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Preface

*Current Medical Diagnosis and Treatment (CMDT)* is the leading internal medicine textbook known for its comprehensive coverage of current inpatient and outpatient care with diagnostic tools relevant to day-to-day practice. These *CMDT Flashcards* provide study aids for 80 of the most common topics in internal medicine. The *CMDT Flashcards* provide a synopsis of the medical topic for a quick review and a study aid for a variety of standardized examinations. As such it will be very useful to medical, nursing, pharmacy, and other health professional students, to house officers, and to practicing physicians. The *CMDT Flashcards* are engaging and patient-centered since all topics begin with presentation of a typical patient to help the reader think in a step-wise fashion through the various clinical problem-solving aspects of the case.

**Outstanding Features**

- 80 common internal medicine topics useful to learners in their preparation for a variety of examinations
- Material drawn from the expert source, *Current Medical Diagnosis and Treatment*
- Concise, consistent, and readable format is organized in a way that allows for quick study
- Medical and nursing students, physician’s assistants, nurse practitioners, house officers, and practicing physicians will find the clear organization and brevity useful

**Organization**

The 80 topics in the *CMDT Flashcards* were selected as core topics because of their relevance to the field of internal medicine and to learners of the discipline.

There are 3 *CMDT Flashcards* for each topic. On the front of the first, a case is presented and the reader is then asked 2 questions regarding the salient features of the patient’s complaints and how to think through the problem, the answers to which are printed upside down on the card. In a similar fashion, the front and back of each of the *CMDT Flashcards* ask questions that develop the learner’s clinical problem-solving skills regarding the case. The questions concern the Essentials of Diagnosis and General Considerations; Symptoms and Signs; Differential Diagnosis; Laboratory, Imaging and Procedural Findings; and Treatments.

The *CMDT Flashcards* follow the organization of *Quick Medical Diagnosis and Treatment* (AccessMedicine and app) and concern disorders in 11 general categories:

- Skin Disorders
- Pulmonary/Ear, Nose & Throat Disorders
- Heart/Hypertension/Lipid Disorders
- Hematologic Disorders
- Gastrointestinal/Liver/Pancreas Disorders
- Gynecologic/Urologic Disorders
- Musculoskeletal Disorders
- Kidney/Electrolyte Disorders
- Nervous System/Psychiatric Disorders
Intended Audience

Medical students on their internal medicine clerkship will find these *CMDT Flashcards* a useful aid as they care for patients with these common medical problems. These *CMDT Flashcards* will assist PA, NP, and medical students taking their internal medicine rotation and house officers to review the core topics as they prepare for standardized examinations. Nurse practitioners and practicing physicians will similarly find these *CMDT Flashcards* useful in order to stay current in clinical problem solving, as well as to review a brief overview of diagnostic studies and treatments.

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San Francisco, CA
A 30-year-old woman presents to her primary care provider with an itchy rash on her hands, wrists, and arms. She states she has had similar rashes before that had gone away with over-the-counter hydrocortisone cream. The first episode occurred when she was very young. Her past medical history includes asthma. She takes loratadine occasionally for allergic rhinitis. Physical examination reveals plaques on the hands, wrists, and antecubital folds that are mildly exudative and without scale. Laboratory testing shows eosinophilia and an elevated serum IgE level.

What are the salient features of this patient’s problems? How do you think through her problems?
Salient features: Pruritic rash in distribution of hands, wrists, antecubital folds; similar symptoms starting in childhood; personal history of atopic conditions (asthma, allergic rhinitis); plaques with exudates and without scale; eosinophilia and elevated serum IgE level

How to think through: It is important to think broadly about possible causes of rash in this patient despite her strong atopic history. Might this be seborrheic dermatitis? (Seborrheic dermatitis typically involves the face and scalp.) A fungal infection? (Prior similar manifestations have resolved with topical corticosteroid treatment, making this unlikely.) Psoriasis? (The distribution and absence of silvery scale makes this unlikely.) Contact dermatitis? (This is a reasonable consideration. Contact dermatitis can be indistinguishable from atopic dermatitis, and in this case, the rash is similarly confined to exposed areas of the body.) What would raise your suspicion for contact dermatitis? (A history of new potential allergen or irritant exposure.) After considering the above, a diagnosis of atopic dermatitis is most likely given the prior atopy (asthma and allergic rhinitis), recurrence of similar symptoms since childhood, eosinophilia, and elevated IgE. How should she be treated? (Midpotency topical corticosteroids twice daily with subsequent tapering to low-potency corticosteroids with emollient applied frequently. This patient’s presentation is unlikely to require oral corticosteroid treatment. An oral antihistamine for itching may be helpful.) How would you counsel this patient to prevent future flares? (Avoid excessive bathing and hand washing. Use mild soaps. Apply emollient after washing. Trim fingernails and wrap affected areas at night to prevent scratching.)
What are the essentials of diagnosis and general considerations regarding atopic dermatitis?
Essentials of Diagnosis

- Pruritic, exudative, or lichenified eruption on the face, neck, upper trunk, wrists, hands, antecubital and popliteal folds
- Personal or family history of allergies or asthma with a tendency to recur
- Onset in childhood in most patients; onset after age 30 years is very uncommon

General Considerations

- Also known as eczema
- Looks different at different ages and in people of different races
- Diagnostic criteria include pruritus, onset in childhood, chronicity, and typical morphology and distribution (flexural lichenification; hand, nipple, and eyelid eczema in adults)
- Also helpful diagnostically are a personal or family history of atopic disease such as asthma, atopic dermatitis or allergic rhinitis, xerosis–ichthyosis, facial pallor with intraorbital darkening, elevated serum IgE, and repeated skin infections
What are the symptoms and signs of atopic dermatitis?
Symptoms and Signs

- Itching may be severe and prolonged.
- Rough, red plaques usually without the thick scale and discrete demarcation of psoriasis affect the face, neck, and upper trunk.
- Flexural surfaces of elbows and knees are often involved.
- In chronic cases, the skin is dry, leathery, and lichenified.
- Pigmented persons may have poorly demarcated hypopigmented patches (pityriasis alba) on the cheeks and extremities.
- In black patients with severe disease, pigmentation may be lost in lichenified areas.
- During acute flares, widespread redness with weeping, either diffusely or in discrete plaques, occurs.
What is the differential diagnosis of atopic dermatitis?
Differential Diagnosis

- Seborrheic dermatitis
- Impetigo
- Secondary staphylococcal infections
- Psoriasis
- Lichen simplex chronicus (circumscribed neurodermatitis)
- Hyper-IgE syndrome
What are the laboratory findings in atopic dermatitis?
Laboratory Tests

- Radioallergosorbent tests (RASTs) or skin tests may suggest dust mite allergy
- Eosinophilia and increased serum IgE levels may be present
What are the treatments for atopic dermatitis?
Medications

- Topical corticosteroids such as triamcinolone or stronger are used, tapering to milder agents such as hydrocortisone.
- Tacrolimus or pimecrolimus are also effective as first-line steroid-sparing agents.
- Systemic and adjuvant therapies include corticosteroids such as prednisone, antihistamines for pruritus, antistaphylococcal antibiotics for superinfections, and phototherapy.
- Oral cyclosporine, mycophenolate mofetil, methotrexate, or azathioprine may be used for the most severe and recalcitrant cases.
- Acute weeping lesions: use soothing soaks and dressings as well as high-potency topical corticosteroids.
- Subacute or scaly lesions (lesions are dry but still red and pruritic): use mid- to high-potency corticosteroids with a taper.
- Chronic, dry lichenified lesions (thickened and usually well-demarcated): require high- to ultra-high potency corticosteroids; occlusion may enhance the initial response.
- Maintenance treatment with moisturizers or weekend use of topical corticosteroids can prevent flares.
A 30-year-old woman presents to the clinic complaining that she has “an itchy rash all over the place.” She noticed that her legs became red, itchy, and blistered about 2 days after she had been hiking in a heavily wooded area. She says that scratching broke the blisters and afterward the rash became much worse and spread all over. She is convinced that the rash could not be poison ivy because once before she was exposed to that plant and did not develop a rash. On examination, there are erythematous vesicles and bullae in linear streaks on both of her legs. Some areas are weepy, with a yellowish crust. There are ill-defined erythematous plaques studded with papulovesicles on the trunk and arms.

What are the salient features of this patient’s problem? How do you think through her problem?
Salient features: Itchy erythematous rash; history of pre-eruption exposure to the outdoors; previous initial exposure to same antigen; vesicles and bullae

How to think through: This patient’s rash is severe, so it is important to think broadly about other causes besides those linked to the outdoor exposure. No symptoms or signs of systemic illness are mentioned, but a complete review of systems and physical examination (with vital signs) are essential. Could this be atopic dermatitis? (Unlikely—there is no history of atopy or prior similar symptoms) Might this be seborrheic dermatitis? (No, because it typically involves the face and scalp.) A fungal infection? (The pace is too rapid, and the rash is more consistent with dermatitis). Scabies? (No, because of the rapid pace and lack of focus in intertriginous areas.) Could this be impetigo? (Yes; careful examination is warranted to exclude impetigo.) What features of this case provide the strongest evidence for contact dermatitis? (Streaked appearance, a pattern confined to exposed areas of the body, and recent possible exposure to poison ivy with prior contact with this antigen.) What are the two classes of causative agents in contact dermatitis? (Irritants and antigens.)

What are other common irritants or antigens?

How should she be treated, topically or systemically? (The weeping and bullae suggest that she may need systemic corticosteroids.) What complications may develop? (Superinfection, especially with Streptococcus spp. and Staphylococcus aureus.)
What are the essentials of diagnosis and general considerations regarding contact dermatitis?
Essentials of Diagnosis
- Erythema and edema, with pruritus, often followed by vesicles and bullae in an area of contact with a suspected agent
- A history of previous reaction to suspected contactant
- A positive result for a patch test with the agent
- May develop secondary infection

General Considerations
- An acute or chronic dermatitis that results from direct skin contact with chemicals or allergens
- Irritant contact dermatitis is red and scaly, but not vesicular, and is usually caused by irritants such as soaps, detergents, or organic solvents
- Allergic contact dermatitis occurs commonly from poison ivy, oak, or sumac; topical medications; hair-care products; preservatives; jewelry (nickel); rubber (latex); vitamin E; essential oils; propolis (from bees); and adhesive tape
- Weeping and crusting are typically caused by allergic, rather than irritant, dermatitis
What are the symptoms and signs of contact dermatitis?
Symptoms and Signs

- The acute phase is characterized by tiny vesicles and weepy and crusted lesions.
- Resolving or chronic contact dermatitis presents with scaling, erythema, and possibly thickened skin; itching, burning, and stinging may be severe.
- The lesions, distributed on exposed parts or in bizarre asymmetric patterns, consist of erythematous macules, papules, and vesicles.
- The affected area is often hot and swollen, with exudation and crusting, simulating—and at times complicated by—infection.
- The pattern of the eruption may be diagnostic (e.g., typical linear streaked vesicles on the extremities in poison oak or ivy dermatitis).
- The location of involvement often suggests the offending agent.
What is the differential diagnosis of contact dermatitis?
Differential Diagnosis

- Impetigo
- Scabies
- Dermatophytid reaction (allergy or sensitivity to fungi)
- Atopic dermatitis
- Pompholyx

Asymmetric distribution, blotchy erythema around the face, linear lesions, and a history of exposure help distinguish contact dermatitis from other skin lesions.

The most commonly confused diagnosis is impetigo, in which case Gram stain and culture rule out impetigo or secondary infection (impetiginization).
What are the laboratory and procedural findings in contact dermatitis?
Laboratory Tests
- Gram stain and culture rule out impetigo or secondary infection (impetiginization).
- After the episode has cleared, patch testing may be useful if the triggering allergen is not known.

Diagnostic Procedures
- If itching is generalized, then consider scraping for scabies.
What are the treatments for contact dermatitis?
Medications

- Acute weeping dermatitis is usually treated with high-potency topical corticosteroids.
- Oral corticosteroids with a 12- to 21-day course and taper are used for severe cases.
- Soothing lotions such as Calamine or Sarna can also be helpful.
- Subsiding or subacute dermatitis is treated with mid- to high-potency topical corticosteroids.
- Chronic dermatitis may require very high-potency topical corticosteroids.

Therapeutic Procedures

- Compresses and wet dressing bandages are often used.
- Removal of the offending irritant is important.
A 25-year-old woman presents with a complaint of rash that has developed over the past several weeks and seems to be progressing. She describes the involved areas as mildly itchy. On examination, she is noted to have several plaque-like lesions over the extensor surfaces of both upper and lower extremities as well as similar lesions on her scalp. The plaques are erythematous with silvery scales and are sharply marginated.

What are the salient features of this patient’s problem? How do you think through her problem?
**Salient features:** Progressive rash; mild itching; plaque-like lesions; extensor surfaces of extremities and scalp distribution; sharp margins with silvery scales

**How to think through:** What are the common skin diseases in the differential diagnosis of this woman’s eruption, and what features about her presentation make psoriasis the most likely diagnosis? (Candidiasis, tinea, and atopic dermatitis are characterized by poorly demarcated lesions and typically present on the extensor surfaces. *Candida,* in particular, is found in the moist body folds and flexural surfaces. This patient’s lesions are described as mildly pruritic, which is more typical of psoriasis than these alternative diagnoses. The scaly scalp plaques are particularly characteristic of psoriasis.) How does her presentation differ from that of seborrheic dermatitis? What other manifestations should you explore? (Nail pitting is common in psoriasis and will help confirm your diagnosis. Joint pain and inflammation would raise the possibility of psoriatic arthritis.)
What are the essentials of diagnosis and general considerations regarding psoriasis?
Essentials of Diagnosis
- Silvery scales on bright red, well-demarcated plaques, usually on the knees, elbows, and scalp
- Nail findings include pitting and onycholysis (separation of the nail plate from the bed)
- Mild itching (usually)
- May be associated with psoriatic arthritis
- Patients with psoriasis are at increased risk for metabolic syndrome and lymphoma
- Histopathology is not often useful and can be confusing

General Considerations
- A common benign, chronic inflammatory skin disease with both a genetic basis and known environmental triggers
- Injury or irritation of normal skin tends to induce lesions of psoriasis at the site (Koebner phenomenon)
- Psoriasis has several variants; the most common is the plaque type
What are the symptoms and signs of psoriasis?
Symptoms and Signs

- There are often no symptoms, but itching may occur.
- Although psoriasis may occur anywhere, examine the scalp, elbows, knees, palms and soles, umbilicus, intergluteal fold, and nails.
- The lesions are red, sharply defined plaques covered with silvery scales; the glans penis and vulva may be affected; occasionally, only the flexures (axillae, inguinal areas) are involved (“inverse psoriasis”).
- Fine stippling (“pitting”) in the nails is highly suggestive; onycholysis may occur.
- Patients with psoriasis often have a pink or red intergluteal fold.
- There may be associated seronegative arthritis, often involving the distal interphalangeal joints.
- Eruptive (guttate) psoriasis consisting of myriad lesions 3 to 10 mm in diameter occurs occasionally after streptococcal pharyngitis.
- Plaque-type or extensive erythrodermic psoriasis with an abrupt onset may accompany HIV infection.
What is the differential diagnosis of psoriasis?
Differential Diagnosis

- Atopic dermatitis (eczema)
- Contact dermatitis
- Nummular eczema (discoid eczema, nummular dermatitis)
- Tinea, candidiasis, or intertrigo
- Seborrheic dermatitis
- Pityriasis rosea
- Secondary syphilis
- Pityriasis rubra pilaris
- Onychomycosis (nail findings)
- Cutaneous features of reactive arthritis
- Cutaneous T-cell lymphoma (mycosis fungoides)
What are the procedural findings in psoriasis?
**Diagnostic Procedures**

- The combination of red plaques with silvery scales on the elbows and knees with scaliness in the scalp or nail pitting or onycholysis is diagnostic.

- Psoriasis lesions are well demarcated and affect extensor surfaces in contrast to atopic dermatitis, which has poorly demarcated plaques in a flexural distribution.

- In body folds, scraping and culture for *Candida* spp. and examination of the scalp and nails will distinguish psoriasis from intertrigo and candidiasis.
What are the treatments for psoriasis?
Medications

- Never use systemic corticosteroids; they may lead to severe rebound flares.
- β-blockers, antimalarial agents, statins, and lithium may flare or worsen psoriasis.

Limited disease (<10% of the body surface)

- Topical corticosteroids or vitamin D analogs such as calcipotriene or calcitriol ointment may be used.
- Occlusion alone clears isolated plaques in 30% to 40% of patients.
- For the scalp, tar shampoo, salicylic acid, and corticosteroid preparations are available.
- Topical tacrolimus or pimecrolimus may be effective in penile, groin, and facial psoriasis.

Moderate disease (10%–30% of the body surface) to severe disease (>30% of the body surface)

- Methotrexate is very effective, and cyclosporine dramatically improves severe cases.
- Acitretin, a synthetic retinoid (and teratogen), is most effective for pustular psoriasis.
- Tumor necrosis factor (TNF) inhibitors, alefacept, and IL-12/23 monoclonal antibodies may be considered.

Therapeutic Procedures

- Ultraviolet (UV) or narrow-band UVB phototherapy can be used with or without coal tar.
- PUVA (psoralen plus ultraviolet A) may be effective even if standard UVB treatment has failed.
A 25-year-old previously well woman presents to your office with complaints of episodic shortness of breath and chest tightness. She has had these symptoms on and off for about 2 years but states that they have worsened lately, occurring two or three times a month. She notes that the symptoms are worse during the spring months and since her new roommate moved in with his cat. She has no exercise-induced or nocturnal symptoms. The patient smokes occasionally when out with friends, drinks socially, and has no history of drug use. Examination is notable for mild end-expiratory wheezing.

**What are the salient features of this patient’s problem? How do you think through her problem?**
**Salient features:** Intermittent shortness of breath and chest tightness; environmental triggers; family history; wheezing on physical examination

**How to think through:** What are other possible causes of shortness of breath, and what makes asthma the most likely cause in this patient? What are common environmental triggers to explore? What associated atopic diseases would you ask about? What are non–allergy-mediated exacerbating factors to explore? How can you best establish the severity of her asthma symptoms and the potential for life-threatening exacerbations? (History of emergency department visits, hospital admissions, and intubations.) If she did not have audible wheezing on examination, what more subtle signs could you look for? (Increased expiratory time, cough induced by rapid expiration.) What would her pulmonary function tests (PFTs) likely show? When you begin treatment of her asthma, what should serve as your barometer for the degree of control? (Number of episodes per week, peak expiratory flow rate [PEFR].) At what point would you add a daily controller medication, and what would be your first choice? Beyond medication, what are other important interventions? (Allergen reduction, smoking cessation.)
What are the essentials of diagnosis and general considerations regarding asthma?
Essentials of Diagnosis
- Episodic or chronic symptoms of airflow obstruction
- Reversibility of airflow obstruction, either spontaneously or after bronchodilator therapy
- Symptoms frequently worse at night or in the early morning
- Prolonged expiration and diffuse wheezes on physical examination
- Limitation of airflow on pulmonary function testing or positive bronchoprovocation challenge

General Considerations
- Hospitalization and death rates highest among blacks
- Affects 5% of the population; prevalence and severity has increased in the United States
What are the symptoms and signs of asthma?
Symptoms and Signs

- Episodic wheezing and difficulty breathing, chest tightness, and cough
- Excess sputum production
- Symptoms are frequently worse at night
- Common aeroallergens include dust mites, cockroaches, cats, and pollen
- Nonspecific precipitants include exercise, respiratory tract infections, rhinitis and sinusitis, postnasal drip, aspiration, gastroesophageal reflux, changes in weather, and stress
- Tobacco smoke increases symptoms and decreases lung function
- Certain medications (including aspirin and nonsteroidal anti-inflammatory drugs) may be triggers
- Nasal findings consistent with allergy and evidence of allergic skin disorders
- Wheezing with normal breathing or a prolonged forced expiratory phase
What is the differential diagnosis of asthma?
Differential Diagnosis

- Vocal cord paralysis or dysfunction
- Foreign body aspiration or laryngotracheal mass
- Tracheal stenosis or tracheomalacia
- Angioedema or airway edema from inhalation injury
- Chronic obstructive pulmonary disease
- Bronchiectasis
- Allergic bronchopulmonary aspergillosis
- Cystic fibrosis
- Eosinophilic pneumonia
- Bronchiolitis obliterans
- Churg-Strauss syndrome
- Psychiatric causes such as conversion disorder
What are the laboratory, imaging, and procedural findings in asthma?
Laboratory Tests

- PFTs: spirometry (forced expiratory volume in 1 second [FEV\textsubscript{1}], forced vital capacity [FVC], FEV\textsubscript{1}/FVC ratio) before and after the administration of a short-acting bronchodilator, with reversibility of obstruction after the bronchodilator.
- PEFR monitoring can quantify severity and guide treatment decisions.
- Arterial blood gases may show a respiratory alkalosis and an increase in the alveolar–arterial oxygen difference; in severe exacerbations, hypoxemia develops, and the PaCO\textsubscript{2} normalizes.
- An increased PaCO\textsubscript{2} and respiratory acidosis may portend respiratory failure.

Imaging Studies

- Chest radiographs usually show hyperinflation but may include bronchial wall thickening and diminished peripheral lung vascular shadows.

Diagnostic Procedures

- Bronchial provocation testing with inhaled histamine or methacholine when asthma is suspected but spirometry is nondiagnostic.
- Exercise challenge and skin testing for environmental allergens may be useful.
What are the treatments for asthma?
Medications

- Long-term control therapies include inhaled corticosteroids, inhaled long-acting β₂-agonists (often in combination with inhaled corticosteroids), systemic corticosteroids, leukotriene modifiers, mediator inhibitors, and phosphodiesterase inhibitors.
- Relief therapy or “rescue” therapies include short-acting inhaled β₂-agonists, inhaled anticholinergics, and systemic corticosteroids.
- Acute exacerbations are treated with inhaled short-acting β₂-agonists with or without systemic corticosteroids depending on the severity.
- Severe exacerbations (PEFR <40% predicted or personal best) may also require oxygen treatment, inhaled ipratropium bromide, and intravenous magnesium sulfate.
- Chronic asthma treatment is guided by asthma severity.
- Mild intermittent asthma treatment requires inhaled short-acting β₂-agonists for rescue.
- Mild persistent asthma treatment includes daily use of a long-term control therapy.
- Moderate persistent asthma treatment requires increased corticosteroid dose or adding long-acting inhaled β₂-agonist.
- Severe persistent asthma treatment requires daily high-dose inhaled corticosteroid and long-acting β₂-agonist.
- Theophylline is a less preferred alternative to long-acting bronchodilators.
A 72-year-old man with chronic obstructive pulmonary disease (COPD) presents to the emergency department with progressively worsening shortness of breath. Using 2 L/min of oxygen at home, he is usually able to walk around the house without limitation. Over the past 4 days, however, he has had increasing dyspnea on exertion and increased cough productive of thick green sputum. He has not had chest pain or worsening of his chronic mild ankle edema. He had smoked 2 packs of cigarettes daily for the past 50 years. Previous pulmonary function tests (PFTs) demonstrated a decreased forced expiratory volume in 1 second (FEV₁) and FEV₁/FVC (forced vital capacity) ratio. Physical examination shows tachycardia, tachypnea, and decreased breath sounds with diffuse wheezing bilaterally. Arterial blood gas (ABG) analysis shows acidemia from a partially compensated respiratory acidosis. He is placed on noninvasive positive-pressure ventilation with marked improvement of his acidemia.

What are the salient features of this patient’s problem? How do you think through his problem?
**Salient features:** Worsening dyspnea; change in cough and sputum; home oxygen use; 100 pack-year smoking history; obstructive pattern on spirometry; wheezing and respiratory distress; lower extremity edema; acidemia with partially compensated respiratory acidosis; improvement on noninvasive positive pressure ventilation

**How to think through:** This patient with COPD presents in respiratory distress. Already on oxygen at home, he has little pulmonary reserve. What test best assesses the severity of his pulmonary status? (ABGs.) His ABGs show acute respiratory acidosis, and noninvasive positive-pressure ventilation is initiated. In addition to ventilatory support, what are the treatment priorities? (Corticosteroid, inhaled β-agonist, inhaled anticholinergic agents.) What clinical developments would necessitate transition to endotracheal intubation? (Altered mental status, failure to decrease \( \text{PaCO}_2 \).) When the patient has recovered to baseline, what therapies decrease COPD exacerbations? (Smoking cessation, inhaled corticosteroids, influenza and pneumococcal vaccinations.) What other therapy decreases the mortality rate? (Home oxygen.)
What are the essentials of diagnosis and general considerations regarding chronic obstructive pulmonary disease?
Essentials of Diagnosis

- History of cigarette smoking
- Chronic cough, dyspnea, and sputum production
- Rhonchi, decreased intensity of breath sounds, and prolonged expiration on physical examination
- Airflow limitation on PFT

General Considerations

- Airflow obstruction is caused by chronic bronchitis, emphysema, or both.
- Obstruction is progressive and may be accompanied by airway hyperreactivity, which is partially reversible.
- Chronic bronchitis is characterized by excessive mucous secretions with productive cough for 3 months or more in at least 2 consecutive years.
- Emphysema is abnormal enlargement of air spaces distal to terminal bronchiole with destruction of bronchial walls without fibrosis.
- Cigarette smoking is the most important cause; 80% of patients have tobacco smoke exposure.
What are the symptoms and signs of chronic obstructive pulmonary disease?
Symptoms and Signs

- Presentation usually at 40-50 years of age with cough, sputum production, and shortness of breath.
- Dyspnea initially occurs only with heavy exertion, progressing to symptoms at rest in severe disease.
- Exacerbation of symptoms is beyond normal day-to-day variation, often including increased dyspnea, an increased frequency or severity of cough, increased sputum volume, or a change in sputum character.
- Infections (viral more commonly than bacterial) precede exacerbations in most patients.
- Late-stage COPD characterized by hypoxemia, pneumonia, pulmonary hypertension, cor pulmonale, and respiratory failure.
- Clinical findings may be absent early.
- Patients are often dichotomized as “pink puffers” or “blue bloaters” depending on whether emphysema or chronic bronchitis predominates.
What is the differential diagnosis of chronic obstructive pulmonary disease?
Differential Diagnosis

- Asthma
- Bronchiectasis, which features recurrent pneumonia and hemoptysis, with distinct radiographic findings
- Bronchopulmonary mycosis
- Central airflow obstruction
- Severe $\alpha_1$-antiprotease deficiency
- Cystic fibrosis, which is usually first seen in children and young adults
What are the laboratory and imaging findings in chronic obstructive pulmonary disease?
Laboratory Tests
- Sputum examination may reveal pathogens, although cultures correlate poorly with exacerbations.
- Electrocardiography shows sinus tachycardia, abnormalities consistent with cor pulmonale in severe disease, or supraventricular tachycardias and ventricular irritability.
- ABGs are unnecessary unless hypoxemia or hypercapnia is suspected and may show a compensated respiratory acidosis with worsening academia during exacerbations.
- Spirometry shows reduced FEV\textsubscript{1} and FEV\textsubscript{1}/FVC ratio in late disease, reduced FVC in severe disease, and increased total lung capacity (TLC) and residual volume (RV) from air trapping.
- Obtaining an α\textsubscript{1}-antiprotease level may reveal a deficiency in young patients with emphysema.

Imaging Studies
- Radiographs in patients with chronic bronchitis may show nonspecific peribronchial and perivascular markings.
- Plain radiographs are insensitive for emphysema; they may show hyperinflation with a flattened diaphragm or peripheral arterial deficiency.
- Computed tomography of the chest is more sensitive and specific for the diagnosis of emphysema.
- Doppler echocardiography estimates pulmonary artery pressure if pulmonary hypertension is suspected.
What are the treatments for chronic obstructive pulmonary disease?
Medications

- Supplemental oxygen in hypoxemic patients increases survival and reduces hospitalizations.
- Bronchodilators offer improvement in symptoms, exercise tolerance, and overall health.
- Ipratropium bromide and short-acting β₂-agonists (e.g., albuterol) are used, often in combination.
- Long-acting β₂-agonists (formoterol, salmeterol) and anticholinergics (tiotropium) are also beneficial.
- Corticosteroids are often used for exacerbations; they are generally not effective in outpatients.
- Antibiotics slightly improve outcomes in acute exacerbations.
- Opioids and sedative–hypnotic drugs can manage severe and refractory dyspnea.

Surgery

- Lung transplantation greatly improves pulmonary function and exercise tolerance.
- Lung volume reduction surgery in highly selected patients results in modest improvements.
- Bullectomy is used for palliation of dyspnea in patients with severe bullous emphysema.

Therapeutic Procedures

- Smoking cessation is the single most important goal.
- Noninvasive positive-pressure ventilation in exacerbation reduces the need for intubation, shortens intensive care unit lengths of stay, and may reduce the risk of health care–associated infections.
A 32-year-old man presents to the urgent care clinic with 4 weeks of cough. He describes a recent illness, coinciding with the onset of his cough, with nasal congestion, sore throat, fatigue, and myalgias. His other symptoms have since subsided, but his cough has continued. He denies any shortness of breath, fevers, or weight loss. He does not smoke cigarettes or use any illicit drugs. His vital signs and physical examination findings are normal.

What are the salient features of this patient’s problems? How do you think through his problems?
Salient features: 4-week time course; recent viral illness with resolution of all symptoms except cough; no shortness of breath, fevers, or weight loss; nonsmoker; normal vital signs and physical examination findings

How to think through: Cough is common and usually benign but can be the presenting symptom of a serious illness. First, consider if the patient has risk factors for a serious underlying cause of his cough. (Here, apparently, there are no risk factors; he is young and a nonsmoker and has no chronic medical problems, immunodeficiency, or recent travel.) Next, think through the serious causes of cough that one must never overlook. What features reassure us that he does not have pneumonia? (Absence of sputum, pleuritic chest pain, dyspnea, fever, hypoxia, tachycardia, or abnormal lung examination, e.g., rales or egophony.) What features reassure us that he does not have cancer? (No smoking history, weight loss, or hemoptysis.) What reassures us that he does not have tuberculosis? Interstitial lung disease? Cardiac disease? Next, consider the most likely diagnoses. Does a duration of 4 weeks qualify as acute, subacute, or chronic cough? Are there infectious causes that fit with his presentation? (Pertussis.) What is the most likely cause? (Postinfectious bronchospasm [or virus-induced wheezing] is common; a minimally productive cough persists for several weeks despite resolution of all other symptoms.)

How should he be counseled and treated? (He should be reassured that prolonged cough after a viral upper respiratory infection is common; bronchodilator therapy is effective for symptom control.) If his cough persists, what additional risk factor information should be gathered? (Explicit travel history, asthma history, occupational or other exposures, HIV risk factors.)
What are the essentials of diagnosis and general considerations regarding cough?
Essentials of Diagnosis
- Age, duration of cough, dyspnea (at rest or with exertion), tobacco use history
- Vital signs (temperature, respiratory rate, heart rate)
- Chest examination

General Considerations
- Cough results from stimulation of mechanical or chemical afferent nerve receptors in the bronchial tree.
- Cough illness syndromes are defined as acute (<3 weeks), persistent (>3 weeks), or chronic (>8 weeks).
- Postinfectious cough lasting 3 to 8 weeks is termed subacute cough to distinguish this distinct clinical entity from acute and persistent cough.
- The prevalence of pertussis infection in adults with a cough lasting more than 3 weeks is 20%, although the exact prevalence is difficult to ascertain because of the limited sensitivity of diagnostic tests.
What are the symptoms and signs of cough?
Symptoms and Signs

- The timing and character of cough are usually not useful in establishing cause
- Dyspnea (at rest or with exertion) may reflect a more serious condition
- Cough-variant asthma: consider in adults with prominent nocturnal cough
- Pneumonia: tachycardia, tachypnea, fever, rales, decreased breath sounds, tactile fremitus, egophony
- Acute bronchitis: wheezing and rhonchi
- Chronic sinusitis: postnasal drip, sore throat, facial pain
- Chronic obstructive pulmonary disease (COPD): cough with phlegm production, abnormal match test (inability to blow out a match from 10 inches away)
- Heart failure: symmetric basilar rales, elevated jugular venous pressure, positive hepatojugular reflux
What is the differential diagnosis of cough?
Differential Diagnosis

Acute cough
- Most often viral upper respiratory infection or postviral infection cough but may be postnasal drip (allergic rhinitis), pneumonia, pulmonary edema, or pulmonary embolism

Persistent cough
- Most common causes: postnasal drip, asthma, gastroesophageal reflux disease (GERD)
- Pulmonary infections: postviral, pertussis, bronchiectasis, eosinophilic bronchitis, tuberculosis, cystic fibrosis, *Mycobacterium avium* complex, *Mycoplasma* or *Chlamydia* infection, respiratory syncytial virus
- Noninfectious pulmonary diseases: asthma (cough-variant), COPD, angiotensin-converting enzyme inhibitors, environmental exposures, endobronchial lesions (e.g., tumor), interstitial lung disease, sarcoidosis, chronic microaspiration, β-blockers (causing asthma)
- Nonpulmonary: GERD, postnasal drip (allergic rhinitis), sinusitis, congestive heart failure, laryngitis, ear canal or tympanic membrane irritation, psychogenic or habit cough
What are laboratory, imaging, and procedural findings in cough?
Laboratory Tests
- Pulse oximetry or arterial blood gas measurement
- Peak expiratory flow rate or spirometry

Imaging Studies
- Chest radiography for abnormal vital signs or chest examination, elderly and immunocompromised persons, and unexplained cough lasting more than 3 to 6 weeks

Diagnostic Procedures
- Pertussis detection by culture and polymerase chain reaction of nasopharyngeal swab
- Reserve procedures for patients with persistent cough who do not respond to therapeutic trials
- Sinus computed tomography scan for cough with postnasal drip, spirometry for wheezing or possible asthma, esophageal pH monitoring for cough with GERD symptoms
What are the treatments for cough?
Medications

Acute cough
- Treatment should target the underlying cause of the illness and the cough reflex itself.
- Amantadine, rimantadine, oseltamivir, and zanamivir may lessen the duration of influenza illness.
- Macrolide or doxycycline should be given for documented *Chlamydia* or *Mycoplasma* infection.
- Acute bronchitis cough severity and duration can be reduced with inhaled $\beta_2$-agonist therapy.
- Dextromethorphan decreases the severity of cough caused by respiratory tract infections.
- Postnasal drip may be treated with antihistamines, decongestants, or nasal steroids.
- GERD may be treated with H$_2$-blockers or proton pump inhibitors.

Persistent cough
- Macrolide antibiotics reduce transmission in pertussis but do not affect the duration of cough if infection has lasted more than 7 to 10 days. (Cough may last up to 6 months.)
- Nebulized lidocaine therapy or oral codeine or morphine sulfate may be given for idiopathic persistent cough.
A 39-year-old woman presents with a gradual onset of shortness of breath over the past 6 months, both at rest (when it is mild) and with exertion (when it can force her to stop activity to “catch her breath”). Previously, she has been healthy; her only hospitalizations were for uncomplicated spontaneous vaginal deliveries at ages 27 and 30 years. She does not smoke cigarettes and has no known allergies. On review of symptoms, she denies pleuritic or exertional chest pain, cough, and wheezing; sometimes she has palpitations with activity. Over the past year, she has had heavy menses, with periods that lasted up to 6 to 7 days, frequently soaking several pads per day. Two weeks ago, she saw her gynecologist, who ordered a complete blood count (CBC) that showed a hemoglobin of 7.2 g/dL and hematocrit of 21%. Pelvic ultrasonography showed a large myomatous uterus. Chest radiography findings were negative.

What are the salient features of this patient’s problem? How do you think through her problem?
Salient features: Premenopausal woman; gradual onset of exertional dyspnea; nonsmoker; no chest pain, cough, or wheeze; heavy menses; severe anemia; abnormal pelvic ultrasonography findings; normal chest radiography findings

How to think through: In patients with subacute progressive dyspnea, cardiopulmonary problems should be excluded first. The absence of pleuritic chest pain, cough, wheezing, and smoking history point away from most pulmonary causes, and absence of chest pain, orthopnea, paroxysmal nocturnal dyspnea, syncope, peripheral edema, and palpitations, from possible cardiac causes. Instead, this patient had another important cause: severe anemia. What other noncardiac causes of dyspnea must be considered? (Respiratory muscle weakness, methemoglobinemia, cyanide ingestion, carbon monoxide [CO] intoxication, metabolic acidosis, chronic pulmonary embolism, and psychogenic [panic or anxiety].) Pulse oximetry usually provides a valuable proxy for the PaO$_2$. What will her oxygen saturation likely be? (With anemia, it should be normal.) How should she be managed? (Iron supplementation and prompt, elective myomectomy. Preoperative transfusion will likely be needed, considering possible surgical blood loss.)
What are the essentials of diagnosis and general considerations regarding dyspnea?
Essentials of Diagnosis

- Fever, cough, chest pain; onset, duration, severity, and periodicity of symptoms
- Vital sign measurement and pulse oximetry; cardiac and chest examination
- Chest radiography; arterial blood gas (ABG) measurement

General Considerations

- Dyspnea is the subjective perception of uncomfortable breathing and may be caused by a wide variety of diseases that increase the effort of breathing or produce compensatory tachypnea (e.g., hypoxemia, acidosis).
What are the symptoms and signs of dyspnea?
**Symptoms and Signs**

- Rapid onset, severe dyspnea: suggests pneumothorax, pulmonary embolism, or flash pulmonary edema
- Pleuritic chest pain: suggests pneumothorax, pulmonary embolism, pericarditis, or pleurisy
- Immobilization, cancer, or lower extremity trauma: suggest pulmonary embolism
- Cough and fever: suggest pulmonary disease, particularly infections, myocarditis, or pericarditis
- Wheezing: suggests acute bronchitis, chronic obstructive pulmonary disease (COPD), asthma, foreign body, or vocal cord dysfunction
- Prominent dyspnea with no accompany features: suggests noncardiopulmonary causes
- Accentuated pulmonic second heart sound (loud P2): suggests pulmonary hypertension or pulmonary embolism
- Also observe respiratory pattern; assess orthopnea and paroxysmal nocturnal dyspnea
What is the differential diagnosis of dyspnea?
Differential Diagnosis

- **Acute**: asthma, pneumonia, pulmonary edema, pneumothorax, pulmonary embolus, metabolic acidosis, acute respiratory distress syndrome, panic attack
- **Pulmonary**: airflow obstruction (asthma, COPD, upper airway obstruction), restrictive lung disease (interstitial lung disease, pleural thickening or effusion, respiratory muscle weakness, obesity), pneumonia, pneumothorax, pulmonary embolism, aspiration, acute respiratory distress syndrome
- **Cardiac**: myocardial ischemia, congestive heart failure, valvular obstruction, arrhythmia, cardiac tamponade
- **Metabolic**: acidosis, hypercapnia, sepsis, CO poisoning
- **Hematologic**: anemia, methemoglobinemia
- **Psychiatric**: anxiety
What are the laboratory, imaging, and procedural findings in dyspnea?
Laboratory Tests
- Serum B-type natriuretic peptide (BNP) testing can help distinguish cardiac from noncardiac causes
- ABG analysis
- Hematocrit or hemoglobin, methemoglobin, or CO measurement as indicated

Imaging Studies
- Chest radiograph is essential
- High-resolution chest computed tomography can evaluate for pulmonary embolism and interstitial and alveolar lung disease

Diagnostic Procedures
- Pulse oximetry at rest and with ambulation (not to supplant ABG and, when indicated, CO and methemoglobin measurements)
- Electrocardiography (ECG)
- Spirometry in patients with suspected obstructive or restrictive airway disease
What are the treatments for dyspnea?
Medications
- Treatment should be aimed at the underlying cause (e.g., transfusion and iron repletion for severe anemia caused by blood loss; inhaled $\beta_2$-agonist, anticholinergic, and corticosteroid for asthma).
- Opioid therapy can relieve dyspnea that occurs in patients nearing the end of life.

