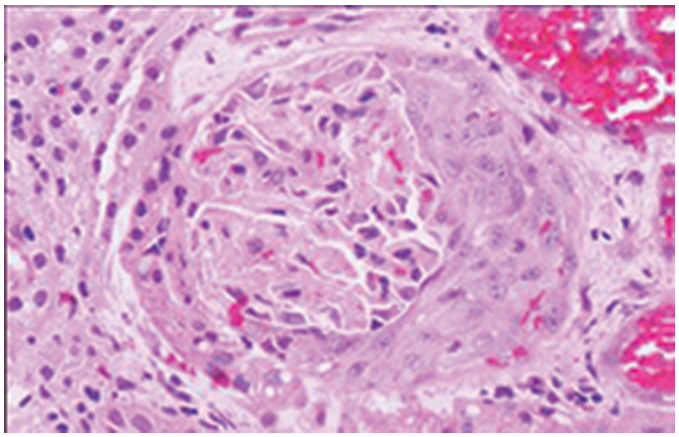

FIGURE 13-12. Microscopic image showing a glomerular crescent, the characteristic histopathologic feature of RPGN. (Reproduced with permission from USMLE-Rx.com.)

What is the pathogenesis of this condition?

Lupus-associated RPGN is rare but likely shares a mechanism similar to other types of lupus renal diseases. Mesangial and subendothelial immune complexes are present, primarily composed of DNA and anti-DNA antibodies. Subsequent activation of complement initiates the immune response.

How does the morphology of urine erythrocytes distinguish upper and lower urinary tract disorders?

Dysmorphic RBCs suggest upper tract bleeding or inflammatory glomerular or tubulointerstitial disease. RBC casts are also an indication of a glomerular disorder. Normal erythrocytes or eumorphic RBCs in urine analysis indicate lower urinary tract bleeding.

Should this patient receive treatment or will the condition self-resolve?

Untreated RPGN typically progresses to end-stage renal disease over weeks to months; therefore, prompt treatment is essential. Although treatment varies based on underlying etiology, empiric steroids should be given to all RPGN patients, sometimes with cyclophosphamide.

CASE 20

A 70-year-old man visits his primary care physician after going to a health fair and discovering that his blood pressure is 170/100 mm Hg. The previous year, his blood pressure was 135/85 mm Hg. The man also has a history of hypercholesterolemia. At the physician's office, his blood pressure is 150/100 mm Hg and heart rate is 80/min. An abdominal bruit is detected in the epigastric region to the right of midline. Laboratory findings are significant for a serum sodium level of 147 mEq/L and a serum potassium level of 3.3 mEq/L.

What is the most likely diagnosis?

The man most likely suffers from renal artery stenosis. The bruit described is in the region of the renal artery; this finding, in addition to the sudden increase in blood pressure and hypokalemia supports the diagnosis of renal artery stenosis. Imaging confirms the diagnosis.

What is the pathogenesis of this condition in this patient and how would it differ in a young woman?

In the elderly population, renal artery stenosis is seen more often in men and is mostly caused by atherosclerotic plaques (secondary to hypercholesterolemia). For younger patients, fibromuscular dysplasia of the renal arteries, seen more in females, would be the likely cause. Hypertension occurs by a similar mechanism in other diseases where there is narrowing of the renal arteries, as in polyarteritis nodosa.

What changes in renin secretion from each kidney are likely?

The kidney ipsilateral to the stenosis will increase renin secretion in response to a perceived decrease in arterial pressure due to decreased flow to the juxtaglomerular apparatus. The contralateral kidney will respond to the patient's resulting hypertension by decreasing its renin secretion (see Figure 13-13).

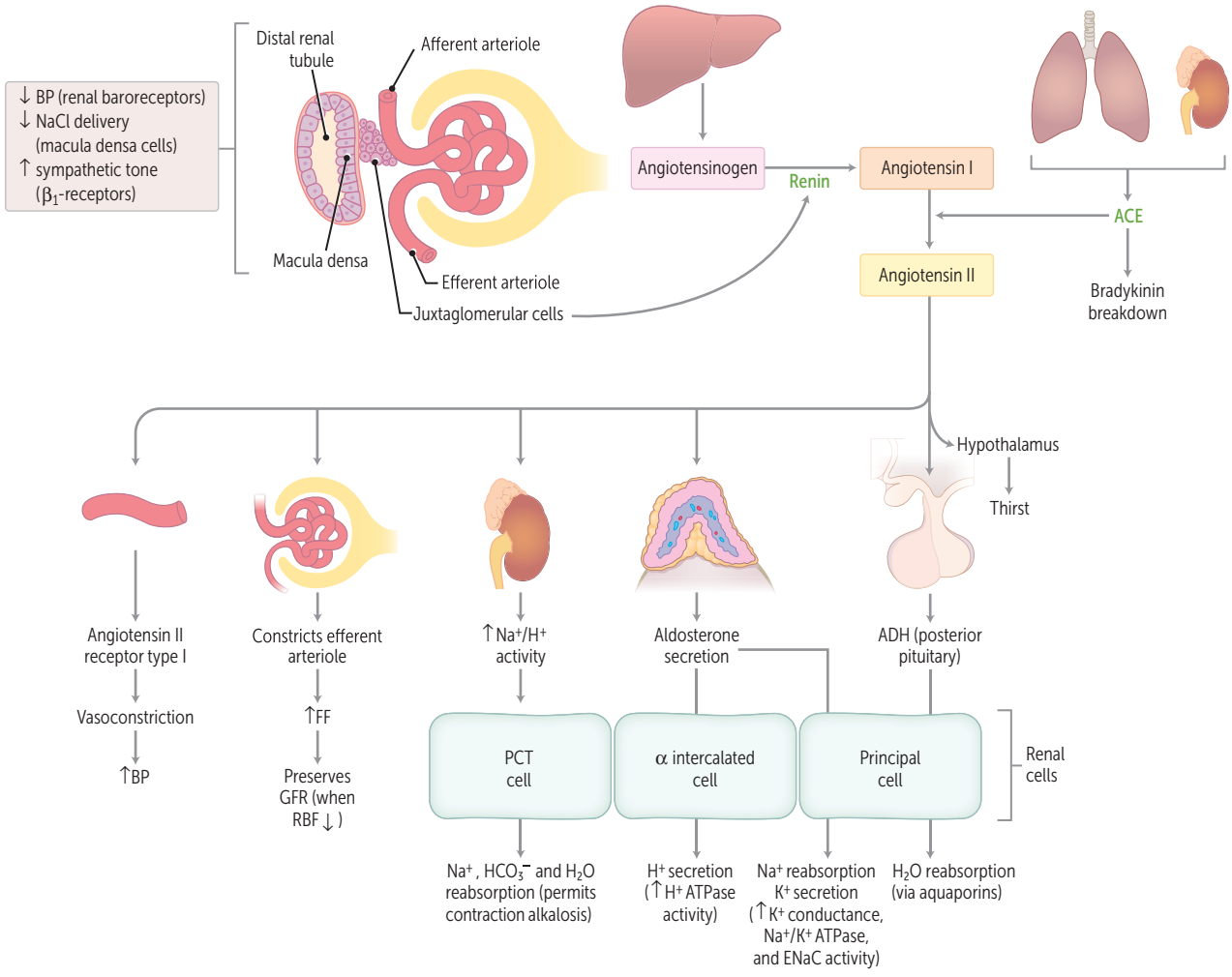

FIGURE 13-13. Renin-angiotensin system. (Reproduced with permission from USMLE-Rx.com.)

How does elevated plasma renin lead to hypertension?

In the plasma, renin converts angiotensinogen (produced in the liver) to angiotensin I. This is converted to angiotensin II by angiotensin-converting enzyme (ACE), which is secreted by pulmonary and renal endothelial cells. **Angiotensin II** acts on vascular smooth muscle to induce vasoconstriction, leading to increased blood pressure. Angiotensin II also acts on the adrenal cortex to stimulate the release of aldosterone, which increases renal absorption of sodium and water to increase blood volume and thus blood pressure.

What electrolyte abnormalities are associated with this condition?

As seen in hyperaldosteronism, the sodium reabsorption is isotonic; therefore, the serum sodium is normal, but hypertension ensues, and hypokalemia is expected as a consequence of renal potassium losses.

What is the medication of choice for this condition?

To correct the increased angiotensin II, an ACE inhibitor, such as lisinopril, or an angiotensin II receptor blocker (ARB), such as losartan, would be the medication of choice. Caution should be used with these drugs when renal artery stenosis is bilateral. Decreased perfusion of the kidneys in the case of a bilateral stenosis is normally compensated for by elevated levels of angiotensin II, which causes vasoconstriction to the glomerular efferent arteriole in order to maintain GFR. With the use of an ACE inhibitor or ARB, this regulatory response is inhibited and GFR can drop significantly.

What four classes of antihypertensive drugs directly target the effects of renin?

- ACE inhibitors (captopril, enalapril, and lisinopril)
- Angiotensin II receptor blockers (losartan, valsartan)
- Aldosterone-antagonizing diuretics (spironolactone, eplerenone)
- Renin inhibitors (aliskiren)

CASE 21

A 5-year-old girl develops a fever of 39°C (102.2°F) 6 months after receiving a well-matched deceased donor renal transplant for focal segmental glomerulosclerosis. Her immunosuppression consists of basiliximab (anti-interleukin-2), prednisone, mycophenolate, and tacrolimus. Blood cultures and viral titers including cytomegalovirus (CMV) are pending.

What is crossmatching?

In transplantation, the process of crossmatching determines whether the recipient has antibodies to the donor's WBCs. This measure prevents hyperacute rejection due to preformed antibodies against graft HLA molecules.

If CMV is present, what fraction of a blood sample will have the highest yield for the virus?

Because CMV invades WBCs, these cells contain the highest titer of the virus. Upon centrifuging a blood sample, a "buffy coat," representing $< 1\%$ of blood and seen between the plasma and hematocrit, will separate out most of the WBCs and platelets. Figure 13-14 shows renal tubular cells infected with CMV, with characteristic intranuclear inclusion bodies that give the appearance of "owl eyes."

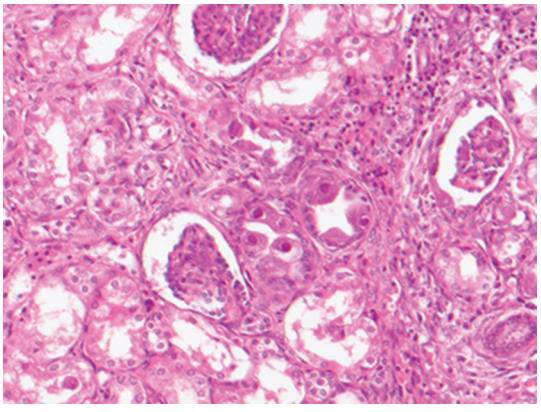

FIGURE 13-14. CMV-infected renal tubular cells with characteristic owl's eye nuclear inclusions. (Reproduced with permission from USMLE-Rx.com.)

Why is CMV of particular concern in this patient?

Approximately 80% of normal adults are infected with CMV yet remain asymptomatic because of their functional immune systems. There is a high likelihood that the donor may have been CMV positive. This girl is immunosuppressed and there is a significant probability that she has been exposed to CMV. As with other members of the herpesvirus family, CMV is more likely to reactivate in an immunosuppressed host. In the immunocompromised host, CMV can cause a variety of syndromes, including a mildly febrile upper respiratory illness, severe gastrointestinal syndrome with mild hepatitis, marked pancytopenia, or pneumonitis. CMV can also directly cause graft dysfunction.

What is the mechanism of action of the antiviral used for initial treatment of CMV in transplant patients?

Ganciclovir is the first-line drug against CMV. It is a guanosine derivative that inhibits CMV DNA polymerase. The most common adverse effects of ganciclovir are hematologic (thrombocytopenia and leukopenia). Foscarnet is an alternative for drug-resistant CMV.

In addition to following routine cancer screening recommendations, this patient should undergo additional screening for what malignancy?

Transplant recipients are at increased risk for skin cancers as a result of their chronic immunosuppression, especially squamous cell and basal cell carcinomas. Routine skin exams are recommended.

How does infection lead to fever in a normal individual?

Pyrogenic cytokines released by phagocytic cells of the immune system trigger the release of cytokines, including tumor necrosis factor-α and interleukin-1, which causes the hypothalamus to increase the set point of core body temperature. A key factor in the ability to mount a fever is the presence of an intact immune system. Infection is often difficult to detect in patients with poor immune function, as their ability to mount a fever is severely blunted.

CASE 22

An 18-month-old boy is brought to the pediatrician with symptoms of his third urinary tract infection (UTI) since birth. His mother reports the child has malodorous urine, a low-grade fever, and poor appetite. Urinalysis reveals bacteria on Gram stain.

What is the most likely diagnosis?

This boy most likely has vesicoureteral reflux (VUR), which is the most common urologic finding in children and cause of recurrent UTIs in the pediatric population. It is seen in 1% of all newborns and almost 50% of young children presenting with a UTI. A renal and bladder ultrasound should be obtained to look for anatomic abnormalities in any child under 2 years with a febrile UTI. If any abnormalities are detected, a voiding cystourethrogram is indicated to diagnose VUR.

Where is the bladder located in men and women?

The bladder sits behind the pubic symphysis and anterior to the rectum in both men and women. In men, the bladder lies anterior to the seminal vesicles above the prostate gland and, in women, is anterior to the uterus.

What are the two regions of the bladder?

The lower region is the trigone or the base of the bladder. The entry of the ureters marks the base of the trigone. The apex of the trigone is where the urethral orifice is surrounded by the internal urethral sphincter. The upper region of the bladder holds urine that enters the bladder via the ureteral orifices. The bladder can expand vertically and horizontally to hold up to 300–400 mL (~20–30 mL/kg) of urine before voiding.

What is the innervation of the bladder?

Afferent innervation involves afferent branches of the visceral nervous system, stretch receptors via parasympathetic nerves, and pain receptors via sympathetic nerves.

Efferent innervation is subdivided into parasympathetic, sympathetic, and somatic innervation (see Figure 13-15).

- Parasympathetic innervation involves **pelvic splanchnic nerves**. The preganglionic axons arise from the lateral horn cells at the S2–S4 levels; postganglionic cell bodies are in the bladder wall. These efferent nerves cause detrusor contraction and internal sphincter relaxation during micturition.
- Sympathetic innervation involves the **sacral splanchnic nerves**. The preganglionic axons arise from lateral horn cell bodies at the T10–T12 and L1–L2 levels. The postganglionic cell bodies are in the inferior mesenteric and hypogastric ganglia. These efferent nerves relax the detrusor and increase the tone of the internal sphincter during bladder filling and prevent reflux of urine into the ureters. In the adult male, these efferents also prevent reflux of semen into the bladder at the ureterovesical junction.
- Somatic innervation involves the **pudendal nerve**, which arises from the ventral rami of the S2–S4 levels. It innervates the external urethral sphincter, which is voluntarily relaxed to allow for micturition.

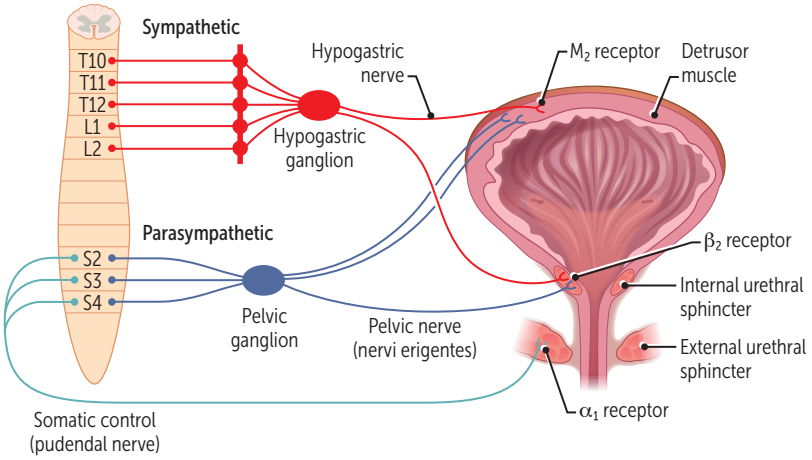

FIGURE 13-15. Bladder innervation. (Reproduced with permission from USMLE-Rx.com.)

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14
Reproductive

CASE 1

A 29-year-old woman G3P2 at 28 weeks' gestation is involved in a motor vehicle accident but does not immediately seek medical attention. Since the accident, she has noticed increasing lower abdominal pain and vaginal bleeding. Upon presentation to the ED, the patient appears uncomfortable and believes she is having prolonged contractions. Her vital signs are notable for mild hypotension and tachycardia. On physical exam, the patient appears anxious and demonstrates bilateral lower abdominal tenderness to palpation. Bright red blood is visible coming from the external os on speculum exam. Relevant laboratory findings are as follows:

Hematocrit: 34% (36%-47%)
Platelet count: 80,000/mm^3 (150-400 $\times$ 10^9/L)
Plasma fibrinogen: 180 mg/dL (400-450 mg/dL)

What is the most likely diagnosis?

Placental abruption. The presence of painful vaginal bleeding in the second or third trimester suggests abruption, and the presence of contractions is an additional clinical hint, as blood is uterotonic, which stimulates the myometrium to contract. She also has a risk factor, having been involved in a motor vehicle accident. The laboratory values, particularly the mild thrombocytopenia (normal platelet count in pregnancy is $>$ 150,000/mm^3) and decreased plasma fibrinogen (normal fibrinogen is $>$ 400 mg/dL in pregnancy), also suggest placental abruption with developing consumptive coagulopathy.

What is the differential diagnosis for vaginal bleeding in the third trimester? (See Table 14-1.)

Table 14-1. Differential Diagnosis for Third Trimester Vaginal Bleeding

Variable	Placental abruption	Placenta previa	Vasa previa
Pathophysiology	**Premature separation** of normally implanted placenta.	**Abnormal placental implantation** (complete, marginal, low lying).	Fetal vessels pass over the internal os due to a **velamentous umbilical cord insertion.**
Symptoms	**Painful, dark bleeding** that is usually sudden onset. **Abdominal pain,** commonly with **uterine contractions.**	**Painless, bright red bleeding.** Usually **no fetal distress** because the bleeding is maternal in origin.	**Painless bleeding** at rupture of membranes. Associated **fetal distress** because bleeding is fetal in origin.
Diagnosis	**Clinical.** Transvaginal ultrasound (TVUS) to look for retroplacental clot and rule out previa.	**Transabdominal US** to look for abnormal placentation.	**TVUS with Doppler** to demonstrate vessels passing over internal os.

What is the pathophysiology of this condition?

Abruptio placentae is the premature separation of a normally implanted placenta from the uterus occurring after 20 weeks' gestation and before delivery. The rupture of maternal blood vessels at the anchoring villi of the placenta causes a separation from the endometrium in which blood can accumulate (see Figure 14-1). The hemorrhage can be external or concealed. This in turn disrupts the fetal blood supply and in severe cases can lead to fetal death.