Therapeutic Procedures
- Supplemental oxygen should be given for patients with hypoxemia; such supplementation in severe COPD with hypoxemia confers a mortality benefit.
- Pulmonary rehabilitation should be done in patients with COPD or interstitial pulmonary fibrosis.
A 73-year-old man presents to his primary care provider with a new cough productive of blood. He reports gradual weight loss of approximately 15 lb over the past 6 months. He has smoked two packs of cigarettes per day for the past 50 years. On physical examination, he has decreased breath sounds and dullness to percussion at the left lung base. His chest radiograph shows a left-sided pleural effusion and consolidation in the left lung.

What are the salient features of this patient’s problem? How do you think through his problem?
Salient features: Older patient; new cough and hemoptysis; weight loss; heavy cigarette smoking history; dull lung base with likely malignant effusion; consolidation on chest radiograph

How to think through: Lung cancer is the leading cause of cancer-related death, has a high mortality rate at the time of detection, and is largely preventable. This patient presents with significant “red flag” features, including a 100 pack-year smoking history, hemoptysis, and weight loss. Other than primary lung cancer, what other disease processes could cause this presentation? (Tuberculosis, pneumonia, lung abscess, lymphoma, metastatic cancer.) What neurologic examination findings suggest complications of lung cancer? (Any mental status, cranial nerve, motor, sensory, or coordination abnormality may indicate brain metastasis; hoarseness or Horner syndrome may indicate compression of the recurrent laryngeal nerve or sympathetic ganglion by an apical [Pancoast] tumor.) What are the next steps in the evaluation of this patient? (Computed tomography [CT] scan to characterize tumor location, plan biopsy, begin staging, and plan possible surgery. Pathologic diagnosis is essential.) What imaging is needed for staging? (CT, positron emission tomography [PET]–CT, and magnetic resonance imaging [MRI] are all used in staging; the brain and abdomen, in addition to the chest, must be assessed.) In the treatment of primary lung cancer, surgery, chemotherapy, and radiation are used, depending on the cancer type and stage. If this patient is not a candidate for surgery or chemotherapy, what palliative therapies should be considered? (Thoracentesis, radiation, oxygen, opioids for pain and dyspnea.)
What are the essentials of diagnosis and general considerations regarding lung cancer?
Essentials of Diagnosis
- New cough or change in chronic cough, dyspnea, hemoptysis, anorexia, weight loss
- Enlarging nodule, mass, or persistent opacity on chest radiograph or CT scan
- Cytologic or histologic findings of lung cancer in sputum, pleural fluid, or biopsy specimen

General Considerations
- Lung cancer is the leading cause of cancer deaths. Cigarette smoking causes more than 90% of cases of lung cancer. Lung cancer is often diagnosed in elderly adults.
- Small cell lung cancer (SCLC) (10%–15%) is aggressive and prone to early hematogenous spread.
- Non–small cell lung cancer (NSCLC) spreads more slowly and has different histologic types.
  - Squamous cell carcinoma (20%) arises from bronchial epithelium (often centrally located).
  - Adenocarcinoma (35%–40%) arises from mucous glands as a peripheral nodule or mass.
  - Large cell carcinoma (3%–5%) is heterogeneous; presents as a central or peripheral mass.
  - Bronchioloalveolar cell carcinoma (2%) arises from epithelial cells distal to the terminal bronchiole and spreads along preexisting alveolar structures (lepidic growth).
What are the symptoms and signs of lung cancer?
Symptoms and Signs

- 75% to 90% are symptomatic at diagnosis; presentation depends on the type and location of the tumor
- Anorexia, weight loss, and asthenia, new or changed cough, hemoptysis, pain from metastases
- Local spread may result in endobronchial obstruction and postobstructive pneumonia, effusions, or a change in voice caused by recurrent laryngeal nerve involvement
- Superior vena cava syndrome
- Horner syndrome
- Brain metastases may present with headache, nausea, vomiting, dizziness, or seizures
- Paraneoplastic syndromes, including the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) (10%–15% of SCLC) and hypercalcemia
What is the differential diagnosis of lung cancer?
Differential Diagnosis

- Pneumonia
- Tuberculosis
- Metastatic cancer to lung
- Benign pulmonary nodule or nodules
- Bronchial carcinoid tumor
- Lymphoma
- *Mycobacterium avium* complex infection
- Fungal pneumonia
- Sarcoidosis
- Foreign body aspiration (retained)
What are the laboratory, imaging, and procedural findings in lung cancer?
Laboratory Tests
- Tissue or cytology specimen is needed for diagnosis.
- Sputum cytology is specific but insensitive; serum tumor markers are not sensitive or specific.
- Pulmonary function tests are required in all NSCLC patients before surgery.

Imaging Studies
- Abnormal findings are seen on chest radiograph or CT scan; CT scan determines staging and resectability.
- For staging, brain MRI, abdominal CT, or PET imaging can look for metastases.

Diagnostic Procedures
- Thoracentesis and cytology of malignant effusions; fine-needle aspiration of lymph nodes
- Bronchoscopy, mediastinoscopy, video-assisted thoracoscopic surgery, or thoracotomy if needed for tissue diagnosis
What are the treatments for lung cancer?
Medications

- Chemotherapy in advance of (neoadjuvant) or after (adjuvant) surgery or radiation in NSCLC, often platinum based
- Bevacizumab and erlotinib can be used in advanced stage NSCLC
- SCLC treated with chemotherapy, usually cisplatin and etoposide

Surgery

- Surgical resection in NSCLC stage I-III; multimodal protocols in stage III; palliative measures in stage IV
- Resection of solitary brain metastases may improve quality of life

Therapeutic Procedures

- Radiation therapy is used as part of multimodal regimens in NSCLC; can also be palliative
A 19-year-old woman presents to her primary care clinic complaining of a sore throat for 2 days. She also reports a fever that reached 38.4°C yesterday. She denies cough. A friend at her place of employment has also had similar symptoms. On physical examination, her neck reveals tender anterior cervical lymphadenopathy, and her tonsils are inflamed and exudative.

What are the salient features of this patient’s problem? How do you think through her problem?
Salient features: Young age; sick contact; sore throat; fever; lack of cough; cervical adenopathy; exudative tonsils

How to think through: Assessment of acute pharyngitis in adults requires the clinician to separate viral pharyngitis from probable group A β-hemolytic streptococcus infection while remaining vigilant for more serious causes of sore throat. Why is it important to identify and treat group A β-hemolytic streptococcal pharyngitis? (Risk of subsequent rheumatic fever and glomerulonephritis.) How many Centor criteria are present in this patient? (Four of four diagnostic criteria: fever, absence of cough, tender cervical lymphadenopathy, tonsillar exudate.) If a rapid strep test result were negative in this case, what would be the appropriate management strategy? (Antibiotic therapy in a patient with four of four the Centor criteria is reasonable regardless of the rapid test result.) What other important infectious diseases present with pharyngitis in young adults and must be considered? (Lemierre’s syndrome [Fusobacterium necrophorum], acute HIV infection, gonococcal pharyngitis, infectious mononucleosis [Epstein-Barr virus or EBV], and cytomegalovirus infection.) If infectious mononucleosis was a consideration, what antibiotic should be avoided because of the high frequency of associated rash? (Ampicillin.) If the patient provides a history of a recent high-risk sexual encounter, should she receive an HIV antibody test now? (No. Detectable antibodies take between 3 weeks and 2 months to form in the majority of infected patients. An HIV viral load nucleic acid test would be more appropriate.)
What are essentials of diagnosis and general considerations regarding pharyngitis?
Essentials of Diagnosis

- Sore throat, fever, anterior cervical adenopathy, and tonsillar exudate suggest group A β-hemolytic streptococcus infection.

General Considerations

- The main concern is to determine whether the cause is group A β-hemolytic streptococcal infection because of the complications of rheumatic fever and glomerulonephritis.
- About one-third of patients with infectious mononucleosis have secondary streptococcal tonsillitis requiring treatment.
- Ampicillin should routinely be avoided if mononucleosis is suspected because it induces a rash.
What are symptoms and signs of pharyngitis?
Symptoms and Signs

- Centor diagnostic criteria for group A β-hemolytic streptococcus infection are fever greater than 38°C, tender anterior cervical adenopathy, lack of cough, pharyngotonsillar exudate.
- Sore throat may be severe, with odynophagia, tender adenopathy, and a scarlatiniform rash.
- Hoarseness, cough, and coryza are not suggestive of group A β-hemolytic streptococcus infection.
- Marked lymphadenopathy and a shaggy white-purple tonsillar exudate, often extending into the nasopharynx, suggest mononucleosis, especially if present in a young adult.
What is the differential diagnosis of pharyngitis?
Differential Diagnosis

- Viral pharyngitis or EBV or infectious mononucleosis
- Primary HIV infection
- Candidiasis
- Necrotizing ulcerative gingivostomatitis (Vincent fusospirochetal disease)
- Retropharyngeal abscess
- Diphtheria
- Other bacterial pharyngitis: *Neisseria gonorrhoeae*, mycoplasma, anaerobic streptococci, *Corynebacterium haemolyticum*
- Epiglottitis
What are the laboratory findings in pharyngitis?
Laboratory Tests

- The presence of the four Centor diagnostic criteria strongly suggests group A β-hemolytic streptococcus infection, and some would treat the patient regardless of laboratory results.
- When three of the four Centor criteria are present, laboratory sensitivity for group A β-hemolytic streptococcus infection rapid antigen testing exceeds 90%.
- When only one Centor criterion is present, group A β-hemolytic streptococcus infection is unlikely.
- With about 90% sensitivity, lymphocyte to white blood cell ratios of greater than 35% suggest EBV infection, not tonsillitis.
- Consider HIV antibody or viral load testing for acute HIV infection.
What are the treatments for pharyngitis?
Medications
- Benzathine penicillin intramuscular injection or oral penicillin V potassium for group A β-hemolytic streptococcus infection
- Macrolides are useful for penicillin-allergic patients
- Analgesic, antiinflammatory drugs (aspirin, acetaminophen)

Surgery
- Removal of tonsils in cases of recurrent abscesses

Therapeutic Procedures
- Avoidance of contact sports in mononucleosis (risk of splenic rupture)
A 67-year-old man with a history of alcoholism presents with a 2-day history of fevers, chills, rigors, shortness of breath, and a cough productive of dark yellow sputum. He had a recent binge of alcohol use that ended 2 days before admission, and he woke up with these symptoms. On physical examination, his temperature is 39.5°C, his respiratory rate is 30 breaths/min, and he is in moderate respiratory distress. His lower right lung field has inspiratory crackles on auscultation. Laboratory testing reveals a white blood cell count of 16,000/mcL. A chest radiograph shows focal consolidation in the right middle and lower lobes.

What are the salient features of this patient’s problem? How do you think through his problem?
**Salient features:** Alcohol history predisposing to aspiration; fever and chills; rigors; shortness of breath; cough with purulent sputum; tachypnea; consolidation on examination and radiograph; leukocytosis

**How to think through:** Pneumonia is a clinical diagnosis in which symptoms, examination, white blood cell count, and chest radiograph are all considered. Although these all point to a diagnosis of pneumonia in this case, what other causes are plausible? (Aspiration pneumonitis, lung neoplasm, lung abscess, acute respiratory distress syndrome, bronchitis, tuberculosis, pulmonary embolism, congestive heart failure, atelectasis, drug reactions.) What are the next diagnostic steps? (Blood cultures; arterial blood gases.) Pathogens and outcomes vary with epidemiologic risk factors. This patient likely has community-acquired pneumonia (CAP), but recent exposure to health care settings and immune status (including HIV testing) should be assessed. His alcoholism may indicate other substance abuse, and both increase the risk of tuberculosis. What pathogens are most likely in this case? (The acuity of his illness is most consistent with “typical” bacterial pneumonia from *Streptococcus pneumoniae, Haemophilus influenzae*, and *Klebsiella pneumoniae*. “Atypical” pneumonia, e.g., *Mycoplasma pneumoniae*, is less likely in patients admitted to the hospital. But empiric antibiotic coverage for both types may be important. Although *Staphylococcus aureus* pneumonia is uncommon, it is associated with morbidity, so coverage for it may be appropriate with severe disease and for patients requiring intensive care.) If this patient responds to antibiotic treatment within the first 2 to 3 days, its duration should be 7 days for most pathogens.
What are the essentials of diagnosis and general considerations regarding pneumonia?
Essentials of Diagnosis

- Fever or hypothermia, tachypnea, cough with or without sputum, dyspnea, chest discomfort, sweats or rigors (or both)
- Bronchial breath sounds or inspiratory crackles on chest auscultation, opacity on chest radiograph
- Leukocytosis
- Purulent sputum
- CAP occurs outside of the hospital; hospital-acquired pneumonia (HAP) occurs more than 48 hours after admission; ventilator-associated pneumonia (VAP) develops in a mechanically ventilated patient; health care–associated pneumonia (HCAP) occurs in community members with high health care facility exposures

General Considerations

- May be bacterial (e.g., *S. pneumoniae*, *M. pneumoniae*, *Chlamydohipha pneumoniae*, *Neisseria meningitides*, *Moraxella catarrhalis*, *K. pneumoniae*) or viral (e.g., influenza, respiratory syncytial virus, adenovirus)
- HAP organisms may include *S. aureus* and *Pseudomonas aeruginosa*
What are the symptoms and signs of pneumonia?
**Symptoms and Signs**

- Acute or subacute onset of fever, cough with or without sputum, and dyspnea may be present.
- Rigors, sweats, chills, pleurisy, chest discomfort, and hemoptysis are common.
- Fatigue, anorexia, headache, myalgias, and abdominal pain may be present.
- Physical findings include fever or hypothermia, tachypnea, tachycardia, decreased oxygen saturation, rales or abnormal breath sounds, and dullness to percussion.
- Symptoms may be more nonspecific in HAP and VAP.
What is the differential diagnosis of pneumonia?
Differential Diagnosis

- Aspiration pneumonia or pneumonitis
- Acute respiratory distress syndrome (ARDS)
- Bronchitis
- Lung abscess or neoplasm
- Tuberculosis
- Pulmonary embolism
- Myocardial infarction or congestive heart failure
- Sarcoidosis
- Interstitial lung disease
- Drug reactions
- Pulmonary hemorrhage
- Atelectasis
What are the laboratory, imaging, and procedural findings in pneumonia?
Laboratory Tests
- Sputum Gram stain, blood cultures, rapid influenza testing, or urine antigen assays for *Legionella pneumophila* and *S. pneumoniae* may guide antibiotic treatment.
- All hospitalized patients should have complete blood count, chemistry panel, and arterial blood gas analysis.
- HIV testing should be considered in all adult patients.

Imaging Studies
- Chest radiograph findings range from patchy airspace opacities to lobar consolidation with air bronchograms to diffuse alveolar or interstitial opacities.
- Clearing of opacities can take 6 weeks or longer.

Diagnostic Procedures
- Sputum induction and fiberoptic bronchoscopy are indicated for patients who cannot provide samples or who may have *Pneumocystis jiroveci* or *Mycobacterium tuberculosis* pneumonia.
- Thoracentesis with pleural fluid analysis should be performed in all patients with effusions.
- Endotracheal aspiration and fiberoptic bronchoscopy with lavage in patients with VAP.
What are the treatments for pneumonia?
**Medications**

- Treatment is based on risk factors and severity of illness.
- Therapy may use a macrolide or doxycycline with or without a β-lactam, or a respiratory fluoroquinolone (e.g., moxifloxacin, gemifloxacin, or levofloxacin).
- Patients in intensive care unit receive both a β-lactam plus azithromycin or a respiratory fluoroquinolone.
- Treatment in patients at risk for *Pseudomonas* infection must include an antipneumococcal, antipseudomonal β-lactam (piperacillin–tazobactam, cefepime, imipenem, meropenem), ciprofloxacin or levofloxacin, and/or an aminoglycoside (gentamicin, tobramycin, amikacin).
- HAP and VAP patients require empiric coverage for both *Pseudomonas* and methicillin-resistant *Staphylococcus aureus* (MRSA).
A 57-year-old man has a right total knee replacement for severe degenerative joint disease. Four days later, he develops shortness of breath and right-sided pleuritic chest pain. He is in moderate respiratory distress with respiratory rate 28 breaths per minute, heart rate 120 beats per minute, blood pressure 110/70 mm Hg, and oxygen saturation 88% on room air. Cardiopulmonary examination is normal. The right leg is postsurgical, healing well, with 2+ pitting edema, calf tenderness, erythema, and warmth; his left leg is normal.

What are the salient features of this patient’s problem? How do you think through his problem?
Salient features: Recent surgery; acute dyspnea; pleuritic chest pain; tachypnea and tachycardia; hypoxia (oxygen desaturation); signs of deep venous thrombosis (DVT) including unilateral calf tenderness and edema.

How to think through: This patient has sudden onset of dyspnea, chest pain, tachypnea, hypoxemia, and tachycardia. What is the differential diagnosis of this scenario? (Myocardial infarction, pneumothorax, cardiac tamponade, pulmonary embolism [PE].) What features make PE more likely? (Pleuritic quality of chest pain, normal cardiopulmonary examinations, post-surgical onset.) What are immediate management and diagnostic priorities in this unstable patient? (Supplemental oxygen, intravenous access; electrocardiogram [ECG], chest radiography.) If ECG shows only sinus tachycardia and chest radiography shows only clear lung fields, how should the possibility of PE be evaluated? (Helical CT scan.) Is there a role for a d-dimer test? (No.) This test is best used for an “intermediate-probability,” rather than this “high-probability,” scenario. His CT scan shows extensive bilateral pulmonary emboli. How do you decide if this is a “massive” or “submassive” PE? (“Massive PE” indicates hemodynamic compromise [cardiogenic shock] and is treated by thrombolysis; in “submassive” PE, the role of thrombolysis is less clear.) In this case, given that his blood pressure is likely below baseline, but he is not in shock, how might you better assess right heart strain? (Echocardiogram.) What treatment should you initiate regardless of the thrombolysis decision? (Heparin or low-molecular weight heparin [LMWH].) Is a workup for thrombophilia indicated? (No. Surgery and stasis more likely “provoked” his PE than did a thrombophilia.) What is the typical duration of anticoagulation for “provoked” venous thromboembolism (VTE)? (6 months).
What are the essentials of diagnosis and general considerations regarding pulmonary embolism?
Essentials of Diagnosis

- Predisposition to venous thrombosis, usually of the lower extremities
- Usually dyspnea, chest pain, hemoptysis, or syncope
- Tachypnea and a widened alveolar–arterial $P_{O_2}$ difference
- Characteristic defects on ventilation/perfusion lung scan, helical CT scan of the chest, or pulmonary angiography

General Considerations

- Third most common cause of death in hospitalized patients; often not recognized antemortem
- Risk factors: immobility, hyperviscosity, increased central venous pressures, vessel damage (trauma, prior DVT, orthopedic surgery), hypercoagulable states
- PE develops in 50% to 60% of patients with proximal lower extremity DVT; 50% are asymptomatic; hypoxemia results from vascular obstruction leading to dead space ventilation, right-to-left shunting, and decreased cardiac output
- Other types of pulmonary emboli: fat embolism, air embolism, amniotic fluid embolism, septic embolism (e.g., endocarditis), tumor embolism, foreign body embolism, and parasite egg embolism (schistosomiasis)
What are the symptoms and signs of pulmonary embolism?
Symptoms and Signs

- Clinical findings depend on the size of the embolus and the patient’s preexisting cardiopulmonary status.
- Dyspnea occurs in 75% to 85% and chest pain in 65% to 75% of patients.
- Tachypnea may be the only sign; it is reliably found in more than 50% of patients.
- Less common symptoms and signs include fever, hemoptysis, cough, crackles (rales), angina, and an accentuated pulmonary component of the second heart sound.
- Homans sign is pain with forced dorsiflexion of the ankle and suggests DVT in the ipsilateral lower extremity; it is a rare finding.
- 97% of patients in the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) study had at least one of the following:
  - Dyspnea
  - Tachypnea
  - Chest pain with breathing
What is the differential diagnosis of pulmonary embolism?
Differential Diagnosis
• Myocardial infarction (heart attack)
• Pneumonia
• Pericarditis
• Heart failure
• Pleuritis (pleurisy)
• Pneumothorax
• Pericardial tamponade
What are the laboratory and imaging findings in pulmonary embolism?
Laboratory Tests

- ECG findings are abnormal in 70% of patients, usually with sinus tachycardia and nonspecific ST-T changes.
- Acute respiratory alkalosis, hypoxemia, and widened arterial–alveolar O_2 gradient (A–a Do_2) may be seen, but these findings are not diagnostic.
- D-dimer testing is very sensitive but is nonspecific for VT.

Imaging Studies

- The most common chest radiography findings are atelectasis, infiltrates, pleural effusions, Westermark sign (focal oligemia with a prominent central pulmonary artery), and Hampton hump (pleural-based area of increased density from intraparenchymal hemorrhage).
- Lung scanning (V/Q scan) can exclude PE if findings are normal or make the diagnosis if high probability; indeterminate scans are common and do not help diagnostic efforts.
- Helical CT arteriography is the initial diagnostic study of choice because it is very sensitive and noninvasive, but it does require administration of intravenous radiocontrast dye.
- Venous thrombosis studies include lower extremity Doppler ultrasonography and may establish the need for treatment, precluding invasive testing in patients with high suspicion for PE.
- Pulmonary angiography is the reference standard for the diagnosis of PE but is invasive.
What are the treatments for pulmonary embolism?
Medications
- Full anticoagulation with heparin should begin with the diagnostic evaluation in patients with a moderate to high clinical likelihood of PE and no contraindications.
- LMWHs are as effective as unfractionated heparin and do not require coagulation monitoring.
- Warfarin is an option for oral anticoagulation therapy.
- The durations of treatment are 6 months for an initial episode with a reversible risk factor, 12 months after initial idiopathic episode, and 6 to 12 months to lifelong in patients with irreversible risk factors or recurrent disease.
- Thrombolytic therapy increases intracranial hemorrhage but is indicated in hemodynamically unstable patients.

Surgery
- Pulmonary embolectomy is an emergency procedure with a high mortality rate performed at few centers.

Therapeutic Procedures
- Catheter devices that fragment and extract thrombus have been used on small numbers of patients.
- Inferior venal caval (IVC) interruption (IVC filters) may be indicated when a significant contraindication to anticoagulation exists or when recurrence occurs despite adequate anticoagulation.
- IVC filters decrease the short-term incidence of PE but increase the long-term rate of recurrent DVT; thus, provision should be made for their removal at the time of insertion.
A 25-year-old man presents to the urgent care clinic with 3 weeks of facial pain and pressure. He describes a right-sided fullness and tenderness over his cheek. He has also had yellow-green drainage from his nose along with subjective fevers, halitosis, and malaise. He felt as though he was getting better 1 week ago, but then his symptoms returned worse than ever. On physical examination, his right maxillary sinus is tender to palpation and percussion.

What are the salient features of this patient’s problem? How do you think through his problem?
**Salient features:** Unilateral facial pain, pressure, and fullness; purulent drainage; fevers and halitosis; partial resolution with subsequent worsening; maxillary sinus tenderness on examination

**How to think through:** Sinus pressure and nasal discharge, accompanied by headache, cough, or subjective fever, are a common constellation of findings in sinusitis. The majority of cases are caused by viral rhinosinusitis, are self-limited, and are treatable symptomatically. The two main tasks for the clinician are to determine the likelihood of bacterial sinusitis and to rule out serious complications. What are the elements of the clinical history associated with bacterial sinusitis? (Unilateral facial pain, purulent drainage, fevers, associated dental pain, partial resolution followed by worsening symptoms [“double worsening”] and duration of >7 days.) What organisms are commonly implicated in bacterial sinusitis? (*Streptococcus pneumoniae*, other streptococci, *Haemophilus influenzae*; possibly *Staphylococcus aureus* or *Moraxella catarrhalis*.) What are the “red flags” for a serious complications? (Eye involvement [proptosis, double vision], altered mental status, and facial erythema suggesting cellulitis. Immune compromise should heighten vigilance for such complications.) When should one consider sinus imaging or referral to an otolaryngologist for nasal endoscopy? (Patients who receive appropriate antibiotic treatment and have no improvement at 4 weeks.) What are first-line antibiotics for treatment of acute bacterial sinusitis? (Amoxicillin, trimethoprim–sulfamethoxazole [TMP–SMZ], doxycycline.) What other treatments can help? (Oral decongestant, intranasal decongestant [for ≤3 days], intranasal steroid spray, and intranasal saline wash.)
What are the essentials of diagnosis and general considerations regarding sinusitis?
Essentials of Diagnosis
- Purulent yellow-green nasal discharge or expectoration and nasal obstruction
- Acute onset (1- to 4-week duration) of facial pain or pressure over the affected sinus or sinuses
- Associated symptoms, including cough, malaise, fever, and headache

General Considerations
- Common disease affecting nearly 20 million Americans annually
- Usually is a result of impaired mucociliary clearance and obstruction of the osteomeatal complex, or sinus “pore”
- Edematous mucosa causes obstruction of the complex, resulting in the accumulation of mucous secretion in the sinus cavity that becomes secondarily infected by bacteria
- The typical pathogens are *S. pneumoniae*; other streptococci; *H. influenzae*; and less commonly, *S. aureus* and *M. catarrhalis*
- Discolored nasal discharge and poor response to decongestants suggest sinusitis
What are the symptoms and signs of sinusitis?
Symptoms and Signs

- Bacterial rhinosinusitis can be distinguished from viral rhinitis when symptoms last longer than 10 days after onset or worsen within 10 days after initial improvement.
- Nonspecific symptoms include fever, malaise, halitosis, headache, hyposmia, and cough.
- Maxillary sinusitis presents with unilateral facial fullness, pressure, and tenderness over the cheek; pain may refer to the upper incisor and canine teeth.
- Ethmoid sinusitis is usually accompanied by maxillary sinusitis; the symptoms are similar.
- Sphenoid sinusitis usually seen in the setting of pansinusitis, or infection of all the paranasal sinuses on at least one side; the patient may complain of headache “in the middle of the head.”
- Frontal sinusitis may cause pain and tenderness of the forehead.
- Hospital-acquired sinusitis may present without any symptoms, is often associated with nasogastric tubes, and is a common source of fever in critically ill patients.
What is the differential diagnosis of sinusitis?
Differential Diagnosis
- Upper respiratory tract infection
- Viral rhinitis
- Allergic rhinitis
- Nasal polyposis
- Dental abscess
- Rhinocerebral mucormycosis
- Otitis media
- Pharyngitis
- Dacryocystitis
- Paranasal sinus cancer
What are the laboratory, imaging, and procedural findings in sinusitis?
Laboratory Tests

- Diagnosis is usually made on clinical grounds alone.

Imaging Studies

- Noncontrast coronal computed tomography scans are more cost effective than conventional films; provide a rapid and effective means to assess all of the paranasal sinuses, identify areas of concern, and direct therapy; and are indicated when symptoms persist longer than 4 to 12 weeks.

- Routine sinus series radiographs are not cost-effective but may be helpful in difficult-to-evaluate cases, when the patient does not respond to appropriate therapy, or when the patient has symptoms or signs of more serious infection (e.g., mucormycosis [infection with *Rhizopus, Mucor, Absidia*, or *Cunninghamamella]*) are noted.

Procedures

- Nasal endoscopy is indicated when symptoms persist longer than 4 to 12 weeks.
What are the treatments for sinusitis?
Medications

- Antibiotics should be given if symptoms last more than 10 to 14 days or if severe symptoms such as fever, facial pain, and periorbital swelling are evident on presentation.
- First-line therapy is amoxicillin, TMP-SMZ, or doxycycline.
- After recent antibiotic use, levofloxacin or amoxicillin–clavulanate is appropriate.
- Second-line therapy includes amoxicillin–clavulanate or moxifloxacin.
- Hospital-acquired infections may require broad-spectrum agents.
- Oral or nasal decongestants may be used for symptom improvement.

Therapeutic Procedures

- For hospital-acquired sinusitis, removal of a nasogastric tube, improved nasal hygiene, and endoscopic or transantral cultures (particularly in HIV-infected or other immunocompromised patients) may be helpful.
A 71-year-old man presents to the emergency department with a sudden onset of substernal chest pain 1 hour ago. He describes the pain as a heavy pressure sensation that radiates down both arms and is 10 of 10 in intensity. His pain started while he was walking around his yard and improved, but did not resolve, with rest. His medical history is significant for diabetes mellitus. He has smoked 1 pack of cigarettes per day for the past 50 years. His mother died of a myocardial infarction (MI) at age 56 years. On heart examination, you hear an S₄ gallop, and on lung examination, you hear bibasilar fine crackles. His electrocardiogram (ECG) shows 3-mm ST-segment elevations in leads II, III, and aVF.

What are the salient features of this patient’s problem? How do you think through his problem?
**Salient features:** Advanced age; sudden onset of substernal chest pain radiating to the arms; pain worse with exertion; cardiac risk factors of diabetes mellitus, smoking, and family history; S₄ gallop and crackles consistent with pulmonary edema; ECG with ST elevations in an inferior distribution

**How to think through:** Acute coronary syndrome (ACS) includes unstable angina, non–ST elevation MI, and ST elevation MI; all result from myocardial ischemia caused by thrombosis at a site of coronary atherosclerosis. There are other causes of MI, but ACS is the most common. This patient has *typical* chest pain, meaning substernal, “pressure” or “squeezing,” exertional, and relieved by rest or nitroglycerin. Radiation to the arms correlates strongly with cardiac chest pain. To evaluate a patient with chest pain, first determine the likelihood of ACS as its cause; then stratify the risk for mortality to ensure timely intervention in high-risk patients. Here the history alone strongly suggests ACS. The patient is deemed to be at high risk because of the ST elevations on ECG. If the ECG showed ST depressions, would he still be considered a high-risk patient? (Yes. Evidence of new heart failure confers high risk.) What medications should be administered upon diagnosis? (Aspirin; clopidogrel, heparin, or low-molecular-weight heparin [LMWH]; nitroglycerin; morphine, if needed.) Should he receive a β-blocker? (No. His new heart failure is a relative contraindication.) If the hospital lacks facilities for cardiac catheterization, how should he be managed? (If transfer to another facility for percutaneous coronary intervention [PCI] within 90 minutes of first medical contact is not possible and barring contraindication, fibrinolytic therapy should be given.)
What are the essentials of diagnosis and general considerations regarding acute myocardial infarction?
Essentials of Diagnosis

- Sudden development of prolonged (>30 minutes) anterior chest discomfort or pressure
- Sometimes masquerading as acute heart failure (HF), syncope, stroke, or shock
- ECG: ST-segment elevation or left bundle branch block
- Immediate reperfusion treatment is warranted with PCI within 90 minutes (preferred) or thrombolysis within 30 minutes of arrival and within 6 to 12 hours of symptom onset

General Considerations

- Results, in most cases, from an occlusive coronary thrombus at the site of a preexisting (although not necessarily severe) atherosclerotic plaque
- More rarely, may result from prolonged vasospasm, inadequate myocardial blood flow (e.g., hypotension), or excessive metabolic demand
- Very rarely, may be caused by embolic occlusion, vasculitis, aortic root or coronary artery dissection, or aortitis
- Cocaine use may cause MI and should be considered in young individuals without risk factors
What are the symptoms and signs of acute myocardial infarction?
Symptoms and Signs

- Recent onset of angina pectoris or alteration in the pattern of angina or chest pressure, squeezing, or “indigestion”
- Pain characteristics: similar to angina in location and radiation but more severe; usually occurs at rest, often in the early morning; builds rapidly; minimally responsive to sublingual nitroglycerin or oral opioids
- Associated symptoms include diaphoresis, weakness, apprehension, syncope or presyncope, dyspnea, orthopnea, cough, wheezing, and nausea and vomiting
- 33% of patients do not experience chest pain, especially older patients, women, and patients with diabetes mellitus
- Marked bradycardia (inferior infarction) to tachycardia (increased sympathetic activity, low cardiac output, or arrhythmia)
- Jugular venous distention indicates right atrial hypertension, often from right ventricular infarction or elevated left ventricular (LV) filling pressures
- S₄ is common; soft heart sounds or S₃ indicates significant LV dysfunction
- Mitral regurgitation murmur usually indicates papillary muscle dysfunction or, rarely, rupture
- Cyanosis and cold temperature indicate low output
What is the differential diagnosis of acute myocardial infarction?
Differential Diagnosis

- Aortic dissection
- Pulmonary embolism
- Tension pneumothorax
- Pericarditis
- Esophageal rupture
- Stress cardiomyopathy (Tako-Tsubo cardiomyopathy or apical ballooning syndrome)
What are the laboratory, imaging, and procedural findings in acute myocardial infarction?
Laboratory Tests
- Quantitative CK-MB (creatine kinase myocardial band), troponin I, and troponin T elevations are seen as early as 4 to 6 hour after onset; they are almost always abnormal by 8 to 12 hours.
- Troponins may remain elevated for 5 to 7 days or longer and are not generally useful for evaluating suspected early reinfarction.

Imaging Studies
- Chest radiograph: signs of CHF, often lagging behind the clinical findings
- Echocardiography: assesses global and regional LV function, wall motion

Diagnostic Procedures
- ECG: classic evolution of changes is from peaked (“hyperacute”) T waves to ST-segment elevation to Q wave development to T wave inversion; this may occur over a few hours to several days
- Angiography: can demonstrate akinesis or dyskinesis, measures ejection fraction, and diagnose coronary artery occlusion
- Swan-Ganz hemodynamic measurements: can be invaluable in managing suspected cardiogenic shock
What are the treatments for acute myocardial infarction?
Medications
- Full-dose aspirin immediately; clopidogrel loading and daily dosage; nitroglycerin for reducing ischemic pain, blood pressure, and pulmonary congestion
- Morphine sulfate if nitroglycerin alone does not relieve pain
- LMWHs (such as enoxaparin) (preferred) or unfractionated heparin, or fondaparinux reduce mortality
- Thrombolytic therapy reduces mortality and limits infarct size in those that cannot get PCI or when PCI will be delayed; greatest benefit occurs if initiated within the first 3 hours
- Glycoprotein IIb/IIIa inhibitors, specifically abciximab, have been shown to reduce major thrombotic events and possibly the mortality rate for patients undergoing primary PCI

Therapeutic Procedures
- ST elevation connotes an acute coronary occlusion and warrants immediate reperfusion therapy.
- Primary PCI is the approach of choice in patients with absolute and many relative contraindications to thrombolytic therapy.
- In patients with cardiogenic shock, early catheterization and percutaneous or surgical revascularization are the preferred management and have been shown to reduce mortality.
- Because an acute interventional approach carries a lower risk of hemorrhagic complications, it may also be the preferred strategy in many older patients.
A 64-year-old man presents to the clinic with a 3-month history of worsening shortness of breath. He becomes short of breath after walking one block or up one flight of stairs. He awakens at night gasping for breath and has to prop himself up with pillows to sleep. On physical examination, his blood pressure is 190/60 mm Hg, and his pulses are hyperdynamic. His apical impulse is displaced to the left and downward. There are rales over both lower lung fields. There are two distinct cardiac murmurs: a high-pitched, early diastolic murmur loudest at the left lower sternal border and a diastolic rumble heard at the apex. Chest radiography shows cardiomegaly and pulmonary edema. Echocardiography shows severe aortic regurgitation (AR) with left ventricular hypertrophy (LVH) and dilatation.

What are the salient features of this patient’s problem? How do you think through his problem?
Salient features: Progressive shortness of breath on exertion, paroxysmal nocturnal dyspnea, orthopnea; pulmonary edema and cardiomegaly indicating heart failure (HF); wide pulse pressure; hyperdynamic pulses; early diastolic murmur at the left sternal border; diastolic rumble at the apex (Austin-Flint murmur); echocardiogram diagnostic of AR with LVH and dilatation

How to think through: This patient has symptoms (dyspnea on exertion, paroxysmal nocturnal dyspnea, and orthopnea) and signs (rales) of HF. Can a clinician generally distinguish between systolic, diastolic, and valvular cause based on symptoms? (Not reliably.) The murmurs suggest a valvular cause. The diastolic murmur at the left upper sternal border and the apical diastolic rumble suggest AR. What other data help in the diagnosis of AR? (The wide pulse pressure, high systolic blood pressure, and hyperdynamic carotid pulse are also characteristic of AR.) What underlying processes cause AR? (Rheumatic heart disease, congenitally bicuspid valve, infective endocarditis, hypertension, cystic medial necrosis, Marfan syndrome, aortic dissection, ankylosing spondylitis, and reactive arthritis.) Echocardiography is key to diagnosis and to monitoring progression of AR. Imaging by contrast computed tomography (CT) may be indicated to assess aortic root diameter or ascending aneurysm. How should this patient be managed? (Blood pressure control with afterload reduction can decrease regurgitation. This patient is symptomatic, and elective valve replacement is indicated.)
What are the essentials of diagnosis and general considerations regarding aortic regurgitation?
Essentials of Diagnosis

- Usually asymptomatic until middle age; then presents with left-sided failure or chest pain
- Wide pulse pressure; diastolic murmur along the left sternal border
- ECG shows left ventricular hypertrophy; radiograph shows left ventricular (LV) dilatation
- Echocardiography with Doppler is diagnostic

General Considerations

- Rheumatic heart disease is less common since the advent of antibiotics.
- Nonrheumatic causes include congenitally bicuspid valve, infective endocarditis, hypertension, cystic medial necrosis, Marfan syndrome, aortic dissection, ankylosing spondylitis, and reactive arthritis.
- LVH occurs from both increased preload and afterload.
What are the symptoms and signs of aortic regurgitation?
Symptoms and Signs

- High-pitched, decrescendo aortic diastolic murmur along the left sternal border without respiratory variation
- Water-hammer or Corrigan pulse: rapid rise and fall from high systolic and low diastolic pressures; Quincke pulses: pulsatile nail beds
- Duroziez sign: to-and-fro murmur over a partially compressed femoral artery
- Musset sign: head bob with each pulse
- Hill sign: leg systolic pressure greater than 40 mm Hg higher than in the arm
- Exertional dyspnea and fatigue are the most frequent symptoms, but paroxysmal nocturnal dyspnea and pulmonary edema may also occur
- Chronic AR is usually slowly progressive; acute AR may present with acute LV failure
What is the differential diagnosis of aortic regurgitation?
Differential Diagnosis

- Aortic dissection
- Graham Steel murmur (pulmonary insufficiency secondary to pulmonary hypertension)
- Mitral stenosis
- Tricuspid stenosis
- Dock’s murmur of stenotic left anterior descending artery
What are the laboratory, imaging, and procedural findings in aortic regurgitation?
Laboratory Tests
- Serum B-type natriuretic peptide may be an early sign of LV dysfunction.

Imaging Studies
- Chest radiography shows cardiomegaly with LV prominence and sometimes aortic dilatation.
- Doppler echocardiography confirms the diagnosis and estimates the severity.
- Serial echocardiographic assessments determine the timing of valve replacement.
- CT or magnetic resonance imaging can estimate aortic root size and exclude aneurysm.

Diagnostic Procedures
- ECG shows LV hypertrophy.
- Cardiac catheterization helps quantify the severity and evaluates the coronary arteries.
What are the treatments for aortic regurgitation?
Medications

- Treatment of hypertension to decrease afterload can reduce the severity of regurgitation.
- β-blockers, angiotensin-converting enzyme inhibitors, or angiotensin II receptor blockers may slow the rate of aortic dilatation in those with Marfan syndrome.

Surgery

- Elective surgery is indicated with symptoms or in those with an ejection fraction below 55% or increasing LV volume.
- Urgent surgery is indicated in patients with acute AR.
- Mechanical valves last longer than tissue valves but require anticoagulation.
A 52-year-old man is brought to the emergency department after a syncopal episode. While running in the park, he suddenly lost consciousness. He had no premonitory symptoms and no symptoms or deficits upon regaining consciousness. For several weeks, he had had substernal chest pressure with exercise. He had no shortness of breath, dyspnea on exertion, orthopnea, or paroxysmal nocturnal dyspnea. As a child, he had had a heart murmur (never further evaluated). On examination, his blood pressure is 110/90 mm Hg, heart rate 95 beats/min, respiratory rate 15 breaths/min, and oxygen saturation 98%. The carotid pulse is weak and delayed in character. Cardiac examination reveals a laterally displaced, sustained apical impulse; a grade 3/6 midsystolic murmur, loudest at the base and radiating to the neck; and an S₄ gallop. The lungs are clear. There is no lower extremity edema. Electrocardiogram shows left ventricular hypertrophy (LVH).

What are the salient features of this patient’s problem? How do you think through his problem?
**Salient features:** Middle age; childhood murmur; syncope without prodrome or postictal phenomena; angina pectoris; no signs of heart failure (yet); narrow pulse pressure; pulsus parvus (weak) et tardus (late); systolic murmur at the base radiating to the carotids; S₄ gallop; electrocardiogram showing LVH

**How to think through:** With recent exertional substernal chest pressure then sudden syncope, what diagnoses are most likely? (Coronary artery disease, acute myocardial infarction (MI), transient ventricular arrhythmia.) However, the physical examination suggests valvular heart disease. The murmur’s radiation to the neck establishes this as aortic stenosis (AS) as opposed to the more common aortic sclerosis. The diminished and delayed carotid artery pulse indicates severe AS. Why does he have a laterally displaced and sustained apical impulse? (LVH caused by a high-pressure gradient across the aortic valve.) His childhood murmur suggests what predisposition to AS? (Bicuspid aortic valve.) What are the next steps in his management? (Cardiac enzymes to rule out MI; echocardiography to assess the aortic valve; consultation to discuss aortic valve replacement.)
What are the essentials of diagnosis and general considerations regarding aortic stenosis?
Essentials of Diagnosis

- Diminished and delayed carotid pulses (pulsus parvus et tardus)
- Soft, absent, or paradoxically split \( S_2 \)
- Harsh systolic murmur, classically crescendo–decrescendo, along the left sternal border, often radiating to the neck and sometimes associated with a thrill
- Electrocardiography (ECG) with LVH; calcified valve on radiography; echocardiography is diagnostic

General Considerations

- Congenital bicuspid valve is the most common etiology in middle-aged patients.
- The cause in elderly patients is usually valvular degeneration from progressive calcification.
- It is more frequent in men, smokers, and patients with hypercholesterolemia and hypertension.
- Coronary artery disease is often coincident because risk factors are the same.
What are symptoms and signs of aortic stenosis?
Symptoms and Signs

- Diminished and delayed carotid pulses (pulsus parvus et tardus); soft, absent, or paradoxically split \( S_2 \)
- Harsh systolic murmur often radiating to carotids and sometimes with ejection click, thrill, or both
- Murmur may be louder at the apex and resemble mitral regurgitation (Gallavardin phenomenon)
- With bicuspid valve, usually asymptomatic until middle or old age and may coincide with coarctation of the aorta or aortic root dilatation
- LVH may lead to myocardial dysfunction
- Patients may present with exertional left ventricular (LV) heart failure, angina pectoris, or syncope
What is the differential diagnosis of aortic stenosis?
Differential Diagnosis

- Other causes of angina pectoris (e.g., coronary artery disease, coronary vasospasm) or chest pain (e.g., pulmonary embolism)
- Other causes of syncope (e.g., cardiac arrhythmia, vasovagal syncope, seizure)
- Other causes of heart failure (HF)
- Systolic murmur of a different cause
- Pulmonary hypertension
- Aortic sclerosis without stenosis
- Coarctation of the aorta
What are the laboratory, imaging, and procedural findings in aortic stenosis?
Laboratory Tests
- B-type natriuretic peptide may be useful in diagnosis and prognostication of HF resulting from AS.

Imaging Studies
- Chest radiography or fluoroscopy may show an enlarged cardiac silhouette and calcified valve.
- Doppler echocardiography is usually diagnostic and can estimate the gradient across the aortic valve.

Diagnostic Procedures
- ECG usually shows LV hypertrophy.
- Cardiac catheterization provides confirmatory data, assesses hemodynamics, and excludes concomitant coronary artery disease.
What are the treatments for aortic stenosis?
Medications
- Medical treatment may stabilize heart failure, but surgical intervention is definitive.
- Lipid-lowering therapy may theoretically slow the progression of AS.
- Control of systemic hypertension is important to reduce excess afterload.

Therapeutic Procedures and Surgery
- Aortic valve replacement is indicated for all symptomatic adult patients and those with LV dysfunction or peak gradient greater than 64 mm Hg by echocardiography or Doppler.
- Balloon valvuloplasty is palliative in adolescents but ineffective for the long term in adults.
- Pericardial valves appear to last longer than porcine valves; neither requires warfarin.
- Mechanical valves have longest life but require warfarin therapy.
- Percutaneous valve replacement may be an option for high surgical risk patients.
A 55-year-old man presents to the clinic complaining of chest pain. For the past 5 months, he has noted intermittent substernal chest pressure radiating to his left arm. The pain occurs primarily when exercising vigorously and is relieved with rest. He has no associated shortness of breath, nausea, vomiting, or diaphoresis. His medical history is significant for hypertension and hyperlipidemia. He is on atenolol and a low-fat diet. His father had died of a myocardial infarction (MI) at age 56 years. He has a 50-pack-year smoking history and is currently trying to quit. His physical examination is normal except for a blood pressure of 145/95 mm Hg; his heart rate is 75 beats/min.

What are the salient features of this patient’s problem? How do you think through his problem?
Salient features: Middle-aged man; intermittent pain with exercise and relieved with rest; substernal location with radiation to the arm; risk factors: hyperlipidemia, hypertension, family history, cigarette smoking

How to think through: When evaluating a patient with chest pain, first determine if the pain is acute in onset (or progressive) with features concerning for acute coronary syndrome (ACS), pulmonary embolism, aortic dissection, pneumothorax, or another emergency. But most patients with chest pain do not require emergent evaluation. This patient’s chest pain has characteristics of typical angina, including substernal location, exertional onset, radiation to the arm, and relief with rest. Risk factors for coronary artery disease (CAD) are weighed along with history, examination, and electrocardiogram (ECG). What are the major CAD risk factors? (Age, sex, family history, tobacco use, diabetes mellitus, hypertension, low high-density lipoprotein [HDL] cholesterol, high non-HDL cholesterol.) Could this be aortic stenosis? (Based on history alone, it could be. Cardiac and carotid pulse examination will help distinguish.) While other causes (esophageal spasm or musculoskeletal pain) are possible, the symptoms, long smoking history, and family history confer a high pretest probability of CAD. There are several noninvasive CAD testing options; all involve a stressor (exercise or pharmacologic) and a detector (ECG, echocardiography, nuclear medicine). Is medical therapy indicated at this point? (Yes: aspirin, statin, β-blocker, and nitroglycerin therapy, given the high suspicion for CAD.)
What are the essentials of diagnosis and general considerations regarding chest pain?
Essentials of Diagnosis
- Chest pain onset, character, location, duration, frequency, and exacerbating and alleviating factors
- Presence of shortness of breath; vital signs; chest and cardiac examination
- ECG and cardiac biomarkers

General Considerations
- Can signify cardiovascular, pulmonary/pleural, esophageal/gastrointestinal, musculoskeletal, or psychiatric disease
- Life-threatening causes: ACS, pericarditis, aortic dissection, pulmonary embolism, pneumonia, tension pneumothorax, and esophageal perforation
- HIV, systemic lupus erythematosus, and rheumatoid arthritis predispose to coronary disease
- Cancer, trauma, recent surgery, immobilization, and history of thrombosis predispose to pulmonary embolism
What are the symptoms and signs of chest pain?
Symptoms and Signs

- Myocardial ischemia: dull, aching, retrosternal, poorly localized; described as pressure, tightness, or squeezing; may radiate to the throat, jaw, shoulders, or arms; precipitated by exertion or stress and relieved by rest or nitroglycerin; dizziness, nausea, diaphoresis, and a feeling of impending doom; elderly adults may complain of fatigue instead of chest pain; hypotension, S₃ or S₄ gallop, pulmonary crackles, elevated jugular venous pressure

- Pericarditis: greater pain supine vs. upright; cardiac friction rub with patient sitting forward

- Aortic dissection: abrupt onset, tearing pain, radiates to the back; differential blood pressures

- Pulmonary embolism: wide ranging presentations; may have normal examination

- Esophageal perforation: recent medical procedures, severe vomiting or retching, subcutaneous emphysema
What is the differential diagnosis of chest pain?
Differential Diagnosis

- Cardiovascular: myocardial ischemia, pericarditis, aortic dissection, aortic stenosis, pulmonary embolism, cardiomyopathy, myocarditis, mitral valve prolapse, pulmonary hypertension, hypertrophic obstructive cardiomyopathy (HOCM), aortic insufficiency
- Pulmonary: pneumonia, pleuritis, bronchitis, pneumothorax, tumor
- Gastrointestinal: esophageal rupture, gastroesophageal reflux disease (GERD), esophageal spasm, Mallory-Weiss tear, peptic ulcer disease, biliary disease, pancreatitis, functional gastrointestinal pain
- Musculoskeletal: cervical or thoracic or shoulder disease, costochondritis, subacromial bursitis
- Other: anxiety or panic attack, herpes zoster, breast disorders, chest wall tumors, thoracic outlet syndrome, mediastinitis
What are the laboratory, imaging, and procedural findings in chest pain?
Laboratory Tests
- Cardiac troponin I for suspected ACS
- D-dimer test, if negative, can rule out pulmonary embolism in patients with low clinical probability

Imaging Studies
- Chest radiography, especially with shortness of breath
- Computed tomography (CT) for diagnosis of esophageal perforation, aortic dissection, and pulmonary embolism
- Ventilation/perfusion scanning for pulmonary embolism if the patient cannot tolerate a CT scan

Diagnostic Procedures
- ECG is warranted in most patients; normal ECG findings do not rule out ACS or other diagnoses
- Exercise stress testing, with perfusion imaging for cardiovascular risk factors and normal testing
What are the treatments for chest pain?
Medications

- Treatment must be guided by underlying etiology
  - Short-acting as-needed nitroglycerin, daily aspirin, β-blocker, long-acting nitrate, statin for stable angina pectoris
  - Empiric trial of high-dose proton pump inhibitor therapy has been reported to improve symptoms in patients with noncardiac chest pain of unknown etiology
A 47-year-old man presents to his primary care provider for a routine checkup. The patient denies any symptoms but is worried about his weight and diet, which consists of many saturated fats. On physical examination, his blood pressure is 153/102 mm Hg, and his body habitus reveals a large amount of abdominal obesity. Blood tests reveal a serum triglyceride level of 321 mg/dL, high-density lipoprotein (HDL) cholesterol level of 24 mg/dL, low-density lipoprotein (LDL) of 132 mg/dL, and hemoglobin A1c of 6.2%.

What are the salient features of this patient’s problem? How do you think through his problem?
**Salient features:** Obese man; large waist circumference; elevated blood pressure; elevated serum triglyceride level; low HDL cholesterol level; insulin resistance consistent with the metabolic syndrome

**How to think through:** Serum LDL and HDL cholesterol, along with triglycerides, are important markers of risk for coronary artery disease (CAD). Elevated LDL cholesterol is associated with increased CAD, and LDL is the primary target of lipid-lowering therapies. This patient has a different, but equally important, pattern of dyslipidemia: low HDL and elevated triglycerides. The degree to which these abnormalities are independent predictors of CAD is debated because they so often travel with other metabolic abnormalities, collectively termed the *metabolic syndrome*. What are the elements of this syndrome? What other secondary causes of hypertriglyceridemia should be considered? (Alcohol abuse, hypothyroidism, nephrotic syndrome, familial disorders of triglyceride metabolism, and medications [e.g., corticosteroids].) What is an important complication of elevated triglycerides, and is this patient likely to experience this complication? (Pancreatitis, which typically occurs with levels greater than 2000 mg/dL.) Should he receive targeted therapy to lower his triglycerides? (Not necessarily.) Weight loss and reduction of CAD risk factors known to improve outcomes is the primary treatment strategy for dyslipidemia. The first interventions should be diet, exercise, blood pressure control, and a statin medication. Targeted triglyceride-lowering therapies are recommended for patients with levels above 500 mg/dL. What medications lower triglycerides? (Fibric acid derivatives [e.g., gemfibrozil, fenofibrate].) What downside might there be to prescribing nicotinic acid for this patient? (Worsened glucose intolerance.)
What are the essentials of diagnosis and general considerations regarding dyslipidemia?
Essentials of Diagnosis
- Elevated serum total cholesterol or LDL cholesterol, low serum HDL cholesterol, or elevated serum triglycerides
- In severe cases associated with metabolic abnormalities, superficial lipid deposition occurs

General Considerations
- Cholesterol and triglycerides are the two main circulating lipids.
- Elevated levels of LDL cholesterol are associated with increased risk of atherosclerotic heart disease; high level of HDL cholesterol are associated with a lower risk.
- Familial genetic disorders are an uncommon, but often lethal, cause of elevated cholesterol.
What are the symptoms and signs of dyslipidemia?
Symptoms and Signs

- Dyslipidemia is usually asymptomatic.
- Extremely high levels of chylomicrons or very-low-density lipoprotein particles are associated with eruptive xanthomas.
- Very high LDL levels are associated with tendinous xanthomas.
- Very high triglycerides (>2000 mg/dL) are associated with lipemia retinalis (cream-colored vessels in the fundus) or pancreatitis.
- The metabolic syndrome consists of a large waist circumference, elevated blood pressure, elevated triglycerides, low HDL cholesterol, and elevated serum glucose level.
What is the differential diagnosis of dyslipidemia?
Differential Diagnosis

Hypercholesterolemia (elevated serum cholesterol)
- Hypothyroidism, diabetes mellitus, Cushing syndrome, obstructive liver disease, nephrotic syndrome, chronic kidney disease, anorexia nervosa, familial hypercholesterolemia, idiopathic
- Drugs: oral contraceptives, thiazides, β-blockers, corticosteroids, cyclosporine

Hypertriglyceridemia (elevated serum triglycerides)
- Alcohol, obesity, metabolic syndrome, diabetes mellitus, chronic renal insufficiency, pregnancy
- Lipodystrophy (e.g., protease inhibitors), familial
- Drugs: oral contraceptives, thiazides, β-blockers, corticosteroids, bile acid–binding resins, isotretinoin
What are the laboratory findings in dyslipidemia?
Laboratory Tests

- Fasting lipid panel; screen for lipid disorders in patients older than age 35 years or with coronary heart disease risk factors, vascular disease, heart failure, or family history of premature heart disease
- Serum thyroid-stimulating hormone to screen for hypothyroidism
- Other tests only as indicated by symptoms and signs suggestive of a secondary cause
- LDL cholesterol (is classified into five categories: optimal, below 100 mg/dL; near optimal, 100 to 129 mg/dL; borderline high, 130 to 159 mg/dL; high, 160 to 189 mg/dL; very high, 190 mg/dL or above

- LDL cholesterol is estimated by the following formula: LDL cholesterol = (Total cholesterol) – (HDL cholesterol) – (Triglycerides/5)
What are the treatments for dyslipidemia?
Medications

- LDL cholesterol threshold for treatment depends on absolute risk of coronary heart disease and LDL level.
- HMG-CoA reductase inhibitors (statins) reduce LDL, coronary events, and mortality.
- Niacin can reduce LDL, increase HDL, and reduce triglycerides but may cause flushing.
- Bile acid–binding resins (e.g., cholestyramine, colestipol) mainly reduce LDL; they have many gastrointestinal side effects.
- Fibric acid derivatives (e.g., gemfibrozil, fenofibrate) reduce LDL and triglycerides and raise HDL; side effects are greater when they are taken with statins.

Therapeutic Procedures

- Low-fat diets may produce a moderate (5%–10%) decrease in LDL cholesterol.
- Substituting monounsaturated fats for saturated fats can lower LDL without affecting HDL.
- Exercise and moderate alcohol consumption can increase HDL levels.
- Reducing alcohol and fatty foods and controlling hyperglycemia are effective for hypertriglyceridemia.
A 75-year-old man with a history of coronary artery disease (CAD) and multiple previous myocardial infarctions (MIs) presents to his primary care provider with increasing shortness of breath. The patient’s exercise tolerance has gone from walking 10 blocks without stopping to needing to catch his breath after walking across the room. He can no longer lie flat at night and uses four pillows to prop himself up in bed. On physical examination, he has bilateral crackles halfway up his lung fields, his jugular venous pulsations (JVPs) are elevated, and his lower extremities have pitting edema.

What are the salient features of this patient’s problem? How do you think through his problem?
Salient features: Elderly man with CAD and previous MIs; shortness of breath; orthopnea; lung crackles from left-sided failure; elevated JVP and lower extremity edema from right-sided failure

How to think through: Heart failure (HF) is a prevalent, important syndrome. Prompt diagnosis and effective management improve morbidity, mortality, and quality of life. As in this case, HF diagnosis typically begins with a complaint of undifferentiated dyspnea on exertion. This patient also describes orthopnea. What additional symptoms also should be elicited? (Exertional chest pain, paroxysmal nocturnal dyspnea, lower extremity edema, syncope or presyncope, palpitations.) What cardiac pathologies can produce HF (as well as the physical examination signs found in this patient)? (Impaired systolic function, impaired diastolic function, and valvular disease.) What physical examination sign should be present with systolic and diastolic dysfunction? (Enlarged, sustained, displaced point of maximal impulse [PMI] at the apex.) After a diagnosis of HF is made, the underlying cause should be identified. In this case, the patient has known CAD, and an echocardiogram or nuclear imaging study may show wall motion abnormalities consistent with ischemia or infarction. What medication classes improve mortality and should be added if not already part of his regimen? (Angiotensin-converting enzyme [ACE] inhibitor, β-blocker, aldosterone receptor blocker.) A loop diuretic should be started for symptomatic relief immediately after assessment of electrolytes and renal function. If this patient proves to have an ejection fraction of less than 35%, what other interventions might help? (Implantable cardiac defibrillator improves mortality. Biventricular pacing can significantly improve symptoms and systolic function in some patients.)
What are the essentials of diagnosis and general considerations regarding heart failure?
Essentials of Diagnosis

Symptoms of left ventricular (LV) or right ventricular (RV) HF

General Considerations

- HF occurs as a result of impaired cardiac output or diastolic dysfunction with fluid retention.
- Acute exacerbations may be caused by excessive salt intake, arrhythmias, or pulmonary emboli.
- High-output HF is caused by thyrotoxicosis, beriberi, severe anemia, or arteriovenous shunting.
- Systolic dysfunction is caused by MI, ethanol abuse, longstanding hypertension, viral myocarditis (including HIV), or Chagas disease or is idiopathic.
- Diastolic dysfunction is associated with abnormal filling of a ("stiff") LV caused by chronic hypertension, LV hypertrophy, and diabetes mellitus.
What are the symptoms and signs of heart failure?
Symptoms and Signs

- LV HF: exertional dyspnea, orthopnea, paroxysmal nocturnal dyspnea, chronic nonproductive cough (often worse in recumbency), nocturia, fatigue and exercise intolerance

- Physical examination in LV HF: crackles and dullness to percussion at bases, parasternal lift, an enlarged and sustained LV impulse, S$_3$ gallop, S$_4$ gallop in diastolic dysfunction

- RV HF: anorexia, nausea, right upper quadrant pain caused by chronic passive congestion of the liver and gut

- Physical examination in RV HF: elevated and abnormal jugular venous pulsations, hepatic enlargement, hepatojugular reflux, ascites, and peripheral pitting edema

- Tachycardia, hypotension, reduced pulse pressure, cold extremities, and diaphoresis

- Long-standing severe HF: cachexia or cyanosis
What is the differential diagnosis of heart failure?
Differential Diagnosis
- Chronic obstructive pulmonary disease (COPD)
- Pneumonia
- Cirrhosis
- Peripheral venous insufficiency
- Nephrotic syndrome
What are the laboratory, imaging, and procedural findings in heart failure?
Laboratory Tests

- Complete blood cell count, serum electrolytes, creatinine, thyroid-stimulating hormone, ferritin
- Electrocardiography (ECG) to look for arrhythmia, MI, LV hypertrophy, conduction delays, repolarization changes
- B-type natriuretic peptide elevated in exacerbation; high negative predictive value

Imaging Studies

- Chest radiography: cardiomegaly, pulmonary edema, and pleural effusions
- Echocardiography: ventricular size and function, valvular abnormalities, pericardial effusions, intracardiac shunts, and segmental wall motion abnormalities
- Stress imaging: indicated if ECG abnormalities or suspected myocardial ischemia

Diagnostic Procedures

- Left heart catheterization to detect CAD
- Right heart catheterization: in patients not responding to standard therapy
What are the treatments for heart failure?
Medications

- ACE inhibitors started at low dosages also decrease mortality; angiotensin II receptor blockers are given for ACE-intolerant patients.
- β-blockers in stable patients (not acute exacerbation) have mortality benefit.
- Aldosterone blockers such as spironolactone or eplerenone decrease mortality.
- Diuretics such as loop or thiazides reduce symptoms of fluid overload.
- Digoxin can reduce symptoms but does not have a mortality benefit.
- Inotropic agents (e.g., dobutamine or milrinone) may be given in cardiogenic shock or awaiting transplantation.

Surgery

- Coronary revascularization, implantable defibrillators, or cardiac resynchronization in select patients
- Cardiac transplantation for advanced HF

Therapeutic Procedures

- Salt and fluid restriction
A 56-year-old black man presents to the clinic for a routine physical examination. On arrival, he is noted to have a blood pressure of 160/90 mm Hg, which you verify after he has sat for 20 minutes in the exam room. You look back in his record and see that during his previous two visits, he had blood pressures of 154/91 and 161/89 mm Hg. He denies any symptoms. He also denies any recent caffeine or other stimulant use.

What are the salient features of this patient’s problem? How do you think through his problem?
Salient features: Elevated blood pressure on multiple occasions and after resting; African American ethnicity; no temporary cause

How to think through: Is this patient's hypertension likely primary or secondary? What are some causes of secondary hypertension? What prescription and over-the-counter medications and other substances might cause hypertension? (Nonsteroidal antiinflammatory drugs [NSAID], oral contraceptives, sympathomimetics.) What dietary and lifestyle factors will most impact his blood pressure? (Alcohol use, sodium intake.) In the absence of other comorbidities, what would be your first choice antihypertensive agent? Is the patient likely to need more than one medication? (With two of three readings >160 mm Hg, this is stage 2 hypertension; multiple agents will likely be necessary.) How would you assess for end-organ damage? What evidence might you find on cardiac and ophthalmic examination, standard laboratory studies, urinalysis, or electrocardiography (ECG)?

What is the treatment goal for systolic blood pressure in this patient? (<140 mm Hg.) What comorbid medical conditions would lower the treatment goal for systolic blood pressure to 130 mm Hg? (Diabetes, coronary artery disease [CAD], and chronic kidney disease.) If this patient's blood pressure did not achieve the treatment goal despite therapy with an angiotensin-converting enzyme (ACE) inhibitor, β-blocker, and a calcium channel blocker, would the patient’s blood pressure be characterized as “resistant hypertension?” (No. Resistant hypertension criteria mandate a regimen of three or more agents, including a diuretic. A thiazide diuretic should generally be the first or second agent.)
What are the essentials of diagnosis and general considerations regarding hypertension?
Essentials of Diagnosis

- Usually asymptomatic but headache at awakening and blurry vision in severe hypertension

General Considerations

- Common disease of which many patients are not aware, and most do not have good control
- More common in African Americans, incidence increases with age
- Classified as normal (blood pressure <120/<80 mm Hg), prehypertension (systolic blood pressure [SBP] 120–139 mm Hg or diastolic blood pressure [DBP] 80–89 mm Hg), stage 1 (SBP 140–159 mm Hg or DBP 90–99 mm Hg), or stage 2 (SBP >160 mm Hg or DBP >100 mm Hg)
- Severe hypertension is usually caused by parenchymal renal disease, renal artery stenosis, endocrine abnormalities, drug use, or abrupt cessation of antihypertensive medications
- Usually there is no identifiable cause of hypertension, although the cause should be searched for
- Resistant hypertension is defined as failure to reach blood pressure control in patients adherent to full doses of a three-drug regimen (including a diuretic)
What are the symptoms and signs of hypertension?
Symptoms and Signs

- Usually asymptomatic
- Headaches are most frequent symptom but are nonspecific
- Elevated blood pressure
- Loud A2 on cardiac examination
- Retinal arteriolar narrowing with “silver-wiring,” arteriovenous nicking
- Flame-shaped hemorrhages
- Laboratory findings usually normal
What is the differential diagnosis of hypertension?
Differential Diagnosis

- Incorrect diagnosis because of “white-coat” hypertension or blood pressure cuff too small
- Adrenal causes: primary hyperaldosteronism, Cushing syndrome, pheochromocytoma
- Renal causes: chronic kidney disease, renal artery stenosis
- Medications: oral contraceptives, NSAIDs, venlafaxine
- Endocrine causes: hyperthyroidism, hypercalcemia, acromegaly
- Coarctation of the aorta
- Obesity
- Increased intracranial pressure
- Obstructive sleep apnea
- Alcohol, cocaine, or amphetamine use
What are the laboratory findings in hypertension?
Laboratory Tests

- Urinalysis
- Serum creatinine, blood urea nitrogen, potassium, fasting glucose, cholesterol, uric acid
- Hemoglobin
- ECG

When a secondary cause is suspected, consider chest radiography, plasma metanephrine levels, plasma aldosterone concentration, plasma renin activity, or urine electrolytes, as indicated.
What are the treatments for hypertension?
**Medications**

- Initiation of drug therapy based on level of blood pressure, presence of target end-organ damage, and overall cardiovascular risk profile.
- Medication classes include diuretics, β-adrenergic blocking agents, ACE inhibitors and angiotensin receptor blockers, calcium channel-blocking agents, α-adrenergic blockers, vasodilators, and centrally acting agents.
- Choice of medication is based on presence of disease-specific indications (e.g., β-blockers in CAD and heart failure, ACE inhibitors in renal disease and heart failure).

**Therapeutic Procedures**

- Weight reduction, alcohol restriction, salt reduction, increased physical activity, smoking cessation
- Dietary changes (DASH diet): high in fruits and vegetables, low fat, low salt
- Aggressive risk factor management, including use of a statin, should be considered in all patients with hypertension
A 58-year-old man presents to the emergency department with 20 minutes of crushing substernal chest pain and marked shortness of breath. Physical examination shows inspiratory crackles over the lower three-quarters of both lung fields, basilar dullness to percussion, hyperdynamic left ventricular (LV) impulse, brisk carotid upstroke, pansystolic murmur at the apex that radiates into the axilla, and S₃ gallop. Electrocardiography (ECG) shows ST-segment elevations in leads II, III, and aVF. Chest radiography shows Kerley B lines and bilateral pleural effusions consistent with acute pulmonary edema. Doppler echocardiography shows severe mitral regurgitation, and transesophageal echocardiography reveals a posterior mitral leaflet prolapsing into the left atrium (LA) and dyskinesis of basal lateral wall segment of the LV. The diagnosis is posterolateral myocardial infarction (MI) with acute mitral regurgitation resulting from papillary muscle ischemia and rupture.

What are the salient features of this patient’s problem? How do you think through his problem?
Salient features: Crushing chest pain and myocardial ischemia; shortness of breath; crackles, dullness to percussion, and S₃ gallop and chest radiography indicating pulmonary edema; hyperdynamic LV, brisk carotid upstroke, and pansystolic murmur at the apex radiating to the axilla; echocardiogram diagnostic of mitral regurgitation

How to think through: This patient presents with an ST-elevation MI and acute left heart failure (HF). What complications of acute MI lead to acute HF? (LV myocardial dysfunction, rupture of the septum or LV free wall with tamponade, arrhythmia, or acute valvular dysfunction.) What examination findings suggest acute mitral regurgitation as the cause of HF? (The character of the murmur, hyperdynamic precordium, and brisk carotid upstroke.) In acute MI, true rupture of the papillary muscles is much less common than papillary muscle dysfunction or displacement (caused by LV dilatation). With dysfunction or displacement, angiography and percutaneous revascularization are often first steps, the mitral regurgitation resolving with reperfusion. Here echocardiography reveals the posterior mitral leaflet prolapsing into the LA, suggesting papillary muscle rupture. What is the optimum intervention? (Emergent coronary artery bypass grafting with mitral valve repair or replacement.)
What are the essentials of diagnosis and general considerations regarding mitral regurgitation?
Essentials of Diagnosis
- Pansystolic murmur at the apex, radiating into the axilla; associated with S₃ when regurgitant volume is great
- ECG with LA abnormality, left ventricular hypertrophy (LVH), and often atrial fibrillation; LA and LV enlargement on radiograph
- Echocardiographic findings are diagnostic and can help decide when to operate

General Considerations
- The cause and acuity of mitral regurgitation determines the clinical presentation; it may be asymptomatic or cause left-sided HF
- Mitral regurgitation results from
  - Ischemia at base or rupture of papillary muscle (myocardial ischemia or infarction or infection [endocarditis])
  - Displacement of papillary muscles (dilated cardiomyopathy)
  - Excessive length of chordae or myxomatous degeneration of leaflets (mitral valve prolapse)
  - Noncontraction of annulus (annular calcification)
  - Scarring (rheumatic fever, calcific invasion)
What are the symptoms and signs of mitral regurgitation?
Symptoms and Signs

- Pansystolic murmur at the apex, radiating into the axilla in most patients
- Hyperdynamic LV impulse, brisk carotid upstroke, and often associated with an S₃ gallop
- May be asymptomatic for many years (or life)
- In acute mitral regurgitation, left atrial pressure rises abruptly, leading to pulmonary edema if severe
- In chronic mitral regurgitation, exertional dyspnea and fatigue worsen gradually over many years
- Chronic LA and LV enlargement may cause subsequent atrial fibrillation and LV dysfunction
- Systemic embolization is relatively unusual compared with other causes of atrial fibrillation
What is the differential diagnosis of mitral regurgitation?
Differential Diagnosis

- Aortic stenosis
- Aortic sclerosis
- Tricuspid regurgitation
- Hypertrophic obstructive cardiomyopathy (HOCM)
- Atrial septal defect
- Ventricular septal defect
What are the laboratory, imaging, and procedural findings in mitral regurgitation?
Laboratory Tests

- B-type natriuretic peptide (BNP) may identify LV dysfunction.

Imaging

- Chest radiography shows left atrial and ventricular enlargement.
- Doppler echocardiography confirms the diagnosis and estimates the severity.
- Transesophageal echocardiography may reveal the cause, identify candidates for repair, and diagnose endocarditis.

Diagnostic Procedures

- ECG shows left atrial abnormality and LV hypertrophy; often atrial fibrillation.
What are the treatments for mitral regurgitation?
Medications
- Vasodilators decreases systemic vascular resistance and may stabilize acute mitral regurgitation while awaiting surgery.

Surgery
- Acute mitral regurgitation resulting from endocarditis, MI, and ruptured chordae tendineae often requires emergency surgery.
- Chronic regurgitation usually requires surgery when symptoms develop or in asymptomatic patients when the LV end-systolic dimension is larger than 4.0 cm or ejection fraction is less than 60%.
- Mitral valve replacement uses mechanical or bioprosthetic valves.

Therapeutic Procedures
- Novel percutaneous approaches to mitral valve repair are being explored.
A 45-year-old woman presents with shortness of breath and an irregular heartbeat. Over the past 2 weeks, she has become easily “winded” with minor activities. She has noted a fast heartbeat and a pounding sensation in her chest. In childhood, she had been ill for several weeks after a severe sore throat. On examination, her pulse rate is noted to be 120 to 130 beats/min, and her rhythm is irregularly irregular. She has distended jugular venous pulses and rales at both lung bases. Cardiac examination also reveals a soft, low-pitched diastolic decrescendo murmur, heard best at the apex in the left lateral decubitus position. An electrocardiogram (ECG) shows atrial fibrillation and left atrial (LA) enlargement.

What are the salient features of this patient’s problem? How do you think through her problem?
**Salient features:** Dyspnea; tachycardic, irregularly irregular rhythm; atrial fibrillation on ECG; possible childhood rheumatic fever; jugular venous distention; pulmonary edema; diastolic decrescendo murmur at the apex and axilla; LA enlargement

**How to think through:** Evaluation of palpitations is more urgent when they are associated with signs of hemodynamic compromise (lightheadedness, syncope, or dyspnea). With the irregularly irregular pulse, an ECG is done, confirming atrial fibrillation. Examination shows left heart failure (HF) with jugular venous distention and pulmonary edema. How might atrial fibrillation lead to subacute HF? (New-onset atrial fibrillation alone may cause inefficient forward flow. Atrial fibrillation also occurs commonly in diastolic HF; with declining ejection fraction in systolic HF, and with LA dilatation, especially in mitral stenosis.) The diastolic murmur here suggests mitral stenosis. Careful history may reveal a decrease in activity level as the mitral stenosis progressed. Should electrical or chemical cardioversion be performed? (No. There is a high risk of systemic embolization in patients with atrial fibrillation for > 48 hours, and those with mitral stenosis are at even higher risk.) How should she be managed? (Initially, rate control and diuresis to improve her symptoms. Echocardiography can characterize the valve area and gradient. Cardiology/cardiac surgery consultations can help decide between percutaneous versus surgical repair.)
What are the essentials of diagnosis and general considerations regarding mitral stenosis?
Essentials of Diagnosis
- Exertional dyspnea, orthopnea, and paroxysmal nocturnal dyspnea; symptoms often precipitated by onset of atrial fibrillation or pregnancy
- Moderate mitral stenosis causes pulmonary edema; severe mitral stenosis presents with pulmonary hypertension and low cardiac output
- ECG may show LA abnormality and atrial fibrillation; echocardiography is diagnostic

General Considerations
- Underlying rheumatic heart disease in almost all patients (although history of rheumatic fever is often absent)
- May also occur because of congenital disease, calcification of the annulus invading the leaflets, or prosthetic valve annular ring mismatch
What are the symptoms and signs of mitral stenosis?
Symptoms and Signs

- An opening snap following A₂ caused by a stiff mitral valve
- Low-pitched diastolic murmur (rumble) at the apex with the patient in the left decubitus position; increased by brief exercise
- Moderate stenosis: exertional dyspnea and fatigue common, especially with tachycardia
- Severe stenosis: pulmonary congestion at rest with dyspnea, fatigue, right-sided HF, orthopnea, paroxysmal nocturnal dyspnea, and occasional hemoptysis
- Sudden increase in heart rate may precipitate pulmonary edema
- Atrial fibrillation is common and may precipitate dyspnea or pulmonary edema
What is the differential diagnosis of mitral stenosis?
Differential Diagnosis

- Mitral valve prolapse
- Atrial myxoma
- Cor triatriatum (congenital atrial anomaly)
What are the imaging and procedural findings in mitral stenosis?
Imaging Studies

- Doppler echocardiography confirms the diagnosis and quantifies the severity based on mitral leaflet thickening and mobility, submitral scarring, and commissural calcium.

Diagnostic Procedures

- ECG typically shows LA abnormality and often atrial fibrillation.
- Cardiac catheterization can detect valve, coronary, or myocardial disease; it is usually done only after a decision to intervene has been made.
What are the treatments for mitral stenosis?
Medications
● Control heart rate to allow for more diastolic filling of the left ventricle
● Anticoagulation with warfarin for patients with atrial fibrillation

Surgery
● Intervention to relieve stenosis indicated for symptomatic disease or pulmonary hypertension
● Surgical valve replacement is done in combined stenosis and regurgitation or when the mitral valve is significantly distorted and calcified

Therapeutic Procedures
● Percutaneous balloon valvuloplasty can be done when there is minimal mitral regurgitation
A young woman is brought to the emergency department by ambulance after a severe motor vehicle accident. She is unconscious. Her blood pressure is 64/40 mm Hg and heart rate is 150 beats/min. She has been intubated and is being hand ventilated. There is no evidence of head trauma. The pupils are 2 mm and reactive. She withdraws to pain. Cardiac examination reveals no murmurs, gallops, or rubs. The lungs are clear to auscultation. The abdomen is tense, with decreased bowel sounds. The extremities are cool and clammy with thready pulses.