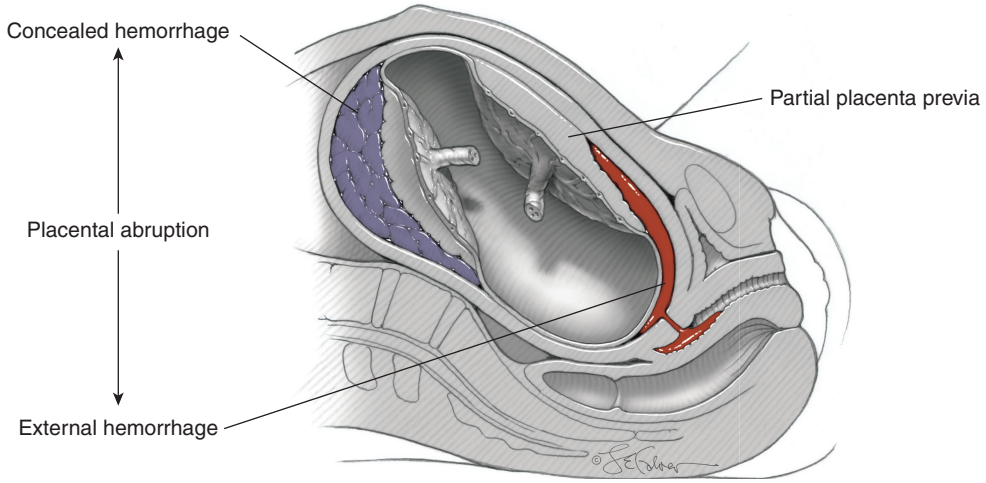

FIGURE 14-1. Schematic of placental abruption. Shown to left is a total placental abruption with concealed hemorrhage. To the right is a partial abruption with blood and clots dissecting between membranes and decidua to the internal cervical os and then externally into the vagina. (Reproduced with permission from Cunningham F, et al. eds. *Williams Obstetrics*, 24th ed, New York: McGraw-Hill; 2013.)

What risk factors are associated with this condition?

Risk factors for placental abruption include trauma, maternal hypertension, cigarette smoking, cocaine use, thrombophilia, increased parity, amniocentesis, prolonged rupture of membranes, and multifetal gestation.

What complication is the patient at greatly increased risk for developing?

Disseminated intravascular coagulation (DIC) occurs in approximately 10%–20% of cases of serious abruption with fetal death. In these cases, it is thought that the death of the fetus releases procoagulants, primarily thromboplastin, into the mother's circulation, triggering DIC. This results in intravascular activation of the coagulation cascade and produces a consumptive coagulopathy, with a prolonged prothrombin time (PT), partial thromboplastin time (PTT), and decreased platelets. Fibrin deposits in microcirculation lead to ischemic organ damage and hemolytic anemia, with subsequent fibrinolysis of the fibrin deposition. Ultimately, this can cause a bleeding diathesis along with clinical manifestations of thrombosis.

CASE 2

A 17-year-old girl presents to the clinic for primary amenorrhea. She reports that she has never had a period. Physical examination reveals normally developed breasts, the lack of axillary and pubic hair, and a small right inguinal mass. Pelvic examination reveals a short vaginal canal with a blind pouch and no palpable uterus or adnexal masses.

What is the most likely diagnosis?

Androgen insensitivity syndrome (also known as testicular feminization syndrome). The gene coding for the androgen receptor is mutated in these individuals, and as such, circulating levels of testosterone are within normal limits but unable to perform their function. Individuals inherit this disease in an X-linked fashion as the gene encoding the AR is found on the X chromosome. The disease affects approximately 1:100,000 **chromosomal males**.

What is the clinical presentation of this condition?

The diagnosis of complete androgen insensitivity is usually made in adolescence or young adulthood and is based on the following constellation of findings:

- Primary amenorrhea
- 46, XY karyotype
- Phenotypically female with normal breast development
- Absent uterus, but testes present
- Serum testosterone in normal adult male range

What is the pathophysiology of this condition?

This disorder results from dysfunction of the androgen receptors in a genetically male patient. The testes are present and secrete testosterone and müllerian inhibiting factor (MIF). However, the person cannot respond to this testosterone because the peripheral receptors are nonfunctional. Instead, the testosterone is converted into estradiol in peripheral tissues (especially adipose tissue), which initiates breast development. The vagina is often present but may be short and blind-ending. The MIF secretion inhibits normal development of the ovaries and uterus. Figure 14-2 illustrates genetic regulation of gonadal development.

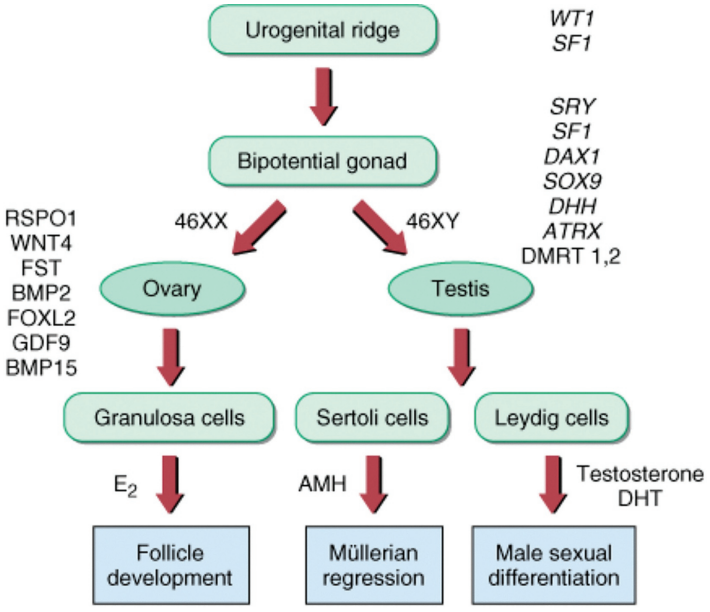

FIGURE 14-2. Transcription factors and cell types responsible for sexual differentiation. AMH, anti-müllerian hormone (müllerian-inhibiting factor); DHT, dihydrotestosterone. (Reproduced with permission from Fauci AS, et al. *Harrison's Principles of Internal Medicine*, 17th ed. New York: McGraw-Hill, 2008: Figure 343-2.)

What would confirmatory testing show in this condition?

- On karyotype, these patients are 46,XY.
- Pelvic ultrasound can show testes and the absence of a uterus and ovaries.
- Polymerase chain reaction assay can show mutations of the androgen receptor.

Testosterone and dihydrotestosterone (DHT) levels should also be measured. Both should be normal or high. Low testosterone may indicate testicular dysgenesis or Leydig cell aplasia/hypoplasia. If testosterone levels are normal but DHT levels are low, 5α-reductase deficiency is suspected because testosterone is converted to DHT by 5α-reductase.

What is the treatment for this condition?

Historically, gonadectomy was performed upon diagnosis. More recently, gonadectomies have begun to be postponed until sexual maturation is complete, as the incidence of testicular cancer in cryptorchid testes is low until after puberty is complete. Hormone treatment with estrogen is indicated in these individuals when gonadectomy is performed, or at the time of expected puberty if gonadectomy was performed before puberty. Psychological therapy is given because of the potential for gender confusion. Surgical reconstruction, such as vaginoplasty, may be needed to create a "functional" vagina, although if found earlier, the use of dilators may obviate surgical intervention.

CASE 3

A 35-year-old woman presents to the clinic with complaints of increased fishy-smelling vaginal discharge. The patient is sexually active with one partner and states that they use condoms for contraception. Physical examination reveals scant, malodorous vaginal discharge that is grayish-white in appearance, but a normal-appearing cervix and vaginal wall. A wet smear of the discharge reveals stippled squamous epithelial cells with smudged borders.

What is the most likely diagnosis?

Bacterial vaginosis (BV). The presence of clue cells, which are squamous epithelial cells with smudged borders, secondary to bacterial studding (see Figure 14-3), is strong evidence that the infection is bacterial in origin. An elevated pH (> 4.5) and a **positive whiff test** (amine release with potassium hydroxide results in a fishy smell) may aid in the diagnosis.

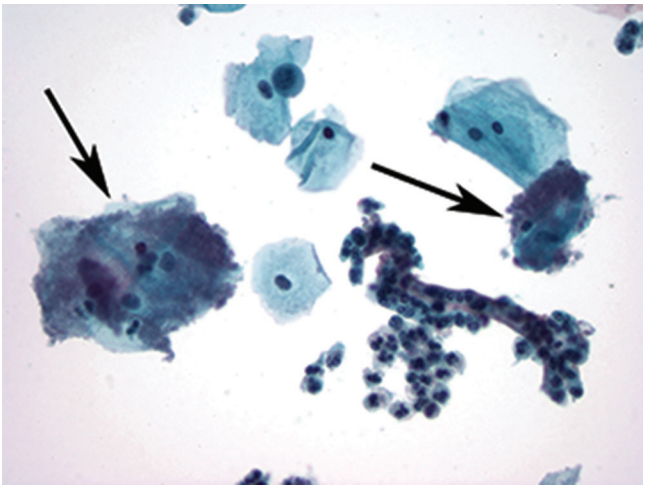

FIGURE 14-3. Pap smear sample showing clue cells. This is caused by an overgrowth of a gram-negative, small bacillus called *Gardnerella*. (Reproduced with permission from USMLE-Rx.com.)

What organism causes this condition?

BV is not generally considered a sexually transmitted infection (STI), and it can also occur in women who have not had intercourse. It is caused by an imbalance of naturally occurring bacterial flora within the vagina, with a decrease in favorable bacteria (lactobacilli) and an overgrowth of existing commensal bacteria (eg, *Gardnerella vaginalis*, *Prevotella* species, *Bacteroides* species).

What other conditions should be considered in the differential diagnosis?

Even with this patient admitting to regular condom use, STIs, such as trichomonas, *Neisseria gonorrhea*, or chlamydia, should still be considered. Most women with chlamydia and gonorrhea are asymptomatic, although they can have cervical motion tenderness on pelvic exam. Trichomonas often causes a frothy discharge with associated "strawberry" petechial on the cervix. Candida is another common cause of vaginitis, which is not sexually transmitted and commonly causes a thick, white, curdy-textured discharge and presents with itching.

What is the treatment for this condition?

Metronidazole (oral or vaginal gel) or vaginal clindamycin can be used to treat bacterial vaginosis (BV). Cervicitis, commonly caused by chlamydia and gonorrhea, is empirically treated with ceftriaxone and azithromycin. PCR-confirmed chlamydia is treated with azithromycin, and PCR-confirmed gonorrhea is treated with ceftriaxone and azithromycin, as ceftriaxone-resistant strains have become increasingly more common in recent years. Candida is treated with fluconazole.

CASE 4

A 64-year-old man goes to his provider's office complaining of difficulty urinating over the past several months. He says he has trouble initiating his stream of urine and after it begins, the flow is hard to maintain. Afterward, his bladder still feels full. The patient states that he often has to rush to the bathroom to make it in time, and the need to urinate awakens him several times each night. He denies seeing any blood in his urine or fever and chills. Other than mild hypertension, the patient's vital signs are stable. On physical exam, digital rectal examination reveals a nontender, uniformly enlarged prostate without distinct nodules or bogginess.

What is the most likely diagnosis?

Benign prostatic hyperplasia (BPH). BPH increases with age and is found in approximately one-half of men 51–60 years of age.

What are the typical signs and symptoms of this condition?

Classic symptoms of BPH include the following:

- Frequency
- Urinary urgency
- Nocturia
- Difficulty initiating and maintaining a stream
- A feeling of fullness in the bladder after voiding
- Dribbling

Classic signs and laboratory findings in BPH include the following:

- Uniformly enlarged prostate on digital rectal exam
- Elevated prostate-specific antigen (PSA) levels of 4–10 ng/mL. A markedly elevated PSA (especially values $>$ 10 ng/mL) raises suspicion for prostate cancer, although some patients with BPH will have normal PSA levels.

What is the pathophysiology of this condition?

The prostate gland has a central region surrounding the urethra and a peripheral region (see Figure 14-4). In BPH the central region hypertrophies in response to stimulation from the growth hormone dihydrotestosterone (DHT). In prostate cancer, it is often the peripheral region that grows. The close proximity of the urethra to the central region is what causes the compressive urinary symptoms classic to BPH, whereas the peripheral nature of the prostatic cancer lesions is linked to the delayed presentation.

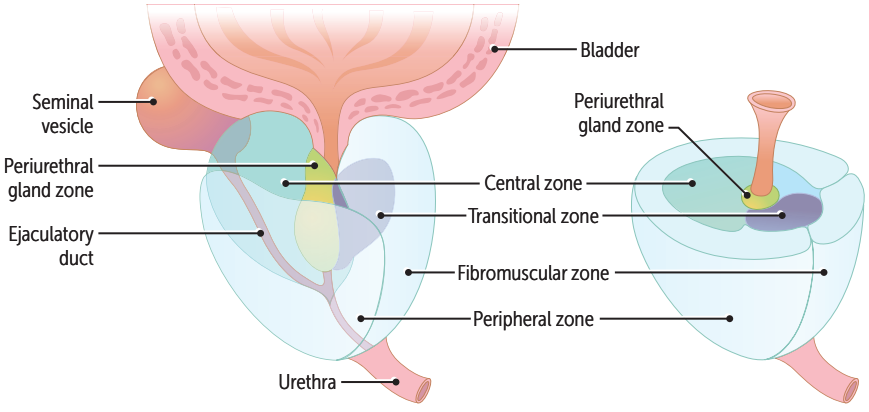

FIGURE 14-4. Prostate zones. (Reproduced with permission from USMLE-Rx.com.)

What are the potential complications of this condition?

Complications of BPH include the following:

- UTI secondary to urine stasis
- Bladder stone formation secondary to urine stasis
- Daytime sleepiness and exhaustion due to repeated nighttime awakenings from nocturia
- Acute urinary retention, which presents with symptoms such as abdominal pain and a suprapubic mass (the filled bladder). This can be spontaneous or secondary to triggers such as anticholinergics, antihistamines, or α-receptor agonists (eg, cold medications), all of which decrease bladder contractility.

What is the treatment for this condition?

Medical options include cholinergics (eg, bethanechol), α-blockers (eg, prazosin), and 5α-reductase inhibitors (eg, finasteride). Cholinergics help increase bladder contractility, whereas α-blockers relax the bladder neck so that urine flows more easily. The 5α-reductase inhibitors prevent the formation of DHT, a potent prostatic stromal and epithelial cell stimulant, so that prostate growth is retarded. Initial medical monotherapy should include α-blockers, but if patients cannot tolerate the adverse effects, such as hypotension and ejaculatory dysfunction, then 5α-reductase inhibitors can be added. Patients should be informed that these medications can take 6-12 months for symptomatic relief.

CASE 5

A 24-year-old woman presents to her physician after recently noticing a lump in her left breast. It seems to change sizes over the course of her menstrual cycle and is associated with some mild tenderness. On physical examination, a 1.0 cm, mobile, firm mass is palpated in the upper lateral quadrant. Bimanual compression of the nipple does not express any discharge, and the skin and nipple are without erythema or dimpling. No axillary lymph nodes are palpable.

What is the most likely diagnosis?

Approximately 90% of breast lumps discovered in women between 20 and 50 years of age are benign. Fibroadenomas are the most common breast tumors seen in women < 35 years old. They are benign, often arise quickly, and reabsorb within several weeks to months. Fibroadenomas do not carry an increased risk of breast cancer in most women. An estimated 20% of cases are bilateral or have multiple fibroadenomas in the same breast. The etiology of fibroadenomas is largely unknown, but a hypothesized estrogen-dependent relation has been proposed as the masses arise during reproductive years, increase during pregnancy, and resolve after menopause.

What are Cooper ligaments?

The superficial and deep pectoral fascia surrounding the breast are connected by fibrous bands known as **Cooper suspensory ligaments**. These ligaments are clinically important as tumor invasion into these structures leads to the physical exam finding of skin dimpling.

What is the structure of breast tissue?

Breast tissue is found between the second and sixth ribs and is made of parenchyma and stroma (see Figure 14-5). The parenchyma has 15–25 lobes, each of which has 20–40 lobules composed of alveoli. Lactiferous ducts offer drainage to the corresponding lobe. The ducts are dilated immediately before the nipple, forming the lactiferous sinuses.

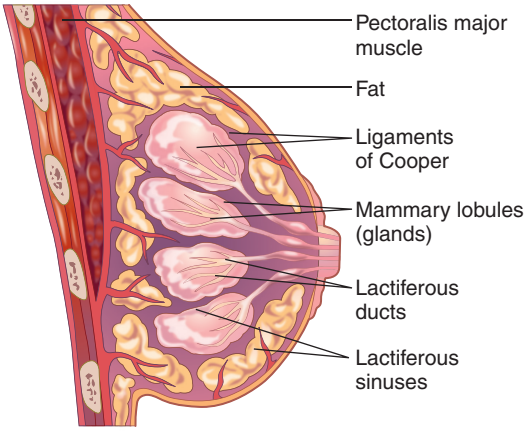

FIGURE 14-5. Breast anatomy. (Modified with permission from USMLE-Rx.com.)

What are the muscles underlying the breast tissue, and how are they innervated? (See Table 14-2.)

Table 14-2. Breast Tissue Muscles and Innervation

Muscle	Innervation
Serratus anterior	Long thoracic nerve
Latissimus dorsi	Thoracodorsal nerve
Pectoralis minor	Medial pectoral nerve
Pectoralis major	Lateral pectoral nerve Medial pectoral nerve

What is the treatment for this condition?

In most situations, these lesions should be biopsied to confirm the diagnosis and to assess the histologic features. Because of their typically benign nature, no treatment is necessary. The risk of breast cancer is slightly increased if the fibroadenoma has complex histology, if there is surrounding proliferative tissue, or if there is a family history of breast cancer. Disadvantages of excision include scarring, dimpling of the breast secondary to mass removal, damage to the duct system, and radiographic changes that could obscure further studies. The patient should be followed up in 3 to 6 months to assess for reabsorption. If concern for breast cancer remains, a needle or excisional biopsy is indicated.

CASE 6

A 17-year-old girl G0P0 is brought to the ED complaining of a 3-day history of nausea, vomiting, and intense abdominal pain. Her last menstrual period was 6 weeks ago, but she has a history of irregular cycles since menarche at age 12. She is not taking oral contraceptives. She is sexually active with her boyfriend and reports that they use condoms infrequently. Her medical history is significant for an appendectomy at age 13. She is afebrile, with a blood pressure of 113/76 and a heart rate of 95 BPM. On physical examination, the patient appears to be in distress, and palpation of the right lower quadrant reveals significant tenderness. Laboratory tests show that the β-human chorionic gonadotropin (β-hCG) level is 2500 mIU/L. Transvaginal ultrasonography reveals no intrauterine pregnancy.

What is the most likely diagnosis?

Ectopic pregnancy (see Figure 14-6). Ectopic pregnancy occurs at a rate of 17:1000 pregnancies. The majority (98%) of cases occur in the fallopian tubes, most often (90%) in the ampulla.

What signs and symptoms are commonly associated with this condition?

- **Non-ruptured ectopic pregnancy:**
  - Abnormal bleeding
  - Abdominal/pelvic pain
  - Nausea/vomiting
  - Pelvic mass
- **Ruptured ectopic pregnancy**
  - Local or generalized abdominal tenderness
  - Orthostatic hypotension
  - Shock
  - Shoulder pain – Kehr Sign (Blood in the abdominal cavity irritates the diaphragm and causes referred pain in the distribution of the phrenic nerve.)
  - Tachycardia

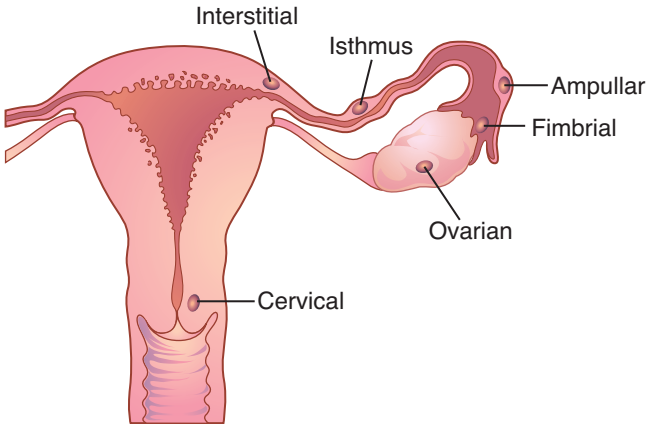

FIGURE 14-6. Common locations of ectopic pregnancies. (Reproduced with permission from USMLE-Rx.com.)

What risk factors are associated with this condition?

Risk factors include conditions causing structural or functional damage to the fallopian tubes:

- Diethylstilbestrol exposure in utero
- In vitro fertilization
- Pelvic inflammatory disease
- Pelvic surgery
- Previous ectopic pregnancy
- Tubal ligation
- Tuboplasty

What are the typical laboratory findings in this condition?

Normal β-hCG levels in pregnancy double every 48-72 hours until reaching 10,000–20,000 mIU/mL. B-hCG levels in an ectopic pregnancy are typically lower and take much longer for serum concentrations to double. The serum progesterone level (typically $<$ 15 ng/mL) is also much lower than in a uterine pregnancy. For diagnostic means, the discriminatory zone is a level of β-hCG for which an ultrasound would reliably visualize an intrauterine pregnancy. In ectopic pregnancies, the discriminatory zone for a transvaginal ultrasound is a β-hCG of 1500–2000 mIU/mL, with a discriminatory zone for transabdominal ultrasound being 6000–6500 mIU/mL.

What are the treatments for this condition?

Treatment may be medical or surgical depending on the clinical situation. The usual medical treatment is methotrexate, which may be given if no fetal heart rate is detected on ultrasound, the β-hCG level is $<$ 5,000 mIU/mL, the ectopic is not suspected to be ruptured, the patient is hemodynamically stable, and the patient's liver and renal tests are normal. β-hCG levels must be checked serially after administration of methotrexate, thus requiring a reliable patient follow-up period, to ensure the proper decline in β-hCG, indicating ectopic demise. Surgery is indicated if the criteria for medical intervention are not met. Surgery may include salpingectomy or salpingostomy, with the former being required if the tube is compromised, bleeding cannot be controlled, or the ectopic seems too large to remove through the salpingostomy.

CASE 7

A 26-year-old woman presents to her physician complaining of intense abdominal pain associated with the start of her menstrual periods. She has been trying unsuccessfully to get pregnant for the past 2 years, despite regular intercourse with her husband. On questioning, she reports pain with intercourse, especially on deep penetration. Her older sister has a similar history.

What is the most likely diagnosis?

Endometriosis.

What signs and symptoms are commonly associated with this condition?

Symptoms of endometriosis include the following:

- Cyclic pelvic pain starting 1–2 days before menses and continuing through the duration of menses, and possibly extending several days after cessation
- Dysmenorrhea
- Dyspareunia
- Abnormal bleeding
- Infertility
- Dyschezia

Signs of endometriosis include the following:

- Uterosacral nodularity
- Palpable adnexal mass
- Definitive laparoscopic evaluation
  - Endometrial implants appear as raspberry lesions or "powder burns." These raised, blue, red, clear or dark brown lesions lead to adhesions.
  - Ovarian cysts can have large collections of old blood called endometriomas or "chocolate cysts."

What is the pathophysiology of this condition?

In endometriosis, endometrial tissue is found outside the endometrial cavity, usually in the ovary and pelvic peritoneum. It is thought that this endometrial tissue is either transported via the lymphatic system, causing peritoneal tissue to undergo metaplastic change to become functional endometrial tissue, or that it is transported through the fallopian tubes in retrograde menstruation. There may also be genetic and immune factors that contribute to development of endometriosis. Endometriosis in premenarchal women also suggests müllerian embryonic rests as a possible etiology. Endometrial tissue causes adhesions, fibrosis, and severe inflammation.

What risk factors are associated with this condition?

Studies have suggested that the prevalence of endometriosis is around 1%–7%, with a much higher incidence (around 50%) in women with infertility. The risk of endometriosis is seven-fold higher in women who have a first-degree relative with the condition. Other risk factors associated with an increased risk of endometriosis include nulliparity, prolonged exposure to estrogen, shorter menstrual periods, heavy menstrual bleeding, and a lower BMI.

What are the treatments for this condition?

Medical treatment includes alleviating symptoms (with nonsteroidal anti-inflammatory drugs) and suppressing menstrual cycles to allow the lesions to involute. This is done with cyclic or continuous oral contraceptive pills, oral or intramuscular medroxyprogesterone (inducing "pseudopregnancy"), androgen derivatives, or gonadotropin-releasing hormone agonists (inducing "pseudomenopause"). Surgical treatment may be necessary in refractory cases, which includes resection or ablation of lesions, or nerve transection.

CASE 8

A 66-year-old man presents to clinic for follow-up on his hypertension. At the end of the visit, he mentions that he has recently had trouble maintaining an erection. The patient denies morning erections as well as any history of diabetes. He wants to know what the treatment options are for treating this condition in order to maintain a sexual relationship with his wife.

What is the most likely diagnosis?

Erectile dysfunction (ED) affects approximately 16% of men 20–75 years of age.

What physiologic factors are necessary to maintain an erection?

Developing and maintaining an erection depends on **neurologic**, **vascular**, **and hormonal factors** (see Figure 14-7). Neurologic control of erectile function is via the dorsal nerve of the penis, a branch of the pudendal nerve that provides autonomic innervation to the pelvis. Vascularly, significant arterial flow into the penis (specifically into the corpora cavernosa and corpora spongiosum) must be maintained and venous outflow prevented. Adequate blood flow is achieved through cyclic guanosine monophosphate (cGMP)-mediated relaxation of the smooth muscle of the corporae, which requires nitric oxide. Hormonally, adequate production of testosterone is required.

What risk factors are associated with this condition?

The main risk factors for developing ED are primarily vascular (hypertension, cardiovascular disease, and diabetes mellitus).

Other risk factors include obesity, smoking, sedentary lifestyle, nerve injury, pelvic trauma/radiation, spinal cord injury, prostate surgery, and psychiatric disorders (eg, depression, performance anxiety, fear of sudden death).

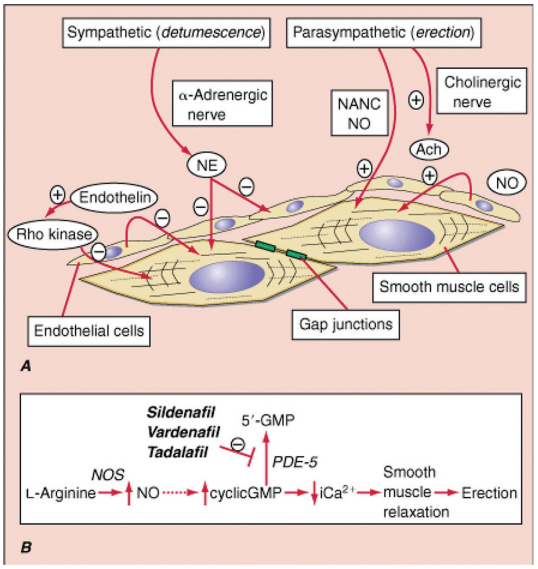

FIGURE 14-7. Innervation and neurotransmitters of penile tumescence and erection. Cyclic GMP, cyclic 3′,5′-guanosine monophosphate; iCa^{2+}, intracellular calcium; NANC, nonadrenergic, noncholinergic pathways; NO, nitric oxide; NOS, nitric oxide synthase; PDE-5, phosphodiesterase type 5. (Reproduced with permission from Fauci AS, et al. *Harrison's Principles of Internal Medicine*, 17th ed. New York: McGraw-Hill, 2008: Figure 49-1.)

What drugs most commonly cause this condition?

- Selective serotonin reuptake inhibitors (SSRIs)
- Spironolactone
- Sympathetic blockers (clonidine, guanethidine, methyldopa)
- Thiazide diuretics
- Ketoconazole
- Cimetidine (but not ranitidine)
- Antipsychotics
- Cholesterol-lowering drugs
- Alcohol
- Nicotine

What is the treatment for this condition?

The main treatment for ED is phosphodiesterase inhibitors, such as sildenafil and vardenafil. These work by preventing the degradation of cGMP, thereby allowing dilatation of the corpora and adequate blood flow into the penis. Patients should not be started on PDE-5 inhibitors if they are currently taking nitrates or α-blockers (tamsulosin, doxazosin, terazosin), as these patients are at increased risk for symptomatic hypotension. Other treatments include vacuum pumps, penile prosthesis, and direct injection of α-blockers (eg, phentolamine) into the penis. Depression should be treated as appropriate. SSRIs and behavioral therapy are helpful in the treatment of performance anxiety.

CASE 9

A 36-year-old woman at 24 weeks' gestation presents to the clinic for a routine prenatal visit. Her fetus is large for gestational age, and she is scheduled for an oral glucose tolerance test (OGTT). She had one previous pregnancy with no complications and is obese but otherwise healthy. Routine 1-hour OGTT revealed a glucose level of 144 mg/dL. Subsequent 3-hour OGTT revealed the following glucose levels:

Fasting: 97 mg/dL
1 hour: 210 mg/dL
2 hours: 190 mg/dL
3 hours: 143 mg/dL

What is the most likely diagnosis?

Gestational diabetes mellitus (GDM) is defined as glucose intolerance first documented in pregnancy.

What is the pathophysiology of this condition?

GDM occurs in approximately 4% of all pregnancies. Normal pregnancy is a pro-diabetic state characterized by insulin resistance and decreased peripheral uptake of glucose. This is mediated by the production of counter-regulatory (anti-insulin) hormones by the placenta, including human placental lactogen, cortisol, and placental growth hormone.

How is this condition diagnosed?

GDM is most often asymptomatic and is usually detected at 24–28 weeks' gestation by a routine OGTT. After failing the 1-hour OGTT, the following 3-hour OGTT levels are diagnostic for GDM:

	Fasting	One-hour	Two-hour	Three-hour
100g load test	> 95 mg/dL	> 180 mg/dL	> 155 mg/dL	> 140 mg/dL

Other signs include glycosuria, hyperglycemia, and fetus large for gestational age.

What risk factors are associated with this condition?

Risk factors include age > 35 years, family or past history of GDM, fetus large for gestational age, glycosuria at first prenatal visit, obesity, polycystic ovarian syndrome, previous stillbirths or abortions, maternal birthweight > 4.1 kg (9 lb), and Hispanic or African-American race.

What are the common fetal complications associated with this condition?

Common fetal complications include:

- Congenital defects
  - Sacral agenesis (associated with maternal diabetes mellitus, not gestational diabetes)
- Macrosomia
- Perinatal mortality (2%–5%)
- Shoulder dystocia

What are the treatments for this condition?

Affected women should adhere to a diabetic diet. Fasting blood glucose and 1-hour or 2-hour postprandial glucose levels should be routinely monitored. If levels remain high for 2 weeks, medical therapy should be instituted with oral agents (eg, glyburide or metformin) or insulin. Fetal growth and well-being should also be monitored.

CASE 10

A 17-year-old woman at 15 weeks' gestation presents to a primary care clinic with painless vaginal bleeding and severe nausea and vomiting. She has not received medical care during her pregnancy. On physical examination, the patient is hypertensive and uterine enlargement is noted, with estimated uterine size consistent with 20 weeks' gestation. Transabdominal ultrasound is performed, and a snowstorm appearance is seen. Lab tests reveal the patient has a markedly elevated β-hCG, and her urinalysis is positive for protein.

What is the most likely diagnosis?

Hydatidiform mole or molar pregnancy. In North American and European countries, rates tend to be 1:1000–1500 pregnancies, whereas in Asian and Latin American countries, the rates are higher, reaching 1:12–500 pregnancies.

What risk factors are associated with this condition?

The main risk factor is extremes of reproductive age (younger than 20 or older than 35 years). A history of molar pregnancy is also predictive.

How does this condition develop?

A **complete mole** develops when an enucleate "empty" egg is fertilized by a haploid sperm that then replicates. This results in 46 chromosomes (all paternal) but no fetal parts. A **partial mole** results from a haploid ovum and two sperm. The karyotype is typically triploid (69 chromosomes) and fetal parts may be present. There are some cases of recurrent moles that are due to a loss of maternal imprinting.

What are the typical signs, symptoms, and clinical presentation of this condition?

Classic presentation includes the following:

- Vaginal bleeding
- Hyperemesis gravidarum (due to high levels of β-hCG)
- Hyperthyroidism

The presence of a molar pregnancy is detected by an overly large uterus, lack of fetal heartbeat, lack of a fetus on ultrasound, very high levels of β-hCG (levels are often > 100,000 mIU/mL), and, occasionally, grapelike clusters exuding from the cervix. The diagnosis is typically made in early pregnancy with evidence of a "snowstorm pattern" on ultrasound, as seen in this patient (see Figure 14-8).

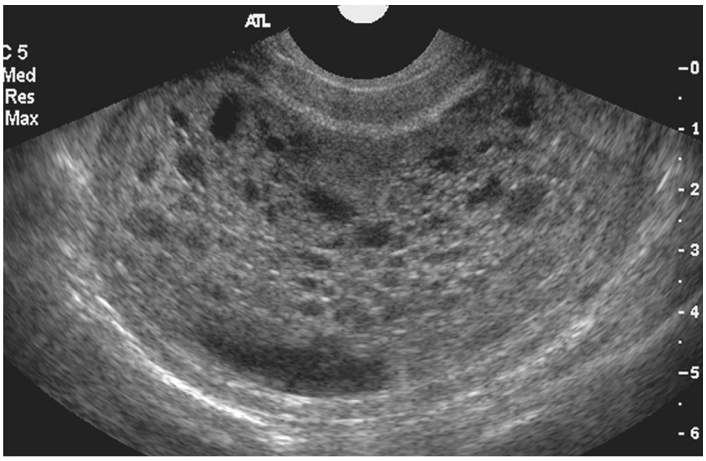

FIGURE 14-8. Sagittal endovaginal ultrasound showing a molar pregnancy. The pattern is described as a bunch of grapes ("cluster of grapes" or "honeycombed uterus" or "snow-storm"). (Reproduced with permission from USMLE-Rx.com.)

What complications are associated with this condition?

- Increased risk for preeclampsia. If a patient develops features of preeclampsia before 20 weeks' gestation, then a molar pregnancy must be considered.
- Ovarian theca-lutein cysts (which are benign and resolve when the mole is removed).
- Respiratory distress (secondary to trophoblastic embolization).
- Choriocarcinoma (other causes of choriocarcinoma are spontaneous or induced abortion, ectopic pregnancy, and normal pregnancy).

What is the treatment for this condition?

Molar pregnancies should be evacuated via suction curettage, regardless of type or presentation date. Patients should be monitored following this procedure via serial β-hCG levels for disease recurrence or incomplete removal. This condition is highly sensitive to chemotherapy (usually methotrexate or actinomycin D), which should be employed following persistently elevated levels of β-hCG. The most common site of metastasis is the lungs, and the metastases also resolve with chemotherapy. Patients who develop choriocarcinoma are asked not to get pregnant for a year so that they can be monitored for recurrence through serial β-hCG levels.

CASE 11

A husband and wife present to a fertility clinic because they have been trying to get pregnant without success for 1 year. The husband is tall and thin. On physical examination, he has sparse axillary and pubic hair, decreased muscle mass, small testes, and gynecomastia. His urinary gonadotropin levels are elevated, and analysis of his sperm reveals azoospermia.

What is the most likely diagnosis?

Klinefelter syndrome.

What is the pathogenesis of this condition?

Klinefelter syndrome is estimated to occur in men at a rate of approximately 1:1000 and is a chromosomal abnormality in which the genotype is **47,XXY**. Dysgenesis of the seminiferous tubules, as well as damage to Leydig cells, causes primary testicular failure with decreased androgen production.

Complications of Klinefelter include the following:

- Azoospermia and infertility
- Gynecomastia
- Small testes and penis
- Loss of libido
- Osteoporosis
- Decreased muscle mass
- Sparse axillary and pubic hair

Risks of Klinefelter include the following:

- Increased risk of developing breast cancer (20x that of the typical male)
- Decreased mental capacity
- Increased risk of anxiety and depression

All of these complications and risks worsen with an increasing number of X chromosomes.

What tests and/or imaging tools could be used to confirm the diagnosis?

- Elevated follicle-stimulating hormone (FSH) levels are a key finding in Klinefelter. Because the seminiferous tubules are unformed, there is a lack of Sertoli cells; therefore, no inhibin (made by Sertoli cells) is produced. Without inhibin, there is a loss of negative feedback on FSH, causing elevated levels (see Figure 14-9). LH levels are also elevated as a result.
- Testosterone levels are low, whereas estradiol levels are high.
- The definitive diagnosis requires karyotype, typically of peripheral leukocytes.

What is the treatment for this condition?

Androgen replacement therapy should begin around puberty. Androgen replacement has been shown to help with virilization, psychosocial development, hair growth, muscle mass, libido, testicular size, and precocious osteoporosis. Also, for younger patients, it may be necessary to include behavioral therapy to help treat concomitant language disorders, difficulties at school, or socialization restrictions.

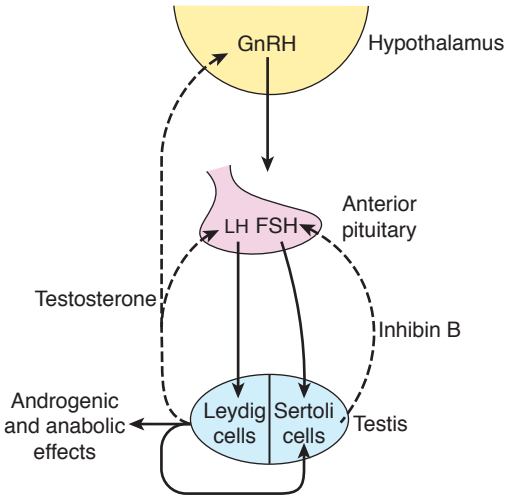

FIGURE 14-9. Hypothalamic-pituitary-gonadal axis. FSH, follicle-stimulating hormone; LH, luteinizing hormone. (Reproduced with permission from Barrett KE, et al. *Ganong's Review of Medical Physiology*, 23rd ed. New York, NY: McGraw-Hill, 2010: Figure 25-20.)

What can be done to increase the fertility of patients with this condition?

Most men with Klinefelter produce small amounts of sperm, but it is typically not found in the ejaculate. Since some sperm are produced, they can be extracted from the testicles for use in in vitro fertilization.

CASE 12

A 42-year-old African-American woman visits her physician complaining of heavy menstrual periods that last for several days. This has been occurring for the past 3 months and is associated with pain and fatigue. She is also complaining of some intermittent constipation and multiple urinary tract infections over the past couple of years. Physical examination reveals an irregularly enlarged uterus with multiple palpable masses. Laboratory tests show that hemoglobin is 11.3 g/dL and hematocrit is 33.3%.

What is the most likely diagnosis?

The heavy vaginal bleeding and palpable masses suggest leiomyomas, or uterine fibroids.

What is the epidemiology of this condition?

Uterine fibroids can be found in 25% of all reproductive-aged women. The incidence of leiomyoma is greatly increased in African-American women (two to three times increased risk compared to white women). Leiomyoma is the most common benign neoplasm in women.

Which cells of the uterus are affected in this condition?

Leiomyomas of the uterus arise from the smooth muscle cells of the myometrium. Fibroids within the uterus can be submucosal, subserosal, or intramural (see Figure 14-10). Submucosal fibroids are most often associated with abnormal bleeding and infertility, whereas subserosal fibroids are most often the cause of pressure due to mass effect. Patients may present with single or multiple fibroids, with the possibility of varying subtypes presenting concurrently.

How does the size of this neoplasm change with age?

The estrogen and progesterone sensitivity of leiomyomas usually results in increased size during the first trimester of pregnancy and shrinkage after menopause.

Is this patient at increased risk for uterine malignancy?

Most leiomyosarcomas arise de novo, and malignant transformation of leiomyomas into leiomyosarcoma is rare. Approximately 9% of uterine malignancies are leiomyosarcomas.

What uterine abnormality is associated with an increased risk of endometrial cancer?

Endometrial hyperplasia, which is characterized by abnormal glandular proliferation, is considered to be a premalignant lesion. This is caused by increased estrogen stimulation and, like uterine fibroids, often presents with abnormal vaginal bleeding. Therefore, its presence must be distinguished from abnormal vaginal bleeding secondary to uterine fibroids. This can be accomplished by histological examination of the endometrium obtained by endometrial biopsy.