What are the salient features of this patient’s problem? How do you think through her problem?
Salient features: Trauma; tachycardia and hypotension; altered mental status; tense abdomen in the setting of trauma suggesting internal bleeding; cool extremities suggesting high systemic vascular resistance; suspicion of hypovolemia because of blood loss

How to think through: Because of the urgency and confusion that accompany a presentation such as this, reliance on protocols is essential and unequivocally improves outcomes. Begin with the ABCDE algorithm, with primary and secondary head-to-toe evaluations. In this case, the evaluation according to protocol reveals hypotension and evidence of poor perfusion—the definition of “shock”—and a rigid abdomen with no other obvious sources blood loss. What are the immediate management priorities? (Intravenous access with rapid fluid resuscitation, blood type and cross-match, central line and arterial line placement, initiation of pressor agents.) What are the immediate diagnostic priorities? (Electrocardiography [ECG], chest radiography, abdominal imaging.) How might the tense abdomen explain the patient’s blood pressure? (Blood loss in the peritoneal space with compression of the inferior vena cava limiting venous return.) To avoid focusing on hypovolemic shock as the only cause, what else might cause or contribute to shock in this patient? (Traumatic aortic dissection, cardiac tamponade, tension pneumothorax, other bleeding source, underlying adrenal insufficiency.) What are the other major classes of shock? (Cardiogenic, obstructive and distributive [septic, anaphylactic, and neurogenic].) What end-organ effects of poor perfusion can one evaluate and monitor during resuscitation? (Mental status; urine output; ECG evidence of cardiac ischemia and arrhythmia; peripheral perfusion with pulses, skin temperature, color, and capillary refill.)
What are the essentials of diagnosis and general considerations regarding shock?
Essentials of Diagnosis
- Hypotension; tachycardia; oliguria; altered mental status; cool, clammy extremities
- Peripheral hypoperfusion and impaired oxygen delivery

General Considerations
- Can be classified as hypovolemic, cardiogenic, obstructive, and distributive (including septic, anaphylactic, and neurogenic)
  - Hypovolemic results from decreased intravascular volume
  - Cardiogenic results from cardiac failure with inability of heart to maintain tissue perfusion
  - Obstructive results from acute decrease in cardiac output
  - Distributive causes include sepsis (most common), anaphylactic, and neurogenic; a reduction in systemic vascular resistance (SVR) results in inadequate cardiac output and tissue hypoperfusion despite normal circulatory volume
    - Septic may be caused by gram-negative or gram-positive bacteria
    - Anaphylactic is caused by an IgE-mediated allergic response
    - Neurogenic caused by spinal cord injury or epidural anesthetic agents
What are the symptoms and signs of shock?
Symptoms and Signs

- Hypotension, weak or thready peripheral pulses, cold or mottled extremities
- Splanchnic vasoconstriction may lead to oliguria, bowel ischemia, and hepatic dysfunction
- Mentation may be normal or altered (e.g., restlessness, agitation, confusion, lethargy, or coma)
- Hypovolemic shock: low jugular venous pressure (JVP) and narrow pulse pressure from reduced stroke volume
- Cardiogenic shock: elevated JVP, global hypoperfusion with oliguria, altered mental status, cool extremities, pulmonary edema if there is left-sided heart failure
- Obstructive shock: central venous pressure (CVP) may be elevated
- Distributive shock: hyperdynamic heart sounds, warm extremities, wide pulse pressure from large stroke volume
  - Septic shock: evidence of infection and organ hypoperfusion (lactic acidosis, oliguria, altered mental status) despite volume resuscitation
  - Anaphylactic shock: evidence of allergen exposure (injected, e.g., venom; ingested, e.g., food; contact, e.g., topical medication; inhaled, e.g., peanut shell dust)
  - Neurogenic shock: evidence of central nervous system injury and hypotension despite volume resuscitation
  - Acute adrenal insufficiency shock: evidence of hypocortisolism
What is the differential diagnosis of shock?
Differential Diagnosis

- Hypovolemic: loss of blood from the gastrointestinal tract, uterus, or urinary tract or loss of fluids and electrolytes as from vomiting or diarrhea
- Cardiogenic: myocardial infarction, cardiomyopathy, myocardial contusion, valvular regurgitation or stenosis, arrhythmias
- Obstructive: cardiac tamponade, tension pneumothorax, massive pulmonary embolism
- Distributive: sepsis, systemic inflammatory response syndrome from burns or severe pancreatitis, anaphylaxis, traumatic spinal cord injury, acute adrenal insufficiency
  - Septic: gram-negative bacteremia, gram-positive cocci, gram-negative anaerobes
  - Anaphylaxis: allergen exposure via injection, ingestion, contact, or inhalation
  - Neurogenic: spinal cord injury, epidural of spinal anesthesia, vagal parasympathetic stimulation leading to hypotension, bradycardia, and syncope (e.g., fright, pain, gastric dilatation)
  - Acute adrenal insufficiency: adrenal crisis in Addison disease or other hypocortisolism
What are the laboratory, imaging, and procedural findings in shock?
Laboratory Tests
- Complete blood count, serum electrolytes and glucose, coagulation parameters
- Arterial blood gas determinations, blood cultures, type and cross-match

Imaging Studies
- Chest radiograph
- Transesophageal echocardiography shows reduced left ventricular filling in hypovolemic and obstructive shock or enlarged left ventricle in cardiogenic shock

Diagnostic Procedures
- ECG
- Arterial line placement for blood pressure and arterial oxygen monitoring
- Foley catheter should be inserted to monitor urinary output
- Pulmonary artery catheter can distinguish cardiogenic from septic shock and monitor effects of volume resuscitation or pressor medications
- CVP measurement can suggest volume status
- Cardiac index is often low in cardiogenic shock and high in septic shock
- SVR is low in septic and neurogenic shock and high in hypovolemic and cardiogenic shock
What are the treatments for shock?
Medications

- Norepinephrine is generally used for vasodilatory shock, but may be used in all causes.
- Dobutamine is the first-line drug for cardiogenic shock.
  - Amrinone or milrinone can be substituted for dobutamine.
  - Dopamine has dopaminergic and β-agonist effect at low doses and α-adrenergic effects at high doses.
- Epinephrine is the treatment of choice in anaphylactic shock and may be used in severe shock and during acute resuscitation.
- Vasopressin is indicated for distributive or vasodilatory shock; it is also used in sepsis if requiring two drugs.
- Broad-spectrum antibiotics are administered in septic shock.

Surgery

- Transcutaneous or transvenous pacing or intraarterial balloon pump for cardiogenic shock.

Therapeutic Procedures

- Volume replacement with fluid or blood products is critical.
- Pulmonary artery catheters are often useful for cardiogenic shock.
- Pericardiocentesis or pericardial window, chest tube placement, or catheter-directed thrombolytic therapy are used as indicated for obstructive shock.
- Correction of acidosis may be accomplished by sodium bicarbonate or hemodialysis.
A 23-year-old woman presents to the emergency department with acute shortness of breath associated with right-sided pleuritic chest pain. She denies fever, chills, cough, and other respiratory symptoms. She has no lower extremity swelling. She has not been ill, bedridden, or immobile for a prolonged period. About 2 years ago, she had a deep venous thrombosis (DVT) in the right lower extremity while taking oral contraceptives. She has been otherwise healthy and is currently taking no medications. On family history, her father died of a pulmonary embolus (PE). On physical examination, she appears anxious and in mild respiratory distress. Her heart rate was 110 beats/min and respiratory rate 20 breaths/min. She has no fever, and her blood pressure is normal. Physical examination findings are normal. Chest radiography findings are normal. Ventilation/perfusion (V/Q) scan reveals a high probability of PE. A hypercoagulable state is suspected.

What are the salient features of this patient’s problem? How do you think through her problem?
**Salient features:** Young woman; acute onset of dyspnea; pleuritic chest pain; personal and family history of DVT; tachycardia; respiratory distress; normal chest radiography; PE on V/Q scan

**How to think through:** This patient’s pleuritic chest pain, tachycardia, history of DVT, and absence of another likely cause of her symptoms confer a high pretest probability of PE. She should be treated with heparin immediately even before confirmation of PE by computed tomography (CT) angiography or V/Q scan. When a removable risk factor for DVT or PE is identified, evaluation for an inherited cause of thrombophilia is not usually performed, and anticoagulation is short term. What are removable risk factors? (Immobility, cancer, recent surgery, or blood vessel wall injury.) This patient’s prior DVT was at first considered to be provoked, given her use of an oral contraceptive. However, the family history of PE suggests a possible inherited cause; evaluation for thrombophilia is appropriate. What tests should be done? (Prothrombin time [PT]; activated partial thromboplastin time [aPTT]; activated protein C resistance; antithrombin [AT], protein C, and protein S levels; lupus anticoagulant test.) Lifelong anticoagulation is indicated, regardless of the evaluation. But evaluation is important for other reasons (e.g., fertility implications, family member guidance).
What are the essentials of diagnosis and general considerations regarding hypercoagulable states?
Essentials of Diagnosis
- Thrombosis, often in the deep veins of the legs
- Personal or family history of clotting, presence of systemic disease, or no provoking factor associated with thrombosis are clues to a hypercoagulable state
- Prolonged clotting times in some diseases

General Considerations
- Hypercoagulable states may be inherited or acquired.
- Activated protein C resistance (factor V Leiden) is the most common inherited problem; protein C and protein S deficiencies, AT deficiency, and prothrombin G20212A mutation are also inherited.
- Lupus anticoagulants may occur in patients with or without systemic lupus erythematosus or other underlying diseases.
- Patients with recurrent or serious thrombosis, a family history of thrombosis, spontaneous abortions, and systemic lupus erythematosus as well as patients without DVT or PE risk factors should be evaluated for hypercoagulable states.
What are the symptoms and signs of hypercoagulable states?
Symptoms and Signs

- Increased risk of thrombosis and recurrent spontaneous abortions with lupus anticoagulants
- Despite the name, no increased bleeding with lupus anticoagulants
- May present with DVT, including pain, swelling, and redness of the limb with normal pulses and extremity perfusion
- May present with pulmonary emboli with or without obvious DVT, including an acute onset of shortness of breath, hypoxemia, tachycardia, and chest pain
- Hypercoagulable states may present with thrombosis at unusual sites (e.g., the central nervous system sagittal sinus, the abdominal mesenteric veins)
What is the differential diagnosis of hypercoagulable states?
Differential Diagnosis

- Inherited causes: Activated protein C resistance (factor V Leiden), prothrombin G20212A mutation, AT deficiency, protein C deficiency, protein S deficiency, hyperhomocysteinemia, dysfibrinogenemia, abnormal plasminogen

- Acquired causes: Immobility or postoperative state, cancer, inflammatory disorders (e.g., ulcerative colitis), myeloproliferative disorder (e.g., polycythemia vera or essential thrombocytosis), estrogens and pregnancy, heparin-induced thrombocytopenia, lupus anticoagulants, nephrotic syndrome, paroxysmal nocturnal hemoglobinuria, disseminated intravascular coagulation, heart failure
What are the laboratory and imaging findings in hypercoagulable states?
Laboratory Tests
- Complete blood count, PT, and aPTT to look for abnormalities
- Assays and polymerase chain reaction are available to measure activated protein C resistance and AT, protein C, and protein S levels
- Lupus anticoagulant: prolonged aPTT that does not correct completely on mixing study (mixing with normal plasma containing clotting factors), indicating the presence of an anticoagulant and not a factor deficiency
- Specialized testing for lupus anticoagulant confirmation: hexagonal phase phospholipid neutralization assay, dilute Russell viper venom time, platelet neutralization assays

Imaging Studies
- Patients with symptoms or signs of DVT or PE should receive ultrasonography with Doppler or helical CT scanning, respectively.
What are the treatments for hypercoagulable states?
Medications

- Anticoagulation with warfarin or heparin in standard doses for most patients with thrombosis.
- If thrombosis is recurrent, lifelong anticoagulation is usually recommended.
- Unfractionated heparin therapy is difficult to monitor in lupus anticoagulant because of the in vitro prolongation of the aPTT in that condition; therefore, low-molecular-weight heparin (LMWH) is preferred.
- During pregnancy, prophylaxis with LMWH should be provided for lupus anticoagulant.

Therapeutic Procedures

- Temporary inferior vena cava filters may be placed in selected clinical situations.
A 65-year-old previously well man presents to the clinic with the complaint of fatigue of 3 months’ duration. Questioning reveals diffuse weakness and feeling winded when walking uphill or climbing more than one flight of stairs. All of his symptoms have slowly worsened over time. Except for light-headedness, the review of systems is negative. The patient has no significant medical history, social history, or family history. On physical examination, he appears somewhat pale, with normal vital signs except for a resting pulse of 118 beats/min. The physical examination is otherwise unremarkable except for his rectal examination, which reveals brown, guaiac-positive stool (consistent with occult blood in the stool). A complete blood count (CBC) reveals a microcytic anemia with low mean corpuscular volume (MCV).

What are the salient features of this patient’s problem? How do you think through his problem?
Salient features: Fatigue, weakness, and dyspnea of insidious onset; pale on physical examination; guaiac-positive stool; microcytic anemia

How to think through: Several of this patient’s symptoms and signs—fatigue, dyspnea, lightheadedness, weakness, and tachycardia—might suggest cardiac and pulmonary causes for your differential diagnosis. But do not forget anemia! After you establish that a patient is anemic, look at the reticulocyte count. Hyperproliferative anemia indicates either hemolysis or active bleeding. Hypoproliferative anemia, which is more common, often indicates a deficiency state. Anemia is further assessed by looking at the MCV. In iron-deficiency anemia, is the MCV low or high? (Low.) What do the serum iron studies—ferritin, iron, transferrin (total iron-binding capacity), and % saturation—show? What does the peripheral smear show? What is the platelet count in iron deficiency? Whenever you determine that the etiology of anemia is iron deficiency, you must investigate its cause. Conceptualize its possible causes by tracing the path from dietary iron intake to absorption to bioavailability to possible (blood) loss. What are the potential pathologies at each stage? For example, where is iron absorbed, and what might disrupt this absorption? Although the gastrointestinal (GI) tract is the most common source of blood loss, be sure to also consider other sources of blood loss (e.g., uterine, urinary, pulmonary).
What are the essentials of diagnosis and general considerations regarding iron-deficiency anemia?
Essentials of Diagnosis
- Serum ferritin <12 mcg/L and response to iron therapy
- Caused by bleeding in adults unless proved otherwise

General Considerations
- Most common cause of anemia worldwide
- More common in women as a result of menstrual losses
- Causes
  - Blood loss (GI, menstrual, repeated blood donation)
  - Dietary deficiency or decreased absorption of iron
  - Increased requirements (pregnancy, lactation)
  - Hemoglobinuria
  - Iron sequestration (pulmonary hemosiderosis)
- Women with heavy menstrual losses may require more iron than can readily be absorbed; thus, they often become iron deficient
- Pregnancy and lactation also increase iron needs, requiring supplementation
- Long-term aspirin use may cause GI blood loss even without documented structural lesion
- Search for a source of GI bleeding if other sites of blood loss are excluded
What are the symptoms and signs of iron-deficiency anemia?
Symptoms and Signs

- Symptoms of anemia (e.g., easy fatigability, tachycardia, palpitations and tachypnea on exertion)
- Skin and mucosal changes (e.g., smooth tongue, brittle nails, and cheilosis) in severe iron deficiency
- Dysphagia resulting from esophageal webs (Plummer-Vinson syndrome)
- Pica (i.e., craving for specific foods [e.g., ice chips, lettuce] often not rich in iron) is frequent
What is the differential diagnosis of iron-deficiency anemia?
Differential Diagnosis

- Microcytic anemia resulting from other causes
  - Thalassemia
  - Anemia of chronic disease
  - Sideroblastic anemia
  - Lead poisoning
What are the laboratory findings in iron-deficiency anemia?
Laboratory Tests

- Diagnosis can be made by
  - Laboratory confirmation of an iron-deficient state
  - Evaluation of response to a therapeutic trial of iron replacement
- Hematocrit is low but MCV is initially normal; later, MCV is low.
- The platelet count may be increased.
- A ferritin value below 12 mcg/L is a highly reliable indicator of depletion of iron stores.
- However, because serum ferritin levels may rise in response to inflammation or other stimuli, a normal ferritin level does not exclude a diagnosis of iron deficiency.
- Serum iron is below 30 mcg/dL, and transferrin saturation is below 15% after iron stores are depleted.
- As deficiency progresses, anisocytosis (variation in red blood cell [RBC] size) and poikilocytosis (variation in RBC shape) develop.
- An abnormal peripheral blood smear shows markedly hypochromic cells, target cells, hypochromic pencil-shaped cells, and occasionally small numbers of nucleated RBCs in severe iron deficiency.
What are the treatments for iron-deficiency anemia?
Medications

- Ferrous sulfate orally is the treatment of choice; it may cause GI side effects, so a low dose initially increases its tolerability.
- Continue iron therapy for 3 to 6 months after restoration of normal CBC to replenish iron stores.
- Failure of response to iron therapy is usually caused by medication nonadherence but may be caused by ongoing blood loss, poor absorption, or incorrect diagnosis (e.g., anemia of chronic disease, thalassemia, celiac disease).
- Indications for parenteral iron are intolerance or refractoriness to oral iron or continued blood loss that cannot be corrected.
- Parenteral iron preparations include iron sucrose or polyglucose sorbitol carboxymethyl ether coated magnetite (ferumoxytol).

Therapeutic Procedures

- Treat the underlying cause of the iron deficiency such as the source of GI bleeding.
A 57-year-old man undergoes total knee replacement for severe degenerative joint disease. Four days after surgery, he develops acute onset of shortness of breath and right-sided pleuritic chest pain. His father died after a pulmonary embolism (PE). The patient is now in moderate respiratory distress with a respiratory rate of 28 breaths/min, heart rate of 120 beats/min, and blood pressure of 110/70 mm Hg. Oxygen saturation is 90% on room air. Lung examination is normal. Cardiac examination reveals tachycardia but is otherwise unremarkable. The right lower extremity is postsurgical, healing well, with 2+ pitting edema, calf tenderness, erythema, and warmth; the left leg is normal.

What are the salient features of this patient’s problem? How do you think through his problem?
**Salient features:** Recent orthopedic surgery; acute dyspnea, pleuritic chest pain, tachycardia and tachypnea suggesting PE; family history of PE; leg edema, tenderness, erythema, and warmth

**How to think through:** Given the postsurgical context, acute symptoms, and vital sign abnormalities, PE is likely, and heparin should be started immediately. Computed tomography (CT) angiography can be performed when the patient is stable. Whether to use thrombolytic therapy is a key question in this case. Thrombolysis is known to improve outcomes in massive PE but is controversial in submassive PE. The patient has tachycardia is not frankly hypotensive at this point. What study would help with this decision? (Echocardiography to characterize the degree of right heart strain.) When a reversible risk factor for deep venous thrombosis (DVT) or PE is identified, such as immobility, cancer, recent surgery, or injury to a blood vessel wall, the event is said to be “provoked,” evaluation for thrombophilia is often not performed, and anticoagulation is prescribed for 3 to 6 months. When a DVT or PE is unprovoked, the risk of recurrence is as high as 7% to 10% per year, and lifelong anticoagulation is typically indicated. In this case, evaluation for a hypercoagulable state is needed to guide duration of anticoagulation; although recent orthopedic surgery is a major reversible risk factor, the family history of PE, suggests a possible inherited thrombophilia. Evaluation should be delayed for 3 months because protein C and S are consumed during acute PE.
What are the essentials of diagnosis and general considerations regarding deep venous thrombosis and thromboembolism?
**Essentials of Diagnosis**

- Predisposition to venous thrombosis
- Pain, swelling, and redness below the level of the thrombus
- Presence of thromboembolic disease such as PE

**General Considerations**

- DVT and PE are two manifestations of the same disease.
- DVT may be in the upper or lower extremity, although it most commonly occurs in the legs.
- DVTs proximal to the knee (popliteal and iliofemoral) embolize more often than distal thrombi.
- Risk factors include venous stasis (e.g., immobility, hyperviscosity, low cardiac output), injury to the vessel wall, and hypercoagulability (e.g., oral contraceptives, inherited hypercoagulable states, malignancy).
What are the symptoms and signs of deep venous thrombosis and thromboembolism?
Symptoms and Signs

- Pain, swelling, and redness below the level of the thrombus; usually unilateral
- Normal arterial pressures and perfusion in the distal extremity
- Homan sign: pain in the calf with dorsiflexion of the ankle (limited sensitivity)
- DVT may be detectable as a palpable cord in the calf
- DVT may be associated with symptoms and signs of PE (e.g., dyspnea, chest pain, tachycardia, and tachypnea)
What is the differential diagnosis of deep venous thrombosis?
Differential Diagnosis

- Muscular strain
- Baker cyst
- Achilles tendon rupture
- Cellulitis
- Superficial thrombophlebitis
- Lymphatic obstruction (e.g., from pelvic tumor)
- Reflex sympathetic dystrophy
- Tumor or fibrosis obstructing venous flow
- May-Thurner syndrome (left iliac vein compressed by the right common iliac artery)
What are the laboratory, imaging, and procedural findings in deep venous thrombosis?
Laboratory Tests

- A negative D-dimer result can rule out DVT in patients with low pretest probability.
- Patients may need further laboratory tests for inherited hypercoagulable disorders. The evaluation should be delayed for 3 months because factors such as protein C and S are consumed during the acute PE.

Imaging Studies

- Ultrasonography with Doppler is diagnostic of DVT and is now the preferred study.
- Magnetic resonance imaging may also be diagnostic and is useful in non-extremity thrombosis.

Diagnostic Procedures

- Venography is the gold standard but is invasive and expensive and rarely used.
- Impedance plethysmography, which relies on changes in electrical impedance between patent and obstructed veins, is comparable to ultrasonography in accuracy.
What are the treatments for deep venous thrombosis and thromboembolism?
Medications

- Anticoagulant therapy is the cornerstone of medical therapy.
- Initial therapy is with low-molecular-weight heparin, fondaparinux, or unfractionated heparin.
- After initial therapy, dose-adjusted vitamin K antagonist (e.g., warfarin) is started.
- Duration of treatment is for a minimum of 3 months for provoked DVT; lifelong treatment should be considered in patients with unprovoked DVT.

Surgery

- Surgical thrombectomy or directed thrombolysis, especially in large iliofemoral thromboses

Therapeutic Procedures

- Inferior vena caval (IVC) filters in patients with absolute contraindication for anticoagulation
A 58-year-old woman presents to the emergency department with complaints of progressive fatigue and weakness for the past 6 months. She is short of breath after walking several blocks. On review of systems, she mentions mild diarrhea. She has noted intermittent numbness and tingling of her lower extremities and a loss of balance while walking. She denies other neurologic or cardiac symptoms and has no history of black or bloody stools or other blood loss. On physical examination, she is tachycardic to 110 beats/min; other vital signs are within normal limits. Head and neck examination is notable for pale conjunctivas and a beefy red tongue with loss of papillae. Neurologic examination reveals decreased sensation to position and vibration in the lower extremities. Laboratory testing shows a low hematocrit level.

What are the salient features of this patient’s problem? How do you think through her problem?
Salient features: Fatigue, weakness and dyspnea of insidious onset; neurologic symptoms, including peripheral neuropathy and ataxia; tachycardia and paleness with anemia; glossitis; posterior column neurologic findings on examination

How to think through: The combination of two clinical presentations should raise the possibility of vitamin $\text{B}_{12}$ deficiency: anemia plus neurologic symptoms. Although peripheral neuropathy is the most common neurologic manifestation, what other neurologic symptoms can result from advanced vitamin $\text{B}_{12}$ deficiency? Regarding the anemia, in what range does the typical mean corpuscular volume (MCV) fall in vitamin $\text{B}_{12}$ deficiency; are there exceptions? What are the other common causes of macrocytic anemia? Specifically, what other metabolic derangements? Medication effects? Toxic ingestions? What are the findings on a peripheral blood smear in vitamin $\text{B}_{12}$ deficiency? What would the reticulocyte count be? Can this patient’s symptoms of fatigue, weakness, and dyspnea be caused by her anemia? In this patient, what would be the most common cause of vitamin $\text{B}_{12}$ deficiency? How would you diagnose it? What might be some other possible causes? Surgical? Infectious? Inflammatory? Dietary?
What are the essentials of diagnosis and general considerations regarding vitamin B$_{12}$ deficiency?
Essentials of Diagnosis

- Macrocytic anemia with serum vitamin B₁₂ level <100 pg/mL
- Macro-ovalocytes and hypersegmented neutrophils on peripheral blood smear

General Considerations

Vitamin B₁₂ is absorbed from the diet (foods of animal origin) in the terminal ileum after binding to intrinsic factor, a protein secreted by gastric parietal cells, and stored in the liver.

Stores take at least 3 years to deplete after vitamin B₁₂ absorption ceases.

Causes of vitamin B₁₂ deficiency

- Decreased intrinsic factor production: pernicious anemia (most common cause), gastrectomy
- Dietary deficiency (only in vegans)
- Competition for vitamin B₁₂ in the gut: blind loop syndrome, fish tapeworm (rare)
- Decreased ileal vitamin B₁₂ absorption: surgical resection, Crohn disease
- Pancreatic insufficiency
- Helicobacter pylori infection
- Transcobalamin II deficiency (rare)

Pernicious anemia is associated with atrophic gastritis and other autoimmune diseases (e.g., immunoglobulin A [IgA] deficiency, polyglandular endocrine failure syndromes).
What are symptoms and signs of vitamin B₁₂ deficiency?
Symptoms and Signs

- Megaloblastic anemia, which may be severe
- Pallor and mild icterus
- Glossitis and vague gastrointestinal disturbances (e.g., anorexia, diarrhea)

Neurologic manifestations

- Peripheral neuropathy usually occurs first.
- Then subacute combined degeneration of the spinal cord affecting posterior columns may develop, causing difficulty with position and vibration sensation and balance.
- In advanced cases, dementia and other neuropsychiatric changes may occur.
- Neurologic manifestations occasionally precede hematologic changes; patients with suspicious neurologic symptoms and signs should be evaluated for vitamin B₁₂ deficiency despite normal MCV and absence of anemia.
What is the differential diagnosis of vitamin B₁₂ deficiency?
Differential Diagnosis

- Folic acid deficiency (other cause of megaloblastic anemia)
- Myelodysplastic syndrome (other cause of macrocytic anemia with abnormal morphology)
- Other cause of peripheral neuropathy, ataxia, or dementia
What are the laboratory and procedural findings in vitamin B$_{12}$ deficiency?
Laboratory Tests
- Anemia of variable severity; hematocrit may be as low as 10% to 15%.
- MCV is strikingly elevated at 110 to 140 fL but may be normal if coexistent thalassemia or iron deficiency is present.
- Low serum vitamin B\textsubscript{12} level establishes diagnosis.
- Serum methylmalonic acid elevations can confirm diagnosis.
- Peripheral blood smear shows macro-ovalocytes, anisocytosis, poikilocytosis, and hypersegmented neutrophils with mean neutrophil lobe count greater than 4 or one or more neutrophil(s) with 6 lobes.
- Reticulocyte count reduced, pancytopenia present in severe cases.
- Serum lactate dehydrogenase (LDH) is elevated, and indirect bilirubin is modestly increased.

Diagnostic Procedures
- Bone marrow morphology shows marked erythroid hyperplasia, megaloblastic changes in erythroid series, and giant metamyelocytes in myeloid series.
What are the treatments for vitamin B$_{12}$ deficiency?
Medications

- For pernicious anemia
  - Vitamin B$_{12}$ intramuscularly at least monthly
  - Oral cobalamin may be tried instead of parenteral therapy but must be continued daily indefinitely
  - Antibiotics if vitamin B$_{12}$ deficiency is caused by bacterial overgrowth in a blind loop.
  - Pancreatic enzymes should be given if deficiency is caused by pancreatic insufficiency.
  - Antihelmintic agent should be given if deficiency is caused by fish tapeworm.
  - Large doses of folic acid may produce hematologic responses in cases of vitamin B$_{12}$ deficiency but allow neurologic damage to progress.
  - Transfusions should generally be avoided because they can lead to heart failure.
A 52-year-old man presents to the emergency department with right upper quadrant (RUQ) abdominal pain for 8 hours. He states that it is steady and unrelenting and began about 1 hour after he ate a hamburger with French fries. Since the pain began, he has experienced episodic nausea and vomited once. On physical examination, he has a fever and marked tenderness to palpation over the RUQ of the abdomen with a positive Murphy sign on inspiration. The white blood cell (WBC) count is 19,000/mcL. Abdominal ultrasonography reveals a thickened gallbladder with multiple gallstones and pericholecystic fluid.

What are the salient features of this patient’s problem? How do you think through his problem?
Salient features: RUQ abdominal pain; onset after a fatty meal; nausea and vomiting; fever and elevated WBC count; positive Murphy sign; thickened gallbladder and pericholecystic fluid on abdominal ultrasonography

How to think through: What causes of RUQ pain are important to consider in differential diagnosis? (Acute cholecystitis, acute pancreatitis, acute hepatitis, intraabdominal abscess, right lower lobe pneumonia, cardiac ischemia.) Could this be biliary colic? (The duration and unrelenting nature of the pain, along with the fever, indicate inflammation rather than the transient obstruction of biliary colic.) How would the presence of jaundice change your assessment? (Cholangitis, hepatitis, and hemolysis would rise in the differential diagnosis.) Is the ultrasound finding of gallstones sufficient to make the diagnosis of cholecystitis? (No. Cholelithiasis is common. The diagnosis of cholecystitis is a clinical one based on the history, examination, WBC, and ultrasound findings. Gallbladder wall edema on ultrasonography strongly suggests cholecystitis.) What are the initial steps in management? (Intravenous [IV] fluids, analgesia, surgical consultation.) Are antibiotics indicated? (Yes, given the fever and leukocytosis. About 40% of patients have positive biliary cultures, especially with *Escherichia coli.*) When should surgery be performed? (Immediate cholecystectomy generally improves outcomes. However, medical comorbidities or septic shock confer high surgical risk and may necessitate delay in surgery.) How are high-risk patients managed? (Often with antibiotics and percutaneous cholecystostomy with subsequent cholecystectomy.)
What are the essentials of diagnosis and general considerations regarding cholecystitis?
Essentials of Diagnosis
- Steady, severe pain, and tenderness in the abdominal RUQ or epigastrium
- Nausea and vomiting; fever and leukocytosis

General Considerations
- Usually occurs when a stone becomes impacted in the cystic duct and inflammation develops behind the obstruction
- Acute calculous cholecystitis should be considered after major surgery or in a critically ill patient without any oral intake for a prolonged period
- May be caused by vasculitis or infectious agents (e.g., cytomegalovirus, cryptosporidiosis, or microsporidiosis) in patients with AIDS or by vasculitis (e.g., polyarteritis nodosa)
What are the symptoms and signs of cholecystitis?
Symptoms and Signs

- The acute attack is often precipitated by a large or fatty meal.
- It consists of relatively sudden, severe, steady pain that is localized to the abdominal RUQ or epigastrium and that may gradually subside over a period of 12 to 18 hours.
- Vomiting occurs in about 75% of patients and affords variable relief in 50%.
- RUQ abdominal tenderness, often with guarding and rebound pain, are seen.
- A palpable gallbladder is present in about 15% of cases.
- Jaundice is present in 25% of cases and suggests possible choledocholithiasis.
- Fever is usually present.
What is the differential diagnosis of cholecystitis?
Differential Diagnosis

- Perforated peptic ulcer
- Acute pancreatitis
- Appendicitis
- Perforated colonic carcinoma or diverticulum of hepatic flexure
- Acute hepatitis or liver abscess
- Pneumonia with pleurisy on right side
- Myocardial infarction
- Radicular pain in a T6 to T10 dermatome (e.g., preeruptive zoster)
What are the laboratory and imaging findings in cholecystitis?
Laboratory Tests

- The WBC count, serum aminotransferase level, and alkaline phosphatase level are often elevated.
- Total serum bilirubin may be mildly elevated even in the absence of bile duct obstruction.
- Serum amylase may also be moderately elevated.

Imaging Studies

- Plain films of the abdomen may show radiopaque gallstones in 15% of cases.
- RUQ abdominal ultrasonography may show gallstones but is only 67% sensitive for acute cholecystitis.
- $^{99m}$Tc hepatobiliary imaging (using iminodiacetic acid compounds; HIDA scan) is useful in demonstrating obstructed cystic duct; the test is very sensitive and specific for acute cholecystitis.
What are the treatments for cholecystitis?
Medications

- Cholecystitis usually subsides on a conservative regimen that includes IV fluids, antibiotics, and analgesics.

Surgery

- Cholecystectomy (generally laparoscopic) should be performed within 2 to 4 days because of the high risk of recurrent attacks.
- Surgical treatment of chronic cholecystitis is the same as for acute cholecystitis.

Therapeutic Procedures

- Ultrasound-guided aspiration, percutaneous cholecystostomy, or an endoscopic stent may postpone or avoid need for surgery in selected patients.
- Cholecystectomy is mandatory when there is evidence of gangrene or perforation.
A 63-year-old man with a long history of alcohol use presents with a 6-month history of increasing abdominal girth, easy bruisability and worsening fatigue. He denies any history of gastrointestinal (GI) bleeding. He drinks three or four cocktails a night but says he is trying to cut down. Physical examination reveals a cachectic man who appears older than his stated age. His blood pressure is 108/70 mm Hg. His scleras are anicteric. His neck veins are flat, and chest examination demonstrates gynecomastia and multiple spider angiomas. There is a protuberant abdomen with detectable fluid wave, shifting dullness, and enlarged spleen. The liver edge is difficult to appreciate. He has trace pitting pedal edema. Laboratory studies show anemia, mild thrombocytopenia, and elevated prothrombin time. Abdominal ultrasonography confirms a shrunken, heterogeneous liver, ascites, and splenomegaly.

What are the salient features of this patient’s problem? How do you think through his problem?
Salient features: Chronic alcohol use; ascites; coagulopathy and thrombocytopenia; edema, gynecomastia; spider angiomas; splenomegaly; ultrasound showing a shrunken liver

*How to think through:* Portal hypertension, inadequate protein synthesis, and inadequate clearance of circulating estrogens explain most of this patient’s symptoms and signs. Which elements are caused by portal hypertension? (Ascites, edema, splenomegaly, and thrombocytopenia caused by splenic sequestration.) What other complications of portal hypertension is he at risk for? (Infection, e.g., bacterial peritonitis, hepatocellular carcinoma [HCC], hepatorenal syndrome, encephalopathy.) How would you determine if he has encephalopathy? What would you expect his liver enzymes to show? His liver biopsy? Besides chronic heavy alcohol intake, what are other major risk factors for cirrhosis? Is his cirrhosis currently compensated or decompensated? How should his ascites be treated? (Sodium restriction; loop diuretic; aldosterone receptor blocker; large-volume paracentesis). What data are needed to establish his prognosis? (Serum creatinine, albumin, bilirubin; imaging to evaluate for HCC and endoscopy for esophageal varices.) What scoring systems can help establish disease severity? Is he a candidate for liver transplantation? (Not while actively drinking alcohol.)
What are the essentials of diagnosis and general considerations regarding cirrhosis?
Essentials of Diagnosis
- End result of injury that leads to both fibrosis and nodular regeneration
- May be reversible if the cause is removed
- Symptoms from hepatic cell dysfunction, portosystemic shunting, and portal hypertension

General Considerations
- Risk factors: chronic viral hepatitis, alcohol, drug toxicity, autoimmune and metabolic liver disease; may have multiple synergistic risk factors
- Three clinical stages: compensated, compensated with varices, and decompensated (ascites, variceal bleeding, encephalopathy, or jaundice)
- Patterns include micronodular, macronodular, and mixed cirrhosis
- Micronodular cirrhosis: most common, with regenerating nodules smaller than 1 mm, typical of alcoholic liver disease (Laennec cirrhosis)
- Macronodular cirrhosis: nodules are several centimeters large; may be posthepatic or follow episodes of massive necrosis and stromal collapse
What are the symptoms and signs of cirrhosis?
Symptoms and Signs

- Can be asymptomatic for long periods; symptoms are usually insidious in onset but may be abrupt.
- Weakness, fatigability, disturbed sleep, muscle cramps, anorexia, and weight loss are common.
- Jaundice—usually not an initial sign—is mild at first, increasing in severity.
- Abdominal pain from hepatic enlargement and stretching of Glisson capsule or from ascites.
- Hematemesis is the presenting symptom in 15% to 25%.
- Fever usually reflects associated alcoholic hepatitis, spontaneous bacterial peritonitis, or intercurrent infection.
- Erectile dysfunction, loss of libido, sterility, and gynecomastia in men; amenorrhea in women.
- Liver may be enlarged and firm with a sharp or nodular edge; splenomegaly occurs in 35% to 50%.
- Ascites, pleural effusions, peripheral edema, and ecchymoses are late findings.
- Encephalopathy is characterized by day–night reversal, asterixis, tremor, dysarthria, delirium, drowsiness and coma; encephalopathy occurs late unless precipitated by an acute insult.
- Skin findings include spider nevi on the upper half of the body, palmar erythema, dilated superficial veins of the abdomen, and glossitis or cheilosis from vitamin deficiencies.
What is the differential diagnosis of cirrhosis?
Differential Diagnosis

- Chronic viral hepatitis
- Alcoholism
- Nonalcoholic fatty liver disease
- Cryptogenic
- Metabolic (e.g., hemochromatosis, α₁-antiprotease deficiency, Wilson disease)
- Primary biliary cirrhosis
- Secondary biliary cirrhosis (chronic obstruction caused by stone, stricture, neoplasm)
- Congestive heart failure or constrictive pericarditis
- Hereditary hemorrhagic telangiectasia
What are the laboratory, imaging, and procedural findings in cirrhosis?
Laboratory Tests
- Macrocytic anemia from suppression of erythropoiesis by alcohol, folate deficiency, hypersplenism, hemolysis, and blood loss from the GI tract
- Thrombocytopenia is secondary to marrow suppression, sepsis, folate deficiency, and splenic sequestration
- Modest elevations of serum aspartate aminotransferase (AST), bilirubin, and alkaline phosphatase; serum albumin is low and prothrombin time prolonged from decreased synthetic function

Imaging Studies
- Ultrasonography to assess liver, detect ascites, masses, or portal hypertension

Diagnostic Procedures
- Esophagogastroduodenoscopy confirms the presence of varices
- Liver biopsy
What are the treatments for cirrhosis?
Medications

- Ascites and edema: restrict sodium and fluid intake; spironolactone and furosemide for diuresis
- Anemia: folic acid and ferrous sulfate
- Severe hypoprothrombinemia: vitamin K or fresh-frozen plasma if there is bleeding or before surgery
- Liver transplantation is indicated in selected cases of irreversible, progressive liver disease
- Absolute contraindications to transplantation include nonhepatic malignancy, sepsis, and advanced cardiopulmonary disease

Therapeutic Procedures

- Abstinence from alcohol, vitamin and diet supplementation, vaccinations for hepatitis A and B viruses
- Large-volume paracentesis (>5 L) is effective in patients with massive ascites refractory to diuretics or with respiratory compromise
- Transjugular intrahepatic portosystemic shunt (TIPS) reduces ascites and portal hypertension but increases hepatic encephalopathy
A 54-year-old man presents to the clinic for a routine checkup. He is well with no physical complaints. The history is remarkable only for a father with colon cancer at age 55 years. Physical examination findings are normal. Cancer screening is discussed, and the patient is sent home with fecal occult blood testing supplies. The fecal occult blood test results are positive. Subsequent colonoscopy reveals a villous adenoma as well as a 2-cm carcinoma.