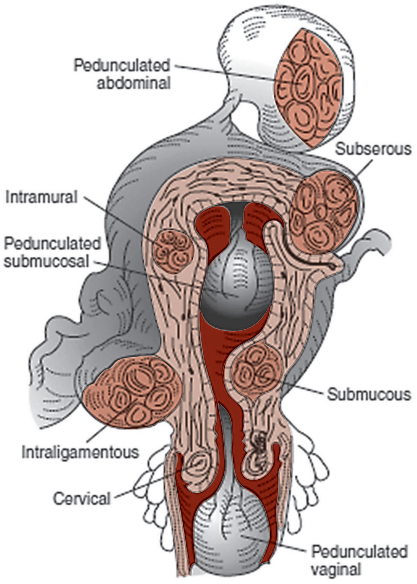

FIGURE 14-10. Myomas of the uterus. (Modified with permission from DeCherney AH, et al., eds. *Current Obstetrics & Gynecology Diagnosis & Treatment*. 8th ed. New York, NY: McGraw-Hill; 1994.)

What is the treatment for this condition?

Expectant management is often considered in mild cases. The most commonly employed hormonal therapy prescribed for symptomatic relief is oral contraceptive pills. Other medical therapy includes nonsteroidal anti-inflammatory drugs for pain relief, as well as the levonorgestrel intrauterine device (IUD) and other hormonal medications (eg, danazol, gonadotropin-releasing hormone [GnRH] analogs, and aromatase inhibitors). For definitive treatment, surgery, including myomectomy or hysterectomy, can be performed. Other possibilities include uterine artery embolization and MRI-guided focused ultrasound surgery.

CASE 13

A 48-year-old woman presents reporting increasing menstrual irregularity. The patient states that she can have up to 3 months between periods and that this irregularity began about 2 years ago. She is also complaining of hot flashes that occur a few times each day and sometimes awaken her at night. She says she is also less interested in sex because she has begun to find it somewhat painful.

What is the most likely diagnosis?

The start of menopause. Menopause is defined as 12 months without a period (amenorrhea) in a woman older than 45 years of age without another cause for amenorrhea. The average age of menopause onset is 51 years. If this occurs in women younger than 40 years of age, it is called premature ovarian failure, and a full workup should be performed to evaluate the cause.

What is the differential diagnosis for irregular vaginal bleeding, and how should it be evaluated?

Vaginal bleeding may be caused by the following:

- Uterine fibroids
- Uterine polyps
- Pregnancy complications
- Menopause
- Thyroid dysfunction
- Endometrial hyperplasia (often secondary to anovulatory cycles and chronic estrogen exposure)
- Endometrial cancer

The gold standard to evaluate these conditions is a uterine biopsy. Transvaginal ultrasound (TVUS), to evaluate the uterine cavity, can also be diagnostic. The endometrial stripe, the uterine lining on TVUS, can be evaluated, with any finding greater than 5 mm an indication for further workup in a postmenopausal woman.

What are the signs, symptoms, and laboratory values associated with this condition?

Signs and symptoms of menopause include a change in menstrual cycle length, skipped periods, hot flashes, sleep disturbance, vaginal dryness (resulting in itching and dyspareunia), and an increase in urinary tract infections (due to increased vaginal pH).

Laboratory values in menopause include elevated follicle-stimulating hormone and decreased estradiol levels. Luteinizing hormone may also be elevated later in the course of menopause.

What complications are associated with this condition?

Patients may have bothersome symptoms, such as vasomotor flushing. Menopause also increases a woman's risk of developing osteoporosis. It is estimated that women can lose up to 20% of their bone density in the years surrounding menopause. This occurs because estrogen, which normally inhibits bone resorption, is decreased. Women undergoing menopause are also at risk for depression. In addition, the risk of cardiovascular disease increases after menopause.

What are the treatments for this condition and its complications?

Short-term estrogen therapy (2–3 years and not more than 5 years) is recommended for moderate to severe vasomotor flushing. Hormone replacement therapy (HRT) is only indicated in patients younger than 60 who are within 10 years of beginning menopause, with no contraindications to HRT (eg, breast cancer, active liver disease, coronary artery disease [CAD]). Long-term therapy is not recommended. Women with an intact uterus need a progestin in addition to estrogen in order to prevent endometrial hyperplasia. The benefits of reducing hot-flash symptoms must be weighed carefully with the increase in cardiovascular adverse events. Topical estrogen can be applied to treat vaginal dryness. For women with osteoporosis or at high risk for the disease, bisphosphonates, which prevent bone resorption, are the preferred first-line agent. The selective estrogen receptor modulator raloxifene is another alternative. These therapies should be used in addition to calcium/vitamin D, exercise, and smoking cessation. Selective serotonin reuptake inhibitors can be given for depressive symptoms.

CASE 14

A 65-year-old woman presents to the clinic with several months of abdominal and pelvic pain, vaginal bleeding, and a change in bowel habits. She has also noticed an increase in her abdominal circumference but states that she has lost weight and experienced night sweats over this time frame. Her physical examination is positive for an abdominal fluid wave and her cancer antigen–125 (CA-125) levels are within normal limits. Despite this, malignancy is suspected, so an abdominal/pelvic CT is ordered, which shows an ovarian mass.

What is the most likely diagnosis?

Ovarian cancer is the second most common gynecologic malignancy. It is also the fifth most likely cause of cancer death in women.

What are the typical signs and symptoms of this condition?

Nonspecific symptoms are characteristic in ovarian cancer and include abdominal and pelvic pain, bloating, vaginal bleeding, and changes in bowel habits. Physical signs are usually present only in advanced disease and include palpable ovarian or pelvic masses, ascites, pleural effusions, and bowel obstruction.

What are the different forms of this condition?

Most ovarian cancers (95%) are epithelial in origin. The two most common types of epithelial ovarian cancer are serous and mucinous. The serous types, which comprise 75% of epithelial carcinomas, are often bilateral. The mucinous type can progress to pseudomyxoma peritonei. Pseudomyxoma peritonei is a condition in which the mucinous adenocarcinoma cells seed the peritoneum. These cells continue to produce mucus and fill the abdominal cavity, eventually obstructing the bowel.

Other types of ovarian cancers include sex cord stromal tumors, germ cell tumors, and metastatic cancer to the ovaries.

What risk factors are associated with this condition?

- Early menarche or late menopause
- Nulligravidity
- Infertility
- Endometriosis
- Family history of ovarian or breast cancer
- *BRCA* mutation or Lynch syndrome

Conversely, protective factors include multiple pregnancies, tubal ligation, breastfeeding, and oral contraceptive pill use. It is theorized that protection against ovarian cancer results from a decreased number of ovulatory cycles.

What tests and/or imaging tools can be used to confirm the diagnosis?

Most women have stage III disease at the time of diagnosis and present with evidence of disease that has spread throughout the peritoneal cavity. Initial tests include transvaginal ultrasound, CT, and screening for the tumor marker CA-125. Common findings on CT include pelvic mass, omental cake, lymphadenopathy, and ascites. CT and ultrasound often miss cancers, however, and CA-125 is better able to detect recurrences than to establish an initial diagnosis. CA-125 can be elevated in a number of benign gynecologic conditions (eg, endometriosis, leiomyomata), and care should be taken when ordering and interpreting this antigen. Diagnostically, CA-125 is of greater benefit when the patient is postmenopausal, as this increases the specificity of the testing. If suspicion remains high even with negative initial testing, exploratory surgery is usually recommended; surgical findings are used to stage the disease.

What is the treatment for this condition?

Treatment is usually debulking surgery followed by chemotherapy, although choice of therapy depends on the clinical presentation of the cancer.

CASE 15

A 57-year-old woman with a history of eczema presents to her primary care physician with a new rash near the nipple of her right breast. She tells her doctor that the rash first appeared 2 months ago and that she had been treating it with the topical corticosteroid prescribed for her eczema. At first the rash improved somewhat, but over the past few weeks it has gotten worse and has expanded in size. Physical examination reveals a raw, scaly lesion around the nipple that is beginning to ulcerate. There is also a palpable mass in the affected breast, a few centimeters deep to the skin lesion.

What is the most likely diagnosis?

Paget disease of the breast, an eczematous skin lesion in the area of the nipple (see Figure 14-11), is associated with underlying ductal carcinoma in situ. In approximately 50% of cases, Paget disease is associated with a palpable breast mass. Paget disease is often mistaken for a benign skin lesion such as eczema.

What is the pathophysiology of this condition?

The skin lesion likely develops from underlying mammary adenocarcinoma cells that migrate through the ducts to the epidermis. However, an alternative theory suggests that epidermal keratinocytes transform into malignant cells independent of the underlying carcinoma.

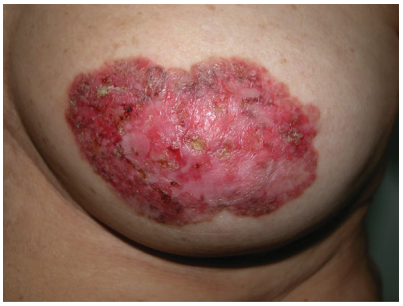

FIGURE 14-11. Paget disease of the breast. Photograph shows the left breast with skin thickening, redness, erythema, erosion of the nipple, and scaling around the nipple areola area. (Reproduced with permission from Muttarak M, et al. Paget's disease of the breast: Clinical, imaging and pathologic findings: A review of 16 patients. *Biomed Imaging Interv J.* 2011;7(2):e16.)

What are the most likely findings on histology?

Histology often shows large cells with a halo of clear cytoplasm surrounding a prominent nucleolus. Additionally, the cytoplasm stains positive for mucin.

What are the most common sites of metastasis for breast carcinoma?

- Bone is the most common site for metastatic disease.
- Other common organ sites include liver and lung.
- Less common sites include bone marrow, brain, ovaries, spinal cord, and eye.

What is the lymphatic drainage of the breast?

Approximately 75% of lymphatic drainage of the breast is to the **axillary lymph nodes**, which include the pectoral (majority of drainage), apical, subscapular, lateral, and central node groups. The nipple drains to the pectoral group. The remaining lymph drains to the infraclavicular, supraclavicular, and parasternal (also known as the internal thoracic) nodes. It should be noted that the inner quadrants of breast tissue have lymphatic connections to the contralateral breast; therefore, metastatic nodes may be present bilaterally depending on the tumor site. To assess for lymph node metastasis in breast cancer, a sentinel lymph node biopsy is performed. To do this, a dye is injected into the tumor, and the first lymph node that the tumor drains into is dyed first. This lymph node is then biopsied to assess for lymphatic invasion.

Molecular analysis of a biopsy reveals that the cells express HER-2/neu in high levels. What is the significance of this, and how does it affect treatment?

The human epithelial growth factor receptor (HER)-2/neu (also known as c-erbB-2) protein is a transmembrane growth factor receptor kinase. Overexpression of this molecule (present in 18%–20% of breast cancers) has been associated with a poorer prognosis. The drug trastuzumab is a humanized recombinant monoclonal antibody directed against this protein. The binding of trastuzumab to the extracellular portion of the molecule stimulates a cytotoxic immune response, leading to death of the cancer cells. Other receptor proteins that may be expressed by breast cancer cells include estrogen (ER) and progesterone (PR). Together with HER-2, a triple-negative cancer, such that the tumor does not express any other of these receptors, confers a worse prognosis.

CASE 16

A 22-year-old woman presents to the ED with a 3-day history of fever, abdominal pain, and vaginal discharge. Her temperature at presentation is 39°C (102.2°F). The patient reports that she is sexually active with a new partner for the last month, and that they do not consistently use condoms. Her last menstrual period ended 5 days ago. On physical examination, her abdomen is diffusely tender in the lower quadrants, without rebound or guarding. Speculum examination reveals mucopurulent drainage from the external cervical os. Cervical motion tenderness is present, as is right-sided adnexal tenderness. Relevant laboratory findings are as follows:

WBC count: 12,500/mm^3
β-hCG: Negative

What is the most likely diagnosis?

Pelvic inflammatory disease (PID). This condition usually occurs as a complication of ascending gonococcal or chlamydial infection; however, regardless of the initiated pathogen, it is thought to be the result of a polymicrobial infection. Ascending infection by these agents can also cause tubo-ovarian abscess or Fitz-Hugh–Curtis syndrome (perihepatitis resulting in right upper quadrant [RUQ] pain).

What signs and symptoms are commonly associated with this condition?

- Fever
- Pelvic pain
- Cervical motion tenderness
- Adnexal tenderness
- WBC elevation
- ESR $>$ 15

What is the pathophysiology of this condition?

Chlamydia is the most common cause of PID. *Neisseria gonorrhoeae* also causes PID. These organisms are thought to initiate the infection, but PID is commonly thought to be polymicrobial in nature.

What risk factors are associated with this condition?

- Cigarette smoking
- High frequency of intercourse
- Multiple partners
- New sexual partner within 1 month of symptom onset
- Recent history of douching
- Use of an intrauterine device
- Young age

What are the likely Gram stain and culture findings?

PCR is the gold standard to detect *Chlamydia* or *N gonorrhoeae*. The sample can be done with a first-catch urine or a cervical swab. Urine PCR is as specific but less sensitive than a cervical swab. Gram staining of *Gonorrhea* will show gram negative, coffee-bean shaped diplococci, whereas *Chlamydia* cannot be viewed using conventional gram staining.

What are the treatments for this condition?

Uncomplicated PID is treated as an outpatient with ceftriaxone and doxycycline with or without metronidazole. If the patient is pregnant, has a tubo-ovarian abscess (visualized via pelvic CT or ultrasound), or is nauseous and cannot tolerate oral medications, she must be hospitalized for administration of intravenous antibiotics, typically cefoxitin or cefotetan plus doxycycline. Surgery or drainage by interventional radiology is indicated in cases of tubo-ovarian abscess.

CASE 17

A 36-year-old African-American woman at 34 weeks' gestation presents to the ED with a 2-day history of headache, blurry vision, and sudden RUQ pain. She reports that her husband has noticed increased swelling of her face since yesterday, and her rings are suddenly too tight. Physical examination is notable for hyperactive deep tendon reflexes and jugular venous distention. Her blood pressure at presentation is 165/110 mm Hg and 4 hours later is 170/110 mm Hg. Relevant laboratory findings are as follows:

Serum transaminase: 2x the upper limit of normal
Serum creatinine: 1.5 mg/dL
Urinalysis: 3+ protein

What is the most likely diagnosis?

Preeclampsia is a multisystem disorder characterized by new onset hypertension and proteinuria during pregnancy after 20 weeks' gestation or postpartum. Eclampsia is preeclampsia with associated seizures. Gestational hypertension is hypertension without proteinuria or other signs/symptoms of preeclampsia. The criteria for diagnosis of preeclampsia is systolic blood pressure > 140/90 mm Hg or diastolic blood pressure > 90 mm Hg on two occasions at least 4 hours apart after 20 weeks' gestation in a previously normotensive patient AND proteinuria (> 300 mg in a 24-hour urine). It may also be diagnosed in the absence of proteinuria, if hypertension is present as described above with the new onset of any of the following: platelets < 100,000/μL, serum creatinine > 1.1 mg/dL, liver transaminases 2x the normal limit, pulmonary edema, or neurologic symptoms (eg, headache, scotoma). Preeclampsia with severe features is severe hypertension (> 160/110 mm Hg) or signs/symptoms of end organ damage such as those listed above.

What signs and symptoms are commonly associated with this condition? (See Table 14-3.)

Eclampsia is characterized by seizures or coma that develop in the setting of preeclampsia.

Table 14-3. Signs and Symptoms of Preeclampsia

	Blood pressure	Urinalysis	Other signs/symptoms
Mild preeclampsia	> 140/90	1+ (> 300 mg/24 hours)	Edema
Severe preeclampsia	> 160/110	3+ (> 5 g/24 hours)	Headache, somnolence, blurred vision, hyperactive reflexes, RUQ pain, elevated liver enzymes, low platelets, IUGR

What is HELLP syndrome?

HELLP is a subcategory of preeclampsia that results in a high rate of stillbirth (10%–15%) and neonatal death (~25%). **HELLP** stands for **H**emolysis, **E**levated **L**iver enzymes, and **L**ow **P**latelets.

What are the treatments for this condition?

If the baby is term, the fetal lungs are mature, or the case is severe, delivery is the best treatment. If the patient is preterm, the risks of preeclampsia progression must be weighed against the risks of prematurity. Prior to 34 weeks, most cases of preeclampsia without features of severe disease are managed with a conservative approach with close monitoring for disease progression in an effort to allow further fetal growth. Conservative treatment may include fetal monitoring, bed rest, and blood pressure control with antihypertensive agents. In preeclampsia with severe features, the patient should be hospitalized, and Mg sulfate should be given for seizure prophylaxis (continued for 24 hours postpartum), in addition to antihypertensive agents. If severe, immediate delivery may be indicated to save the life of the mother. If delivery is indicated prior to 37 weeks, betamethasone should be given for fetal lung development.

CASE 18

A 17-year-old boy is awakened from his sleep by sudden, sharp, left-sided scrotal pain. In the ED, the patient says he feels nauseous but denies any vomiting. On physical examination, he is afebrile, and there is evidence of swelling and erythema of the scrotum. He has a negative cremasteric reflex on the left. No transillumination of the scrotum is present.

What is the most likely diagnosis?

Testicular torsion. Testicular torsion is usually seen in adolescent males aged 16–18 years, although it can also occur in infancy. Approximately 50% of instances occur during sleep, but it can also occur at rest or with physical activity. Some patients have repeated episodes that spontaneously resolve (presumably because the testis is undergoing repeated torsion and detorsion).

What signs and symptoms are typically associated with this condition?

Symptoms of testicular torsion include the following:

- Sudden, acute onset of pain in the scrotum, often unilateral
- Swelling/erythema of the scrotum
- Abdominal pain
- Nausea/vomiting

Signs of testicular torsion include the affected side's being higher than the other and horizontal in orientation (Bell clapper's deformity) as well as absent cremasteric reflex.

What conditions should be included in the differential diagnosis? (See Table 14-4.)

Table 14-4. Differential Diagnosis of Testicular Pain

DDx	Features
Epididymitis	Normal Doppler examination, + Prehn sign (pain relieved with scrotal elevation), usually secondary to STDs or prostatitis
Orchitis	Systemic symptoms, typically bilateral, may occur with other signs of mumps (parotitis)
Hydrocele	Secondary to patent processus vaginalis, will transilluminate on ultrasonography
Varicocele	"Bag of worms" on physical examination, more often left-sided, will not transilluminate
Hernia	Typically painless (unless incarcerated), will not transilluminate
Tumor	Painless mass, insidious presentation, patients may present after trauma (but likely secondary to patient feeling the mass after the trauma)

What complications are associated with this condition?

Testicular torsion results in the twisting of the spermatic cord, which contains the testicular artery, pampiniform plexus, and vas deferens. The main danger is the twisting of the testicular artery, which cuts off the blood supply to the testicle. If this is not reversed rapidly, it will result in **testicular atrophy and necrosis**. This is a true surgical emergency.

What is the treatment for this condition?

Manually untwisting the testis will produce immediate and dramatic pain relief if successful. The success of this method can be confirmed by evidence of return of blood flow to the testis on Doppler ultrasound. Even if successful, surgery should be performed to suture the testis in place to prevent repeated torsion, known as orchiopexy. If manual detorsion does not work, emergent surgery must be performed. Treatment must be initiated within 6 hours of presentation to assure viability of the testicle. If it is not treated within 24 hours, there is decreased chance of the testicle's viability.

CASE 19

A 16-year-old girl is brought to her pediatrician because of an absence of menarche. She has short stature, a webbed neck, and a square chest. Physical examination reveals breast buds and female external genitalia. Upper extremity blood pressures are equal, 117/76, but femoral blood pressures are found to be 85/66. CT scan reveals a small uterus and atretic, fatty ovaries. There is no known history of this condition in her family.

What is the most likely diagnosis?