What are the salient features of this patient’s problem? How do you think through his problem?
Salient features: Family history of colon cancer at similar age; routine screening after age 50 years; positive fecal occult blood test result; subsequent colonoscopy with both an adenoma and a carcinoma

How to think through: What are the recommended colon cancer screening modalities? When does screening start for a patient with no family history of polyposis or colon cancer? When should screening have begun for the patient in this case? (10 years earlier than the age at which his father was diagnosed.) What pathological characteristics of polyps found on colonoscopy are considered high risk for progression to cancer? (Tubular adenoma, villous adenoma.) In addition to family history, what are the other known risk factors for colon cancer? (Inflammatory bowel disease; diets low in fiber and high in red meat and fat; black > white race.) How does right-sided colon cancer present? How does left-sided colon cancer present? What is the next step for this patient? (Computed tomography [CT] scan of the chest, abdomen, and pelvis for preoperative staging.) For which stages of colon cancer is chemotherapy a recommended part of the treatment?
What are the essentials of diagnosis and general considerations regarding colorectal cancer?
Essentials of Diagnosis
- Personal or family history of adenomatous polyps or colorectal cancer are important risk factors
- Symptoms or signs depend on tumor location; proximal colon cancer causes fecal occult blood and anemia, distal colon cancer causes change in bowel habits and hematochezia
- Diagnosis established with colonoscopy

General Considerations
- Second leading cause of death from malignancy in the United States
- Many adenocarcinomas (~50%) occur within reach of detection by flexible sigmoidoscopy
- Most colorectal cancers arise from malignant transformation of an adenomatous polyp (tubular, tubulovillous, or villous adenoma) or serrated polyp (traditional serrated adenoma, or sessile serrated adenoma)
- Up to 5% are caused by polyposis syndromes or hereditary nonpolyposis colorectal cancer
- Risk factors include older age, personal or family history, inflammatory bowel disease (ulcerative colitis and Crohn colitis), high-fat and red meat diets, and race (blacks > whites)
What are the symptoms and signs of colorectal cancer?
Symptoms and Signs

- Adenocarcinomas grow slowly and may be asymptomatic.
- Right-sided colon cancers cause iron-deficiency anemia, fatigue, and weakness from blood loss.
- Left-sided colon cancers cause obstructive symptoms, colicky abdominal pain, changes in bowel habits, constipation alternating with loose stools, and stool streaked with blood.
- Rectal cancers cause rectal tenesmus, urgency, and recurrent hematochezia.
- Weight loss is uncommon unless disease is metastatic.
- Physical examination findings are usually normal except in advanced disease in which a mass may be palpable in the abdomen.
- Hepatomegaly suggests metastatic spread.
What is the differential diagnosis of colorectal cancer?
Differential Diagnosis

- Diverticulosis or diverticulitis
- Hemorrhoids
- Adenomatous polyps
- Ischemic colitis
- Inflammatory bowel disease
- Irritable bowel syndrome
- Infectious colitis
- Iron deficiency from other cause
What are the laboratory, imaging, and procedural findings in colorectal cancer?
Laboratory Tests

- Positive fecal occult blood test results; complete blood cell count may reveal iron-deficiency anemia
- Elevated liver function tests, particularly alkaline phosphatase, are suspicious for metastatic disease
- Carcinoembryonic antigen (CEA) level should normalize after complete surgical resection; persistently elevated levels suggest persistent disease

Imaging Studies

- Barium enema or CT colonography (“virtual colonoscopy”) for initial diagnosis if standard colonoscopy is not available
- Chest, abdominal, and pelvic CT scan for preoperative staging
- Pelvic magnetic resonance imaging and endorectal ultrasonography may guide operative management of rectal cancer

Diagnostic Procedures

- Colonoscopy visualizes the entire colon and permits biopsy of lesions.
- Staging by the TNM (tumor, node, metastasis) system determines therapy and estimates the patient’s long-term survival.
What are the treatments for colorectal cancer?
Medications

- Adjuvant chemotherapy reduces recurrence in stage II disease and increases survival in stage III disease.
- FOLFOX (oxaliplatin, fluorouracil, and leucovorin) is preferred for stage III disease.
- FOLFOX or FOLFIRI (addition of irinotecan to fluorouracil and leucovorin) is used in stage IV (metastatic) disease.
- Biological agents (bevacizumab, cetuximab, and panitumumab) demonstrate further improvement in tumor response rates in stage IV disease.

Surgery

- Resection of the primary colonic or rectal cancer with lymph node removal for staging
- For unresectable rectal cancer, diverting colostomy, radiation therapy, laser fulguration, or placement of an expandable wire stent
- For metastatic disease, resection of isolated liver or lung metastases

Therapeutic Procedures

- Combined adjuvant pelvic radiation and chemotherapy with resection
- Local ablative techniques (cryosurgery, embolization) for unresectable hepatic metastases
A 28-year-old woman arrives in the urgent care clinic complaining of cramping abdominal pain. She has had the pain intermittently over the past 5 months, accompanied by diarrhea. During this time period, she lost 16 lb and had significant malaise. On examination, she has a diffusely tender abdomen, worst in the right lower quadrant (RLQ), but no rebound or guarding. Complete blood count (CBC) reveals anemia, and her serum vitamin B$_{12}$ level is low. Her stool culture and ova and parasites examination results are negative. She is referred for colonoscopy, partly to exclude inflammatory bowel disease (IBD).

What are the salient features of this patient’s problem? How do you think through her problem?
**Salient features:** Chronic cramping abdominal pain and diarrhea; weight loss; malaise; anemia (presumably from poor vitamin B$_{12}$ absorption in the terminal ileum); negative stool test results

**How to think through:** Diarrhea, a common symptom, requires consideration of its time course and a framework for clinical reasoning to determine its cause. This patient has chronic diarrhea. In chronic diarrhea, what are the common pathologic categories to frame the differential diagnosis? (Common causes: infectious, inflammatory, functional, malabsorption, and medication side effects. Less common causes: vasculitis, neuroendocrine tumors; may be explored after the common causes.) What characteristics make IBD likely in this patient? (Chronic abdominal pain; weight loss; and low serum vitamin B$_{12}$ level, indicating possible involvement of the terminal ileum). Is fecal leukocyte testing useful in diagnosis of IBD? (No. Test specificity is poor; fecal leukocytes also occur in infectious diarrhea.) What extraintestinal symptoms and signs would increase your suspicion for IBD? (Fever, uveitis, arthritis, oral ulcers, erythema nodosum.) Ulcerative colitis commonly causes hematochezia, and Crohn disease causes heme-positive stools without gross blood. Her anemia may be caused by anemia of chronic disease, iron deficiency from gastrointestinal blood loss, or vitamin B$_{12}$ deficiency. Do the gross and pathologic colonoscopic findings differ between Crohn disease and ulcerative colitis? (Yes.) What are the most serious complications of Crohn disease? (Fistulae, intraabdominal abscesses, and intestinal obstruction.) What are the common steroid-sparing agents used in the treatment of Crohn disease? (Azathioprine; mercaptopurine; methotrexate; infliximab.)
What are the essentials of diagnosis and general considerations regarding Crohn disease?
Essentials of Diagnosis
- Insidious onset of intermittent bouts of low-grade fever, diarrhea, and RLQ pain
- Radiographic evidence of ulceration, stricturing, or fistulas of the small intestine or colon

General Considerations
- Crohn disease is a transmural process.
- Crohn disease may involve the small bowel only, colon alone, or both; it is most common in the terminal ileum.
- It is a chronic illness with exacerbations and remissions.
- One-third of patients have associated perianal disease (fistulas, fissures, abscesses).
- Fewer than 5% of patients have symptomatic involvement of the upper intestinal tract.
What are the symptoms and signs of Crohn disease?
Symptoms and Signs
- Cramping abdominal pain and tenderness, nonbloody diarrhea, liquid bowel movements
- Intestinal obstruction: postprandial bloating, cramping pains, and loud borborygmi
- Intraabdominal or retroperitoneal abscesses: fevers, chills, abdominal mass, leukocytosis
- Sinus tracts and fistulas: bladder or vagina recurrent infections, cutaneous fistulas
- Perianal disease: skin tags, anal fissures, perianal abscesses and fistulas
- Extraintestinal manifestations: arthralgias, arthritis, iritis or uveitis, pyoderma gangrenosum, erythema nodosum, oral aphthous lesions, gallstones, nephrolithiasis
What is the differential diagnosis of Crohn disease?
Differential Diagnosis

- Ulcerative colitis
- Irritable bowel syndrome
- Appendicitis
- *Yersinia enterocolitica* enteritis
- Mesenteric adenitis
- Intestinal lymphoma
- Segmental colitis caused by ischemic colitis, tuberculosis, amebiasis, *Chlamydia*
- Diverticulitis with abscess
- Nonsteroidal antiinflammatory drug–induced colitis
What are the laboratory, imaging, and procedural findings in Crohn disease?
Laboratory Tests
- Anemia of chronic inflammation, blood loss, iron deficiency, or vitamin B<sub>12</sub> malabsorption
- Leukocytosis with abscesses; sedimentation rate or C-reactive protein elevated
- Stool for routine pathogens, ova and parasites, leukocytes, fat, and *Clostridium difficile* toxin

Imaging Studies
- Barium upper gastrointestinal series with small bowel follow-through
- Computed tomography enterography or capsule (video) imaging of small intestine

Diagnostic Procedures
- Colonoscopy; biopsy of intestine reveals granulomas in 25%
What are the treatments for Crohn disease?
Medications
- Loperamide, atropine, or tincture of opium for symptomatic diarrhea
- Broad-spectrum antibiotics if bacterial overgrowth or microperforations with exacerbations
- 5-Aminosalicylic acid agents such as mesalamine work for colonic but not small bowel disease
- Ileal-release preparation budesonide
- Corticosteroids such as prednisone are the mainstay for treatment of severe exacerbations
- Immunomodulatory drugs such as azathioprine, mercaptopurine, infliximab, or methotrexate

Surgery
- Indications for surgery: intractability to therapy, intraabdominal abscess, bleeding, obstruction

Therapeutic Procedures
- Diet high in fiber and low in fat and lactose; vitamin B₁₂ supplementation
DIARRHEA  31A

A 62-year-old woman presents to her primary care provider with complaints of 2 weeks of diarrhea, starting after a recent hospitalization for pneumonia. She describes the diarrhea as watery stool mixed with small amounts of blood, large in volume, and occurring seven to 10 times per day. She was treated in the hospital with antibiotics for her pneumonia and for this diarrheal episode received a recent course of a ciprofloxacin from an urgent care clinic without resolution. On physical examination, she has dry mucous membranes and a diffusely tender abdomen.

What are the salient features of this patient’s problem? How do you think through her problem?
**Salient features:** Frequent stools; 2-week time course; recent hospitalization and antibiotic use; large-volume watery stool with blood; no resolution with ciprofloxacin; dehydration and abdominal tenderness

**How to think through:** Acute diarrhea is defined as occurring for less than 2 weeks. Given that this patient was recently hospitalized and received two courses of antibiotics, what are the most likely causes of her diarrhea? (Direct medication toxicity vs. infectious diarrhea, specifically, *C. difficile* colitis or another hospital-acquired pathogen.) When after antibiotic exposure does diarrhea caused by *C. difficile* typically begin? (5–10 days, although the interval can be up to several weeks.) What are the next diagnostic steps? (Send *C. difficile* toxin assay immediately Stool culture for *Campylobacter*, *Shigella*, and *Salmonella* is reasonable. There are no risk factors for parasitic disease. A complete blood count and serum electrolytes and creatinine should be sent.) What is the next treatment step? (Because of the high prevalence of *C. difficile*—up to 20% of hospitalized patients are carriers—and the potential severity of the complications, empiric antibiotic treatment for *C. difficile* is appropriate. Her dry mucous membranes on examination suggest dehydration, and based on her vital signs and overall assessment, readmission to the hospital for supportive care should be strongly considered.) What are the serious sequelae of *C. difficile* colitis? (Fulminant colitis with systemic toxicity; toxic megacolon.) What clinical signs would prompt imaging and escalation of care? (High fever, severe pain, leukocytosis [white blood cell count of 15,000/mcL is typical for mild to moderate disease; 40,000/mcL is more consistent with fulminant disease], and shock.)
What are the essentials of diagnosis and general considerations regarding diarrhea?
Essentials of Diagnosis

- Acute diarrhea has a duration of less than 2 weeks; chronic diarrhea is present for more than 4 weeks.
- Traveler’s diarrhea is usually a benign, self-limited disease occurring about a week into travel.

General Considerations

- Acute diarrhea is most commonly caused by infectious agents, bacterial toxins, or drugs.
- Recent exposures, ingestions, medical history, and travel may suggest causes of diarrhea.
- Inflammatory diarrhea is distinguished from noninflammatory diarrhea by the presence of fecal blood and leukocytes.
- Medications that can commonly cause diarrhea include metformin, allopurinol, orlistat, selective serotonin reuptake inhibitors, cholinesterase inhibitors, proton pump inhibitors, and nonsteroidal antiinflammatory drugs.
- Osmotic diarrheas resolve during fasting; secretory diarrheas do not.
- Immunocompromised patients are susceptible to many infectious causes of diarrhea.
- Traveler’s diarrhea is a risk factor for development of irritable bowel syndrome.
What are the symptoms and signs of diarrhea?
Symptoms and Signs

- Increased stool frequency or liquidity
- Physical examination may reveal abdominal tenderness or peritonitis
- When the cause is invasive bacterial pathogens (e.g., *Shigella, Campylobacter, Salmonella*), stools may be bloody, and fever may be present
- Osmotic diarrheas: abdominal distention, bloating, flatulence
- Secretory diarrhea: high-volume, watery diarrhea; dehydration; electrolyte imbalance
- Inflammatory conditions: abdominal pain, fever, weight loss, hematochezia
- Malabsorption syndromes: weight loss, steatorrhea, nutritional deficiencies
What is the differential diagnosis of diarrhea?
Differential Diagnosis

Acute Diarrhea

- Infectious: viruses (Norwalk, rotavirus, adenovirus), preformed toxin (*Staphylococcus aureus*, *Bacillus cereus*, *Clostridium perfringens*), toxin production (*enterotoxigenic Escherichia coli*, *Vibrio cholera*), protozoa (*Giardia lamblia, Cryptosporidium, Cyclospora, Isospora*), invasive or inflammatory (*Shigella, Salmonella, Campylobacter, E. coli O157:H7, C. difficile*)
- Noninfectious: drugs, antibiotics, inflammatory bowel disease, laxative abuse, radiation colitis

Chronic Diarrhea

- Osmotic: lactase deficiency, medications (antacids, lactulose, sorbitol, olestra), factitious
- Secretory: hormonal (carcinoid, VIPoma, medullary thyroid carcinoma, adrenal insufficiency)
- Inflammatory conditions: inflammatory bowel disease, microscopic colitis, radiation colitis
- Malabsorption: celiac sprue, small bowel resection, pancreatic insufficiency, bacterial overgrowth, reduced bile salts
- Motility disorders: irritable bowel syndrome, postsurgical, systemic disease such as diabetes mellitus
- Chronic infections: giardiasis, amebiasis, strongyloidiasis
What are the laboratory, imaging, and procedural findings in diarrhea?
Laboratory Tests
- Often self-limited, but prompt evaluation is warranted with fever, bloody diarrhea, abdominal pain, dehydration, immunocompromised or frail older patients, or health care-associated diarrhea
- Stool cultures, ova and parasites, fecal leukocytes, complete blood count, serum electrolytes, albumin, thyroid-stimulating hormone
- If malabsorption suspected, obtain serum folate, vitamin B\textsubscript{12}, iron, vitamin A and D levels, prothrombin time or international normalized ratio
- Stool \textit{C. difficile} toxin assay if recent history of antibiotic exposure or hospitalization
- Rectal swab cultures in sexually active patients with suspected proctitis
- Serologic testing for celiac sprue with IgA tissue transglutaminase or anti-endomysial antibody
- 24-hour stool collection and fecal fat may help with chronic diarrhea to elucidate cause

Imaging Studies
- Abdominal computed tomography for suspected chronic pancreatitis, pancreatic cancer, neuroendocrine tumors

Diagnostic Procedures
- Sigmoidoscopy or colonoscopy with mucosal biopsy
What are the treatments for diarrhea?
**Medications**

- Patients with bloody diarrhea, high fever, or systemic toxicity should not receive antidiarrheal medications
- Opioids, loperamide, bismuth, or diphenoxylate with atropine are effective for symptomatic treatment
- Octreotide subcutaneously for secretory diarrheas caused by neuroendocrine tumors
- Cholestyramine resin for patients with bile salt-induced diarrhea
- Empiric antibiotic treatment with fluoroquinolones, azithromycin, doxycycline, or trimethoprim-sulfamethoxazole
- Specific antimicrobial treatment for shigellosis, cholera, salmonella, *C. difficile*, giardiasis
- Antibiotics are not recommended in nontyphoid *Salmonella, Campylobacter, Aeromonas, Yersinia*, or *E. coli* O157:H7 infection except in severe disease

**Therapeutic Procedures**

- Bland diet with avoidance of high-fiber foods, fats, mild products, caffeine, and alcohol
- Rehydration with oral electrolyte solutions (e.g., Pedialyte, Gatorade) or intravenous fluids
A 53-year-old man comes to the emergency department with a 3-hour history of bright red blood per rectum. The man states that he had been feeling well until 3 hours before when he had the sudden urge to defecate and passed a large amount of bright red blood that seemed to fill the toilet bowl. After the initial episode, he passed similar amounts of blood mixed with stool four more times. He is feeling lightheaded but denies abdominal pain, nausea, vomiting, hematemesis, and melena. He had a similar but less severe episode some years ago that resolved quickly without treatment. His medical history includes diverticulosis coli, diagnosed on a prior computed tomography scan. On physical examination, his heart rate is 130 beats/min.

What are the salient features of this patient’s problem? How do you think through his problem?
**Salient features:** Hematochezia (recurrent episodes); no melena; painless; history of diverticulosis coli and prior episode of self-limited bleeding; symptoms and signs of volume depletion (lightheadedness, tachycardia)

**How to think through:** Gastrointestinal (GI) bleeding is common, and rapid initial triage is essential. What single feature in the case indicates the need for urgent management, and what is your first priority? (The heart rate of 130 beats/min indicates hypovolemia; rapid intravenous [IV] access is needed.) Would a normal hematocrit reassure you that a hemorrhage is insignificant? (No. The hematocrit in acute blood loss is often normal.) Are lower GI sources of blood loss more or less common than upper GI sources? Do they generally present higher or lower risk of death? (Lower GI sources are less common and generally less morbid.) What features make a lower GI source more likely in this case? (Bright red blood; history of diverticulosis coli.) What are the common causes of lower GI bleeding, and which of these fit with the data in this case? Would you assess risk factors for upper GI bleeding as well? (Yes. A brisk upper GI bleed may appear as red blood per rectum.) If hematochezia continues with persistent tachycardia despite transfusions, what are further diagnostic and treatment options? (Rapid purge colonoscopy and angiography and embolization by interventional radiology.) Is intervention typically needed in lower GI bleeding? (No. The majority of lower GI bleeds stop spontaneously. Supportive care and subsequent colonoscopy are the more common course.)
What are the essentials of diagnosis and general considerations regarding lower gastrointestinal bleeding?
Essentials of Diagnosis

- Hematochezia is usually present, although 10% of hematochezia is caused by an upper GI source.
- Stable patients can be evaluated by colonoscopy.
- Massive active bleeding calls for evaluation with sigmoidoscopy, upper endoscopy, angiography, or nuclear bleeding scan.

General Considerations

- Lower GI bleeding is defined as that arising below the ligament of Treitz (i.e., small intestine or colon; ≤95% of cases arise in the colon).
- Lower GI bleeding is less common than upper GI bleeding and tends to be more benign.
- Spontaneous cessation occurs in more than 85%; the hospital mortality rate is less than 4%.
- The most common causes in patients younger than age 50 years are infectious colitis, anorectal disease, and inflammatory bowel disease.
- The most common causes in patients older than age 50 years are diverticulosis coli (50%), colonic vascular ectasias, neoplasms, ischemia, varices, and ulcers.
- In 20% of cases, no source of bleeding can be identified.
What are the symptoms and signs of lower gastrointestinal bleeding?
Symptoms and Signs

- Brown stools mixed or streaked with blood suggest a rectosigmoid or anal source.
- Maroon stools suggest a right colon or small intestine source.
- Black stools (melena) suggest a source proximal to the ligament of Treitz, but dark maroon stools arising from small intestine or right colon may be misinterpreted as “melena.”
- Bright red blood per rectum with upper GI bleeding is almost always in the setting of massive hemorrhage with shock.
- Bloody diarrhea associated with cramping abdominal pain, urgency, or tenesmus suggests inflammatory bowel disease (especially ulcerative colitis), infectious colitis, or ischemic colitis.
- Diverticular bleeding is acute, painless, and usually subsides spontaneously, although it may recur.
- Vascular ectasias (angiodyplasias) cause painless occult blood loss, melena, or hematochezia.
- Neoplasms cause chronic occult blood loss or intermittent anorectal hematochezia.
- Anorectal disease often produces small amounts of bright red blood on the toilet paper or blood streaking of the stool.
What is the differential diagnosis of lower gastrointestinal bleeding?
Differential Diagnosis

- Diverticulosis coli
- Vascular ectasias (angiodyplasias), such as idiopathic arteriovenous malformations, CREST (calcinosis, Raynaud syndrome, esophageal dysmotility, sclerodactyly, and telangiectasia) syndrome, hereditary hemorrhagic telangiectasias
- Colonic polyps
- Colorectal cancer
- Inflammatory bowel disease (ulcerative colitis, Crohn disease)
- Hemorrhoids
- Anal fissure
- Ischemic colitis
- Infectious colitis
- Radiation colitis or proctitis
- Nonsteroidal antiinflammatory drug–induced ulcers of the small bowel or right colon
What are the laboratory, imaging, and procedural findings in lower gastrointestinal bleeding?
Laboratory Tests
- Complete blood cell count, platelet count, international normalized ratio, type and cross-match for transfusion
- Serum creatinine, blood urea nitrogen

Imaging Studies
- Nuclear technetium-labeled red blood cell scan may be helpful in patients with significant active bleeding but is often nondiagnostic
- Selective mesenteric angiography in patients with massive bleeding or positive technetium scans

Diagnostic Procedures
- Nasogastric tube aspiration or upper endoscopy to exclude upper tract source
- Anoscopy
- Colonoscopy in patients in whom bleeding has ceased and in patients with moderate active bleeding (often after rapid purge with polyethylene glycol solution)
- Small intestine push enteroscopy or video capsule imaging in patients with unexplained recurrent hemorrhage of obscure origin suspected as originating from the small intestine
What are the treatments for lower gastrointestinal bleeding?
**Surgery**
- Surgery is indicated in patients with ongoing bleeding that requires more than 6 units of blood transfusion within 24 hours or more than 10 total units in whom endoscopic or angiographic therapy has failed
- Limited resection of the bleeding segment of small intestine or colon, if possible
- Total abdominal colectomy with ileorectal anastomosis if the bleeding site cannot be precisely identified

**Therapeutic Procedures**
- Excellent vascular access with (usually) two 18-gauge (or larger) peripheral IV lines
- Volume repletion with IV fluids
- Close monitoring of blood counts and coagulation panel with transfusion support as needed
- Therapeutic colonoscopy: high-risk lesions (e.g., diverticulum with active bleeding or a visible vessel; vascular ectasia) can be treated endoscopically with saline or epinephrine injection, cautery (bipolar or heater probe), or application of metallic clips or bands
- Angiography with selective embolization achieves immediate hemostasis in more than 95% of patients when a bleeding lesion is identified
A 74-year-old man with severe osteoarthritis presents to the emergency department reporting two episodes of melena (black stools) without hematochezia (bright red blood in the stools) or hematemesis (bloody vomitus). He takes 600 mg of ibuprofen three times a day to control his arthritis pain. He denies alcohol use. On examination, his blood pressure is 150/70 mm Hg, and his resting pulse is 96 beats/min. His epigastrium is minimally tender to palpation. Rectal examination reveals black tarry stool in the vault, grossly positive for occult blood. Endoscopy demonstrates a 3-cm gastric ulcer. *Helicobacter pylori* is identified on biopsies of the ulcer site.

What are the salient features of this patient’s problem? How do you think through his problem?
**Salient features:** Melena; nonsteroidal antiinflammatory drug (NSAID) use; mild tachycardia from anemia; tender epigastrium, stool occult blood positive; endoscopy showing gastric ulcer; biopsy positive for *H. pylori*

**How to think through:** Upper gastrointestinal (GI) bleeding is a common clinical problem, and rapid initial triage is essential. As soon as melena is confirmed by physical examination, you must determine if the patient is hemodynamically stable. What is the most sensitive marker of a hemodynamically significant hemorrhage? (An elevated heart rate.) What are key factors in determining if an urgent upper endoscopy is indicated? (Evidence of hemodynamic instability; ongoing bleeding.) How could you assess ongoing hemorrhage? (Nasogastric lavage.) Does hematochezia rule out the upper GI tract as a bleeding source? (No. A brisk upper GI tract bleed may appear as red blood.) Would a normal hematocrit reassure you that a hemorrhage is insignificant? (No.) What is the first priority if you suspect a significant GI bleed? (Intravenous [IV] access.) What are important risk factors to consider for upper GI bleeding? (Alcohol use and other risk factors for cirrhosis, NSAID use, retching [Mallory-Weiss tear], *H. pylori* risk factors, and symptoms suggesting gastric cancer.) What raises the likelihood of *H. pylori*? (Patients born in an endemic country; older age.) How is *H. pylori* treated?
What are essentials of diagnosis and general considerations regarding upper gastrointestinal bleeding?
Essentials of Diagnosis

- Melena or hematemesis; hematochezia can occur in large, brisk upper GI tract bleeds.
- Use volume (hemodynamic) status to determine the severity of blood loss; hematocrit is a poor early indicator of blood loss.
- Endoscopy is diagnostic and may be therapeutic.

General Considerations

- Hematemesis is either bright red blood or brown “coffee grounds” material.
- Melena develops after as little as 50 to 100 mL of blood loss.
- Hematochezia requires more than 1000 mL of blood loss.
- Upper GI bleeding is self-limited in 80% of cases; urgent medical therapy and endoscopic evaluation are required in the remainder.
- Peptic ulcers account for about 50% of cases; variceal bleeding accounts for 10% to 20% of cases.
What are the symptoms and signs of upper gastrointestinal bleeding?
Symptoms and Signs

- Signs of chronic liver disease implicate bleeding caused by portal hypertension, but a different lesion is identified in 25% of patients with cirrhosis.
- Dyspepsia, NSAID use, or history of previous peptic ulcer suggests peptic ulcer disease.
- Heavy alcohol ingestion or retching suggests a Mallory-Weiss tear.
What is the differential diagnosis of upper gastrointestinal bleeding?
Differential Diagnosis

- Hemoptysis
- Peptic ulcer disease
- Esophageal or gastric varices
- Erosive gastritis (e.g., NSAIDs, alcohol, stress)
- Mallory-Weiss syndrome
- Portal hypertensive gastropathy
- Vascular ectasias (angiodyplasias), such as idiopathic arteriovenous malformation, CREST (calcinosis, Raynaud syndrome, esophageal dysmotility, sclerodactyly, and telangiecasis) syndrome, hereditary hemorrhagic telangiectasias
- Gastric cancer
- Rare causes include erosive esophagitis, duodenal varices, aortoenteric fistula, Dieulafoy lesion (aberrant gastric submucosal artery), hemobilia (from hepatic tumor, angioma, penetrating trauma, pancreatic cancer, and hemosuccus pancreaticus [pancreatic pseudoaneurysm])
What are the laboratory and procedural findings in upper gastrointestinal bleeding?
Laboratory Tests
- Complete blood cell count, platelet count, prothrombin time or international normalized ratio (INR)
- Serum creatinine and liver enzymes
- Blood typing and screening or cross-matching
- Hematocrit is not a reliable indicator of the severity of acute bleeding

Diagnostic Procedures
- Assess volume (hemodynamic) status using blood pressure, heart rate, and postural hypotension.
- Upper endoscopy should be done after the patient is hemodynamically stable to identify the source of bleeding, determine risk of rebleeding, guide triage, and render endoscopic therapy.
- Consider biopsy for *H. pylori* at time of endoscopy.
What are the treatments for upper gastrointestinal bleeding?
Medications
- IV proton pump inhibitor (e.g., esomeprazole or pantoprazole) for those admitted
- High doses of oral proton pump inhibitors may also be effective
- Octreotide bolus and continuous drip for bleeding related to portal hypertension
- Terlipressin may be preferred to octreotide in countries where available

Therapeutic Procedures
- Insert two 18-gauge or larger IV lines, fluid repletion as needed for hemodynamics
- Nasogastric tube placed for aspiration and serial monitoring of blood counts
- Packed red blood cells to maintain a hemoglobin of 6 to 10 g/dL, platelets to keep count above 50,000/mcL, and fresh-frozen plasma for patients with coagulopathy (INR >1.8)
- Transfuse blood in patients with brisk active bleeding regardless of the hematocrit
- Uremic patients with active bleeding should be given desmopressin (DDAVP)
- Endoscopic therapy such as cautery, injection of a sclerosant or epinephrine, or application of a rubber band or metallic clips
- Consider intraarterial embolization or transvenous intrahepatic portosystemic shunts (TIPS) procedures in those for whom endoscopic therapy has failed
A 27-year-old woman presents to her primary care clinician complaining of nausea and vomiting. She returned 1 week ago from an international trip to South America where she ate at local restaurants and food carts. On physical examination, her skin is jaundiced, her abdomen is tender to palpation in the right upper quadrant (RUQ), and there is mild hepatomegaly. Serum bilirubin and aminotransferases are elevated. Anti–hepatitis A virus (HAV) IgM antibody is positive.

What are the salient features of this patient’s problem? How do you think through her problem?
Salient features: Nausea, vomiting; recent travel with possibly unsanitary food exposure; jaundice; tender abdomen; hepatomegaly; elevated serum bilirubin and aminotransferase tests; positive anti-HAV IgM

How to think through: Acute nausea and vomiting in a returning traveler can be attributable to infectious gastroenteritis, but the overlap of nausea and jaundice places hepatitis high in the differential diagnosis. When considering hepatitis of any cause, what risk factors should be assessed? (Acetaminophen use, alcohol use, possible Amanita mushroom consumption [toxin induced], sexual risk factors—hepatitis B virus [HBV] > HAV > hepatitis C virus [HCV]—injection drug use, tattoos, or blood transfusion [HBV, HCV.]) The duration of travel and of her symptoms should be elicited. The incubation period of the hepatitis viruses varies, and will help narrow the differential diagnosis. All can cause the acute symptoms seen in this patient. What viral hepatitis serologies are detectable during the acute illness and would be most informative here? (Anti-HAV IgM; HBV surface antigen [HBsAg] and anti-HBc IgM; anti-HCV and, if a high suspicion, assay for HCV RNA.) If all of these study results are negative in this patient, what other infectious causes of hepatitis should be considered? (Mononucleosis [Epstein-Barr virus], cytomegalovirus [CMV], leptospirosis, brucellosis, yellow fever.) Would a serum alanine aminotransferase level above 1000 IU/dL or a bilirubin level above 8 mg/dL suggest that the diagnosis of viral hepatitis be reconsidered? (No. this degree of elevation is common.) How should she be managed? (Supportive care, intravenous [IV] hydration and glucose if needed, avoidance of alcohol and hepatotoxic medications.) What is the likelihood of developing fulminant hepatic failure? (Very rare except in patients with underlying HCV or cirrhosis.) Hand washing by the patient and care providers is important.
What are the essentials of diagnosis and general considerations regarding hepatitis?
Essentials of Diagnosis

- Prodrome of anorexia, nausea, vomiting, malaise, aversion to smoking
- Fever, enlarged and tender liver, jaundice
- Normal to low white blood cell count; markedly elevated aminotransferases
- Hepatitis C is often asymptomatic

General Considerations

- Transmission of HAV is by the fecal–oral route; incubation averages 30 days.
- HBV contains an inner core protein (hepatitis B core antigen [HBcAg]) and outer surface coat (HBsAg).
- Coinfection with HCV is common in persons infected with HIV.
- HBV is usually transmitted by blood, sexual contact, or vertical transmission; it has an insidious onset.
- HCV is mostly transmitted by injection drug use, but body piercing, tattoos, and hemodialysis are risk factors.
What are the symptoms and signs of hepatitis?
Symptoms and Signs

- Onset may be abrupt or insidious
- Malaise, myalgia, arthralgia, easy fatigability, upper respiratory symptoms, and anorexia
- Nausea and vomiting are frequent, and diarrhea or constipation may occur
- Abdominal pain mild and constant in the RUQ
- Jaundice, hepatomegaly, splenomegaly, acholic stools
- Enlarged cervical or epitrochlear lymph nodes
- HCV infection may be asymptomatic
What is the differential diagnosis of hepatitis?
Differential Diagnosis

- Viral: hepatitis A, B, C, D (in the presence of B), E, infectious mononucleosis, CMV, herpes simplex virus, parvovirus B19, yellow fever
- Other infections: leptospirosis, secondary syphilis, brucellosis, Q fever
- Alcoholic hepatitis
- Toxins (predictable): acetaminophen, *Amanita* mushrooms, tetracycline, valproic acid
- Toxins (idiosyncratic): isoniazid, nonsteroidal antiinflammatory drugs, statins, azole antifungals, halothane, ecstasy, kava
- Vascular: right-sided heart failure, shock liver, portal vein thrombosis, Budd-Chiari syndrome
- Metabolic: Wilson disease, acute fatty liver of pregnancy, Reye syndrome
- Autoimmune hepatitis
- Lymphoma or metastatic cancer
What are the laboratory findings in hepatitis?
Laboratory Tests

- Elevated serum aspartate or alanine aminotransferase is followed by elevated bilirubin and alkaline phosphatase.
- Prolongation of prothrombin time indicates synthetic dysfunction and severe disease.
- Anti-HAV IgM indicates acute illness; IgG may indicate previous exposure or immunity if not associated with symptoms.
- HBsAg (surface antigen) indicates chronic HBV infection in patients without acute disease.
- Anti-HBs (surface antibody) alone indicates HBV immunity because the vaccine has only surface proteins and no core proteins.
- Anti-HBc (core antibody) indicates HBV exposure and is diagnostic in acute hepatitis.
- HBV DNA can be used for prognosis and consideration of treatment.
- Antibodies to HCV are first used for diagnosis; HCV RNA assay confirms diagnosis and establishes disease activity.
What are the treatments for hepatitis?
Medications

- IV hydration and glucose can be given if needed; parenteral nutrition can be used if nausea and vomiting are pronounced or if oral intake is low for a prolonged period.
- Corticosteroids produce no benefit.
- Chronic hepatitis B can be treated with antivirals (entecavir, tenofovir, lamivudine, adefovir, and telbivudine) in selected patients.
- In hepatitis C, treatment with interferon alfa or peginterferon with or without the addition of ribavirin can be considered when HCV RNA has not cleared from serum in 3 to 4 months (doses as for chronic hepatitis C).

Therapeutic Procedures

- Avoidance of strenuous physical exertion, alcohol, and hepatotoxic agents
A 58-year-old woman presents to the emergency department with a 2-day history of epigastric abdominal pain, fever, anorexia, and nausea. Serum amylase and lipase levels are markedly elevated. Two months ago, she had an episode of right upper quadrant abdominal pain and ultrasound imaging demonstrated multiple gallstones without gallbladder wall edema. She is admitted to the hospital. On hospital day 3, the physician is called urgently to evaluate her for hypotension and shortness of breath. Respiratory failure ensues, requiring endotracheal intubation and mechanical ventilation. A chest radiograph and severe hypoxia support the diagnosis of acute respiratory distress syndrome (ARDS).

What are the salient features of this patient’s problems? How do you think through her problems?
Salient features: Fever; epigastric abdominal pain; anorexia, nausea, history of gallstones; markedly elevated serum lipase and amylase levels; associated ARDS

How to think through: Undifferentiated abdominal pain is a common clinical challenge. In this case, markedly elevated serum amylase and lipase levels point to a diagnosis of acute pancreatitis. What are the leading causes of acute pancreatitis? (Alcohol abuse, gallstones, hypertriglyceridemia, medications, pancreatic duct stricture or obstruction, pancreatic or other malignancy, or compressive adenopathy.) Given her age, sex and prior evaluation, cholelithiasis is most likely. Nevertheless, alcohol use should be assessed. What does initial treatment entail? (Nothing by mouth, intravenous [IV] hydration, and pain control.) A major challenge is to identify the 15% to 25% of cases that will progress to severe, necrotizing pancreatitis. Predictive models, such as the Ranson criteria, are used but have low specificity. Should the patient have imaging when her condition deteriorates? (Yes. Imaging may be omitted at presentation if the diagnosis is clear cut, but worsening clinical status is an indication for computed tomography [CT] or magnetic resonance cholangiopancreatography [MRCP]. Both can distinguish necrosis from edema.) Does development of shock and ARDS indicate necrosis or infection? (Necrosis is likely; a cytokine-mediated systemic inflammatory response syndrome can precipitate these complications even in the absence of infection.) What are the treatments for severe pancreatitis? (Opioids; calcium gluconate for tetany; fresh-frozen plasma [FFP] for coagulopathy with bleeding; vasopressors for shock; nutritional support; antibiotics and debridement for infection.)
What are the essentials of diagnosis and general considerations regarding acute pancreatitis?
Essentials of Diagnosis
- Abrupt onset of deep epigastric pain, often with radiation to the back
- Nausea, vomiting, sweating, weakness, fever, abdominal tenderness and distention
- Leukocytosis, elevated serum amylase, elevated serum lipase
- History of previous episodes, often related to alcohol intake

General Considerations
- Most often caused by a passed gallstone, usually less than 5 mm in diameter, or heavy alcohol intake
- Rarely, may be the initial manifestation of a pancreatic or ampullary neoplasm
- Pathogenesis may include edema or obstruction of the ampulla of Vater, bile reflux into pancreatic ducts, and direct injury of the pancreatic acinar cells
What are the symptoms and signs of acute pancreatitis?
Symptoms and Signs

- Sometimes a history of alcohol intake or a heavy meal immediately preceding the attack or a history of milder similar episodes or biliary pain in the past
- Severe, epigastric abdominal pain, abrupt in onset, usually radiating to the back
- Pain often made worse by walking and lying and better by sitting and leaning forward
- Upper abdominal tenderness, most often without guarding, rigidity, or rebound
- Abdominal distention and absent bowel sounds from paralytic ileus
- Nausea and vomiting; weakness, sweating, and anxiety in severe attacks
- Fever of 38.4° to 39.0°C; tachycardia; hypotension (even true shock); pallor; and cool, clammy skin if severe
What is the differential diagnosis of acute pancreatitis?
Differential Diagnosis

- Acute cholecystitis
- Acutely perforated duodenal ulcer
- Acute intestinal obstruction
- Leaking aortic aneurysm
- Renal colic and acute mesenteric ischemia
What are the laboratory, imaging, and procedural findings in acute pancreatitis?
Laboratory Tests
- Serum amylase and lipase are increased, usually more than three times normal.
- Leukocytosis, proteinuria, granular casts, glycosuria, hyperglycemia, and elevated bilirubin are present.
- Blood urea nitrogen (BUN) and serum creatinine and alkaline phosphatase may be elevated.
- Hypocalcemia correlates with the severity of disease.

Imaging Studies
- Plain abdominal radiographs may show gallstones, a “sentinel loop,” or the “colon cutoff sign.”
- Ultrasonography may identify gallstones but is otherwise often unhelpful for diagnosis.
- CT can differentiate from other catastrophes and assess prognosis and complications.
- Endoscopic ultrasonography is useful for occult biliary disease (e.g., small stones, sludge).

Diagnostic Procedures
- Endoscopic retrograde cholangiopancreatography (ERCP) can be done if there is associated cholangitis.
What are the treatments for acute pancreatitis?
Medications

- Meperidine intramuscularly as needed for pain
- Nothing by mouth and IV fluids until patient is pain free and has bowel sounds
- Then begin clear liquids and gradually advance to a low-fat diet, as tolerated
- For severe pancreatitis, large amounts of IV fluids to maintain intravascular volume
- IV calcium gluconate for hypocalcemia with tetany
- FFP or serum albumin may be needed for coagulopathy or hypoalbuminemia
- Imipenem, ciprofloxacin and metronidazole, or cefuroxime for pancreatic necrosis or infection

Surgery

- For mild pancreatitis with cholelithiasis, cholecystectomy or cholecystotomy
- Debridement of infected pancreatic necrosis
A 52-year-old man with a 20-year history of alcohol abuse presents to the clinic complaining of recurrent episodes of epigastric and left upper quadrant (LUQ) abdominal pain. Over the past month, his pain has become almost continuous; he requests morphine for pain control. Recently, his stool has been bulky and foul smelling. He has a history of alcohol-related acute pancreatitis. Examination reveals a 10-lb weight loss and mild epigastric tenderness to palpation and guarding. Bowel sounds are decreased. Serum amylase and lipase are mildly elevated. A plain abdominal film shows pancreatic calcifications.

What are the salient features of this patient’s problem? How do you think through his problem?
Salient features: Long-standing alcohol abuse; repeated acute pancreatitis episodes; chronic epigastric abdominal pain; bulky and foul-smelling stool (steatorrhea from pancreatic insufficiency); epigastric tenderness; elevated serum amylase and lipase; pancreatic calcifications

How to think through: Epigastric pain has a broad differential diagnosis, highlighting the importance of the history—the pattern and timing of abdominal pain, alcohol use, prior episodes of acute pain, nausea, and anorexia—and careful physical examination. If the serum amylase and lipase levels were normal, could the patient still have chronic pancreatitis? (Yes. Although these enzymes are often mildly elevated in chronic pancreatitis, their sensitivity and utility are far greater in acute pancreatitis.) How could you confirm your diagnosis? (Diagnosis of steatorrhea and pancreatic calcifications on radiography provide sufficient confirmation. Computed tomography [CT], magnetic resonance cholangiopancreatography [MRCP], and endoscopic retrograde cholangiopancreatography [ERCP] are available, if needed.) Should he be assessed for endocrine dysfunction? (Yes. Such patients can develop impaired glucose tolerance and eventually diabetes mellitus.) What lifestyle modification will improve his symptoms? (Abstinence from alcohol; small meals; low-fat diet.) What medication might help? (Pancreatic enzymes.) Are there procedural interventions that might help his symptoms? (ERCP with stenting of the pancreatic duct; sphincterotomy; celiac plexus nerve block.) What complications might arise for this patient? (Opioid addiction; diabetes; pancreatic pseudocyst, abscess or cancer; bile duct stricture; cholestasis; malnutrition; peptic ulcer.)
What are the essentials of diagnosis and general considerations regarding chronic pancreatitis?
Essentials of Diagnosis
- Epigastric pain, steatorrhea, weight loss, abnormal pancreatic imaging

General Considerations
- Chronic pancreatitis occurs most often with alcoholism; the risk increases with the duration and amount of consumption.
- Tobacco smoking may accelerate progression of alcoholic chronic pancreatitis.
- Pancreatitis develops in about 2% of patients with hyperparathyroidism.
- Tropical pancreatitis, related to malnutrition, is a common cause in Africa and Asia.
- A stricture, stone, or tumor obstructing the pancreas can lead to obstructive chronic pancreatitis.
- Autoimmune pancreatitis is associated with hypergammaglobulinemia.
- The pathogenesis may be related to a first episode of acute pancreatitis, which initiates an inflammatory process that results in injury and then fibrosis.
- Genetic factors may predispose to chronic pancreatitis in some cases (e.g., CFTR gene mutations).
What are the symptoms and signs of chronic pancreatitis?
**Symptoms and Signs**

- Persistent or recurrent episodes of epigastric and LUQ pain with referral to the upper left lumbar region may occur.
- Anorexia, nausea, vomiting, constipation, flatulence, and weight loss are common.
- During attacks tenderness over the pancreas, mild muscle guarding, and ileus may be noted.
- Attacks may last only a few hours or as long as 2 weeks; pain may eventually be almost continuous.
- Steatorrhea (as indicated by bulky, foul, fatty stools) may occur late in the course.
What is the differential diagnosis of chronic pancreatitis?
Differential Diagnosis

- Cholelithiasis
- Diabetes mellitus
- Malabsorption from other causes
- Intractable duodenal ulcer
- Pancreatic cancer
- Irritable bowel syndrome
What are the laboratory, imaging, and procedural findings in chronic pancreatitis?
Laboratory Tests

- Serum amylase, lipase, alkaline phosphatase, and bilirubin may be elevated
- Normal amylase and lipase does not exclude the diagnosis even in an acute attack
- Excess fecal fat in stool or pancreatic insufficiency on secretin stimulation
- Genetic tests for the major trypsinogen gene mutations
- Elevated IgG4 levels, antinuclear antibody, and antibodies to lactoferrin and carbonic anhydrase II are often seen in cases of autoimmune pancreatitis

Imaging Studies

- Plain radiographs show calcifications caused by pancreaticolithiasis in 30% of patients.
- CT may show calcifications, ductal dilatation, and heterogeneity or atrophy of the gland.
- MRCP or endoscopic ultrasonography (EUS)

Diagnostic Procedures

- ERCP is the most sensitive study
What are the treatments for chronic pancreatitis?
Medications
- Steatorrhea is treated with pancreatic enzyme supplements at meals.
- H₂-receptor antagonists and proton pump inhibitors may further decrease steatorrhea.
- Pain may be alleviated by the use of pancreatic enzymes or octreotide subcutaneously.
- Autoimmune pancreatitis is treated with prednisone.

Surgery
- Correctable coexistent biliary tract disease should be treated surgically.
- Surgery may drain persistent pseudocysts, treat other complications, or relieve pain.
- In advanced cases, subtotal or total pancreatectomy may be considered as a last resort but has variable efficacy and is associated with a high rate of pancreatic insufficiency and diabetes mellitus.

Therapeutic Procedures
- Institute a low-fat diet, alcohol avoidance; treat associated complications such as diabetes
- Dilation or stenting of the duct via ERCP; sphincterotomy
- Celiac plexus nerve block may be considered
A 43-year-old man presents to the urgent care clinic with bloody diarrhea. He has had five or six stools per day for the past 7 days associated with crampy abdominal pain and a feeling of incomplete emptying of his bowels. He has had similar episodes in the past, although this one is particularly severe. Physical examination shows a diffusely tender abdomen and blood on digital rectal examination. His blood hemoglobin is 8.3 g/dL. Sigmoidoscopy reveals a friable colonic mucosa, and biopsies show inflammation confined to the mucosal surface.

**What are the salient features of this patient’s problem? How do you think through his problem?**
**Salient features:** Bloody diarrhea; abdominal pain and tenesmus; abdominal tenderness; blood on rectal examination; anemia; friable colonic mucosa; colonic mucosal surface, not transmural, inflammation on biopsy

**How to think through:** What is the differential diagnosis here? (Infectious colitis caused by *Escherichia coli* O157:H7, *Shigella*, *Campylobacter*, or *Salmonella* spp.; inflammatory bowel disease [IBD]; ischemic colitis; colon cancer; and diverticulosis.) Although the friable mucosa in ischemic colitis can resemble IBD, this patient is atypically young for ischemic colitis and lacks atherosclerotic risk factors. The tempo does not fit colon cancer. Diverticular bleeding is usually painless. What medical history helps distinguish IBD from infection? (His prior similar episodes favor the diagnosis of IBD.) What extraintestinal symptoms and signs increase suspicion for IBD? (Fever, uveitis, arthritis, ankylosing spondylitis, erythema nodosum, pyoderma gangrenosum, sclerosing cholangitis, thromboembolism.) What studies should be obtained? (A complete blood count [CBC] to assess for anemia; serum electrolytes and creatinine to assess for diarrhea-related dehydration and hypokalemia; stool culture to exclude infection. Without a risk factor [e.g., travel to an endemic region or men who have sex with men], stool ova and parasite testing is low yield. Fecal leukocyte testing is not useful because of poor specificity. Sigmoidoscopy is diagnostic and easier and safer than pancolonoscopy in acute colitis.) How should his IBD be treated? (For mild disease, rectal or oral 5-ASA derivatives (e.g., sulfasalazine); for severe disease, corticosteroids, mercaptopurine, azathioprine, or infliximab.)
What are the essentials of diagnosis and general considerations regarding ulcerative colitis?
Essentials of Diagnosis
- Bloody diarrhea, lower abdominal cramps, fecal urgency
- Anemia, low serum albumin, negative stool culture results
- Sigmoidoscopy is key to diagnosis

General Considerations
- Ulcerative colitis is an idiopathic inflammatory condition that involves the mucosal surface of the colon, resulting in diffuse friability and erosions with bleeding.
- It may involve the rectosigmoid region, left side of the colon, or the entire colon.
- Most affected patients experience periods of symptomatic flare-ups and remissions.
What are the symptoms and signs of ulcerative colitis?
Symptoms and Signs

- Bloody diarrhea, cramps, abdominal pain, fecal urgency and tenesmus
- Tenderness, evidence of peritoneal inflammation, bright red blood on digital rectal examination
- Severity of symptoms depends on severity of disease
- Toxic megacolon can occur with colonic dilatation, signs of toxicity, and risk of perforation
- Extracolonic manifestations occur in 50%: oral ulcers, erythema nodosum, pyoderma gangrenosum, uveitis, spondylitis or sacroiliitis, arthritis, sclerosing cholangitis
What is the differential diagnosis of ulcerative colitis?
Differential Diagnosis

- Infectious colitis: *Salmonella*, *Shigella*, *Campylobacter*, amebiasis, *Clostridium difficile*, enteroinvasive *Escherichia coli*
- Ischemic colitis
- Crohn disease
- Diverticular disease
- Colon cancer
- Antibiotic-associated diarrhea or pseudomembranous colitis
- Infectious proctitis: gonorrhea, *Chlamydia*, herpes, syphilis
- Radiation colitis or proctitis
- Cytomegalovirus colitis in immunocompromised persons
What are the laboratory, imaging, and procedural findings in ulcerative colitis?
Laboratory Tests
• Hemoglobin, sedimentation rate, and serum albumin reflect disease severity
• Stools for bacterial (including *C. difficile*) culture, ova and parasites

Imaging Studies
• Abdominal radiographs; barium enema is not useful and may precipitate toxic megacolon

Diagnostic Procedures
• Sigmoidoscopy establishes the diagnosis.
• Colonoscopy should not be performed in patients with fulminant disease because of the risk of perforation but is recommended after improvement.
What are the treatments for ulcerative colitis?
Medications
- Mesalamine orally or by rectal suppository; balsalazide or sulfasalazine orally
- Corticosteroid therapy and cyclosporine for moderate to severe disease
- Toxic megacolon: broad-spectrum antibiotics, intravenous corticosteroids, infliximab or cyclosporine
- Mercaptopurine, azathioprine, or infliximab for refractory or severe disease

Surgery
- Total proctocolectomy with ileostomy required in 25% of patients
- Indications for surgery include severe refractory disease, perforation, or neoplasia

Therapeutic Procedures
- Regular diet with limited caffeine and gas-producing vegetables; may require NPO (nothing by mouth) status in severe exacerbations
A 53-year-old nulliparous woman presents to her primary care clinician for evaluation of a painless breast lump that she first noted a few months ago. She came for evaluation when she noticed bloody discharge from the ipsilateral nipple. She takes no medications, and her family history is remarkable for her mother and sister having breast cancer. On physical examination, there are a firm 2-cm mass with poorly defined margins in the left breast and firm left axillary lymph nodes.

What are the salient features of this patient’s problem? How do you think through her problem?
Salient features: Nulliparous woman; painless and firm breast lump; nipple discharge; family history of breast cancer in first-degree relatives; ipsilateral firm axillary lymphadenopathy

How to think through: Breast cancer is the second most common cause of cancer death in women and is a major source of morbidity. This woman’s presentation is highly concerning, and prompt evaluation is essential. This patient is nulliparous with a strong family history. What other factors increase a woman’s risk for breast cancer? (Total duration of menses, i.e., early menarche and late menopause; alcohol use, high dietary fat, and lack of exercise; high breast density on mammography.) If the physical examination is accurate, this patient’s presentation is concerning for invasive breast cancer, stage IIIa or greater, as defined by T2 (2-cm mass), N2 (ipsilateral matted axillary lymph nodes), with no comment on possible distant metastasis. Fortunately, fewer than 10% of women present with metastatic disease. How should she be evaluated? (Bilateral mammography and ultrasonography of breast and axilla; core needle biopsy of the mass [preferred over fine-needle biopsy].) What special studies should be conducted on the biopsy tissue? (Assays for hormone receptors and human epidermal growth factor receptor 2 [HER2] expression, both of which guide treatment and prognosis.) Computed tomography (CT), possibly with positron emission tomography (PET), is needed to detect metastases. Treatment will depend on histology, tumor markers, metastatic disease, and comorbidities but may include surgery, chemotherapy, radiation, and hormonal therapy. Should the patient or her family members undergo genetic testing for BRCA1 mutations? (A family history of breast cancer is common because of its prevalence. Although only 10% of breast cancers are associated with inherited genetic mutations, referral to genetic counseling is important in this case because two first-degree relatives had it.)
What are the essentials of diagnosis and general considerations regarding breast cancer?
Essentials of Diagnosis
- Early findings include a single nontender, firm mass or a mammographic abnormality.
- Later findings include skin or nipple retraction, axillary lymphadenopathy, breast enlargement, redness, edema, pain, and fixation of a mass to the skin or chest wall.

General Considerations
- Second most common cancer and cause of death in women
- Risk is higher with advancing age, positive family history, nulliparity or late first pregnancy (after age 30 years), early menarche (before age 12 years) or late natural menopause (after age 55 years), alcohol use, high dietary fat, lack of exercise, high breast density on mammogram, fibrocystic disease when accompanied by proliferative changes, papillomatosis, atypical epithelial hyperplasia on biopsy, history of uterine cancer
- Estimated 85% lifetime risk in women with BRCA1 gene mutations
What are the symptoms and signs of breast cancer?
Symptoms and Signs

- Presenting complaint is a lump (usually painless) in 70%
- Less frequently: breast pain, nipple discharge, erosion, retraction, enlargement, or itching
- With metastatic disease, back or bone pain, jaundice, or weight loss
- Physical findings include nontender, firm or hard mass with poorly delineated margins; skin or nipple retraction or dimpling; breast asymmetry; erosions of nipple epithelium (Paget disease of breast); watery, serous, or bloody discharge
- Metastatic disease suggested by firm or hard axillary nodes that are larger than 1 cm or fixed to skin or deep structures
- Advanced stage (stage III or IV) suggested by ipsilateral supraclavicular or infraclavicular lymphadenopathy
What is the differential diagnosis of breast cancer?
Differential Diagnosis

- Fibrocystic condition of breast
- Fibroadenoma
- Intraductal papilloma
- Lipoma
- Fat necrosis
What are the laboratory, imaging, and procedural findings in breast cancer?
Laboratory Tests
- Alkaline phosphatase is increased in liver or bone metastases; hypercalcemia occurs in advanced disease
- Carcinoembryonic antigen (CEA) and CA 15-3 or CA 27-29 are markers for recurrent disease

Imaging Studies
- Mammography
- Breast ultrasonography may differentiate cystic from solid masses
- MRI and ultrasonography may be useful in women at high risk for breast cancer
- CT, bone scans, and PET scans can detect metastatic disease

Diagnostic Procedures
- Fine-needle aspiration (FNA), core biopsy, open biopsy, or ultrasound-guided biopsy
- Cytologic examination of breast nipple discharge may be helpful on rare occasions
What are the treatments for breast cancer?
Medications

- Chemotherapy is used in curable disease and in metastatic disease.
  - CMF (cyclophosphamide, methotrexate, fluorouracil)
  - AC (Adriamycin [doxorubicin], cyclophosphamide) with taxanes (docetaxel or paclitaxel)
- Tamoxifen or aromatase inhibitors are used in hormone receptor–positive patients.
- Bisphosphonates are used to decrease disease recurrence and treat metastases to the bone.
- Trastuzumab and lapatinib bind to HER-2/neu receptors for HER-2/neu–expressive cancers.

Surgery

- Surgery is indicated for stage I and II cancers; breast-conserving therapy is indicated in selected patients.
- Sentinel node biopsy for invasive cancer can be used as an alternative to axillary dissection.

Therapeutic Procedures

- Radiotherapy is usually used after surgical therapy.
A 68-year-old man presents to the primary care clinician with a complaint of urinary frequency. The patient has noted increased urinary urgency and frequency for approximately 1 year, which have progressively worsened. He now seems to have to urinate “all the time,” including four times each night, and often feels like he has not completely emptied his bladder. In addition, in the past month, he sometimes has postvoid dribbling. The family history is negative for malignancy. On examination, he appears healthy. His prostate is diffusely enlarged without focal nodule or tenderness.

What are the salient features of this patient’s problem? How do you think through his problem?
**Salient features:** Man of advancing age; chronic progressive urinary frequency and urgency; poor bladder emptying; nocturia; postvoid dribbling; prostate enlargement without nodules or tenderness

**How to think through:** Progressive lower urinary tract symptoms are so common in older men that clinicians must maintain a broad differential diagnosis before reaching a diagnosis of benign prostatic hyperplasia (BPH). In addition to BPH, what other processes could account for this patient’s symptoms? (Urinary tract infection [UTI], prostatitis, polyuria caused by metabolic disturbance such as diabetes mellitus or insipidus, neurogenic bladder, urethral stricture, anticholinergic and sympathomimetic medications, or bladder or prostate cancer.) Is BPH a risk factor for prostate cancer? (Because both are common, analysis of data is complicated, but evidence suggests that it is not.) How should this patient be evaluated? (Thorough review of systems, including constitutional symptoms and bone pain suggesting cancer; family history; abdominal examination; prostatic digital rectal examination [DRE]; neurologic examination; urinalysis [to detect infection or blood]. If there is concern for urinary retention, obtain a postvoid ultrasound of the bladder for residual urinary volume and serum creatinine.) How should he be treated? (α-Blockers are the first-line therapy; 5-α-reductase inhibitors are adjunct agents, taking several months for maximal effect and being minimally effective without concurrent α-blocker. Surgical intervention, such as transurethral resection of the prostate, is considered for refractory symptoms, urinary retention, recurrent UTI, and obstructive nephropathy.)
What are the essentials of diagnosis and general considerations regarding benign prostatic hyperplasia?
Essentials of Diagnosis

- Obstructive or irritative voiding symptoms in absence of infection, neurologic disorder, urethral stricture, or prostate or bladder malignancy
- May have enlarged prostate on rectal examination that is smooth, firm, and elastic

General Considerations

- Etiology is multifactorial, including aging and relating to dihydrotestosterone (DHT)
- Prevalence: ~20% men ages 41 to 50 years; ~50% men ages 51 to 60 years; >90% men ages >80 years
- At age 55 years, ~25% of men report obstructive voiding symptoms
- At age 75 years, 50% of men report a decrease in the force and caliber of the urinary stream
What are the symptoms and signs of benign prostatic hyperplasia?
Symptoms and Signs

- Obstructive symptoms: hesitancy, decreased force and caliber of stream, sensation of incomplete bladder emptying, double voiding (urinating a second time within 2 hours), straining to urinate, postvoid dribbling
- Irritative symptoms: urgency, frequency, nocturia
- American Urological Association (AUA) Symptom Index can be used for patients starting therapy
What is the differential diagnosis of benign prostatic hyperplasia?
Differential Diagnosis

- Prostate cancer
- UTI
- Neurogenic bladder
- Urethral stricture
What are the procedural findings in benign prostatic hyperplasia?
Diagnostic Procedures
- History to exclude other possible causes of symptoms
- Physical examination, DRE (note size and consistency of the prostate), and a focused neurologic examination
- Examine lower abdomen for a distended bladder
- If possibility of cancer, further evaluation is needed by serum prostate-specific antigen (PSA), transrectal ultrasonography, and biopsy
What are the treatments for benign prostatic hyperplasia?
Medications
- α-Blockers such as prazosin, terazosin, doxazosin, and tamsulosin work quickly for symptoms.
- 5-α-Reductase inhibitors such as finasteride require 6 months of therapy for maximum effect.
- Combination therapy of an α-blocker and 5-α-reductase inhibitor is better than either one alone.

Surgery
- Surgery is indicated for refractory retention, recurrent infections, kidney failure, and bladder stones.
- Transurethral resection of the prostate (TURP) is effective, but complications include retrograde ejaculation (75%), erectile dysfunction (5%–10%), urinary incontinence (<1%).
- Transurethral incision of the prostate (TUIP) and open prostatectomy are also available.
- Minimally invasive approaches include laser surgery, needle ablation, and microwave therapy.

Therapeutic Procedures
- With watchful waiting, about 10% of patients progress to urinary retention and 50% improve.
A 24-year-old woman presents to the clinic complaining of painful menses. She states that for the past several years, she has had cramping pain in the days preceding her menses as well as during her menses. In addition, she notes bloating and weight gain in the week before her menses, with swelling of her hands and feet. She has irritability and severe mood swings during that time; she cries easily and for no reason becomes enraged at her family or boyfriend. On review of systems, she denies urinary symptoms, vaginal discharge, and gastrointestinal symptoms. She has no significant medical history. She has never been pregnant and never had a sexually transmitted disease. She is monogamous with her long-standing boyfriend and states that they always use condoms. She takes no medications. Her physical examination findings are unremarkable.

What are the salient features of this patient’s problems? How do you think through her problems?
Salient features: Young woman; chronic painful menses that are cramping in character; bloating and weight gain with mood disturbance before menses; normal physical examination findings (suggests primary dysmenorrhea)

How to think through: Primary dysmenorrhea needs to be differentiated from secondary dysmenorrhea in this patient. Primary dysmenorrhea begins in adolescence. Symptoms begin 0 to 2 days before the onset of menses and last up to 3 days; associated symptoms of nausea, back pain, fatigue, and headache are characteristic. Exclusion of secondary causes of menstrual pain often does not require additional testing, but careful assessment of risk factors, history, and pelvic examination is needed. What history, not present in this case, would alert the clinician to possible secondary dysmenorrhea? (Onset after age 25 years, worsening of symptoms over time, unilateral pain, abnormal uterine bleeding.) Why is the low-risk sexual history important in this case? (Pelvic inflammatory disease [PID] is an important cause of secondary dysmenorrhea.) What are the other major secondary causes to consider? (Endometriosis is most common; adenomyosis.) What is the natural history of primary dysmenorrhea, and how should this patient be counseled? (Improvement over time is typical, often with marked improvement after parity.) What are the two major pharmacologic treatment strategies? (Hormonal contraception and nonsteroidal antiinflammatory drug [NSAIDs].) What nonpharmacologic treatments have the greatest evidentiary support? (Application of heat and physical activity.)
What are the essentials of diagnosis and general considerations regarding dysmenorrhea?
**Essentials of Diagnosis**

- Primary dysmenorrhea is menstrual pain associated with ovular cycles in the absence of pathologic findings.
- Secondary dysmenorrhea is menstrual pain for which an organic cause exists, such as endometriosis.

**General Considerations**

- Primary dysmenorrhea usually occurs in young women; begins within 1 to 2 years of menarche; and is caused by uterine vasoconstriction, anoxia, and sustained contractions mediated by prostaglandins.
- Secondary dysmenorrhea usually begins well after menarche even in the third or fourth decades of life.
What are the symptoms and signs of dysmenorrhea?
Symptoms and Signs

Primary Dysmenorrhea

- Low, midline, wave-like, cramping pelvic pain often radiating to the back or inner thighs
- Cramps may last for 1 or more days and may be associated with nausea, diarrhea, headache, and flushing
- No pathologic findings on pelvic examination

Secondary Dysmenorrhea

- The history and physical examination may suggest endometriosis or PID
What is the differential diagnosis of dysmenorrhea?
Differential Diagnosis

- Endometriosis
- Adenomyosis
- PID
- Uterine leiomyomas (fibroids)
- Intrauterine device (IUD)
- Pelvic pain syndrome
- Endometrial polyp
- Cervicitis
- Cervical stenosis
- Cystitis
- Interstitial cystitis
What are the imaging and procedural findings in dysmenorrhea?
Imaging Studies

- Magnetic resonance imaging (MRI) is the most reliable method to detect submucous myomas.
- Ultrasonography or, preferably, MRI is useful in identifying adenomyosis.

Diagnostic Procedures

Secondary Dysmenorrhea

- Laparoscopy is often needed to differentiate endometriosis from PID.
- Submucous myomas can be detected by saline infusion hysterography, by hysteroscopy, or by passing a sound or curette over the uterine cavity during a dilatation and curettage.
What are the treatments for dysmenorrhea?
Medications

- NSAIDs or cyclooxygenase-2 inhibitor started before menses
- Oral contraceptives, depot-medroxyprogesterone acetate, or levonorgestrel-containing IUDs for primary dysmenorrhea
- Oral contraceptives, danazol, and gonadotropin-releasing hormone agonists for endometriosis
- Levonorgestrel-releasing intrauterine system (LNG-IUS), uterine artery embolization, or hormonal approaches to treat adenomyosis

Surgery

- Laparoscopy or laparotomy with or without hysterectomy is often performed

Therapeutic Procedures

- Local heat and high-frequency transcutaneous electrical nerve stimulation
A 73-year-old African American man presents to a primary care clinician to establish care. He has not seen a doctor for some time, but low back pain and difficulty initiating and maintaining a stream of urine have prompted his visit today. His family history is notable for his father having prostate cancer. On physical examination, he has tenderness to palpation over the lumbar spine, and his digital rectal examination (DRE) reveals a large focal hard prostate nodule. His laboratory testing reveals a serum prostate-specific antigen (PSA) concentration of 21.3 ng/mL.

What are the salient features of this patient’s problem? How do you think through his problem?
**Salient features:** Older African American man; obstructive urinary symptoms; focal prostatic nodule; highly elevated PSA; low back pain and tenderness over the lumbar spine suggesting bony metastasis

**How to think through:** Prostate cancer detection is challenging. For every clinically important case of prostate cancer identified, routine PSA testing detects many cancers that will not progress to clinically significant disease. Prostate cancer, however, is a leading cause of cancer-related death among men. What risk factors for prostate cancer are present in this patient? (Family history and African American heritage.) What is the most potentially alarming finding on physical examination in this case? (Lumbar tenderness suggesting metastatic disease.) What are the next diagnostic steps? (Transrectal ultrasonography and biopsy of the prostate, computed tomography [CT] of the abdomen and pelvis, and radionuclide bone scan.) Without the significant elevation in PSA, would a biopsy be warranted in this case? (Yes. Asymmetry or nodules on DRE should be evaluated histologically.) Does the high PSA value in this case increase the likelihood of extracapsular extension? (Yes. Although PSA levels are challenging to interpret because of fluctuation and overlap with benign prostatic hypertrophy, a level >10 ng/mL is a strong indication of extracapsular disease.) To what sites does prostate cancer metastasize? (Usually bone.) Are bony metastases in prostate cancer osteolytic or osteoblastic, and do they cause elevated serum alkaline phosphatase? (Osteoblastic. Yes, serum alkaline phosphatase and calcium may be elevated.) How is prostate cancer classified to guide treatment and prognosis? (The TNM [tumor, node, metastasis] staging system, incorporating the Gleason score for pathologic tumor grade, and the PSA value.)
What are the essentials of diagnosis and general considerations regarding prostate cancer?
Essentials of Diagnosis

- Prostatic induration on DRE or elevated level of serum PSA
- Most often asymptomatic; rare systemic symptoms (weight loss, bone pain)

General Considerations

- Most common non-dermatologic cancer and second leading cause of cancer-related death in American men
- Incidence increases with age: ~30% of men ages 60 to 69 versus 67% in men ages 80 to 89 years have prostate cancer
- Risk factors: African American ethnicity, family history of prostate cancer, high dietary fat intake
- Majority of prostate cancers are adenocarcinomas
What are the symptoms and signs of prostate cancer?
Symptoms and Signs

- Obstructive voiding symptoms
- Focal nodules or areas of induration within the prostate on DRE
- Lymph node metastases
- Lower extremity lymphedema
- Back pain or pathologic fractures
- Rarely, signs of urinary retention (palpable bladder) or neurologic symptoms as a result of epidural metastases and cord compression
What is the differential diagnosis of prostate cancer?
Differential Diagnosis

- Urinary obstruction (e.g., urethral stricture, stone, bladder neck contracture)
- Prostatitis
- Benign prostatic hyperplasia
- Prostatic stones
- Bladder cancer
What are the laboratory, imaging, and procedural findings in prostate cancer?
Laboratory Tests
- Elevated serum PSA (normal <4 ng/mL)
- PSA correlates with the volume of both benign and malignant prostate tissue
- Elevated blood urea nitrogen or serum creatinine with urinary retention or urethral obstruction
- Elevated serum alkaline phosphatase or calcium in patients with bony metastases

Imaging Studies
- Magnetic resonance imaging or transrectal ultrasonography (TRUS) can detect capsular penetration and local invasion.
- CT imaging and radionuclide bone scan can be useful in detecting metastases.

Diagnostic Procedures
- TRUS-guided biopsy in men with abnormal DRE or elevated PSA
What are the treatments for prostate cancer?
Medications

- Androgen deprivation is used for advanced or metastatic disease via antiandrogens, surgical orchiectomy or medical orchiectomy with gonadotropin-releasing hormone agonists or antagonists.
- Ketoconazole or corticosteroids can suppress adrenally produced sex hormones.
- Chemotherapy with docetaxel or other taxanes may improve survival in those with castrate-resistant disease.

Therapeutic Procedures

- Surveillance (watchful waiting) may be appropriate for low–stage or low-grade disease
- Surgery: radical prostatectomy; lower stages have lowest recurrence rates
- Radiation therapy with external beams or transperineal implantation (brachytherapy)
- Combination therapy with androgen deprivation and surgery, irradiation, or both
A 45-year-old man presents to the urgent care clinic complaining of low back pain. He was moving heavy boxes at work the day before when he had a sudden onset of low back pain that radiates down into his left buttock and left posterior thigh. His medical history is unremarkable, and he takes no medications. He denies bowel and bladder incontinence. On physical examination, he has decreased sensation on the posterior left thigh, decreased strength on left ankle dorsiflexion, and an absent left ankle jerk deep tendon reflex. He has no saddle anesthesia and normal rectal tone. His straight-leg raise test result positive, with pain reproduced on passive elevation of the right (contralateral) leg.

What are the salient features of this patient’s problem? How do you think through his problem?
**Salient features:** Acute onset of low back pain; radiation down the left buttock and posterior thigh with decreased sensation and loss of ankle jerk reflex; positive straight-leg raise test result (suggestive of disc herniation); no warning signs of cauda equina syndrome

**How to think through:** Acute low back pain is common in both primary care and emergency medicine settings. The challenge is to identify the high-risk patient who needs urgent further evaluation from the low-risk patient who may be equally uncomfortable but for whom a trial of conservative management is appropriate. Even with an apparent mechanical cause, key risk factors must be assessed. What are the major causes of high-risk back pain? (Infection [vertebral osteomyelitis, epidural abscess], metastatic cancer, rheumatologic spondylitis, cauda equina syndrome, fracture.) This patient has no notable medical history, history of cancer, corticosteroid use, or osteoporosis. What additional risk factor must be assessed? (Injection drug use.) What are the key “red flag” symptoms to elicit? (Fever, weight loss, nocturnal pain, change in bowel or bladder function, lower extremity or sphincter weakness.) What is the most likely cause of this patient’s pain? (An L5–S1 radiculopathy, likely caused by disk herniation. Less likely causes, given his age, include pyriformis syndrome, osteoarthritis, and fracture.) What examination finding specifically supports the diagnosis of disk herniation? (Positive contralateral straight-leg raise.) Should he receive imaging? (No. He is very likely to improve with conservative management, including nonsteroidal antiinflammatory drugs [NSAIDs], heat, and physical therapy, within 6 weeks.)
What are the essentials of diagnosis and general considerations regarding low back pain?
Essentials of Diagnosis

- A precise diagnosis cannot be made in the majority of cases even when anatomic defects are present because such defects are common in asymptomatic patients.
- Most patients with acute onset of low back pain will improve in 1 to 4 weeks and need no evaluation beyond the initial history and physical examination.

General Considerations

- Low back pain is exceedingly common; it is experienced at some time by up to 80% of the population.
- Chronic low back pain from degenerative joint disease is rare before age 40 years.
What are the symptoms and signs of low back pain?
Symptoms and Signs

- Worsening with rest and improvement with activity is characteristic of seronegative spondyloarthropathies; degenerative disease usually improves with rest and is worse with activity.
- Radiation down the buttock and below the knee, loss of reflexes, and a positive crossed straight-leg raise test result suggests nerve root irritation from a herniated disc.
- Straight-leg raise test: passive ipsilateral hip flexion reproduces pain and indicates nerve root irritation.
- Crossed straight-leg raise: passive contralateral hip flexion reproduces pain; not very sensitive but is specific for disc herniation.
- Deficits of multiple nerve roots suggest a cauda equina tumor or epidural abscess.
- Bilateral leg weakness, saddle area anesthesia, bowel or bladder incontinence, or erectile dysfunction indicates cauda equina syndrome.
What is the differential diagnosis of low back pain?
Differential Diagnosis

- Muscular strain
- Herniated disk
- Lumbar spinal stenosis
- Compression fracture
- Degenerative joint disease
- Infectious diseases (e.g., osteomyelitis, epidural abscess, subacute bacterial endocarditis)
- Neoplastic disease (vertebral metastases)
- Seronegative spondyloarthropathies (e.g., ankylosing spondylitis)
- Leaking abdominal aortic aneurysm
- Renal colic
What are the imaging and procedural findings in low back pain?
**Imaging Studies**

- Radiographs are warranted promptly for those with suspected infection, cancer, fractures, or inflammation and those who do not improve after 2 to 4 weeks of conservative therapy.
- Personal history or symptoms of malignancy or nocturnal or supine pain should warrant imaging.
- Magnetic resonance imaging is needed urgently in any patient suspected of having an epidural mass or cauda equina tumor, but most routine disk herniation will improve over 4 to 6 weeks of conservative therapy.

**Diagnostic Procedures**

- If the history and physical examination do not suggest the presence of infection, cancer, inflammatory back disease, major neurologic deficits, or pain referred from abdominal or pelvic disease, further evaluation can be deferred while conservative therapy is tried.
What are the treatments for low back pain?
Medications

- NSAIDs are given for analgesia; severe pain may require opioids.
- Limited evidence supports short course of “muscle relaxants” such as diazepam, cyclobenzaprine, carisoprodol, or methocarbamol in patients who do not respond to NSAIDs.

Surgery

- Surgical consultation is done urgently for any patient with a large or evolving neurologic deficit.
- For sciatica caused by disk herniation, conservative treatment and surgery achieve similar 1-year outcomes; however, pain relief and perceived recovery are obtained more quickly with surgery.

Therapeutic Procedures

- Epidural corticosteroid injections can provide short-term relief of sciatica.
- Corticosteroid injections into facet joints are ineffective for chronic low back pain.
A 58-year-old man with a long history of treated essential hypertension and mild renal insufficiency presents to the urgent care clinic complaining of pain in the right knee. His primary care provider saw him 1 week ago and added a thiazide diuretic to improve his blood pressure control. He had been well until the night before the clinic visit, when he noted some redness and slight swelling of his knee. He later awakened with significant pain and swelling. He was able to walk only with assistance. There was no history of knee trauma. Physical examination confirmed the presence of a swollen right knee, with erythema and warmth. Joint aspiration recovered copious dark yellow, cloudy synovial fluid. Microscopic analysis demonstrated 30,000 leukocytes/mcL; negative Gram stain results; and many needle-shaped, negatively birefringent crystals.

What are the salient features of this patient’s problem? How do you think through his problem?
Salient features: Chronic kidney disease; monoarticular joint pain, warmth and erythema; thiazide use; synovial fluid with white blood cell (WBC) count of 30,000/mcL, negative Gram stain, needle-shaped negatively birefringent (urate) crystals

How to think through: A septic joint is the first consideration in patient with monoarticular joint pain and inflammation (rubor [redness], dolor [pain], calor [warmth], tumor [swelling])—that is, a true arthritis. The other two major causes of monoarticular arthritis are trauma and crystal-induced arthropathies. Does the patient fit the demographic profile for gout? (Yes.) Is his joint one typically affected by gout? (Yes, most common are the great toe, midfoot, and knee.) What is the tempo of the onset of pain in gout? (Rapid escalation.) What are the risk factors for gout? (Thiazides, myeloproliferative disorders, alcohol intake.) Can patients with gout have fever? (Yes.) How does synovial fluid analysis help? (Both gout and infection can cause a WBC count >50,000/mcL. Although the joint fluid Gram stain and culture help to rule out infection, finding crystals establishes the diagnosis of gout definitively.) Where on the body you might find tophi? (Cartilage, external ears, hands, feet, olecranon and prepatellar bursae, tendons, and bone.) What might radiography show in gout? (Erosions.)
What are the essentials of diagnosis and general considerations regarding gout?
Essentials of Diagnosis

- Acute onset, usually monoarticular, often involving the first metatarsophalangeal (MTP) joint
- Polyarticular involvement more common with long-standing disease
- Hyperuricemia in most; identification of urate crystals in joint fluid or tophi is diagnostic
- Dramatic therapeutic response to nonsteroidal antiinflammatory drugs (NSAIDs)

General Considerations

- Common in Pacific Islanders (e.g., Filipinos)
- 90% of patients with primary gout are men
- Causes a recurring acute arthritis and later a chronic deforming arthritis
- Secondary gout from acquired hyperuricemia from:
  - Medications (diuretics, low-dose aspirin, cyclosporine, and niacin)
  - Myeloproliferative disorders, multiple myeloma, hemoglobinopathies
  - Chronic kidney disease
  - Hypothyroidism, psoriasis, sarcoidosis, and lead poisoning
- Alcohol ingestion increases urate production and decreases renal excretion of uric acid
What are the symptoms and signs of gout?
Symptoms and Signs

- Sudden onset of arthritis, frequently nocturnal
  - Often the MTP joint of the great toe joint (“podagra”) is affected.
  - Other common joints include the feet, ankles, and knees.
- As the attack progresses:
  - Pain becomes intense.
  - Joints are red, tender, and swollen.
  - Fever is common.
- Tophi may be found in cartilage, external ears, hands, feet, olecranon, prepatellar bursae, tendons, and bone after several attacks of acute arthritis.
- Asymptomatic periods of months or years commonly follow the initial attacks.
- Years of recurrent severe attacks can evolve into a chronic, deforming disease that mimics rheumatoid arthritis.
What is the differential diagnosis of gout?
Differential Diagnosis

- Septic arthritis
- Pseudogout (calcium pyrophosphate deposition disease)
- Rheumatoid arthritis
- Reactive arthritis
- Osteoarthritis
- Cellulitis
- Chronic lead poisoning (saturnine gout)
- Bursitis or bunion of the first MTP joint (podagra)
- Sarcoidosis (podagra or tophi)
- Polyarteritis nodosa or erythema nodosa (tophi)
What are the laboratory, imaging, and procedural findings in gout?
Laboratory Findings

- Serum uric acid is elevated (>7.5 mg/dL) in 95% of patients who have serial measurements.
- A single uric acid determination is normal in up to 25% of cases, so it cannot exclude gout.