Turner syndrome, characterized by gonadal dysgenesis secondary to the presence of a single X chromosome **(XO)** (see Figure 14-12). This syndrome is the most common cause of primary amenorrhea. This genetic disorder affects 3% of all conceptions, but only 1:1000 45X embryos survives to term.

What other conditions can cause primary amenorrhea?

Primary amenorrhea refers to the complete absence of menstruation by 16 years of age with 2° sexual development or absence of 2° sexual characteristics by age 14 (compared with secondary amenorrhea, which is cessation of menstruation for more than 6 months after menarche). Other causes of amenorrhea include the following:

- Absence of uterus, cervix, and/or vagina (müllerian agenesis)
- Hypothalamic hypogonadism (secondary to anorexia, exercise, stress, or gonadotropin-releasing hormone deficiency)
- Ovarian failure (gonadal dysgenesis)
- Pituitary disease
- Polycystic ovarian syndrome
- Transverse vaginal septum or imperforate hymen

What diagnostic test is indicated based on the patient's clinical features?

Serum FSH should be tested, and if elevated, is consistent with probable gonadal dysgenesis such as in Turner syndrome. Karyotype analysis should also be performed.

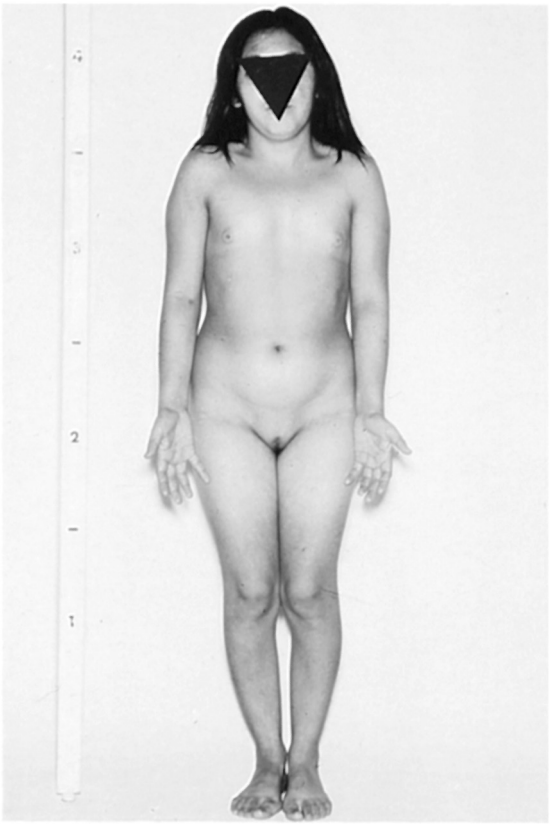

FIGURE 14-12. Turner syndrome. (Reproduced, with permission, from Le T, et al. *First Aid for the USMLE Step 1: 2019*. New York: McGraw-Hill, 2019.)

What other conditions are associated with this syndrome?

- Coarctation of the aorta
- Bicuspid aortic valve
- Hypothyroidism
- Sensorineural hearing loss
- Horseshoe kidney
- Lymphedema, primarily of hands and feet
- Osteoporosis

What are the treatments for this condition?

Recombinant human growth hormone and hormone replacement therapy can initiate puberty and complete growth. Treatment of other associated conditions is also advised.

15
Respiratory

CASE 1

A 4-year-old boy is brought to the ED by his mother because he is lethargic, drooling, and having difficulty breathing. Physical examination reveals an elevated temperature and a high-pitched upper airway wheeze. Further questioning of the patient's mother reveals that the child has not received any immunizations. A lateral x-ray of the neck shows soft tissue swelling (see Figure 15-1).

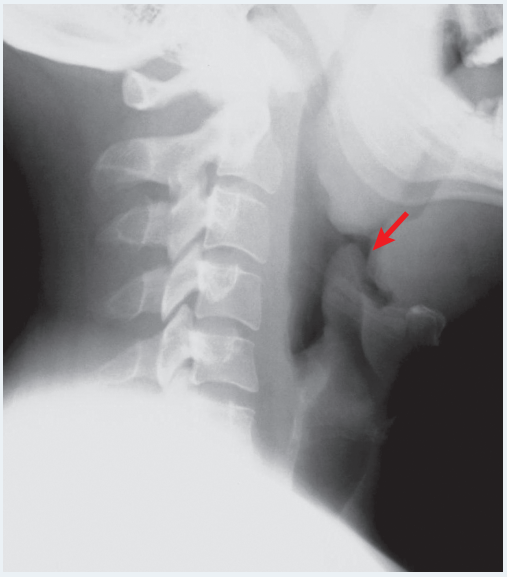

FIGURE 15-1. (Reproduced with permission from USMLE-Rx.com.)

What is the most likely diagnosis?

The stridor found on lung examination and the drooling—findings consistent with both tracheal and esophageal obstruction—suggest acute epiglottitis. The obstruction is due to swelling of the epiglottis caused by infection and is a medical emergency. The x-ray in Figure 15-1 shows the classic **"thumbprint"** sign caused by the thickening and swelling of the epiglottis.

What is the likely source of this infection?

Given the child's unimmunized status, the most likely cause is type b *Haemophilus influenzae* infection. *H influenzae* is considered part of the normal flora of the nasopharynx and can thus be spread by direct contact with respiratory secretions and by airborne droplet contamination. Epiglottitis may also represent a primary infection of the epiglottis rather than invasion from the nasopharynx.

What additional microorganisms can cause this presentation?

H influenzae remains the most common cause in both immunized and unimmunized individuals in the absence of trauma. However, epiglottitis can also be caused by *Pasteurella multocida,* which is often transmitted from dog or cat bites, herpes simplex virus type 1, *Streptococcus pneumoniae*, and *Staphylococcus aureus*.

What is the main virulence factor of the causative organism in this case?

The polysaccharide capsule is the major virulence factor of *H influenzae,* which has both encapsulated and nonencapsulated strains. The nonencapsulated forms are limited to local infections, such as otitis media in children and mild respiratory infection in adults. The encapsulated strains are significantly more virulent and can cause disseminated diseases such as meningitis, epiglottitis, and septic arthritis. There are six capsular types of *H influenzae,* designated a through f. The b-type capsule accounts for approximately 95% of serious *H influenzae* infections in children; hence, the childhood vaccine Hib (*H Influenzae, b).*

How has the vaccine for this infection been redesigned to improve its efficacy?

The Hib vaccine consists of a purified b-type capsule conjugated to diphtheria toxin. The diphtheria toxin activates T lymphocytes, which are required for adequate antibody production against the capsular antigen. The original vaccine consisted only of b capsule and was not effective in eliciting an antibody response because it consisted only of polysaccharide with no peptide component.

CASE 2

While working in a laboratory, a medical student accidentally opens a canister of highly corrosive gas and inhales a large quantity of the gas. He immediately goes to the ED for evaluation and treatment. Physical examination shows labored breathing and tachypnea as well as scattered crackles and tachycardia.

What conditions should be included in the differential diagnosis?

Given this patient's history, the differential diagnosis should include noncardiogenic pulmonary edema, acute pneumonitis, and acute respiratory distress syndrome (ARDS). Onset of symptoms may take up to several days depending on the severity of the insult.

If protein-rich exudate is found in the alveoli, what diagnosis is likely and what is the mechanism of the disease?

Protein-rich exudate in the alveoli suggests diffuse alveolar damage, which may lead to ARDS. The alveolar damage results from toxic neutrophilic substances, oxygen-derived free radicals, and activation of the coagulation cascade, all of which are stimulated by some inciting agent (eg, corrosive gas). As a result, the alveolar capillaries become more permeable, allowing the leakage of protein-rich exudate into the alveolar space and the subsequent formation of intra-alveolar hyaline membranes, seen histologically (see Figure 15-2). The hyaline membranes interfere with oxygenation, producing hypoxemia.

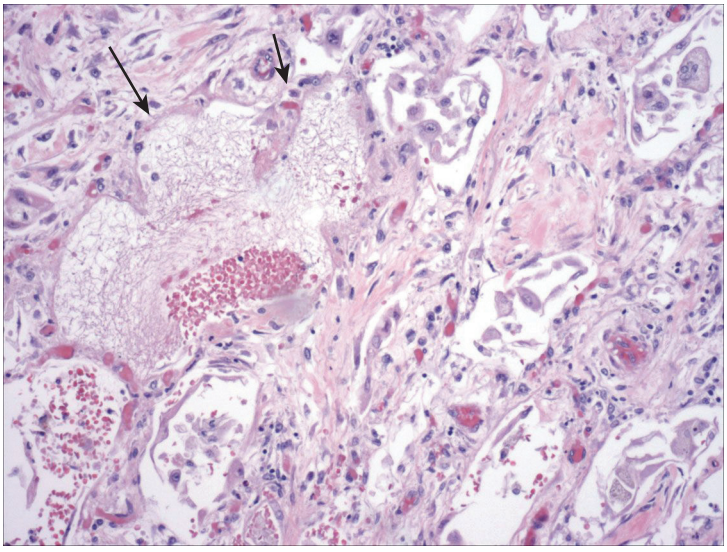

FIGURE 15-2. Histopathology of ARDS; arrows pointing to eosinophilic hyaline membranes lining the alveolar spaces. (Modified with permission from USMLE-Rx.com.)

If this condition does not resolve, what complications can arise?

If left untreated, the persistent inflammation and hyaline membranes promote organization of the damaged tissue, resulting in **irreversible fibrosis**.

What causes this condition and what is the treatment?

There are many causes of ARDS, including pancreatitis, aspiration, pneumonia, sepsis, trauma, and shock. Treatment of ARDS must address the unique underlying cause; however, oxygenation using some form of mechanical ventilation is typically the cornerstone of acute management.

How are the other conditions in the differential diagnosis characterized?

- Noncardiogenic pulmonary edema is pulmonary edema caused by injury to the lung parenchyma (such as pulmonary contusion, aspiration, or inhalation of toxic gas).
- Acute interstitial pneumonitis is a severe lung disease that begins abruptly with cough, fever, and difficulty breathing and progresses to respiratory failure within days to weeks.

CASE 3

A newborn boy has been diagnosed by prenatal ultrasound with a congenital cystic adenomatoid malformation (CCAM) in the right lower lobe of his lung. CCAMs are hamartomas of terminal bronchioles. Because of the risks of CCAM-associated complications, the boy undergoes a right lower lobe resection.

How many lobes of lung tissue will remain after the right lower lobe is removed?

There are five total lung lobes: three on the right and two on the left (see Figure 15-3). Four lobes of lung parenchyma will remain following the surgery.

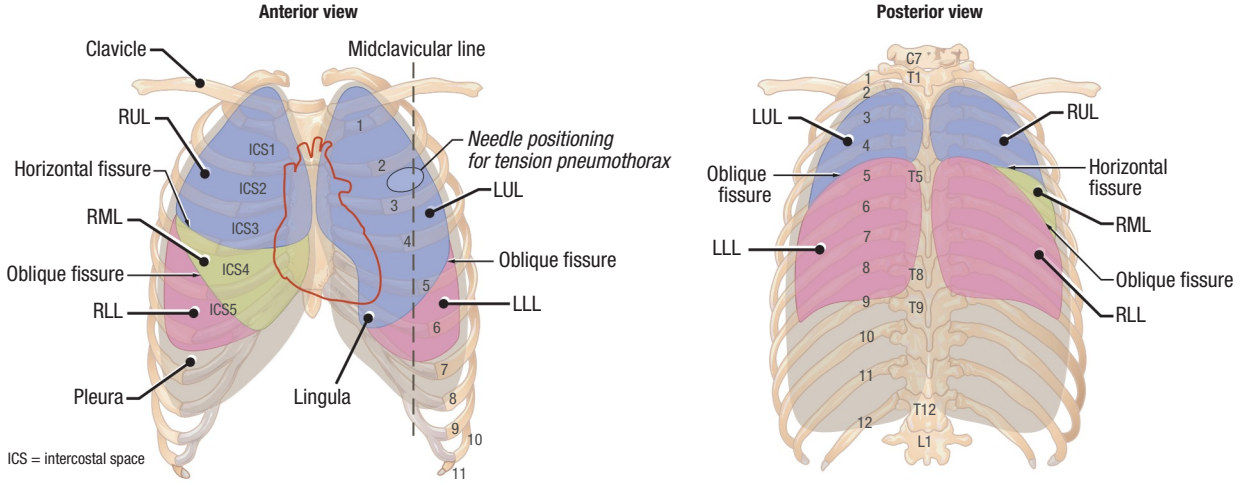

FIGURE 15-3. Lobes of the lung. RUL, right upper lobe; RML, right middle lobe; RLL, right lower lobe; LUL, left upper lobe; LLL, left lower lobe. (Reproduced with permission from Le T, et al. *First Aid for the USMLE Step 1: 2018*. New York: McGraw-Hill, 2018: 645.)

Which vessels supply arterial and venous branches to the lungs, and what paths do the branches follow to supply each lung segment?

The lung alveoli are supplied by branches of the pulmonary artery and vein. The bronchial tree, however, receives its arterial supply from the bronchial arteries from the aorta and venous drainage from bronchial veins that feed into the azygos and accessory hemiazygos veins. Pulmonary and bronchial arteries follow the airways into the periphery. Pulmonary veins course in the septa between adjacent lung segments.

When entering the thoracic cavity through an intercostal space, the surgeon preserves the intercostal nerves and vessels. What is the anatomic relationship between the intercostal nerves and vessels and the ribs?

The intercostal nerves and vessels lie in the costal groove inferior to each rib. They are positioned between the innermost intercostal and internal intercostal muscles for the length of those muscles. Thus, when a patient's thoracic cavity needs to be accessed, it is important to place the needle just above the superior border of a rib in order to avoid damage.

During development, the pulmonary arteries arise from which aortic arch?

The sixth aortic arch gives rise to the pulmonary arteries, and the left sixth aortic arch also gives rise to the ductus arteriosus.

During which week of gestation are the bronchial buds formed from the foregut?

Bronchial buds are formed in the fourth week of gestation. Depending on the histology and other associated anomalies, different types of CCAMs are suspected to result from insults at varying stages of development. For example, **type 2 CCAMs** are associated with anomalies such as esophageal fistulas and bilateral renal agenesis. Thus, type 2 CCAMs are thought to arise early in organogenesis, during the fourth week of gestation.

CASE 4

A 7-year-old boy is brought to the ED after awakening in the middle of the night with difficulty breathing. He has a 2-day history of worsening productive cough and wheezing. The patient is found to have dyspnea, tachypnea, and a decreased inspiratory/expiratory ratio. Lung examination reveals diffuse rhonchi and expiratory wheezes in addition to pulsus paradoxus. He is afebrile and has no recent history of fever. This is the patient's second visit to the ED with these symptoms; his first visit was 2 years ago.

What is the most likely diagnosis?

Asthma exacerbation. Asthma is a form of obstructive lung disease that is commonly associated with allergic rhinitis and eczema.

What is the pathophysiology of this condition?

Acutely, bronchial hyperresponsiveness leads to episodic, **reversible bronchoconstriction**. Specifically, smooth muscle contraction in the airways leads to expiratory airflow obstruction. Chronically, airway inflammation leads to histologic changes in the bronchial tree.

What are other obstructive lung diseases, and how do they differ from this condition?

- **Bronchiectasis** is a disease state in which bronchi become inflamed and dilated, causing obstructed airflow (wide airways impair laminar outflow) and impaired clearance of secretions. It is often associated with AIDS, cystic fibrosis, and Kartagener syndrome.
- **Emphysema** is a long-term, progressive disease in which the small airways and alveoli (which maintain the lung's functional shape) are destroyed, leading to airway collapse on expiration and air trapping. This is usually the result of smoking but can also be due to α-1-antitrypsin deficiency, a genetic disorder.
- **Chronic bronchitis** is chronic inflammation of the bronchi that causes a persistent and productive cough that lasts for at least 3 months in 2 consecutive years. The excess mucus itself narrows the airways and serves as an obstruction. Smoking is almost always the cause.

Unlike these diseases, the airway obstruction seen in asthma is usually reversible.

What histologic findings in the lung are associated with this patient's diagnosis?

Histologic examination is most remarkable for smooth muscle hypertrophy and increased inflammatory cell recruitment (particularly eosinophils), but goblet cell hyperplasia and thickening of basement membranes can also be appreciated (see Figure 15-4). Grossly, dilated bronchi may have mucous plugs, and histologically, will be filled with neutrophils.

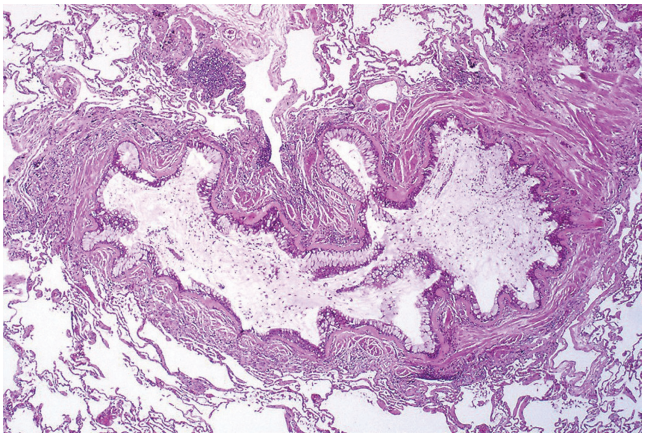

FIGURE 15-4. Histologic findings in asthma. (Reproduced courtesy of Dr. Yale Rosen.)

What are common triggers of this condition?

Triggers of asthma exacerbation include stress, cold, exercise, dust, animal dander, mold, and viral upper respiratory tract infections.

What is the treatment for this condition?

For acute episodes, albuterol, a short acting β_2-agonist (SABA), helps relax bronchial smooth muscle and decrease airway obstruction. However, for long-term control of persistent symptoms, inhaled corticosteroids are ideal because they target the inflammation.

CASE 5

A patient comes to his physician with a hacking cough and purulent sputum. His history is positive for a genetic birth defect called Kartagener syndrome in which ciliary motion is either abnormal or absent. The patient also claims to have a constantly runny nose, a prior diagnosis of chronic bronchitis, and numerous bouts of pneumonia. Before making a diagnosis, the physician orders a high-resolution CT scan of the patient's lungs (see Figure 15-5).

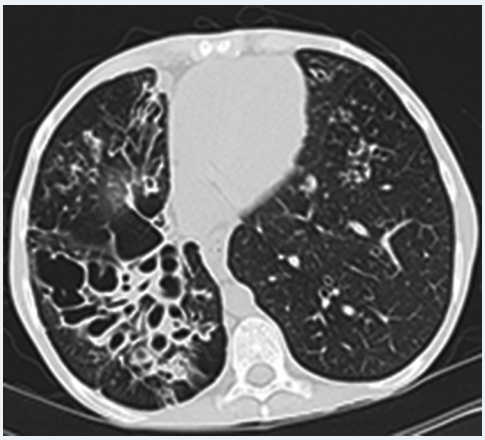

FIGURE 15-5. (Reproduced with permission from USMLE-Rx.com.)

What is the most likely diagnosis?

Bronchiectasis.

What radiologic findings can help diagnose this condition?

In bronchiectasis, a "tree-in-bud" pattern is commonly seen on high-resolution CT scans (see Figure 15-5). This represents the plugging of small airways with mucus and bronchiolar wall thickening. When bronchiectasis is associated with situs inversus and chronic rhinosinusitis, the triad of findings is referred to as Kartagener syndrome.

What is the genetic defect in this condition?

The microtubules that compose a cilium are connected via dynein arms. In primary ciliary dyskinesia, the dynein arm is defective, impairing the back-and-forth motility of the cilia. As a result, all physiologic functions reliant upon cilia are impaired (eg, airway expulsion, sperm motility and ovulation, hearing).

What are the possible etiologies of this condition?

Etiologies include chronic bronchial necrotizing infections, cystic fibrosis, bronchial obstruction from granulomatous disease or neoplasms, α_1-antitrypsin deficiency, impaired host defense (eg, AIDS), airway inflammation (eg, bronchiolitis obliterans), and even certain medications (eg, amiodarone). Additionally, tuberculosis and primary ciliary dyskinesia should be evaluated.

What complications are associated with this condition?

Complications of bronchiectasis include hemoptysis, infections, amyloidosis, and because it is an obstructive lung disease, hypoxemia, dyspnea, and cor pulmonale.

What is the treatment for this condition?

If an infection is thought to be the cause, then antibiotics should be given. If the bronchiectasis is localized, surgery may be an option. For routine management, however, measures include postural drainage and chest percussion.

CASE 6

A 60-year-old man comes to the ED with new-onset headaches and dizziness that developed suddenly as he was working on his car in a closed garage 2 hours ago. He denies fever, cough, shortness of breath, falls, or toxic ingestions. On physical examination, his skin is noted to appear bright pink and his lungs are clear to auscultation. His neurologic exam is unremarkable, and no focal deficits are noted. A pulse oximeter demonstrates 100% saturation, and an arterial blood gas analysis confirms the diagnosis.

What is the most likely diagnosis?

Carbon monoxide poisoning.

What is the pathophysiology of this condition?

Carbon monoxide is a noxious gas that originates from many sources, such as fires, car exhaust, gas heaters, and furnaces. It binds to normal human hemoglobin in the oxygen-binding site, **reducing the oxygen-binding capacity** of hemoglobin molecules; however, it also increases the affinity of the other binding sites for oxygen. The net effect is a decrease in the total oxygen-binding potential of hemoglobin, which ultimately reduces the amount of oxygen able to be delivered to the tissues. This causes tissue hypoxia despite "normal" saturation of hemoglobin binding sites by oxygen and carbon monoxide.

What is the treatment for this condition?

Hyperbaric oxygen and 100% oxygen are the standard treatments for carbon monoxide poisoning, as the elevated pressure and fraction of oxygen helps hasten the dissociation of carbon monoxide from hemoglobin oxygen-binding sites to allow for resaturation with oxygen instead.

What do shifts in the oxygen dissociation curve represent?

Shifts in the curve (see Figure 15-6) represent changes in affinity of the hemoglobin binding sites for oxygen. A left shift represents increased affinity, whereas a right shift represents decreased affinity. A rightward-shifted curve is ideal in peripheral tissues, as the decreased affinity allows greater oxygen unloading. Tissue products such as acid and CO_2 cause a rightward shift of the curve and ultimately more oxygen unloading; this principle is known as the Bohr effect. Conversely, a leftward-shifted curve is ideal in the pulmonary capillary beds, as the increased affinity allows greater oxygen binding. In the pulmonary circulation, binding of oxygen promotes release of CO_2 being carried by the red blood cells, which is also known as the Haldane effect.

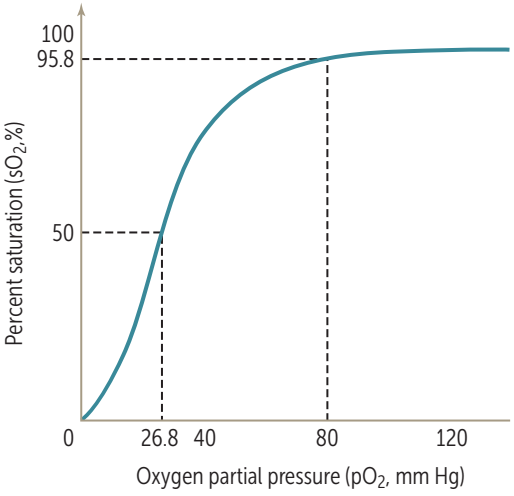

FIGURE 15-6. Oxygen dissociation curve. (Reproduced with permission from USMLE-Rx.com.)

CASE 7

A 50-year-old man visits a community health clinic because of a 1-month history of cough productive of yellow sputum. On questioning, he says he has had several periods of cough lasting 4–6 consecutive months each year for the past 5 years. He has smoked two packs of cigarettes per day for the past 30 years. On examination, the man's breathing is shallow, and he exhales slowly with pursed lips. His jugular venous pulse is visible to the jawline when he is reclined at an angle of 45°. Auscultation of the chest demonstrates wheezing and distant heart sounds. A positive hepatojugular reflux is demonstrated, as is 2+ pitting edema up to the knees. X-ray of the chest is shown in Figure 15-7.

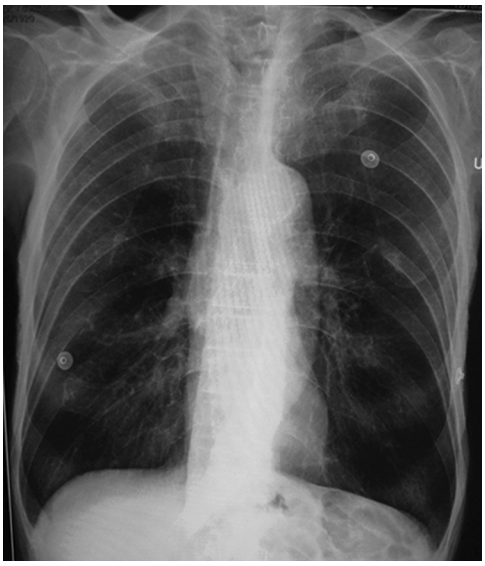

FIGURE 15-7. (Reproduced courtesy of Dr. James Heilman.)

What is the most likely diagnosis?

The chronicity of the productive cough (suggestive of chronic bronchitis) and the accompanying pursed-lip breathing (suggestive of emphysema) indicate chronic obstructive pulmonary disease (COPD).

What radiologic findings can help diagnose this condition?

In patients with COPD, x-rays of the chest often reveal lung hyperinflation and flattening of the diaphragm due to expiratory airflow obstruction and subsequent air trapping, as seen in Figure 15-7. Additionally, there are decreased peripheral vascular markings due to pulmonary hypertension. If a lateral view is obtained, an increased anteroposterior (AP) diameter may also be appreciated due to the hyperinflation of the lungs.

What abnormalities would be expected on pulmonary function testing?

- In **obstructive lung diseases** such as COPD, the forced expiratory volume in 1 second (FEV_1) is decreased, forced vital capacity (FVC) is near normal or only slightly decreased, and the FEV_1/FVC ratio is $< 70\%$ of predicted.
- In **restrictive lung disease**, decreased vital capacity and total lung capacity result in a FEV_1/FVC ratio of $> 80\%$.
- In a **mixed obstructive-restrictive lung** disease, both the FEV1/FVC ratio and FVC will be significantly reduced.

How would this condition affect the patient's arterial blood gas levels (pH, PaO_2, $PaCO_2$, and SaO_2)?

The pH decreases as a result of respiratory acidosis. Although pH may be normal in a patient with chronic compensated COPD, it is low in a patient with an acute exacerbation. Arterial oxygen tension (PaO_2) decreases, arterial carbon dioxide tension ($PaCO_2$) increases, and oxygen saturation (SaO_2) decreases secondary to impaired gas exchange (from destruction of alveolar septae and pulmonary capillary bed).

Why is breathing with pursed lips adaptive in this condition?

Breathing with pursed lips maintains positive end-expiratory pressure (PEEP), preventing the alveolar and small airway collapse that is common in emphysema. Positive airway pressure can also be achieved with continuous positive airway pressure, bilevel positive airway pressure, or intubation and ventilatory support. Respiratory therapy often provides supplemental oxygen via a mask or nasal prongs.

What complication of this condition is suggested by the patient's enlarged neck veins, hepatomegaly, and edema?

Cor pulmonale, or right heart failure due to chronic primary pulmonary hypertension from hypoxic vasoconstriction-induced vascular remodeling. Right heart failure leads to systemic venous congestion, which presents with the symptoms mentioned here. This complication occurs only in patients with severe COPD who develop pulmonary hypertension. Pulmonary hypertension can also occur secondary to left heart disease due to backup of blood from the left atrium into the pulmonary veins, as well as congenital heart diseases that overload the pulmonary arteries beyond their capacities (eg, large ventricular septal defects). "Cor pulmonale," however, is used only to designate right heart failure that is the result of pulmonary hypertension of a primary pulmonary etiology rather than a secondary cardiac etiology.

CASE 8

A 15-year-old girl is brought to the ED in acute respiratory distress and is stabilized with treatment. On questioning, she reports an increasingly productive cough over the past few days. Her pulse oximetry shows 93% oxygen saturation on 2 L of oxygen, and she often gasps for air midsentence. Examination shows nostril flaring, subcostal retractions, and clubbing of the fingers. A birth history reveals she had a meconium ileus.

What genetically transmitted condition does this patient likely have?

The patient likely has cystic fibrosis (CF), which is caused by loss-of-function mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) protein, a chloride channel found in all exocrine tissues. As a result of these mutations, secretions in the lung, intestine, pancreas, and reproductive tract are extremely viscous, impairing normal functioning of these organs.

What test was likely conducted to confirm the diagnosis?

Most likely, a genetic screen was conducted in the patient's infancy, checking for elevated levels of immunoreactive trypsinogen. The diagnostic test to confirm a screen is the sweat chloride test. Because the CFTR protein in the sweat glands normally absorbs chloride, patients with CF have an excess amount of chloride in the sweat, contributing to the salty taste of their sweat. It may, however, be difficult to collect an adequate amount of sweat in a baby.

What is the probable etiology of the patient's current symptoms?

The lungs in patients with CF are colonized at an early age with various bacteria not normally found in the lung. Therefore, patients suffer from repeated pulmonary bacterial infections (most commonly *Staphylococcus aureus*, *Haemophilus influenzae*, and *Pseudomonas aeruginosa*), which increase production of viscous secretions. These increased secretions lead to increased cough and inflammation, which over time cause dilation of the airway walls, or bronchiectasis; pulmonary obstruction is a complication of bronchiectasis and manifests as acute respiratory distress. CT findings of a patient with cystic fibrosis will show bronchiectasis with mucous plugs from the increased secretions (see Figure 15-8).

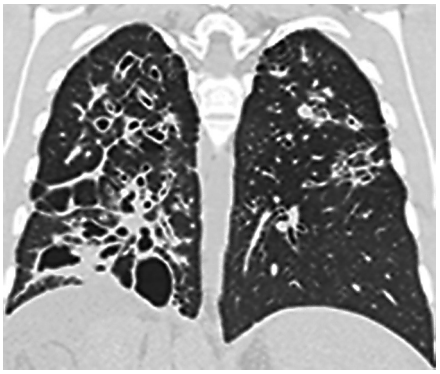

FIGURE 15-8. Bronchiectasis and mucous plugging in CF. (Reproduced with permission from USMLE-Rx.com.)

What vitamin supplements do patients with this condition usually require?

Patients with CF have pancreatic insufficiency because the thick secretions block the release of pancreatic enzymes needed to absorb fats. Thus, patients will generally require the fat-soluble vitamins A, D, E, and K.

What information can be provided if this patient asks for genetic counseling?

The frequency of CF in white people is 1:2000; the carrier rate of CF in white people is 1:25. CF is an autosomal recessive disease, so all children of a patient with CF at a minimum become carriers. Approximately 95% of men with CF are infertile because of defects in the transport of sperm; however, the sperm itself is normal. Infertility affects as many as 20% of women due to abnormally thick cervical mucus and amenorrhea from malnutrition.

What is the prognosis for patients with this condition?

Prognosis for patients with CF is fair, and most patients are able to survive into their 30s and lead relatively normal lives. Death in adulthood is almost always due to severe pulmonary infections, such as those caused by *Pseudomonas,* typically occurring in the 30s.

CASE 9

A 70-year-old woman with a 65-pack-year smoking history complains to her physician of worsening dyspnea. The dyspnea has now become so severe that she is experiencing shortness of breath at rest. She also admits that her cough is now occasionally productive of small amounts of thin sputum. Physical examination reveals a thin woman with an increased thoracic anteroposterior diameter. The physician notes that she breathes through pursed lips, has an increased expiratory phase, and is using her accessory muscles to breathe.

What is the most likely diagnosis?

- The most likely diagnosis is COPD with features of emphysema. Other obstructive lung diseases that should be on the differential include chronic bronchitis and asthma.
- By definition, a patient with chronic bronchitis experiences a cough with sputum production on most days for 3 months of a year for at least 2 consecutive years. Patients with chronic bronchitis also experience hypoxia that results in cyanosis of the skin and lips as well as fluid retention.
- Patients with asthma experience reversible and episodic airway obstruction, which is characterized by acute wheezing, coughing, and shortness of breath. Symptoms usually respond to treatment with an inhaled β_2-agonist and can often be prevented by avoiding triggers, such as allergens and irritants.

What is the pathophysiology of this condition?

Normally, the alveoli contain antiprotease enzymes to prevent damage to the alveolar walls. When someone smokes, however, the inhaled irritants activate inflammatory cells to release proteases, exceeding the capacity of the antiproteases to protect the alveoli. As a result, the walls between individual alveoli get destroyed, resulting in enlargement of air spaces. Figure 15-9 demonstrates emphysematous lung tissue with dilated air spaces on the left and preserved alveolar tissue on the right.

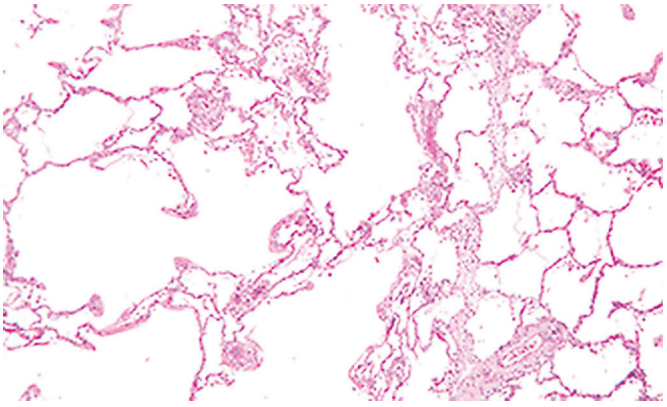

FIGURE 15-9. Centrilobular emphysema. (Reproduced courtesy of Dr. Michael Bonert.)

The destruction of lung parenchyma also decreases the intrinsic elastic recoil of the lungs, increasing airway collapsibility and resulting in expiratory obstruction. As a result, patients with emphysema often find it easier to exhale through pursed lips (which maintains a high end-expiratory pressure, thereby stenting the alveoli open); hence the term "pink puffers," as patients with pure emphysema are not typically cyanotic. Because of chronic hyperinflation though, the lungs are expanded close to total lung capacity with little inspiratory reserve, and diaphragms are flattened to a point of significant mechanical disadvantage.

What findings are expected on lung and heart examination?

Air trapped in the lungs causes the chest to sound hyperresonant to percussion. Patients with COPD also have decreased breath sounds, wheezing, a prolonged expiratory phase, diminished heart sounds, and a point of maximal impulse (PMI) that may be displaced centrally. The hyperinflation of the lungs causes the chest to appear "barrel-shaped," which can be appreciated on a lateral x-ray of the chest through a widened AP diameter (see Figure 15-10). In general, patients are often very thin due to the excess calories burned from the increased work of breathing.

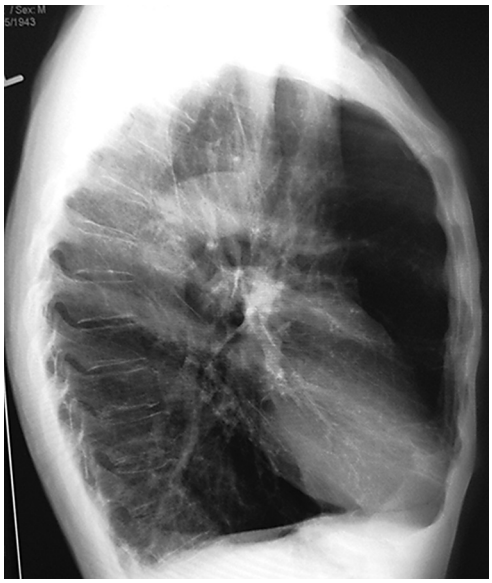

FIGURE 15-10. Emphysema, widened AP diameter. (Reproduced courtesy of Dr. James Heilman.)

What pattern of lung parenchymal destruction is likely to be found in this patient?

Smoking results in a destruction pattern termed **centrilobular emphysema**, which affects the respiratory bronchioles and central alveolar ducts. Figure 15-10 demonstrates this pattern, as some of the alveolar tissue is spared. **Panacinar emphysema** is associated with α_1-antitrypsin deficiency and results in destruction throughout the acinus.

How do pulmonary function test results help distinguish this condition from other lung diseases?

In COPD, pulmonary test results are likely to be consistent with obstructive lung disease findings: dramatically reduced forced expiratory volume in 1 second (FEV_1) and reduced forced vital capacity (FVC), resulting in an FEV_1/FVC ratio of < 70%. By contrast, in restrictive lung diseases, both the FEV_1 and the FVC are reduced, resulting in a normal FEV_1/FVC.

CASE 10

A pregnant woman at 31 weeks' gestation suffering from markedly elevated blood pressure and thrombocytopenia suddenly starts having seizures. She is rushed to the delivery room, where she is determined to have eclampsia, and then immediately taken to the operating room for cesarean section. Her baby is delivered prematurely and found to have increased work of breathing and an elevated heart rate. The baby is intubated, a drug is administered, and x-ray of the chest is taken (see Figure 15-11).

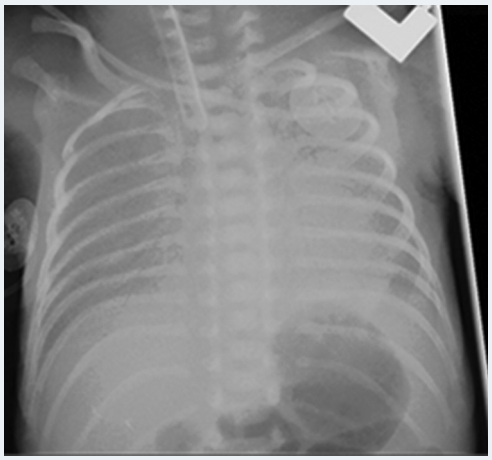

FIGURE 15-11. (Reproduced with permission from USMLE-Rx.com.)

What is the most likely diagnosis?

The baby is suffering from neonatal respiratory distress syndrome (NRDS), a disease in which parts of the baby's lungs are deficient in surfactant, a compound that reduces surface tension in the alveoli and helps keep them inflated. This deficiency results in collapsed air spaces, incomplete expansion of the lungs (ie, atelectasis), hyaline membranes, and vascular congestion. Clinically, patients present with tachypnea, tachycardia, and cyanosis immediately after birth. X-ray of the chest of a baby with NRDS will show "ground-glass opacities," resembling the atelectatic alveoli, and air bronchograms (see Figure 15-11).

What drug was most likely given to this baby to promote lung expansion?

Surfactant, normally produced late in fetal life (around week 28), can be given to the newborn baby directly. Surfactant lowers the surface tension between alveoli, helping the lung to expand. Dexamethasone can be used antenatally to aid in surfactant production; it is given to women at risk for preterm delivery to reduce the risk of respiratory distress syndrome.

What are risk factors associated with the development of this condition?

Cortisol promotes surfactant production, while insulin impairs it. Thus, C-section delivered babies (less stress than vaginal deliveries) and infants of diabetic mothers are more vulnerable. Premature babies are also vulnerable because surfactant begins to form around week 28 of gestation and reaches mature levels around week 35.

What are the primary types of atelectasis?

- **Adhesive atelectasis** occurs in patients with insufficient surfactant.
- **Obstructive atelectasis** involves obstruction of an airway, commonly at the level of the smaller bronchi, with collapse of the alveoli distal to the obstruction. A common cause for this type of atelectasis is secretions or exudates.
- **Cicatricial atelectasis** occurs in an area of scarred lung tissue.
- **Passive atelectasis** occurs because of poor ventilation (eg, after surgery).
- **Compressive atelectasis** is due to a space-occupying mass in the thorax that compresses a region of lung tissue.