Imaging Studies

- Early in the disease, radiographs show no changes.
- Later, punched-out erosions with an overhanging rim of cortical bone (“rat bite”) develop.

Diagnostic Procedures

- Sodium urate crystals in joint fluid or material aspirated from a tophus establishes the diagnosis.
- The crystals are needle-like and negatively birefringent when examined by polarized light microscopy and may be extracellular or found within neutrophils.
What are the treatments available for gout?
Asymptomatic hyperuricemia should not be treated.

**Acute Attack**
- NSAIDs are the treatment of choice
- Opioids for severe pain
- Intraarticular corticosteroids for monoarticular disease
- Corticosteroids may also be given intravenously or orally
- Bed rest to prevent early recurrence

**Prevention**
- Reduce reversible causes, including a high-purine diets, obesity, frequent alcohol consumption, and trigger medications (diuretics, niacin, low-dose aspirin).
- Colchicine can be used daily to prevent future attacks or prevent exacerbation when other treatments are initiated.
- Probenecid and sulfinpyrazone are uricosuric drugs that can increase excretion of uric acid in those with intact renal function.
- Allopurinol and febuxostat are xanthine oxidase inhibitors that can decrease uric acid production.
- Pegloticase given for refractory, chronic gout converts uric acid to (readily excreted) allantoin

**Surgery and Therapeutic Procedures**
- Surgical excision of tophi rarely offers mechanical improvement in select cases.
A 41-year-old man presents to urgent care clinic complaining of right medial knee pain. His pain began after he twisted his knee playing soccer 1 month ago. At the time, he had a significant amount of swelling and difficulty in bearing weight, both of which slowly resolved after 1 week of ice and rest. Since then, he has had both pain and frequent “locking” and “catching” of the joint when walking. On examination, he has tenderness to palpation at the medial joint line and a positive McMurray test result.

What are the salient features of this patient’s problem? How do you think through his problem?
**Salient features:** Medial knee pain; trauma with twisting; immediate effusion; “locking” and “catching” sensation; positive McMurray test result

**How to think through:** When evaluating any acute arthritis, begin with a mental checklist of systemic illnesses that can manifest as acute arthritis. Otherwise, acute joint pain will be erroneously attributed to trauma. If knee joint swelling and pain developed without clear-cut trauma, what study will likely provide the most important data? (Arthrocentesis.) Provided that the patient denies fevers and constitutional symptoms and the history supports trauma as the mechanism, the clinician’s tasks are to identify the injured structure, weigh the utility of imaging, and assess the need for early intervention. Key history to be elicited here include the mechanism of injury, ability to bear weight after the injury, degree of swelling and pain, and presence of “locking” and “catching.” The exact location of the pain (best obtained by asking the patient to point with one finger) should also be assessed. The tempo of swelling onset was not reported. (When swelling develops rapidly after injury, hemorrhathrosis should be considered, possibly from an acute ligamentous tear.) “Catching” and “locking” strongly suggest what pathology? (A meniscal tear.) What internal knee joint structures should be evaluated on the physical examination? (Ligaments, meniscus.) How is the meniscus assessed? (Two commonly performed tests load and stress the meniscus: McMurray test and Thessaly test.) What imaging modality is preferred if meniscus injury is suspected? (Magnetic resonance imaging [MRI].)
What are the essentials of diagnosis and general considerations regarding knee pain?
Essentials of Diagnosis

- Examination of range of motion, effusions, meniscus, and ligaments
- Evaluation of aspirated joint fluid if indicated

General Considerations

- Injuries may be caused by trauma, inflammation, infection, or degenerative changes.
- Ligaments, menisci, synovium, or bursa may be affected.
- Effusions can occur with intraarticular pathology (e.g., osteoarthritis, tears of meniscus or cruciate ligament, or patellar fracture).
- Overuse syndromes of the knee, such as anserine bursitis, iliotibial band syndrome, and popliteal or patellar tendinitis, occur often in runners who overtrain or who are not properly conditioned.
What are the symptoms and signs of knee pain?
Symptoms and Signs

- History of overuse, trauma, sports, or previous injuries can help suggest a diagnosis.
- Fever or risk factors for sexually transmitted diseases (e.g., gonorrhea) suggest an infectious origin.
- Grinding, clicking, or popping may indicate osteoarthritis or patellofemoral syndrome.
- “Locking” or “catching” during walking suggests a meniscal injury or loose body in the knee joint.
- Pain with bending and walking downstairs suggests patellofemoral joint dysfunction.
- Pain after rising from prolonged sitting suggests a problem with patellar tracking.
- Overuse syndromes worsen with continued use; iliotibial band syndrome often has “snapping.”
What is the differential diagnosis of knee pain?
Differential Diagnosis

- Meniscal injury
- Ligamentous tear or sprain
- Osteoarthritis
- Patellar dysfunction or misalignment
- Fracture of the patella or tibia
- Inflammatory arthritis
- Septic arthritis
- Ruptured popliteal (Baker) cyst
- Prepatellar or anserine bursitis
What are the laboratory, imaging, and procedural findings in knee pain?
Laboratory Tests
- Complete blood count (CBC), uric acid level, and anti-CCP (anti–cyclic citrullinated protein) antibody testing may help identify infection, gout, or rheumatoid arthritis as the cause of an inflammatory arthritis.
- Laboratory testing of aspirated joint fluid is extremely helpful.

Imaging Studies
- Plain weight bearing radiographs may show degenerative changes or fractures.
- MRI helps to evaluate soft tissues, menisci, and ligaments.

Diagnostic Procedures
- Physical examination includes palpating the relevant sites around the knee and special tests.
  - Lachman test, anterior drawer test, and pivot shift test for anterior cruciate ligament tear
  - Varus and valgus stress tests for collateral ligament tears
  - Posterior drawer test and “sag sign” for posterior cruciate ligament tear
  - McMurray test, modified McMurray test, and Thessaly test for meniscal tear
  - Apprehension sign for patellofemoral joint instability
- Arthrocentesis of joint fluid effusions should be done.
What are the treatments for knee pain?
Medications

* Symptomatic treatment aimed at the underlying cause

Surgery

* Ligamentous or meniscal repair
* Knee replacement surgery in patients with osteoarthritis or rheumatoid arthritis with significant disability

Therapeutic Procedures

* In overuse syndromes, rest and abstention from the causative physical activities for a period of days to weeks are essential, with subsequent gentle stretching to prevent recurrence.
* Joint aspiration (arthrocentesis) is often both diagnostic and therapeutic.
A 47-year-old woman presents to the clinic with a 4-week history of fatigue, bilateral hand pain and stiffness, and hand and wrist joint swelling. About 1 month before presentation, she noticed that her hands were stiffer in the morning but thought that it was because of too much typing. However, the stiffness has worsened, and she now needs about 1 hour each morning to “loosen up” her hands. As the day goes on, the stiffness improves, although it does not go away entirely. She has also noticed that her knuckles and wrists are swollen and feel somewhat warm. Physical examination reveals warm, erythematous wrists and metacarpal joints bilaterally. Hand radiographs show periarticular demineralization and erosions, and blood test results are significant for mild anemia, elevated erythrocyte sedimentation rate (ESR), and positive rheumatoid factor (RF) and anti-CCP (anti–cyclic citrullinated protein) antibodies.

What are the salient features of this patient’s problem? How do you think through her problem?
Salient features: Polyarticular joint pain and swelling; stiffness worse in the morning and lasting more than 30 minutes; wrist and metacarpophalangeal (MCP) joint involvement; bilaterality of joint involvement; radiographs with demineralization and erosions; elevated ESR and rheumatoid factor and anti-CCP antibodies.

How to think through: Is this arthralgia (joint pain) or arthritis (joint inflammation)? What four things indicate joint inflammation (rubor [redness], dolor [pain], calor [warmth], tumor [swelling])? How many joints are involved (mono- vs. oligo- vs. polyarthritis)? What is the pattern of joint involvement: small versus large versus both? Which joints are involved (distal interphalangeal [DIP] vs. proximal interphalangeal [PIP] vs. MCP)? Is there morning stiffness for at least 30 minutes and prominent afternoon fatigue? Are there features of lupus (sicca symptoms, oral ulcers, malar rash, photosensitivity, chest pain, or Raynaud phenomenon)? Are there symptoms of psoriasis or inflammatory bowel disease? ESR, although nonspecific, is useful marker of inflammation in subtle cases. A positive RF result and characteristic erosions on hand radiographs strengthen the case for rheumatoid arthritis (RA), and positive anti-CCP antibodies are highly specific for the diagnosis. Would arthrocentesis help? If so, what might the synovial fluid show in this patient?
What are essentials of diagnosis and general considerations regarding rheumatoid arthritis?
Essentials of Diagnosis

- Insidious onset with morning stiffness and symmetric joint pain
- Polyarthritis with predilection for the small joints of the hands and feet
- Radiographic juxtaarticular osteoporosis; joint erosions and narrowing
- RF and anti-CCP antibodies in 70% to 80%
- Extraarticular manifestations, including subcutaneous nodules, interstitial lung disease, pleural effusion, pericarditis, splenomegaly with leukopenia, vasculitis

General Considerations

- A chronic systemic inflammatory disease of unknown cause with synovitis of multiple joints
- Pathological findings include chronic synovitis with pannus formation
- The pannus erodes cartilage, bone, ligaments, and tendons
- Females > males almost 3:1, peak onset in the fourth and fifth decades for women and sixth to eighth decade for men
What are the symptoms and signs of rheumatoid arthritis?
Symptoms and Signs

- **Joint symptoms**
  - Insidious onset, symmetric, polyarticular with tenderness, pain
  - Stiffness persisting for more than 30 minutes (and usually many hours) is prominent in the morning, recurs after inactivity or strenuous activity
  - PIP joints of the fingers, MCP joints, wrists, knees, ankles, and metatarsophalangeal joints most often involved
  - Synovial cysts and rupture of tendons and nerve entrapment may occur
  - Neck can be affected, but the spine and sacroiliac joints usually spared
  - In advanced disease, atlantoaxial (C1–C2) subluxation can lead to myelopathy

- Rheumatoid nodules over bony prominences, bursae, tendon sheaths, and other tissues are present in about 20% of patients.

- Extraarticular manifestations correlate with the presence of RF in serum.

- Ocular symptoms include scleritis, episcleritis, and dryness.

- Other extraarticular manifestations include palmar erythema, vasculitis, interstitial lung disease, pericarditis, and pleural disease.
What is the differential diagnosis of rheumatoid arthritis?
Differential Diagnosis

- Gout with tophi (mistaken for nodules)
- Systemic lupus erythematosus
- Infections such as parvovirus B19, Lyme disease, or rubella
- Osteoarthritis or inflammatory osteoarthritis
- Polymyalgia rheumatica
- Hemochromatosis (MCP and wrist joints)
- Rheumatic fever
- Hepatitis B or C
- Palindromic rheumatism
- Hypertrophic pulmonary osteoarthropathy (paraneoplastic)
- Systemic vasculitis, especially polyarteritis nodosa, mixed cryoglobulinemia or antineutrophil cytoplasmic antibody (ANCA)–associated vasculitides
What are the laboratory, imaging, and procedural findings in rheumatoid arthritis?
Laboratory Tests
- Anti-CCP and rheumatoid factor are present in 70% to 80% with established RA but only 50% in early disease.
- Anti-CCP antibodies are the most specific blood test (specificity ~95%).
- Approximately 20% of patients have antinuclear antibodies (ANA).
- ESR and C-reactive protein are typically elevated in disease activity.
- Anemia, leukopenia with splenomegaly (e.g., Felty syndrome), and elevated platelets are common.

Imaging Studies
- Radiographic changes are specific but insensitive, especially early in disease.
- The earliest changes are swelling and juxtaarticular demineralization in the wrists or feet.
- Joint space narrowing and erosions develop later in disease.

Diagnostic Procedures
- Arthrocentesis is needed to diagnose superimposed septic arthritis, a common complication of RA.
What are the treatments for rheumatoid arthritis?
Medications

- Nonsteroidal antiinflammatory drugs (NSAIDs) and cyclooxygenase (COX)-2 inhibitors provide some symptomatic relief but do not prevent erosions or alter disease progression.
- Disease-modifying antirheumatic drugs (DMARDs) should be started as soon as the diagnosis is certain.
- Methotrexate is the initial DMARD of choice.
- Tumor necrosis factor inhibitors such as etanercept, infliximab, adalimumab, and golimumab are DMARDs that work faster than methotrexate.
- Hydroxychloroquine is useful for patients with mild disease.
- Corticosteroids are effective, but side effects limit long-term use.
- Leflunomide is a pyrimidine synthesis inhibitor nonbiologic DMARD.
- Sulfasalazine is a second-line nonbiologic agent.
- Other biologics include abatacept (CTLA4-Ig), rituximab (anti-CD20), and tocilizumab (IL-6).

Surgery

- Joint replacements for long-standing, severe, erosive disease with destruction

Therapeutic Procedures

- Physical and occupational therapy, joint rest, heat and cold, exercise, splinting, and assistive devices
- Intraarticular corticosteroids may be helpful if symptoms are confined to a few joints
A 22-year-old African American woman reports intermittent joint pain in her right knee and the joints of the fingers of her right hand, especially the proximal interphalangeal (PIP) joints, as well as a rash on her cheeks and nose that appears after sun exposure. On review of systems, she reports chest pain with deep breaths. On physical examination, she has painless oral ulcers on her palate; a pleural friction rub; and a facial rash, sparing the nasolabial folds. Her urine dipstick reveals 3+ protein, and laboratory testing reveals a white blood cell count of 3400/mcL, a platelet count of 89,000/mcL, a positive rapid plasma reagin (RPR) test result, a positive antinuclear antibody (ANA) test result with a titer of 1:320, and a positive anti-Smith antibody test result.

What are the salient features of this patient’s problem? How do you think through her problem?
Salient features: Young African American woman; symmetric, intermittent arthritis involving the fingers and knee; malar rash that spares the nasolabial folds; photosensitivity; signs and symptoms of pleuritis (chest pain, friction rub); oral ulcers; renal involvement (proteinuria); leukopenia and thrombocytopenia; false-positive syphilis test result; positive ANA result with high titer; positive anti-Smith test result

How to think through: Which populations are most affected by lupus? What are the typical timing and pattern of progression in lupus? What features of lupus are found on history? (Recall the common symptoms by building a mental image of the affected areas of the body—cognition, conjunctivitis or vision change, hair loss, sicca symptoms, oral ulcers, malar rash, photosensitivity, pleuritis, pericarditis, gastrointestinal symptoms, joint pain, Raynaud phenomenon). How might you assess involvement of the kidneys? (Urinalysis, renal biopsy.) What are the important serologies for lupus? (ANA is 99% positive but is nonspecific; anti-Smith and anti–double-stranded DNA have low sensitivity but high specificity.) How is the complete blood count useful? Will complement levels be elevated or decreased? What features of rheumatoid arthritis (RA) and lupus overlap? (Arthritis, pleural inflammation, leukopenia.) How can you differentiate RA from lupus? (The arthritis in RA more often affects the small joints of the hands and feet; is symmetrical; and shows evidence of inflammation on examination—rubor [redness], dolor [pain], calor [warmth], tumor [swelling]—and erosions on radiographs).
What are the essentials of diagnosis and general considerations regarding systemic lupus erythematosus?
Essentials of Diagnosis

- Multiple system involvement
- Occurs mainly in women, more common in young and African American women
- Rash over areas exposed to sunlight
- Joint symptoms in 90% of patients
- Anemia, leukopenia, thrombocytopenia
- ANA with high titer to double-stranded DNA

General Considerations

- Systemic lupus erythematosus (SLE) is an inflammatory autoimmune disorder.
- The clinical course is marked by spontaneous remission and relapses.
- Four features of drug-induced lupus separate it from SLE.
  - The sex ratio is nearly equal.
  - Nephritis and central nervous system (CNS) features are not ordinarily present.
  - Hypocomplementemia and antibodies to double-stranded DNA are absent.
  - It usually reverts toward normal when the offending drug is withdrawn.
What are the symptoms and signs of systemic lupus erythematosus?
Symptoms and Signs

- Fever, anorexia, malaise, and weight loss
- Skin lesions: alopecia, characteristic malar “butterfly” rash
- Raynaud phenomenon (20% of patients) often antedates other symptoms
- Joint symptoms, with or without active synovitis occur in more than 90% and are often the earliest manifestation
- Ocular: conjunctivitis, photophobia, blurring of vision, transient or permanent monocular blindness
- Pulmonary: pleurisy, pleural effusion, bronchopneumonia, pneumonitis, restrictive lung disease
- Cardiac: pericarditis, myocarditis, arrhythmias, verrucous endocarditis of Libman-Sacks
- Mesenteric vasculitis: aneurysms in medium-sized blood vessels, abdominal pain (particularly postprandial), ileus, peritonitis, and perforation may result
- Neurologic: psychosis, cognitive impairment, seizures, peripheral and cranial neuropathies, transverse myelitis, strokes, severe depression may be exacerbated by the administration of large doses of corticosteroids
- Glomerulonephritis: several forms may occur, including mesangial, focal and diffuse proliferative, and membranous
What is the differential diagnosis of systemic lupus erythematosus?
Differential Diagnosis

- Drug-induced lupus (especially procainamide, hydralazine, and isoniazid)
- Scleroderma
- Rheumatoid arthritis
- Inflammatory myopathy, especially dermatomyositis
- Rosacea
- Vasculitis (e.g., polyarteritis nodosa)
- Endocarditis
- Lyme disease
What are the laboratory and procedural findings in systemic lupus erythematosus?
Laboratory Tests

- Production of many different autoantibodies is seen.
- ANA test results are sensitive but not specific for systemic lupus (i.e., they are positive in most patients with lupus but are also positive in many patients with nonlupus conditions such as RA, autoimmune thyroid disease, scleroderma, and Sjögren syndrome).
- Antibodies to double-stranded DNA and to Sm are specific for SLE but not sensitive because they are present in only 60% and 30% of patients, respectively.
- Depressed serum complement—a finding suggestive of disease activity—often returns toward normal in remission.
- Three types of antiphospholipid antibodies occur.
  - The first causes the biologic false-positive test results for syphilis.
  - The second is lupus anticoagulant, a risk factor for venous and arterial thrombosis and miscarriage.
  - The third is anticardiolipin antibody.
- Abnormality of urinary sediment is almost always found in association with renal lesions. Red blood cells, with or without casts, and mild proteinuria are frequent.

Diagnostic Procedures

- Renal biopsy is useful in deciding whether treatment may be beneficial
What are the treatments for systemic lupus erythematosus?
Medications

- Skin lesions often respond to the local administration of corticosteroids.
- Minor joint symptoms can usually be alleviated by rest and nonsteroidal antiinflammatory drugs.
- Antimalarials (hydroxychloroquine) may be helpful in treating rashes or joint symptoms and appear to reduce the incidence of severe disease flares.
- Corticosteroids are required for the control of certain serious complications, such as thrombotic thrombocytopenic purpura, hemolytic anemia, myocarditis, pericarditis, glomerulonephritis, alveolar hemorrhage, and CNS involvement.
- Immunosuppressive agents such as cyclophosphamide, chlorambucil, and azathioprine are used in cases resistant to corticosteroids.
  - Cyclophosphamide improves renal survival, but overall survival is no better than in those treated with prednisone.
- Systemic corticosteroids are not usually given for minor arthritis, skin rash, leukopenia, or the anemia associated with chronic disease.

Therapeutic Procedures

- Patients with SLE should avoid sun exposure and use sunscreen.
A 61-year-old woman presents to the emergency department with 3 days of shortness of breath and lower extremity swelling. She has been previously healthy with no history of heart disease. Two weeks ago, she had been treated in the hospital for pneumonia and group A streptococcus bacteremia, from which she recovered. On physical examination now, her blood pressure is 170/100 mm Hg, and she has crackles in both lower lung fields, a normal cardiac examination, and 2+ pitting edema of both lower extremities. Urinalysis shows mild proteinuria and hematuria, with many dysmorphic red blood cells (RBCs) with some RBC casts. An echocardiogram shows normal systolic function.

What are the salient features of this patient’s problem? How do you think through her problem?
**Salient features:** Lower extremity edema and volume overload; hypertension; mild proteinuria, hematuria and RBC casts; normal cardiac function; recent streptococcal infection suggesting possible postinfectious glomerulonephritis (GN)

**How to think through:** When a patient presents with new edema, it is important to consider causes other than heart failure. Fortunately, the clinician here obtained a urinalysis looking for both hematuria and proteinuria. Given the abnormal result, microscopic evaluation of urine sediment, preferably by a nephrologist, should follow. What is the most serious cause of a case such as this? (Rapidly progressive glomerulonephritis [RPGN], one cause of which is poststreptococcal glomerulonephritis [GN].) What laboratory studies help define the cause of RPGN? (Serum complement levels, ASO titer, anti-GBM antibody, antinuclear antibody [ANA] titer, antineutrophil cytoplasmic antibody [ANCA], cryoglobulins, hepatitis B surface antigen, hepatitis C antibody.) Complement levels help narrow the differential diagnosis of RPGN. Postinfectious GN, lupus nephritis, and cryoglobulinemia all consume complement by forming immune complexes. By contrast, normal complement levels are found in ANCA-associated ("pauci-immune"), anti-GBM (Goodpasture syndrome), and IgA nephropathies. Renal biopsy will demonstrate characteristic light microscopy, immunofluorescence, and electron microscopy findings but is not always performed in patients with recent streptococcal infection. However, in this severe case, it could be considered if it would change treatment. Other causes of RPGN are treated with corticosteroids or other immunosuppressive medications or, in the case of mixed cryoglobulinemia, plasmapheresis.
What are the essentials of diagnosis and general considerations regarding glomerulonephritis?
Essentials of Diagnosis

- Hematuria, dysmorphic red cells, RBC casts, and mild proteinuria
- Acute renal insufficiency, dependent edema, and hypertension

General Considerations

- Postinfectious GN commonly appears 1 to 3 weeks after pharyngitis or impetigo.
- Pauci-immune necrotizing GN is caused by granulomatosis with polyangiitis (formerly Wegener granulomatosis), microscopic polyangiitis, or Churg-Strauss syndrome.
- Membranoproliferative GN is an idiopathic renal disease that usually presents with nephritic features ranging from asymptomatic glomerular hematuria and proteinuria to episodes of gross hematuria to the acute nephritic syndrome.
- Essential (mixed) cryoglobulinemia is associated with cold-precipitable immunoglobulins (cryoglobulins) precipitating in glomerular capillaries.
- Rapidly progressive acute GN requires rapid identification and treatment.
What are the symptoms and signs of glomerulonephritis?
Symptoms and Signs

- Hypertension
- Edema, first in body parts with low tissue tension such as the periorbital and scrotal regions
- Dark urine and oliguria
- Hematuria and proteinuria
- Cryoglobulinemia may have purpuric or necrotizing skin lesions, arthralgias, hepatosplenomegaly
- Pauci-immune causes may have mononeuritis multiplex or hemoptysis
- Hemoptysis occurs in granulomatosis with polyangiitis
- Membranoproliferative GN may have hypocomplementemia and recent history of upper respiratory tract infection
What is the differential diagnosis of glomerulonephritis?
Causes

- IgA nephropathy (Berger disease)
- Peri-infectious or postinfectious GN
- Endocarditis
- Lupus nephritis
- Cryoglobulinemic GN (often associated with hepatitis C virus)
- Membranoproliferative GN
- Acute interstitial nephritis (AIN)
- Acute tubular necrosis (ATN)
What are the laboratory, imaging, and procedural findings in glomerulonephritis?
Laboratory Tests
- Urinalysis showing hematuria, RBC casts, moderate proteinuria (usually <3 g/day)
- Serum creatinine can rise over days to months
- Other abnormal findings (depending on underlying cause): complement levels (C3, C4, CH50), antistreptolysin O (ASO) titer, anti-GBM antibody level, ANA titer, serum cryoglobulins, hepatitis B surface antigen or hepatitis C virus antibody, C3 nephritic factor, ANCA

Imaging Studies
- Renal ultrasonography

Diagnostic Procedures
- Renal biopsy can distinguish types of GN based on patterns identified on light microscopy, immunofluorescence, and electron microscopy.
What are the treatments for glomerulonephritis?
Medications
- Specific therapy is aimed at the underlying cause.
- Supportive measures include antihypertensive medications, salt restriction, diuretics, and antibiotics as indicated for infections.
- Corticosteroids in high doses and cytotoxic agents such as cyclophosphamide, depending on the nature and severity of disease, may be required.

Therapeutic Procedures
- The diagnosis of cryoglobulinemia calls for aggressive treatment of the underlying infection, including α-interferon for hepatitis C–related cryoglobulinemia in some patients, as well as pulse corticosteroids, plasma exchange, and cytotoxic agents.
- Renal transplantation is an option in membranoproliferative disease but the disease may recur in the transplanted kidney.
A 45-year-old woman presents to the emergency department after 5 days of nausea, vomiting, and diarrhea. She states that she has only been able to drink water occasionally, and her vomiting and diarrhea have been profuse. On review of systems, she complains of fatigue and muscle cramps. Her medical history includes hypertension, for which she takes hydrochlorothiazide (HCTZ). Physical examination reveals symmetric hyporeflexia of the extremities. An electrocardiogram (ECG) reveals broad and flattened T waves with a prominent U waves. Her serum K$^+$ is measured at 2.5 mEq/L.

**What are the salient features of this patient’s problem? How do you think through her problem?**
**Salient features:** Vomiting and diarrhea causing extrarenal potassium losses; fatigue and muscle cramps; thiazide diuretic use, causing kaliuresis; hyporeflexia on examination; ECG with flattened T waves and U waves; low serum potassium level

**How to think through:** The patient’s symptom of fatigue can be attributed to her poor oral intake in the setting of acute illness. What factors in her history and physical examination prompt you to consider an electrolyte abnormality? (Protracted vomiting in combination with diarrhea, muscle cramps, and hyporeflexia.) Is the underlying cause of her hypokalemia, intrarenal or extrarenal? (Both, but mainly extrarenal.) What diagnostic test can help differentiate between an intrarenal and extrarenal cause of the potassium loss? (Measurement of urine $K^+$ concentration and calculation of the transtubular potassium gradient.) What role does the thiazide diuretic likely play here? (The gastrointestinal [GI] losses are likely the primary cause of the potassium loss, with HCTZ limiting her ability to retain sufficient potassium to compensate. Given the combination of losses, measurement of urine $K^+$ and calculation of the transtubular potassium gradient are not necessary.) How should the patient be managed initially? (Oral repletion of potassium, reserving intravenous repletion [which can be dangerous] if the patient does not tolerate oral potassium. Hydration intravenously or orally. Suspension of HCTZ until full recovery.) If her potassium level were to remain low after initial repletion, is there another electrolyte abnormality that should be explored? (Yes. Look for a low serum magnesium level.)
What are the essentials of diagnosis and general considerations regarding hypokalemia?
Essentials of Diagnosis

- Serum K$^+$ is below 3.5 mEq/L (< 3.5 mmol/L).
- Severe hypokalemia may induce dangerous arrhythmias and rhabdomyolysis.
- Transtubular potassium concentration gradient (TTKG) can distinguish renal from nonrenal loss of potassium.

General Considerations

- GI loss from infectious diarrhea is the most common cause.
- Potassium shift into the cell is transiently stimulated by insulin and glucose and facilitated by β-adrenergic stimulation; α-adrenergic stimulation blocks potassium shift into the cell.
- Aldosterone increases potassium secretion in the distal renal tubule.
- Magnesium is a cofactor for potassium uptake and is required for maintenance of potassium levels; magnesium depletion should be suspected in persistent or refractory hypokalemia.
What are the symptoms and signs of hypokalemia?
Symptoms and Signs

- Muscular weakness, fatigue, and muscle cramps are common in mild to moderate hypokalemia.
- Constipation or ileus may result from smooth muscle involvement.
- Flaccid paralysis, hyporeflexia, hypercapnia, tetany, and rhabdomyolysis may be seen in severe hypokalemia (serum K\(^+\) < 2.5 mEq/L).
- Hypertension may result from aldosterone or mineralocorticoid excess.
- Renal manifestations include nephrogenic diabetes insipidus and interstitial nephritis.
What are the causes of hypokalemia?
Causes

- Potassium shift into cell: insulin excess; alkalosis; β-adrenergic agonists; trauma; hypokalemic periodic paralysis; barium or cesium intoxication

- Renal potassium loss (urine $K^+ > 40$ mEq/L)
  - Increased aldosterone (mineralocorticoid) effects from primary or secondary hyperaldosteronism, renovascular or malignant hypertension, Cushing syndrome, European licorice (inhibits cortisol), renin-producing tumors, or congenital abnormalities of steroid metabolism (e.g., adrenogenital syndrome, 17α-hydroxylase defect)
  - Increased urine flow at the distal nephron from diuretics (furosemide, thiazides) or salt-losing nephropathy
  - Hypomagnesemia, often from a medication effect (e.g., aminoglycoside, cetuximab, cisplatin, amphotericin B, pentamidine)
  - Renal tubular acidosis (type I or II) from Fanconi syndrome, interstitial nephritis, or metabolic alkalosis (bicarbonaturia)
  - Genetic disorder of the nephron such as Bartter or Liddle syndrome

- Extrarenal potassium loss (urine $K^+ < 20$ mEq/L): vomiting, diarrhea, laxative abuse, villous adenoma, Zollinger-Ellison syndrome
What are the laboratory and procedural findings in hypokalemia?
Laboratory Tests

- Serum K⁺ is below 3.5 mEq/L (< 3.5 mmol/L).
- Urinary potassium concentration is low (<20 mEq/L) as a result of extrarenal loss and inappropriately high (>40 mEq/L) with renal loss.
- Calculating TTKG is a rapid method to evaluate net potassium secretion.

\[
TTKG = \frac{\text{Urine K⁺/Plasma K⁺}}{\text{Urine osm/Plasma osm}}
\]

- Hypokalemia with TTKG above 4 suggests renal potassium loss with increased distal K⁺ secretion.
  - In such cases, plasma renin and aldosterone levels are helpful in differential diagnosis.
  - The presence of nonabsorbed anions, including bicarbonate, also increases the TTKG.

Diagnostic Procedures

- ECG can show decreased amplitude and broadening of T waves, prominent U waves, premature ventricular contractions, and depressed ST segments.
What are the treatments for hypokalemia?
Medications

- Oral potassium is the safest way to treat mild to moderate deficiency.
- Dietary potassium is almost entirely coupled to phosphate—rather than chloride—and does not correct potassium loss associated with chloride depletion, such as from diuretics or vomiting.
- In the setting of abnormal kidney function and mild to moderate diuretic dosage, daily oral potassium therapy is generally sufficient to prevent hypokalemia.
- Indications for intravenous potassium replacement include severe, life-threatening hypokalemia or an inability to tolerate oral supplementation.
- Coexisting magnesium and potassium depletion can result in refractory hypokalemia despite potassium repletion if there is no magnesium repletion.
A 75-year-old man with small cell carcinoma of the lung presents to the emergency department with altered mental status. The patient’s wife states that over the past few days, he has become progressively more lethargic. His appetite has been poor, but he willingly ingests water, consuming 2 to 3 quarts per day. On examination, the patient is a cachectic man in mild respiratory distress. He is lethargic but arousable. He is oriented to person only. His temperature is 38°C, blood pressure is 110/60 mm Hg, heart rate is 88 beats/min, respiratory rate is 18 breaths/min, and oxygen saturation is 96% (on 3 L of O₂). His mucous membranes are moist. Breath sounds are decreased in the left lower posterior lung field with rales in the upper half. Extremities are without edema. Neurologic examination shows only bilateral positive Babinski reflexes and asterixis. Laboratory studies reveal a serum sodium level of 118 mEq/L.

What are the salient features of this patient’s problem? How do you think through his problem?
Salient features: Altered mental status; lethargy; increased free water intake; low serum sodium; an underlying diagnosis (lung cancer) associated with the syndrome of inappropriate antidiuretic hormone secretion (SIADH)

How to think through: In “true” hyponatremia (hypotonic hyponatremia), which hormone causes the problem? (ADH.) In normal physiology, how does the body regulate osmolarity? (By retaining water via ADH.) How does the body regulate intravascular volume? (By retaining sodium via the reninangiotensin–aldosterone axis, but ADH can be a powerful regulator of volume as well). What laboratory characteristic is shared by all patients with hyponatremia? (Urine osmolarity > serum osmolarity.) How do we classically break down the differential diagnosis of hyponatremia? (By volume status.) What are indications of volume status in this case? (Blood pressure, heart rate, mucous membranes, absence of edema.) What are the causes of euvolemic hyponatremia? (Water intoxication, SIADH.) What diseases are associated with SIADH? What is the appropriate initial treatment? (Free water restriction.)
What are the essentials of diagnosis and general considerations regarding hyponatremia?
Essentials of Diagnosis
- Serum Na⁺ is below 130 mEq/L (<130 mmol/L).
- Hyponatremia usually reflects excess water retention relative to sodium rather than sodium deficiency.
- The patient’s volume status and serum osmolality are essential to determine the cause.
- Hypotonic fluids commonly cause hyponatremia in hospitalized patients.

General Considerations
- It is the most common electrolyte abnormality observed in a general hospitalized population.
- Most cases reflect water imbalance and abnormal water handling, not sodium imbalance.
- ADH plays a primary role in the pathophysiology of hyponatremia.
- A diagnostic algorithm using serum osmolality and volume status separates the causes of hyponatremia into therapeutically useful categories.
What are the symptoms and signs of hyponatremia?
Symptoms and Signs

- Mild hyponatremia (plasma sodium 130–135 mEq/L) is usually asymptomatic.
- As the serum sodium concentration drops, nausea and malaise progress to headache, lethargy, and disorientation.
- The most serious symptoms of severe and rapidly developing hyponatremia are:
  - Seizure
  - Coma
  - Permanent brain damage
  - Respiratory arrest
  - Brainstem herniation
  - Death
What are the causes of hyponatremia?
Isotonic Hyponatremia or Pseudohyponatremia
- Severe hyperlipidemia and hyperproteinemia interfering with sodium measurement

Hypotonic Hyponatremia
- **Hypovolemic**: renal or extrarenal volume loss with hypotonic fluid replacement; cerebral salt wasting seen in patients with intracranial disease
- **Euvolemic**: SIADH, postoperative hyponatremia, hypothyroidism, adrenal insufficiency, psychogenic polydipsia, beer potomania, drug reaction (thiazides, angiotensin-converting enzyme inhibitors), endurance exercise, reset osmostat
- **Hypervolemic**: heart failure, cirrhosis, nephrotic syndrome, advanced kidney disease

Hypertonic Hyponatremia
- Hyperglycemia and mannitol administration for increased intracranial pressure; Glucose and mannitol osmotically pull intracellular water into the extracellular space
What are the laboratory findings in hyponatremia?
Laboratory Tests

- Serum Na\(^+\) below 130 mEq/L (<130 mmol/L)
- Obtain other serum electrolytes, serum creatinine, serum osmolality, and urine sodium
- Thyroid and adrenal function tests may occasionally be necessary to enable diagnosis of SIADH
What are the treatments for hyponatremia?
Medications

- Regardless of volume status, restrict free water and hypotonic fluid intake.
- For hypovolemic patients, fluid resuscitation with isotonic fluids (either normal saline or lactated Ringer solution) is given.
- For cerebral salt wasting, hypertonic saline or normal saline and fludrocortisone are given.
- For hypervolemic patients, loop diuretics, dialysis, or both are given.
- Euvolemic patients may respond to free water restriction alone.
- Correct glucose and discontinue inciting medications (if possible).
- Symptomatic and severe hyponatremia may require medications, hypertonic saline, or both.
- Too rapid of correction can lead to central pontine myelinolysis; frequent monitoring and slow correction are necessary when initiating treatment.
- Demeclocycline inhibits ADH and is used in those who cannot restrict water or who do but do not respond.
- Vasopressin antagonists such as tolvaptan mediate the diuretic effect of ADH.
A 36-year-old woman with diabetes mellitus sustained a fall onto her arm at a construction site. In the emergency department, she had radiography showing a complex radial fracture and then a preoperative computed tomography (CT) scan with contrast. She subsequently underwent pinning and reconstructive surgery of her arm with perioperative broad-spectrum antibiotics. Her blood pressure remained normal throughout her surgery. On the second hospital day, there was a doubling of her serum creatinine, from 0.8 to 1.9 mg/dL. Her urine output dropped to 20 mL/hr. Serum creatine kinase returned at 600 units/L.