How does obstructive atelectasis differ from compressive atelectasis?

In obstructive atelectasis, the mediastinum shifts toward the atelectasis due to loss of lung volume in that area, so an x-ray of the chest will show greater opacities on the side of the atelectasis. By contrast, the mediastinum shifts away from the atelectasis with compression, so an x-ray of the chest will show greater lucencies on the side of the atelectasis.

During atelectasis, to what is the patient commonly predisposed?

Atelectasis results in mucus trapping and a decrease in ventilation, thereby predisposing the patient to **infections**.

CASE 11

A 70-year-old man with a history of laryngeal cancer presents to the ED with shortness of breath. He complains that for the past 3 days he has been unable to lie flat to sleep, and last night he woke up suddenly gasping for air. An x-ray of the chest is shown in Figure 15-12.

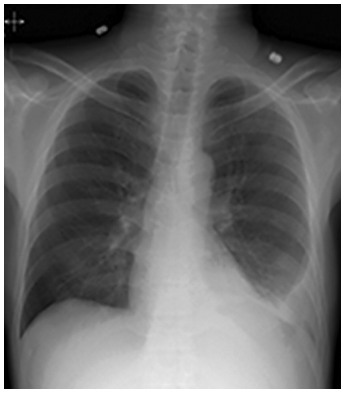

FIGURE 15-12. (Reproduced with permission from USMLE-Rx.com.)

What is the most likely diagnosis?

A pleural effusion consists of fluid accumulation in the pleural space (between the visceral pleura and the parietal pleura) of the lung. Normally, the pleural space is only a potential space, with a small amount of fluid. In a decubitus x-ray, layering of the fluid can be seen, as shown in Figure 15-12.

How is this condition classified?

There are two types of pleural effusion:

- **Transudative pleural effusions** are caused by increased hydrostatic pressure of the pleural capillaries (as in congestive heart failure) or by a decrease in plasma oncotic pressure (as in disorders with decreased plasma albumin levels, such as renal and hepatic failure).
- **Exudative pleural effusions** are caused by a change in the permeability of the pleural surface (such as secondary to inflammatory or neoplastic changes).

Laboratory analysis of the effusion can identify it as a transudate or exudate based on certain properties, as specified in Table 15-1.

Table 15-1. Properties of Transudates and Exudates

	Transudate	Exudate
Protein content	Low (< 2.5 g/dL)	High (> 2.9 g/dL)
Cell density	Hypocellular (clear)	Cellular (cloudy)
LDH	High (< serum)	High (> serum)

What are the common causes of this condition?

- Common causes of transudative pleural effusion include congestive heart failure, cirrhosis, constrictive pericarditis, nephrotic syndrome, and pulmonary embolism (PE).
- Common causes of exudative pleural effusion include infection (pneumonia, tuberculosis), malignancy (primary or metastatic lung cancer or mesothelioma), collagen vascular disease, and PE (note that PE can cause both transudative and exudative pleural effusions).

What are the typical laboratory findings in this condition?

Analysis of pleural effusion fluid includes measuring pH, total protein, lactate dehydrogenase (LDH), glucose, cell count, gram stain, and culture. Cytology can also be performed to identify malignant causes. Meeting any one of the three Light's criteria qualifies the effusion as an exudate:

- Protein effusion/serum ratio > 0.5
- LDH effusion/serum ratio > 0.6
- Pleural LDH level greater than two-thirds the upper limit of serum LDH level

What are the treatments for this condition?

Thoracentesis performed by needle insertion into the pleural space is both diagnostic and therapeutic. The needle is inserted through an intercostal space superior to the rib to avoid the intercostal nerve and vessels, which lie in the intercostal groove at the inferior border of the rib. The pleural space begins at the 6th rib in the midclavicular line, the 8th rib in the midaxillary line, and the 10th rib in the paravertebral line, and extends 2 ribs downward in each line. Care should be taken to remain within these borders to avoid damage to surrounding structures.

Other treatments include pleurodesis (in which the pleura is made adherent and closed by chemicals such as talc or doxycycline or physical abrasion) and permanent catheter insertion into the pleural space for periodic fluid drainage.

CASE 12

A 60-year-old man visits his doctor complaining of recurrent fever, chest pain, and difficulty breathing. He states that his symptoms wax and wane but never completely resolve. The patient's occupational history is significant for 30 years as a shipyard worker. Suspecting an occupational exposure to hazardous material, the physician orders an x-ray of the chest (see Figure 15-13).

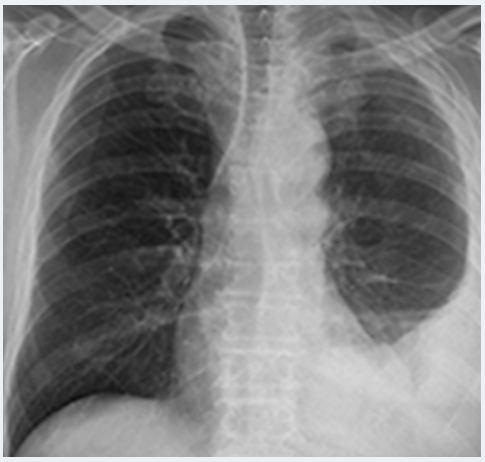

FIGURE 15-13. (Reproduced with permission from USMLE-Rx.com.)

What is the most likely diagnosis?

The pleural thickening and associated pleural effusion in the right lung (see Figure 15-13) in addition to a history of exposure to asbestos make the diagnosis of malignant mesothelioma of high concern. Benign pleural plaques may present with a similar thickening, but without the pleural effusion. As the malignant mesothelioma progresses, the lung is surrounded and compressed by a thick layer of tumor. Although mesotheliomas are rare, an exposure history greatly increases the risk. Common features of the disease include dyspnea, chest pain, and pleural effusions, as seen in this patient.

What is the pathophysiology of this condition?

When asbestos fibers are inhaled, they become surrounded by alveolar macrophages and coated by a protein-iron complex, forming asbestos or **"ferruginous"** bodies, as seen in Figure 15-14. These bodies eventually undergo fibrosis, causing the lung tissue to become diffusely fibrotic and rigid and the airways to become distorted.

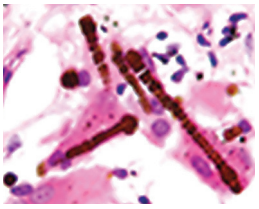

FIGURE 15-14. Asbestos bodies. (Reproduced courtesy of Dr. Michael Bonert.)

What occupations put patients at risk for exposure to the suspected agent?

Asbestos exposure is commonly seen in pipe fitters, shipyard workers, welders, plumbers, and construction workers. In addition to malignant mesothelioma, asbestos is associated with benign pleural plaques, interstitial lung disease, pleural effusions, and bronchogenic carcinoma. Most asbestosis-related cancers tend to be bronchogenic carcinomas; however, most mesotheliomas tend to be of an asbestosis-related etiology. The diseases typically manifest several decades after asbestos exposure.

What are the typical findings on pulmonary function testing in this condition?

Pulmonary function testing reveals a restrictive pattern. Tumor growth decreases lung expansion and total lung capacity. Both forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC) are decreased, but the FEV_1/FVC ratio is preserved.

What is the prognosis for patients with this condition?

Given only supportive care, the median survival for patients with malignant mesothelioma is approximately 6–12 months. With very aggressive therapies, such as extrapleural pneumonectomy plus chemotherapy and radiation, the median survival can be as high as 34 months.

How do the pneumoconioses differ radiographically?

Asbestosis is the only pneumoconiosis to involve the base of the lungs, whether it be with asbestos bodies or pleural plaques. Silicosis, coal workers' pneumoconiosis, and berylliosis tend to affect the upper zones of the lungs. Each of the pneumoconioses has certain unique features that help make the diagnosis from imaging and the history, as listed in Table 15-2.

Table 15-2. Pneumoconioses

	Exposure	Chest x-ray findings
Asbestosis	Asbestos (eg, shipbuilding)	• Pleural thickening, plaques, effusions • Nodules in the LOWER zones
Silicosis	Silica dust (eg, sandblasters, mine workers)	• Multiple small nodules in the UPPER zones • Hilar "eggshell" calcifications
Coal workers' pneumoconiosis	Coal dust (eg, urban/industrial cities)	• Large masses of dense fibrosis in the UPPER zones
Berylliosis	Beryllium (eg, beryllium miners, fluorescent light bulbs)	• Small granulomas in the UPPER zones

CASE 13

A 67-year-old man comes to the ED complaining of a 3-day history of cough and fever and a 1-day history of shaking chills. He has smoked about half a pack of cigarettes per day for the past 45 years. For the past 9 months, the man has had an increasingly severe cough that has been productive of clear sputum. His cough now produces rusty sputum. On physical examination, he is found to have a respiratory rate of 24/min and a temperature of 39°C (102.2°F). An x-ray of the chest shows lung consolidation (see Figure 15-15).

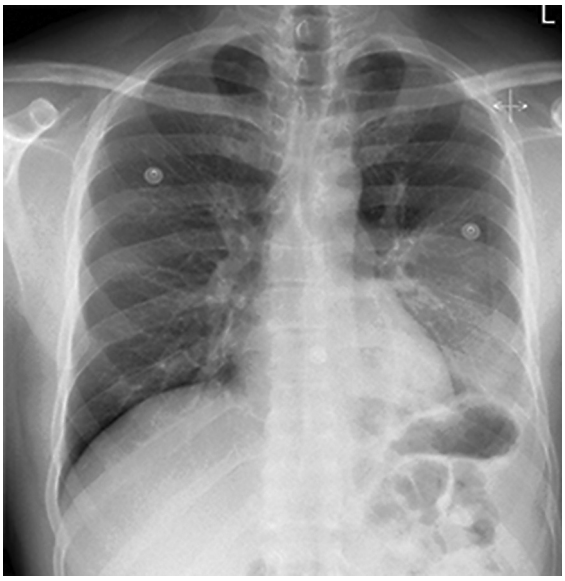

FIGURE 15-15. (Reproduced with permission from USMLE-Rx.com.)

What is the most likely diagnosis?

This patient presents with several classic findings of community-acquired pneumonia (CAP): a productive cough, fever, rigors (shaking chills), and tachypnea. His risk factors include an advanced age and a significant smoking history.

What are the likely lung examination findings?

On physical exam, decreased breath sounds, crackles, dullness to percussion, and increased tactile fremitus are probable findings, indicating areas of consolidation (ie, areas filled with fluid). On x-ray of the chest, lobar-shaped opacities (see Figure 15-15), interstitial markings, or patchy infiltrates may be visible, depending on the etiology of the pneumonia.

What are the most likely causative organisms?

In general, *Streptococcus pneumoniae* is the most common causative organism of community-acquired pneumonia. However, different age groups are prone to different organisms:

- **Neonates**: group B *Streptococci*, *Escherichia coli*
- **Children**: Viruses (RSV), *Mycoplasma*
- **Adults**: *Mycoplasma, H influenzae, Staphylococcus aureus*
- **Elderly**: *Legionella,* influenza virus

Gram stain of the sputum reveals gram-positive cocci in pairs and short chains. Additional testing reveals that the organism is optochin sensitive and the Quellung reaction is positive. What is the causative organism?

S pneumoniae, a gram-positive bacterium, is an encapsulated organism, hence the positive Quellung reaction, which is performed by adding anticapsular antisera that cause the capsule to swell. The organism is also catalase negative, α-hemolytic (partial hemolysis; the blood turns greenish), and optochin sensitive (which differentiates it from *Streptococcus viridans,* which is also α-hemolytic).

What is the treatment for this condition?

Penicillin V and amoxicillin are rarely used in clinical practice because resistance with these drugs is an increasing problem. The typical treatment is either a macrolide in combination with a cephalosporin or fluoroquinolone monotherapy.

What factors would indicate hospitalization for a patient with this condition?

Factors that increase the need for hospitalization are known as the "**CURB65**" criteria, which include age older than **65** years, altered mental status or **C**onfusion**,** abnormally high kidney function tests **(**ie, creatinine and blood **U**rea nitrogen**),** fast **R**espiratory rate, and low **B**lood pressure. Patients with these findings likely need intravenous antibiotics in the hospital rather than oral antibiotics at home.

CASE 14

An 18-year-old man comes to his physician complaining of a 3-week history of worsening dry and nonproductive cough. He also has a throbbing headache and a mild fever and complains of malaise and a sore throat. Treatment with penicillin has not relieved his symptoms.

What is the most likely diagnosis?

Mycoplasma pneumoniae, which causes primary atypical pneumonia ("walking pneumonia"), is the most common cause of pneumonia in teenagers (see Table 15-3). This organism is the smallest free-living bacterium. It has no cell wall, and its membrane is the only bacterial membrane containing cholesterol, a human cell membrane compound.

Table 15-3. Most Common Causes of Pneumonia According to Age

6 Weeks–18 Years	18–40 Years	40–65 Years	> 65 Years
Viral (RSV)	*M pneumoniae*	*S pneumoniae*	*S pneumoniae*
M pneumoniae	*C pneumoniae*	*H influenzae*	Viral
C pneumoniae	*S pneumoniae*	Anaerobes	Anaerobes
S pneumoniae		*M pneumoniae*	*H influenzae*

What diagnostic tests can help confirm the diagnosis?

A high titer of cold agglutinins (IgM) and growth on **Eaton agar** (which is specific for growing *M pneumoniae* and contains penicillin for selectivity) indicate *M pneumonia* infection.

What clinical findings are commonly associated with this condition?

Infection with *M pneumoniae* typically results in mild upper respiratory tract disease, including low-grade fever, malaise, headache, and a dry, nonproductive cough. Symptoms gradually worsen over a few days and can last for more than 2 weeks. It is often referred to as a "walking" pneumonia, given the mild and indolent course of the illness. Fewer than 10% of patients develop more severe disease with lower respiratory tract symptoms. Classically, x-ray of the chest in these patients looks worse than would be predicted by their physical appearance, with interstitial and patchy infiltrates rather than lobar ones.

What is the pathogenicity of this organism?

M pneumoniae is an extracellular organism that attaches to respiratory epithelium. As the superficial layer of respiratory epithelial cells is destroyed, the normal ability of the upper airways to clear themselves is lost. As a result, the lower respiratory tract becomes contaminated by microbes and is mechanically irritated. Close contact allows for spread of the organism, which is why outbreaks are common in schools and military bases.

What hematologic condition can develop secondary to this infection?

Autoimmune hemolytic anemia due to cold agglutinins (usually IgM autoantibodies that are able to agglutinate RBCs at temperatures below 35°C) can lead to lysis and mild anemia. Cold agglutinin production peaks during the third week of *M pneumoniae* infection and resolves spontaneously. Because the antibodies only agglutinate in the cold, the patient will test positive on an indirect Coombs test.

What are the treatments for this condition?

Azithromycin is most commonly prescribed to treat *Mycoplasma* infection. Tetracycline, clarithromycin, or erythromycin may be prescribed as well; however β-lactam antibiotics such as amoxicillin (a common treatment for pneumonia) must be avoided, as the organism lacks the target of β-lactams, a cell wall.

CASE 15

A 55-year-old man comes to the ED after suddenly experiencing severe right-sided chest pain followed by profound difficulty breathing. He informs the physician that he has severe emphysema due to an extensive history of tobacco use. On physical examination, the patient is markedly tachypneic and tachycardic. His breath sounds are diminished at the right apex, and his chest wall is hyperresonant to percussion on the right and normoresonant on the left. No tactile fremitus is noted. Arterial blood gas analysis demonstrates a partial pressure of oxygen (PO_2) of 60 mm Hg and a partial pressure of carbon dioxide (PCO_2) of 50 mm Hg.

What is the most likely diagnosis?

Pneumothorax—more specifically, secondary spontaneous pneumothorax. Whereas primary spontaneous pneumothorax occurs in the absence of underlying lung disease, secondary spontaneous pneumothorax occurs in the setting of chronic lung parenchymal disruption.

What is the pathophysiology of this condition?

Spontaneous pneumothorax is most likely caused by rupture of a subpleural bleb (a pocket of air caused by destruction of lung parenchyma near the pleural surface), which allows air to escape into the pleural cavity. A **tension pneumothorax** ensues when a one-way valve is created, allowing air to progressively accumulate in the pleural space with each inspiration. This expanded and pressurized pleural compartment shifts and compresses other intrathoracic structures, including the alveoli, which rely on a negative intrapleural pressure to remain inflated.

What diseases most often underlie this condition?

The most common underlying condition is COPD. Additionally, patients with AIDS, *Pneumocystis jiroveci* pneumonia, cystic fibrosis, and tuberculosis are at higher risk for spontaneous pneumothorax. Of note, mechanical ventilation, a therapeutic measure, can also induce pneumothorax through barotrauma when the settings of ventilation are excessive.

What is the most common clinical presentation of this condition?

Dyspnea with pleuritic chest pain on the same side of the pneumothorax is a common presentation. Typical physical examination findings include diminished breath sounds, hyperresonance, and absent fremitus over the pneumothorax. Arterial blood gas testing typically shows hypoxia and hypercapnia.

What are the typical radiologic findings in this condition?

Partial collapse of the lung on the side of the pneumothorax with a thin line parallel to the chest wall (representing air escaping into the pleural space) is usually visible. In a tension pneumothorax, tracheal and mediastinal deviation can be present away from the pneumothorax. In a nontension pneumothorax, however, the trachea and mediastinum will remain unchanged or shift toward the side of the collapsed lung (see Figure 15-16).

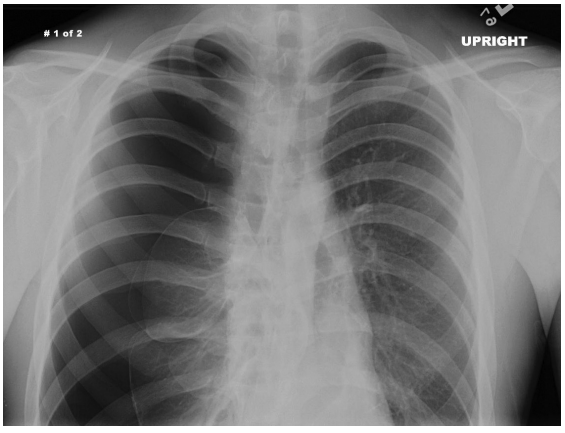

FIGURE 15-16. Right-sided tension pneumothorax, leftward mediastinal shift. (Reproduced with permission from USMLE-Rx.com.)

What is the treatment for this condition?

For a tension pneumothorax, needle decompression at the second intercostal space at the midclavicular line is the initial treatment. Then, as with other pneumothoraces, a chest tube (thoracotomy) is placed at the fifth intercostal space at the midaxillary line. Small pneumothoraces may be treated with high concentration oxygen to facilitate nitrogen resorption and followed clinically and radiographically. In the case of repetitive pneumothoraces, parenchymal sclerosing agents, such as physical and chemical irritants, are used to adhere the layers of the pleura to each other in a process called pleurodesis; this obliteration of the potential space prevents air from accumulating, effectively preventing future pneumothoraces.

CASE 16

A 55-year-old woman with a history of COPD presents to the local hospital complaining of fatigue and weakness. On admission, she is found to have the following laboratory values:

Serum:
- Sodium: 144 mEq/L
- Chloride: 96 mEq/L
- Bicarbonate: 40 mEq/L
- Potassium: 4.2 mEq/L
- Blood urea nitrogen/creatinine ratio: 18:1

Arterial blood gas analysis:
- pH: 7.32
- Partial pressure of carbon dioxide (P_{CO_2}): 91 mm Hg

What is the most likely cause of these symptoms?

The patient has respiratory acidosis (pH $<$ 7.4 and P_{CO_2} $>$ 40 mm Hg) with compensatory metabolic alkalosis (elevated bicarbonate). Respiratory acidosis can be caused by states of poor ventilation, such as COPD, airway obstruction, and high altitude (low partial pressure of O_2). The resulting pH and electrolyte disturbances can produce nonspecific symptoms, including fatigue, headache, dizziness, confusion, and lethargy.

What is the most likely diagnosis?

The patient has a chronic respiratory acidosis due to her underlying COPD. It is considered chronic because she has already compensated for the elevated P_{CO_2} through bicarbonate retention and production. A patient undergoing a more acute process is not able to compensate as quickly, and so the pH would be more acidotic and the bicarbonate levels would be in the normal range.

In Figure 15-17, which area corresponds to respiratory acidosis, respiratory alkalosis, metabolic acidosis, and metabolic alkalosis?

Letter A: metabolic alkalosis (with a rapid respiratory compensation evidenced by the elevated P_{CO_2})
Letter B: acute respiratory alkalosis (without metabolic compensation)
Letter C: chronic respiratory alkalosis (with metabolic compensation evidenced by the significantly lower bicarbonate levels)
Letter D: metabolic acidosis (with a rapid respiratory compensation evidenced by the lower P_{CO_2})
Letter E: acute respiratory acidosis (without metabolic compensation)
Letter F: chronic respiratory acidosis (with metabolic compensation evidenced by the significantly higher bicarbonate levels)

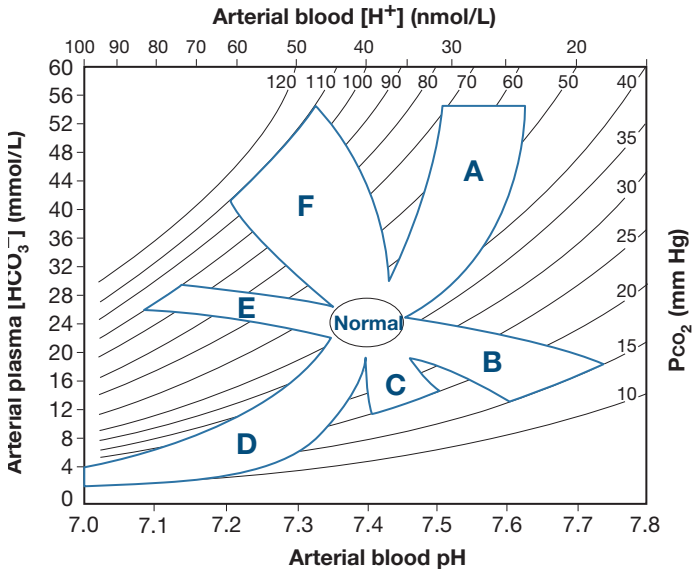

FIGURE 15-17. Acid-base nomogram. (Reproduced with permission from USMLE-Rx.com.)

How is this condition distinguished from metabolic acidosis?

In respiratory acidosis, the primary disturbance is an increase in P_{CO_2} due to inadequate ventilation, to which the body responds by increasing renal bicarbonate reabsorption, which can take 24-48 hours to compensate. In metabolic acidosis, the primary disturbance is a decrease in bicarbonate, which is compensated for by much more immediate hyperventilation, resulting in a decreased P_{CO_2}.

What is the anion gap, and what factors can increase the anion gap in this condition?

The anion gap is defined as $[Na^+] - ([HCO_3^-] + [Cl^-])$ and is normally 8-12. Calculation of the anion gap is often helpful in reaching the correct diagnosis. In this case, it is $[144] - ([40] + [96]) = 8$, which is within the normal range. Causes of increased anion-gap metabolic acidosis include renal failure, diabetic ketoacidosis, lactic acidosis, and salicylate ingestion. Causes of normal anion-gap metabolic acidosis include diarrhea, renal tubular acidosis, and hyperchloremia. Normal anion-gap metabolic acidoses are also often referred to as hyperchloremic metabolic acidoses because the chloride levels rise rather than a metabolically produced anion.

CASE 17

A 35-year-old African-American man presents to his primary care physician with progressive dyspnea on exertion. He has no history of congestive heart failure or asthma and has had no known contact with any individuals known to have tuberculosis. His laboratory results reveal normal creatinine kinase (CK), CK-MB fraction, and troponin levels. An x-ray of the chest shows bilateral hilar lymphadenopathy and evidence of interstitial lung disease (ILD). A bronchoscopic lung biopsy was performed and is shown in Figure 15-18.

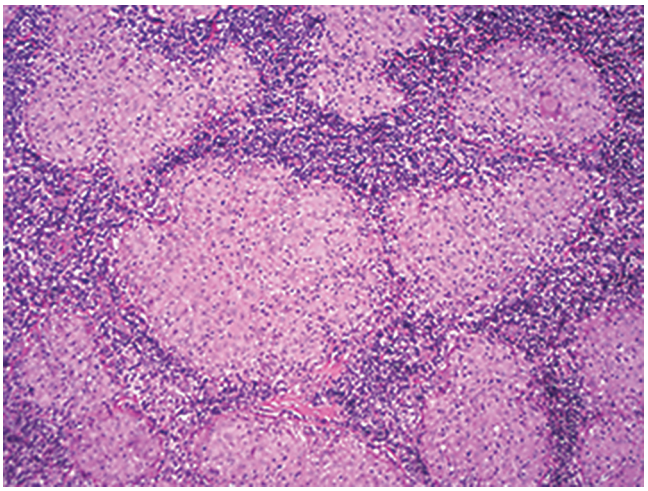

FIGURE 15-18. (Reproduced with permission from USMLE-Rx.com.)

What is the most likely diagnosis?

Sarcoidosis. Sarcoidosis is a form of interstitial lung disease (ILD) that presents with bilateral hilar lymphadenopathy and reticular opacities on x-ray of the chest, classically in African-American women. Lung tissue biopsy demonstrates multiple small noncaseating granulomas (discrete collections of tissue macrophages termed "histiocytes" organized into multinucleated giant cells without central necrosis), seen in Figure 15-18.

What is ILD and what are the common causes?

The term "ILD" is generically used to describe a collection of diseases that involve diffuse scarring and/or inflammation of lung tissue. Common causes of ILD are as follows:

- Prolonged exposure to occupationally inhaled inorganic agents such as silicone, coal, asbestos, talc, mica, aluminum, and beryllium
- Idiopathic pulmonary fibrosis
- Connective tissue disease (eg, Wegener granulomatosis, systemic lupus erythematosus, scleroderma, Sjögren disease)
- Sarcoidosis
- Hypersensitivity pneumonitis, such as "farmer's lung" or "bird-breeder's lung," in which an immune reaction to an organic dust induces a type III or type IV hypersensitivity reaction
- Radiation-induced disease
- Antitumor drugs (eg, bleomycin)

What laboratory abnormalities may be found in this patient's condition?

Macrophages in the noncaseating granulomas contain 1α-hydroxylase activity and are thus able to activate 24-hydroxycholecalciferol (24-OH-D) into its active form, 1,25-dihydroxycholecalciferol (or calcitriol). As a result, patients often have hypercalcemia. Additionally, the macrophages secrete angiotensin-converting enzyme, so those levels will also be elevated. In the bronchoalveolar lavage fluid, a predominance of CD4+ T cells may be noted, too.

What pulmonary function testing findings are expected?

In ILD, lung compliance is decreased, reflecting increased stiffness from the diffuse alveolar wall inflammation and fibrosis. Thus, all ILDs present with features characteristic of restrictive lung disease: a decreased tidal volume and total lung capacity. Diffusion capacity is also decreased as a result of inflammatory destruction of the air-capillary interface. Unlike most ILDs, however, sarcoidosis also has features of obstruction in addition to restriction.

What are some extrapulmonary manifestations of this patient's ILD?

Common extrapulmonary manifestations of sarcoidosis are in the eye (anterior uveitis) and skin (papules and erythema nodosum), but granulomas can also occur in the heart, brain, lung, and peripheral lymph nodes.

What is the treatment for this condition?

Corticosteroids.

CASE 18

A 56-year-old man presents to his physician complaining of generalized weakness, cough, and a 9.1-kg (20-lb) weight loss that has occurred over the past 8 weeks. His voice is hoarse, and he is unable to keep up with his work as a construction worker. The patient has a 30-pack-year smoking history. Serum sodium is 119 mEq/L. The physician orders posteroanterior and lateral chest radiographs (see Figure 15-19).

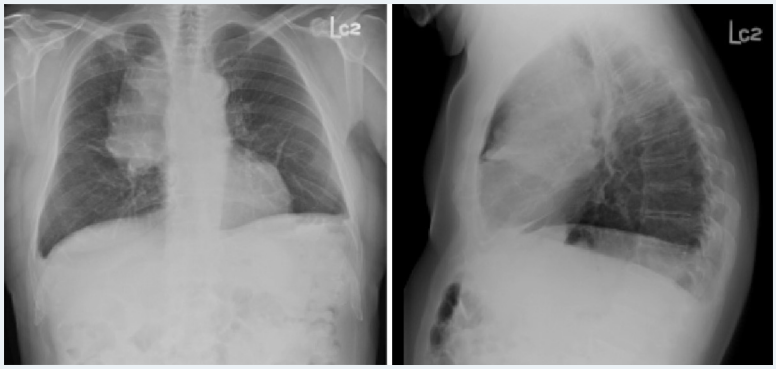

FIGURE 15-19. (Reproduced with permission from Kantarjian HM, et al. *MD Anderson Manual of Medical Oncology*. New York: McGraw-Hill, 2006: 239.)

What is this most likely diagnosis?

Small cell lung cancer is strongly suggested by the central, hilar nature of the lung mass, as seen in Figure 15-19; a significant weight loss; an extensive smoking history; and a serum sodium of 119 mEq/L, as a result of syndrome of inappropriate antidiuretic hormone (SIADH), a paraneoplastic process.

Which other paraneoplastic processes are associated with this condition?

Small cell lung cancer causes hormonally mediated Cushing syndrome due to ectopic secretion of adrenocorticotropic hormone. In addition, some patients with small cell lung cancer develop Lambert-Eaton myasthenic syndrome, a neuromuscular junction disorder in which muscle weakness improves with use; and subacute cerebellar degeneration due to autoantibodies generated against neurons.

What additional symptoms can arise from an intrathoracic cancer?

Symptoms for tumors within the thoracic cavity derive from their location and the structures they displace or disrupt, and include superior vena cava obstruction, hoarseness of the voice due to recurrent laryngeal nerve compression, phrenic nerve palsy resulting in dyspnea (the phrenic nerve innervates the diaphragm), dysphagia from esophageal compression, and stridor due to tracheal compression.

What would a biopsy of this patient's condition show?

Small cell lung cancer is a neuroendocrine tumor, and as with all neuroendocrine tumors, a biopsy will show small round blue cells. Immunohistochemically, the cells stain positive for neuron markers, such as chromogranin A and neuron-specific enolase.

To which areas does this condition commonly metastasize?

Small cell lung cancer, like all other lung cancers, is notable for its metastases to the central nervous system, liver, bone, and uniquely the adrenal glands. As a result, patients may present with bone pain, neurologic symptoms such as seizures or focal deficits, pain in the right upper quadrant, and adrenal insufficiency (inadequate cortisol and/or mineralocorticoids)

What is the prognosis for patients with this condition?

Untreated patients with this disease have a median survival of only 6–17 weeks. However, with combination chemotherapy, median survival may increase to up to 70 weeks. The prognosis largely depends on the tumor's reaction to chemotherapy; drugs include etoposide and cisplatin. Surgery is not an option in small cell lung cancer because of its early and highly aggressive metastasis.

CASE 19

A 62-year-old woman presents to the ED with acute-onset shortness of breath. She also complains of "stabbing" pleuritic right-sided chest pain. The woman had a stroke 3 months ago but is otherwise healthy. Her temperature is 36.7°C (98.1°F), blood pressure is 90/60 mm Hg, heart rate is 110/min, respiratory rate is 40/min, and oxygen saturation is 80% on room air. Physical examination reveals jugular venous distention, and cardiovascular examination reveals a fast rate with regular rhythm and no murmurs. The woman's lungs are clear bilaterally with decreased breath sounds in the right middle lobe.

What is the most likely diagnosis?

This is a case of pulmonary embolism (also known as venous thromboembolism, or VTE).

What other conditions should be included in the differential diagnosis?

The differential diagnosis of chest pain includes the following:

- **Cardiac**: Myocardial infarction, unstable angina, pericarditis (all less likely to present with such a low oxygen saturation)
- **Pulmonary**: Pneumonia, pneumothorax (tension pneumothorax especially needs to be ruled out), exacerbation of COPD
- **Musculoskeletal**: Costochondritis (presents with point tenderness reproducible on physical exam)
- **Gastrointestinal**: gastroesophageal reflux (nocturnal upper abdominal or substernal pain presenting without exertion)

What is the Virchow triad?

The Virchow triad refers to the three factors that increase the risk for venous thrombosis: endothelial injury, hypercoagulability, and stasis. It is believed that patients with VTE are predisposed to venous thrombosis; triggers include pregnancy, limb immobility, and surgery.

What is the most likely finding on microscopic examination?

Under low-power magnification, characteristic lines of Zahn (alternating pale lines of platelets and fibrin with red lines of RBCs) may be visible in the thrombus, as shown in Figure 15-20. Lines of Zahn occur only in thrombi formed before death, unlike post-mortem thrombi, which occur secondary to stasis.

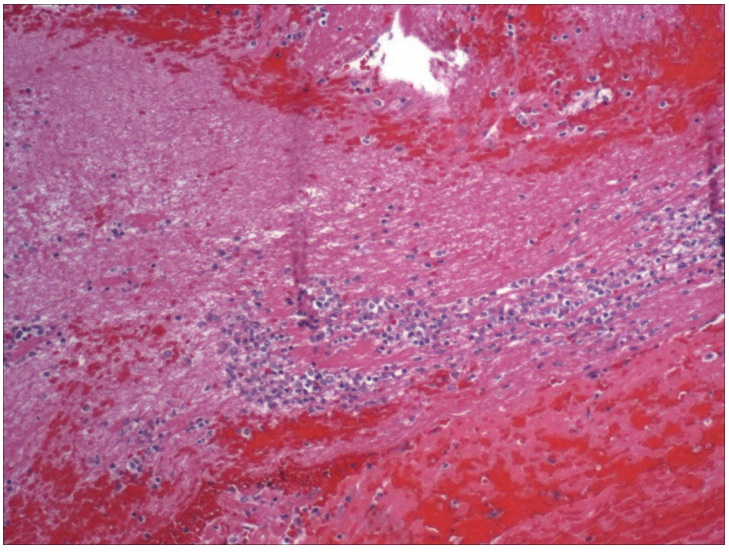

FIGURE 15-20. Lines of Zahn, premortem thrombus. (Reproduced with permission from USMLE-Rx.com.)

What test remains the gold standard for diagnosing this condition?

Pulmonary CT angiography remains the most specific test available for definitively diagnosing VTE; a positive finding for VTE would be a filling defect. However, because of the invasiveness of angiography, CT of the chest with thin cuts is the most frequently used diagnostic test. A ventilation-perfusion lung scan (V/Q scan) is still often used. A lung scan showing normal perfusion virtually excludes VTE, as a VTE always occludes some pulmonary vessel. An x-ray of the chest can show signs of VTE including Hampton hump (a wedge-shaped opacity indicating infarction of an area served by an occluded vessel) and Westermark sign (oligemia distal to a VTE); however, neither sign is specific. Additional imaging would still be necessary to confirm the diagnosis.

Plasma D-dimer levels have a negative predictive value in cases of low clinical suspicion but are elevated in more than 90% of patients with VTE. This assay is nonspecific, and levels may also be elevated in conditions such as myocardial infarction or sepsis.

When the basis for ordering imaging is unclear, the Wells criteria can be used to strengthen the diagnosis of a pulmonary embolism, based on various criteria, such as hemoptysis, tachycardia, history of deep venous thromboses, and pure clinical suspicion.

What are the treatments for this condition?

VTE is treated with hospitalization and therapeutic levels of heparin for at least 5 days unless there is a contraindication to anticoagulation (eg, recent surgery). In most patients, warfarin and heparin are started together, and the patient continues taking oral warfarin for outpatient anticoagulation for 3 months. In patients who have unprovoked VTEs (in the absence of Virchow's triad risk factors), oral anticoagulation may be continued for longer. If there is a contraindication to anticoagulation or a high risk of recurrence of VTE, an inferior vena cava filter is recommended for control.

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APPENDIX

CASE INDEX

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Tao developed a passion for medical education as a medical student. He currently edits more than 15 titles in the *First Aid* series. In addition, he is Founder and Chief Education Officer of USMLE-Rx for exam preparation and ScholarRx for undergraduate medical education. As a medical student, he was editor-in-chief of the University of California, San Francisco (UCSF) *Synapse*, a university newspaper with a weekly circulation of 9000. Tao earned his medical degree from UCSF in 1996 and completed his residency training in internal medicine at Yale University and fellowship training at Johns Hopkins University. Tao subsequently went on to cofound Medsn, a medical education technology venture, and served as its chief medical officer. He is currently chief of adult allergy and immunology at the University of Louisville.

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Richard is a family medicine resident physician at the University of Alabama. Over the course of his medical career, Richard has always been drawn towards teaching medical students through lecture series and informal didactics. He is a graduate of St. George's University School of Medicine. While at St. George's, Richard was actively involved in teaching other medical students in various subjects of basic sciences. During his clinical years, Richard became involved with the First Aid team and has worked on several projects with them, including being senior editor of the USMLE-Rx Step 1 question bank and being an author for *First Aid for the Family Medicine Boards* and *First Aid for the Basic Sciences: General Principles*. Richard looks forward to a career as a hospitalist as well as in academic medicine. Being Italian, Richard enjoys spending time with his family, watching soccer with his dad, eating, weight lifting, playing video games, and spending time with his friends and girlfriend.

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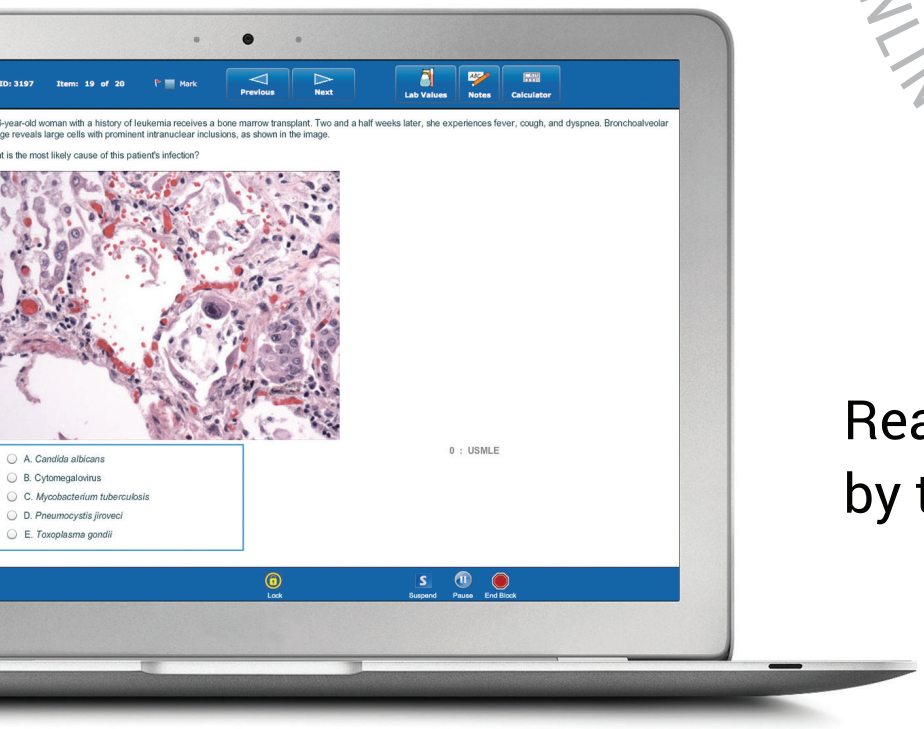

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