What are the salient features of this patient’s problem? How do you think through her problem?
Salient features: Increase in serum creatinine concentration; oliguria; traumatic injury and moderately elevated creatine kinase; administration of iodinated contrast and antibiotics

How to think through: Serum creatinine is an indirect measure of glomerular filtration rate (GFR). What are the limitations to its use as a measure of GFR? (It accurately reflects GFR only when renal function is at a steady state. This patient’s creatinine rose from 0.8 to 1.9 mg/dL in 24 hours, indicating complete cessation of renal function—a GFR of 0!) How would you rank possible causes of acute kidney injury (AKI) in this case? (Contrast nephropathy > rhabdomyolysis > acute tubular necrosis [ATN].) Iodinated contrast can cause rapid onset of AKI, especially in those with diabetes and chronic kidney disease. Rhabdomyolysis generally causes an elevated serum creatine kinase (into the thousands), more often in substance abuse or prolonged stasis. Could the antibiotics have caused ATN? (Possibly, but its onset is typically slower.) Could they have caused acute interstitial nephritis? (Again, the onset is too fast, and there was no evidence of fever, rash, or white blood cell casts.) What are key elements of the workup for AKI? (Urinalysis microscopic examination for red blood cells, white blood cells, and casts; urine protein, creatinine, and sodium; renal ultrasonography.) How is AKI managed? (Daily weights; input and output; volume status; strict monitoring of electrolytes; adjustment of medication doses; avoidance of nonsteroidal antiinflammatory drugs (NSAIDs), angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers, and diuretics; low-potassium diet.)
What are the essentials of diagnosis and general considerations regarding acute kidney injury?
Essentials of Diagnosis
- Defined as a sudden decrease in kidney function, resulting in an inability to maintain acid–base, fluid, and electrolyte balance and to excrete nitrogenous wastes
- Sudden increase in blood urea nitrogen (BUN) or serum creatinine
- Oliguria often associated
- Symptoms and signs depend on cause

General Considerations
- 5% of hospital admissions and 30% of intensive care unit admissions have AKI.
- 25% of hospitalized patients develop AKI.
- Serum creatinine concentration can typically increase 1.0 to 1.5 mg/dL daily.
- There are three categories of AKI: prerenal, intrinsic renal, and postrenal causes.
What are the symptoms and signs of acute kidney injury?
Symptoms and Signs

- Nausea, vomiting, malaise
- Hypertension
- Pericardial friction rub, effusions, and cardiac tamponade
- Arrhythmias
- Rales and volume overload
- Abdominal pain and ileus
- Bleeding secondary to platelet dysfunction
- Encephalopathy, altered sensorium, asterixis, seizures
- Oliguria, defined as urinary output below 500 mL/day or below 20 mL/hr
What is the differential diagnosis of acute kidney injury?
Differential Diagnosis

Prerenal Causes
- Dehydration, hemorrhage, heart failure, renal artery stenosis, NSAIDs, ACE inhibitors

Postrenal Causes
- Obstruction (e.g., benign prostatic hyperplasia, bladder tumor)

Intrinsic Renal Disease
- ATN: ischemia, toxins (e.g., NSAIDs, antibiotics, radiographic contrast, rhabdomyolysis, chemotherapy, multiple myeloma)
- Acute glomerulonephritis: immune complex, pauci-immune (antineutrophil cytoplasmic antibody positive), antiglomerular basement membrane
- Vascular: malignant hypertension, atheroembolism, thrombotic thrombocytopenic purpura
- Acute interstitial nephritis (AIN): drugs (sulfa, NSAIDs, β-lactams, allopurinol, diuretics, rifampin), infections, immune (systemic lupus erythematosus, Sjögren syndrome, sarcoidosis, cryoglobulinemia)
What are the laboratory, imaging, and procedural findings in acute kidney injury?
Laboratory Tests
- Serum creatinine and BUN elevated
- Hyperkalemia, hyperphosphatemia, hypocalcemia, anion gap metabolic acidosis
- BUN:creatinine ratio above 20:1 in prerenal, postrenal causes, and acute glomerulonephritis
- Fractional excretion of sodium (FE$_{Na}$) with oliguria: low (< 1%) in prerenal causes; high (> 1%) in ATN

Imaging Studies
- Renal ultrasonography to exclude obstruction or other anatomic abnormalities; check renal size and echo texture
- CT or magnetic resonance imaging if retroperitoneal fibrosis from tumor or radiation is suspected

Diagnostic Procedures
- Electrocardiogram: peaked T waves, PR prolongation, and QRS widening in hyperkalemia, long QT with hypocalcemia
What are the treatments for acute kidney injury?
Therapeutic Procedures

- Prerenal insults: maintain euvoemia, monitor electrolytes, avoid nephrotoxins, treat cause
- Postrenal causes: relief of obstruction if present with catheters or stents
- Intrinsic renal disease: treatment depends on cause; hold offending agents
- Hemodialysis, peritoneal dialysis indications include:
  - Uremic symptoms such as pericarditis, encephalopathy, or coagulopathy
  - Fluid overload unresponsive to diuresis
  - Refractory hyperkalemia
  - Severe metabolic acidosis (pH <7.20)
  - Neurologic symptoms such as seizures or neuropathy
A 58-year-old obese woman with hypertension, type 2 diabetes mellitus, and chronic kidney disease (CKD) is admitted to the hospital after a right femoral neck fracture sustained in a fall. Recently, she has been complaining of fatigue and was started on epoetin alfa subcutaneous injections. Her other medications include an angiotensin-converting enzyme (ACE) inhibitor, a β-blocker, a diuretic, calcium supplementation, and insulin. On review of systems, she reports mild tingling in her lower extremities. On examination, her blood pressure is 148/60 mm Hg.

What are the salient features of this patient’s problem? How do you think through her problem?
Salient features: Hypertension; diabetes mellitus; anemia, responsive to epoetin alfa injections; lower extremity tingling suggestive of neuropathy

How to think through: What are the likely contributors to this patient’s CKD? (Hypertension, leading to glomerulosclerosis or to renal artery stenosis [or both], along with diabetic nephropathy, both likely contribute. Obesity-related kidney disease presents a third, independent possibility.) What studies would be appropriate? (Urinalysis with microscopy, urine protein measurement, renal ultrasonography.) How can urine protein be estimated? (The ratio of spot urine protein to urine creatinine approximates the number of grams of protein lost per day. A ratio >3.5 indicates nephrotic range proteinuria, which would be unexpectedly high for the above causes.) Is a renal biopsy needed? (No. In the absence of unexpected findings on the above studies or an unexpected course, the diagnosis of CKD is based on epidemiologic risk factors.) What treatments are known to slow the progression of CKD? (ACE inhibitor or angiotensin receptor blocker [ARB]; control of hypertension with a goal systolic blood pressure of ≤130 mm Hg; optimal control of diabetes.) What are the important aspects of management of this patient’s CKD while she is in the hospital? (Adjustment of all medication dosing. Monitoring of electrolytes, weight, volume status, input and output. Avoidance of nonsteroidal antiinflammatory drugs.)
What are the essentials of diagnosis and general considerations regarding chronic kidney disease?
Essentials of Diagnosis

- Decline in the glomerular filtration rate (GFR) over months to years
- Persistent proteinuria or abnormal renal morphology
- Bilateral small kidneys on ultrasonography in advanced disease

General Considerations

- Rarely reversible, progressive decline in renal function
- Affects more than 20 million Americans, or one in nine adults
- More than 70% of cases of stage 5 CKD and end-stage renal disease (ESRD) in the United States are caused by diabetes mellitus or hypertension
- Glomerulonephritis, cystic diseases, other urologic diseases account for another 12% and unknown causes ~15%
What are the symptoms and signs of chronic kidney disease?
Symptoms and Signs

- Symptoms develop slowly and are nonspecific; patients are often asymptomatic until advanced CKD
- Uremia: fatigue, weakness, malaise, anorexia, nausea, vomiting, pruritus, metallic taste in mouth
- Neurologic irritability, difficulty concentrating, insomnia, subtle memory defects, restless legs, paresthesias, and twitching
- Decreased libido, menstrual irregularities
- Chest pain can occur with pericarditis (rare)
- Hypertension is the most common sign
- Renal osteodystrophy (osteitis fibrosa cystica), osteomalacia, and adynamic bone disease
What is the differential diagnosis of chronic kidney disease?
Differential Diagnosis

- Primary glomerular diseases (e.g., focal and segmental glomerulosclerosis, IgA nephropathy)
- Secondary glomerular diseases (e.g., diabetic nephropathy, amyloidosis, sickle cell nephropathy, HIV-associated nephropathy)
- Tubulointerstitial nephritis (e.g., drug hypersensitivity, analgesic nephropathy, chronic pyelonephritis)
- Hereditary disease (e.g., polycystic kidney disease, Alport syndrome, medullary cystic disease)
- Obstructive nephropathies (e.g., prostatic disease, nephrolithiasis, congenital)
- Vascular diseases (e.g., hypertensive nephrosclerosis, renal artery stenosis)
What are the laboratory, imaging, and procedural findings in chronic kidney disease?
Laboratory Tests
- Serum creatinine and blood urea nitrogen (BUN) are elevated with evidence of previous elevation
- Anemia, platelet dysfunction, bleeding time prolongation
- Metabolic acidosis
- Hyperphosphatemia, hypocalcemia, hyperkalemia
- Isosthenuria, proteinuria, urinary sediment with broad waxy casts

Imaging Studies
- Renal ultrasonography for anatomic abnormalities, kidney size, and echogenicity

Diagnostic Procedures
- Possible renal biopsy if etiology is unclear
What are the treatments for chronic kidney disease?
Medications
- Hyperkalemia is treated with sodium polystyrene sulfonate.
- Acid–base disorders can be treated with sodium bicarbonate.
- Hypertension is treated with ACE inhibitors or ARBs, if serum potassium and GFR permit, and often diuretics.
- Anemia is treated with iron supplementation (if evidence of iron deficiency) and erythropoietin or darbepoetin.
- Coagulopathy may be helped acutely with desmopressin (DDAVP) and chronically by dialysis.
- Renal osteodystrophy and osteomalacia are treated with phosphorous-binding agents, vitamin D, and calcitriol.

Therapeutic Procedures
- Diet: low sodium, low potassium, low phosphorus, water restriction to maintain fluid balance
- Kidney transplantation
- Hemodialysis or peritoneal dialysis for end-stage CKD manifesting fluid overload, hyperkalemia, metabolic acidosis, or severe uremia (e.g., pericarditis, neuropathy, other neurologic symptoms)
A 48-year-old man presents to the emergency department with severe, colicky right flank pain. He denies dysuria and fever. He does report significant nausea without vomiting. He has never experienced anything like this before. On examination, he is afebrile, his blood pressure is 160/80 mm Hg, and his pulse rate is 110 beats/min. He is writhing on the gurney, unable to find a comfortable position. His right flank is mildly tender to palpation, and abdominal examination is benign. Urinalysis is significant for 1+ blood, and microscopy reveals 10 to 20 red blood cells (RBCs) per high-power field. Nephrolithiasis is suspected, and the patient is intravenously hydrated and given pain medication with temporary relief.

What are the salient features of this patient’s problems? How do you think through his problems?
Salient features: Flank pain; first episode in the fourth decade of life; nausea and vomiting; writhing in discomfort; afebrile; flank tender to palpation; benign abdominal examination; hematuria

How to think through: The colicky pain with the hematuria suggests nephrolithiasis. The patient also has demographic risk factors. (Stones occur in men > women; ages 30–50 years.) What feature in this case makes nephrolithiasis more likely than an acute abdomen? (The patient is moving continually.) Why is he hypertensive and tachycardic? (Most likely because of pain.) What is the most common type of renal calculi? (Calcium oxalate.) Treatment and dietary interventions vary based on the type of stone. Although serum and urine studies can help ascertain the type of stone, as can radiographic lucency and appearance, analysis of a recovered stone is best. Which stones are radiolucent on plain abdominal radiography? (Uric acid stones.) What radiographic study is preferred? (Noncontrast helical computed tomography [CT].) The largest stone that can pass spontaneously is 6 mm. Can any medications facilitate the passage of a stone? (α-Blockers and calcium channel blockers.) Pain control with nonsteroidal antiinflammatory drugs and opioids is the other key component of treatment. What developments in this case would serve as indications for further intervention? (Failure to pass the stone; intractable pain and nausea; fever.) What are some of the interventions available? (Extracorporeal shock wave or percutaneous lithotripsy.) What dietary modification should be recommended to prevent recurrence? (Low-salt diet; decreased animal protein intake; increased fluid intake.)
What are the essentials of diagnosis and general considerations regarding kidney stone disease?
Essentials of Diagnosis

- Flank pain, hematuria, nausea and vomiting
- Identification of stone on noncontrast spiral CT scan

General Considerations

- Kidney stones affect men more often than women; high-protein and high-salt diets and genetic factors such as cystinuria and distal renal tubular acidosis contribute to stone formation
- Five types of kidney stones: calcium oxalate, calcium phosphate, struvite, uric acid, cystine
- Most urinary stones contain calcium (85%) and are radiopaque; uric acid stones are radiolucent
- Uric acid calculi: from malignancy, uricosuric medications, abrupt weight loss, low urine pH
- Struvite calculi ("staghorn" calculi) occur with recurrent urinary tract infections with urease-producing organisms, including *Proteus*, *Pseudomonas*, and *Providencia* spp.
- Cystine calculi: an inherited disorder with recurrent stone disease
What are the symptoms and signs of kidney stone disease?
Symptoms and Signs

- Symptoms include severe, colicky, episodic pain in the flank radiating to the abdomen with nausea and vomiting.
- Patients are constantly moving in sharp contrast to those with an acute abdomen.
- With a stone in the ureter, pain may be referred into the ipsilateral testis or labium.
- With a stone at the ureterovesical junction, marked urinary urgency and frequency occur.
- After the stone passes into the bladder, there is minimal pain with passage through the urethra.
- Stone size does not correlate with the severity of symptoms.
What is the differential diagnosis of kidney stone disease?
Differential Diagnosis

- Cholecystitis
- Appendicitis
- Diverticulitis
- Epididymitis
- Pyelonephritis
- Prostatitis
- Pancreatitis
- Lower lobe pneumonia
- Abdominal aortic aneurysm
- Musculoskeletal pain
What are the laboratory and imaging findings in kidney stone disease?
Laboratory Tests

- Urinalysis: microscopic or gross hematuria in 90%
- Urinary pH: <5.5 suggests uric acid or cystine stones; ≥7.2 suggests a struvite stone; between 5.5 and 6.8 typically indicates calcium-containing stones
- Serum calcium, electrolytes, and uric acid; stone analysis of any recovered stones
- Recurrent stones or family history may require 24-hr urine collection for volume, pH, calcium, uric acid, oxalate, phosphate, sodium, and citrate; serum parathyroid hormone if hypercalciuria is documented

Imaging Studies

- Plain radiography of the abdomen and renal ultrasonography will diagnose most stones
- Spiral CT is often first-line tool; only indinavir-related calculi are not visible
What are the treatments for kidney stone disease?
Medications

- Renal hypercalciuria: thiazides (effective long term)
- Hyperoxaluric calcium nephrolithiasis: oral calcium supplements
- Uric acid calculi: alkalinization of the urine and allopurinol for hyperuricemia
- Struvite calculi: stone extraction, consideration of suppressive antibiotics
- Cystine calculi: alkalinization of the urine, increase fluid intake, penicillamine and tiopronin

Surgery

- Ureteral obstruction with infection requires antibiotics and surgical drainage
- Stones smaller than 6 mm usually pass spontaneously; tamsulosin, ibuprofen, and corticosteroids may aid passage
- Renal calculi may require extracorporeal shock wave or percutaneous lithotripsy
- Resorptive hypercalciuria: surgical resection of the parathyroid adenoma
A 43-year-old man with severe depression is brought into the emergency department after being found collapsed at home. His family states that he had been recently despondent, and they had not heard from him for 3 days. On physical examination, he is unresponsive and tachypneic with a respiratory rate of 41 breaths/min despite a normal lung examination. His chest radiograph findings are unremarkable. An arterial blood gas (ABG) analysis shows a pH of 6.93, $\text{Pa}_2$ of 20 mm Hg, $\text{Pa}_2$ of 100 mm Hg, and a $\text{HCO}_3^-$ of 4 mEq/L. Serum electrolyte tests show an anion gap of 35.

What are the salient features of this patient’s problem? How do you think through his problem?
Salient features: Severe depression; tachypnea without evidence of lung disease; acidemia with decreased PaCO₂ and increased anion gap

How to think through: The emergency room team has obtained the most crucial test for a nonresponsive, tachypneic patient: the ABG analysis. ABG interpretation is complex, and the test is typically obtained during inherently stressful clinical circumstances, necessitating a systematic approach. Is the patient hypoxic? (No.) Is he acidemic or alkyleneic? (Acidemic.) Is the primary cause metabolic or respiratory? (Metabolic. He is hyperventilating, effectively reducing the PaCO₂ well below the normal value of 40 mm Hg.) Is there an anion gap? (Yes, the anion gap is 35.) The disorder can now be named anion-gap metabolic acidosis with compensatory respiratory alkalosis. What is the differential diagnosis of this disorder? (Diabetic or alcoholic ketoacidosis, uremia, lactic acidosis, ethylene glycol or methanol ingestion, salicylate or paraldehyde intoxication, isoniazid or iron overdose.) The history of depression raises the concern for a suicide attempt by an ingestion. Which of the above should be prioritized, and what should be the next diagnostic steps? (An osmol gap would support methanol or ethylene glycol ingestion. The serum salicylate level should also be checked.) What is the treatment for methanol or ethylene glycol ingestion? (Fomepizole, a competitive inhibitor of alcohol dehydrogenase; hemodialysis.) When ingestion of any substance is suspected, co-ingestion should be considered (e.g., the serum acetaminophen level should always be checked).
What are the essentials of diagnosis and general considerations regarding metabolic acidosis?
Essentials of Diagnosis

- Metabolic acidosis can be classified by either an increased or normal anion gap.
- Anion gap = Na\(^+\) – (HCO\(^3\)\(^-\) + Cl\(^-\))
- The hallmark of anion gap metabolic acidosis is that the low HCO\(^3\)\(^-\) is associated with either normal or increased serum Cl\(^-\) so that the anion gap increases or remains normal, respectively.

General Considerations

- Calculation of the anion gap is useful in determining the cause of the metabolic acidosis.
- A normochloremic (increased anion gap) metabolic acidosis generally results from addition to the blood of organic acids such as lactate, acetoacetate, \(\beta\)-hydroxybutyrate, and exogenous toxins (e.g., ethylene glycol, methanol, or salicylate).
- Most common causes of non–anion gap acidosis are gastrointestinal (GI) HCO\(_3\)^\(^-\) loss and defects in renal acidification (renal tubular acidoses).
What are the symptoms and signs of metabolic acidosis?
Symptoms and Signs

- Symptoms are mainly those of the underlying disorder or toxicity.
- Compensatory hyperventilation may be misinterpreted as a primary respiratory disorder.
- When severe, Kussmaul respirations (deep, regular, sighing respirations indicating intense stimulation of the respiratory center) occur.
- Acid–base disorders may be mixed; mixed acid–base disorder occurs frequently in alcoholism.
- Three major types of renal tubular acidosis (RTA) can be differentiated by the clinical setting: urinary pH, urinary anion gap, and serum K⁺ level.
What is the differential diagnosis of metabolic acidosis?
Differential Diagnosis

*Anion Gap*
- Lactic acidosis (type A: cardiogenic, septic, shock; type B: metabolic causes and toxins)
- Diabetic ketoacidosis
- Alcoholic ketoacidosis
- Uremic acidosis (usually at glomerular filtration rate <15–30 mL/min)
- Ethylene glycol toxicity
- Methanol toxicity
- Salicylate toxicity (mixed metabolic acidosis with respiratory alkalosis)

*Non–Anion Gap*
- GI HCO$_3^-$ loss
- Defects in renal acidification (RTA types I, II, or IV)
What are the laboratory findings in metabolic acidosis?
Laboratory Tests

- Blood pH, serum HCO$_3^-$, and Pco$_2$ are decreased; hyperkalemia may be seen.
- Anion gap is increased (normochloremic), normal, or decreased (hyperchloremic).
- In lactic acidosis, lactate levels are at least 4 to 5 mEq/L but are commonly 10–30 mEq/L.
- The diagnosis of alcoholic ketoacidosis is supported by the absence of a diabetic history and no evidence of glucose intolerance after initial therapy.
- Urinary anion gap from a random urine sample (urine [Na$^+$ + K$^+$] – Cl$^-$) helps differentiate between renal and GI etiologies of non–anion gap acidosis. The urinary anion gap is negative if the cause is GI HCO$_3^-$ loss (diarrhea) since renal acidification remains normal and NH$_4$Cl excretion increases. If the cause is distal RTA, the urinary anion gap is positive since the kidney cannot excrete NH$_4$Cl.
What are the treatments for metabolic acidosis?
Medications

- The underlying disorder should be treated (e.g., restoration of tissue perfusion, volume resuscitation).
- In salicylate intoxication, alkali therapy helps to convert salicylate to salicylic acid and thus to prevent central nervous system damage.
- In methanol intoxication, fomepizole, ethanol, or both are used to inhibit alcohol dehydrogenase and mitigate toxicity.
- Treatment of RTA is mainly achieved by administration of alkali (either as bicarbonate or citrate).
- The addition of thiazides in RTA may reduce the amount of alkali required.
- Fludrocortisone may be effective in RTA cases with hypoaldosteronism.
A 40-year-old woman with Hodgkin lymphoma is admitted to the hospital because of anasarca. She has no known history of renal, liver, or cardiac disease. Her serum creatinine level is 1.4 mg/dL, serum albumin level is 2.8 g/dL, and liver test results are normal. Urinalysis shows no red or white blood cell casts but 4+ protein. A 24-hour urine documents a protein excretion of 4 g/24 hr. She is diagnosed with nephrotic syndrome. Renal biopsy shows minimal change disease. Corticosteroids and diuretics are instituted, with gradual improvement of edema. Her hospital course is complicated by a deep venous thrombosis of the left calf and thigh that requires systemic anticoagulation.

What are the salient features of this patient’s problem? How do you think through her problem?
Salient features: Anasarca; elevated serum creatinine; hypoalbuminemia; bland urine sediment; proteinuria above 3 g/24 hr; minimal change disease on renal biopsy; resolution with corticosteroid therapy; associated thrombosis from hypercoagulability

How to think through: In a patient with new edema, the urinalysis is essential in diagnosis of possible nephritic or nephrotic syndromes. What is the criterion for nephrotic range proteinuria? (>3.5 g/d.) Along with proteinuria, what are the other components of nephrotic syndrome? (Hypoalbuminemia <3.0 g/dL; edema, periorbital edema, pulmonary edema, pleural effusion, and anasarca; hyperlipidemia with fat bodies in the urine; hypercoagulability.) Acute kidney injury does not always accompany nephrotic syndrome, and a normal serum creatinine level should not halt investigation. What are the four most common causes of nephrotic syndrome? (Minimal change disease, focal glomerular glomerulosclerosis, membranous nephropathy, membranoproliferative glomerulonephropathy.) What common medication may precipitate nephrotic syndrome, mimic minimal change disease, and increase the chance of acute kidney injury? (Nonsteroidal antiinflammatory drugs.) Patients with nephrotic syndrome have impaired immune defenses, and a significant fraction have a thrombotic event. Why? (Urinary loss of proteins [IgG, antithrombin, and plasminogen] likely plays a role.) Was renal biopsy needed in this case? (Yes. A firm diagnosis is needed to choose the correct treatment.) With the biopsy result, how should she be managed? (Corticosteroids, tapered over several months; diuretic; angiotensin-converting enzyme [ACE] inhibitor; warfarin; and low-sodium diet.)
What are the essentials of diagnosis and general considerations regarding nephrotic syndrome?
Essentials of Diagnosis
- Bland urine sediment with few, if any, cells or casts; may have oval fat bodies
- Proteinuria >3 g/day, serum albumin <3 g/dL, edema
- Hyperlipidemia is typical

General Considerations
- Often associated with diabetes mellitus, amyloidosis, or systemic lupus erythematosus
- Four most common lesions:
  - Minimal change disease
  - Focal glomerular glomerulosclerosis
  - Membranous nephropathy
  - Membranoproliferative glomerulonephropathy
What are the symptoms and signs of nephrotic syndrome?
Symptoms and Signs

- Peripheral edema with serum albumin <3 g/dL
- Edema is initially dependent but may become generalized and include periorbital edema
- Dyspnea caused by pulmonary edema, pleural effusions
- Abdominal distention occurs from ascites, which may worsen dyspnea
- Increased susceptibility to infection from urinary loss of immunoglobulins and complement
- Increased risk of venous thrombosis from loss of anticoagulant factors in urine protein
What is the differential diagnosis of nephrotic syndrome?
Differential Diagnosis

- Heart failure
- Cirrhosis
- Venous insufficiency
- Protein-losing enteropathy
- Malnutrition
- Hypothyroidism
What are the laboratory and procedural findings in nephrotic syndrome?
Laboratory Tests

- Serum creatinine may or may not be elevated depending on severity and chronicity
- Urinalysis with proteinuria; few cellular elements or casts; oval fat bodies appear as “grape clusters” under light microscopy and “Maltese crosses” under polarized light
- Serum albumin <3 g/dL, serum protein <6 g/dL; hyperlipidemia; elevated erythrocyte sedimentation rate
- Send serum complement levels, serum and urine protein electrophoresis, antinuclear antibodies, and serologic tests for hepatitis, as indicated

Diagnostic Procedures

- Renal biopsy is indicated in adults with new-onset idiopathic nephrotic syndrome
What are the treatments for nephrotic syndrome?
Medications
- Corticosteroids and cytotoxic agents as indicated for primary renal lesion
- Loop and thiazide diuretics in combination and often in large doses
- ACE inhibitors and angiotensin receptor blockers
- Antilipidemic agents
- Warfarin for patients with thrombosis for at least 3 to 6 mo

Therapeutic Procedures
- Dietary protein intake should replace total daily urinary protein losses; salt restriction helps edema
An 82-year-old woman with mild dementia is hospitalized in the intensive care unit (ICU) for urosepsis and treated with intravenous antibiotics. On hospital day 3, despite improvement of her sepsis, she becomes acutely confused. Her other medications include opiates for pain and diphenhydramine for insomnia. On physical examination, she is alert and can remember her name but has poor attention and believes that she is in a grocery store and that the year is 1952. Her neurologic examination findings are otherwise normal. She appears agitated and has been aggressive with the nursing staff. On subsequent examination later in the day, her symptoms are significantly better.

What are the salient features of this patient’s problem? How do you think through her problem?
Salient features: Elderly woman with underlying dementia; ICU admission; confusion despite appropriate treatment of underlying disease; opioid and anticholinergic use; disoriented with poor attention; non-focal neurologic examination; agitation; waxing and waning course

How to think through: Altered mental status is common among patients, disarming for clinicians, and alarming to families. A patient in the emergency department with altered mental status requires a broad diagnostic approach. We have more information about this hospitalized patient. What is the term for her constellation of features? (Delirium.) What are the defining features of delirium? (Acute onset or waxing and waning course and inattention and one of the following: disorganized thinking or altered level of consciousness.) How is attention assessed? (Serial 7s or spelling WORLD backwards.) What are common risk factors that predispose patients to delirium? (Baseline cognitive impairment, older age, severe illness, pain, presence of a Foley catheter, use of restraints, and polypharmacy.) What are the three most common medicine classes that contribute to delirium in elderly adults? (Benzodiazepines, opioids, and anticholinergics.) How should this patient be managed? (Discontinue medications with central nervous system [CNS] activity when possible. Nonpharmacologic interventions are the mainstay, including frequent reorientation of patient; family involvement; darkness and quiet at night, minimizing vital signs and other disruptions; manual tasks for distraction during daytime. Use of neuroleptic medications is controversial [because of increased mortality] and so is limited to patients with agitation that places them at risk of harm or that causes distress.)
What are the essentials of diagnosis and general considerations regarding altered mental status?
Essentials of Diagnosis

- Altered mental status broadly refers to a change in level of consciousness and can include delirium, stupor, and coma.
- Delirium is a transient global disorder of attention, often as a result of a systemic problem.
- Stuporous patients respond only to repeated vigorous stimuli; comatose patients are unarousable and unresponsive.

General Considerations

- Delirium may be a primary brain disease or a secondary manifestation of some general disorder.
- Delirium can coexist with dementia and should be considered a syndrome of acute brain dysfunction analogous to acute kidney injury.
- Coma is a major complication of serious CNS disorders.
- Abrupt onset of coma suggests intracerebral hemorrhage or brainstem stroke.
What are the symptoms and signs of altered mental status?
Symptoms and Signs

- Delirium usually has a rapid onset with marked deficit of memory and recall, fluctuating mental status (“waxing and waning”), and often anxiety and irritability.
- In stupor, response to painful stimuli may indicate intact sensory and motor pathways.
- Decorticate posturing occurs with lesions of the internal capsule, midbrain, pons, or cerebral peduncle.
- Pupils may suggest disease (e.g., pinpoint [opioids], ipsilateral fixed and dilated [herniation or atropine or scopolamine], small but responsive [metabolic encephalopathy]).
- Eye movements: deviation to side may suggest an ipsilateral lesion.
- Oculomotor responses to passive head turning (doll’s eyes) are impaired with brainstem lesions.
- Oculovestibular reflex tested by caloric stimulation may be absent in brainstem impairment.
- Respiratory patterns may include Cheyne-Stokes, hyperventilation, atactic, or apneustic.
ALTERED MENTAL STATUS  55D

What is the differential diagnosis of altered mental status?
Differential Diagnosis

- Drugs: opioids, alcohol, sedatives, antipsychotics
- Metabolic: hypoxia, hypo- or hyperglycemia, hypercalcemia, hypo- or hypernatremia, uremia, hepatic encephalopathy, hypo-or hyperthyroidism, vitamin B$_{12}$ or thiamine deficiency, carbon monoxide poisoning, Wilson disease
- Infectious: meningitis, encephalitis, bacteremia, urinary tract infections, pneumonia, neurosyphilis
- Structural: space-occupying lesion (e.g., brain tumor, subdural hematoma, hydrocephalus)
- Vascular: stroke, subarachnoid hemorrhage, hypertensive encephalopathy, CNS vasculitis, thrombotic thrombocytopenic purpura, disseminated intravascular coagulation, hyperviscosity
- Psychiatric: schizophrenia, depression
- Other: seizure, hypothermia, heat stroke, ICU psychosis or delirium, brain death, locked-in syndrome, persistent vegetative state
What are the laboratory, imaging, and procedural findings in altered mental status?
Laboratory Tests
- Physical examination for neurologic abnormalities, infection, or hypoxia
- Routine laboratory tests: serum electrolytes, glucose, creatinine, blood urea nitrogen, liver tests, thyroid function tests, complete blood count, arterial blood gas analysis, serum vitamin B\textsubscript{12}, and folate, urinalysis, blood cultures, cerebrospinal fluid analysis

Imaging Studies
- Urgent noncontrast computed tomography (CT) scanning of the head to identify hemorrhage, brain herniation, or mass
- Electroencephalography may be helpful for identifying seizures
- Magnetic resonance imaging can help identify abnormalities not seen on CT

Diagnostic Procedures
- Lumbar puncture if CT scan unrevealing to exclude subarachnoid hemorrhage or meningitis
What are the treatments for altered mental status?
Medications

- The aim of treatment is to identify and correct the underlying causal medical problem.
- Discontinue delirium-inducing drugs such as analgesics, corticosteroids, anticholinergics, and depressants.
- Delirious patients may require haloperidol; treat alcohol withdrawal with benzodiazepines.
- Dextrose, naloxone, and thiamine should be given intravenously without delay in patients with stupor or coma.

Therapeutic Procedures

- Stabilize patients with respiratory and circulatory support as needed.
- For delirium, a pleasant, comfortable, nonthreatening, and physically safe environment with adequate nursing or attendant services should be provided.
A 73-year-old man is brought in by his wife, who is concerned about his worsening memory. A retired engineer, he has recently been getting lost in the neighborhood where he has lived for 30 years. He has often been found wandering and been brought home by neighbors. When asked about this, he becomes upset and defensive and says that he was just trying to get some exercise. He has had trouble dressing himself and balancing his checkbook. A physical examination is unremarkable, except that he scores 18 of 30 points on the Mini-Mental Status Examination. A metabolic evaluation is normal. A computed tomography (CT) scan of the head shows generalized brain atrophy, although perhaps only what would be expected for his age, without focal lesion. He is diagnosed with dementia, likely from Alzheimer disease.

What are the salient features of this patient’s problem? How do you think through his problem?
**Salient features:** Age older than 65 years; worsening memory; wandering; loss of abilities in activities of daily living (ADLs); abnormal cognitive function test; normal metabolic evaluation; brain atrophy on head imaging studies

**How to think through:** Patients with impaired cognitive function and personality change are commonly encountered in both inpatient and outpatient settings. Before dementia can be diagnosed, delirium must be excluded. What are the distinguishing features of each? (Delirium is acute in onset, waxing and waning, with inattention and either an altered level of consciousness or disorganized thinking. Dementia is subacute in onset and marked by progressive decline in short-term memory and at least one other cognitive domain.) What other disorders may mimic dementia? (Medication toxicities, depression and psychotic disorders, thyroid disease, vitamin $B_{12}$ deficiency, HIV, syphilis, malignancy.) After Alzheimer disease is diagnosed, how should the patient be treated? (The effectiveness of cholinesterase inhibitors is modest at best. Close attention to the patient’s level of function and safety become paramount, with ADL and I-ADL assistance and emphasis on structure and routine.) The use of antipsychotic medications to control difficult behavioral symptoms is controversial. What are the two key toxicities of these medicines in patients with dementia? (Arrhythmia from prolonged QT interval and stroke.) Complications of end-stage dementia include anorexia, dysphagia, and aspiration; hospice care at this stage is often appropriate.
What are the essentials of diagnosis and general considerations regarding dementia?
Essentials of Diagnosis

- Progressive decline of intellectual function
- Loss of short-term memory and at least one other cognitive deficit
- Deficit severe enough to cause impairment of function
- Not delirious (no waxing or waning in level of consciousness)

General Considerations

- A progressive, acquired impairment in multiple cognitive domains, at least one of which is memory
- The deficits must be significant enough to interfere with work or social life
- Frequently coexists with depression and delirium
- Patients have little cognitive reserve and can have acute cognitive or functional decline with a new medical illness
- Risk factors include older age, family history, lower educational level, and female sex
- Alzheimer disease most common cause in the United States followed by vascular dementia
- Prevalence of Alzheimer disease increases precipitously with increasing age
What are the symptoms and signs of dementia?
Symptoms and Signs

Symptoms and signs consist of memory impairment with at least one or more of the following: aphasia (word-finding difficulty), apraxia (inability to perform previously learned tasks), agnosia (inability to recognize objects), or impaired executive function (poor planning, judgment, mental flexibility).

Alzheimer disease is characterized by memory and visuospatial deficits in early disease, although social graces may be retained despite cognitive decline; personality and behavioral difficulties occur as the disease progresses; end-stage disease is characterized by mutism and complete loss of function.

“Subcortical” dementias have psychomotor slowing, reduced attention, early loss of executive function, and personality changes.

Lewy body dementia may be confused with delirium and is characterized by rigidity and bradykinesia; visual, often bizarre hallucinations; and (rarely) tremor.

Frontotemporal dementias have personality change and compulsive behaviors with preserved visuospatial function.

Dementia with motor findings, such as extrapyramidal features or ataxia, may represent a less common disorder (e.g., progressive supranuclear palsy, corticobasal ganglionic degeneration, olivopontocerebellar atrophy).
What is the differential diagnosis of dementia?
Differential Diagnosis

- Depression (so-called pseudodementia)
- Mild cognitive impairment
- Delirium
- Medication side effects
What are the laboratory, imaging, and procedural findings in dementia?
Laboratory Tests
- Recommended tests include complete blood count, serum thyroid-stimulating hormone, vitamin B<sub>12</sub>, electrolytes, creatinine, glucose, and calcium.
- Testing for HIV, syphilis (e.g., fluorescent treponemal antibody [FTA] test), heavy metal screen, and liver biochemical tests may be informative but are not considered routine.

Imaging Studies
- Magnetic resonance imaging is beneficial for younger patients and those with acute onset or neurologic signs.
- Noncontrast CT is sufficient in older patients with a more classic presentation of Alzheimer disease.

Diagnostic Procedures
- Evaluate for deficits related to cardiovascular accidents, parkinsonism, or peripheral neuropathy
- Screening tests of cognitive function such as “clock draw” and “three-item recall”
- If patient fails a screening test, more formal cognitive testing is indicated (e.g., Mini-Mental Status Examination or more formal neurocognitive evaluation)
What are the treatments for dementia?
Medications

- Acetylcholinesterase inhibitors (donepezil, galantamine, rivastigmine) give modestly improved cognitive function in mild to moderate dementia but do not prevent disability.
- Choose other medications based on symptoms (depression, anxiety, psychosis).
- Haloperidol and atypical antipsychotic agents (risperidone, olanzapine, quetiapine, aripiprazole, clozapine, ziprasidone) may reduce aggressive behaviors but carry significant risks.
- The Food and Drug Administration has issued black box warning about the risk of QTc prolongation and torsades de pointes and thus the potential for sudden death with both haloperidol and atypical antipsychotic agents.

Therapeutic Procedures

- Provide structure and routine; speak simply to the patient.
- Discontinue all nonessential drugs and correct, if possible, any sensory (visual, hearing) deficits.
- Exclude unrecognized delirium, pain, urinary obstruction, or fecal impaction.
A 57-year-old woman presents to her primary care clinician complaining of insomnia for 4 months. She reports that she can often fall asleep but awakens very early in the morning and cannot get back to sleep. She has a lack of interest in things that she previously enjoyed, frequent feelings of guilt and hopelessness, decreased energy, and occasional thoughts of “ending it all.” Her symptoms are making it hard for her to perform well at her place of employment. She denies any drug or alcohol use. A physical examination, including thyroid examination, is normal. Laboratory test results, including a thyroid-stimulating hormone (TSH), are normal.

What are the salient features of this patient’s problem? How do you think through her problem?
Salient features: Sleep disturbance with early awakening; anhedonia; decreased energy; guilt and hopelessness; suicidal ideation; functional disturbance; normal examination and laboratory results; no substance use disorder

How to think through: The prevalence of depression is high; unaddressed depression is a significant cause of morbidity and impediment to successful management of other chronic diseases. This patient’s initial complaint is sleep disturbance, which is common. What are her other symptoms and signs of depression? (Loss of interest, dysphoria, decreased energy, suicidal ideation.) When considering depression, what are the other crucial psychiatric diagnoses to consider? (Bipolar disorder, adjustment disorder, dysthymia, seasonal affective disorder, and substance abuse or dependence.) What medical disorder most commonly causes symptoms that mimic depression? (Hypothyroidism.) What are the treatment options? (Psychotherapy and pharmacotherapy are equivalent in efficacy; a combination of the two is superior to either alone.) What are the classes of pharmacotherapy? (Selective serotonin reuptake inhibitors [SSRIs], tricyclics, and monoamine oxidase inhibitors [MAOIs].) What is most serious potential adverse effect of these medications? (Serotonin syndrome may occur when taken in conjunction with MAOIs or selegiline or with other serotonergic agents.) What are the common side effects of SSRIs? (Headache, nausea, tinnitus, insomnia, nervousness, and sexual dysfunction.) While monitoring treatment, one must screen for suicidal ideation.
What are the essentials of diagnosis and general considerations regarding depression?
Essentials of Diagnosis
- Up to 30% of primary care patients have depressive symptoms.
- In most depressions:
  - Mood varies from mild sadness to intense guilt, worthlessness, and hopelessness
  - Difficulty in thinking and concentration, with rumination and indecision
  - Loss of interest, with diminished involvement in activities
  - Somatic complaints, anxiety, and disrupted sleep
  - Loss of energy, appetite, and sex drive
- In some severe depressions, psychomotor disturbance, delusions, withdrawal from activities, or suicidal ideation may manifest.

General Considerations
- Sadness and grief are normal responses to loss; depression is not.
- Unlike grief, depression is marked by a disturbance of self-esteem, with a sense of guilt and worthlessness.
- Dysthymia is a chronic depressive disturbance with milder symptoms than major depression.
What are the symptoms and signs of depression?
Symptoms and Signs
- Anhedonia
- Withdrawal from activities
- Feelings of guilt
- Poor concentration and cognitive dysfunction
- Anxiety
- Chronic fatigue and somatic complaints
- Diurnal variation with improvement as the day progresses
- Vegetative signs such as insomnia, anorexia, and constipation
- Occasionally, severe agitation and psychotic ideation
- Atypical features include hypersomnia, overeating, lethargy, and rejection sensitivity
What is the differential diagnosis of depression?
Differential Diagnosis

- Bipolar disorder or cyclothymia
- Adjustment disorder with depressed mood
- Dysthymia
- Premenstrual dysphoric disorder
- Major depression with postpartum onset: usually 2 weeks to 6 months postpartum
- Seasonal affective disorder
  - Carbohydrate craving
  - Lethargy
  - Hyperphagia
  - Hypersomnia
What are the laboratory findings in depression?
Laboratory Tests

Tests to be completed to exclude medical causes of depression include:

- Complete blood cell count
- Serum TSH
- Red blood cell folate
- Toxicology screen may be indicated
What are the treatments for depression?
**Medications**

- SSRIs such as paroxetine, fluoxetine, sertraline, fluvoxamine, escitalopram, and citalopram are generally first-line therapy and have few side effects (insomnia, nervousness, sexual dysfunction); clinical response varies from 2 to 6 weeks.
- Tricyclic antidepressants (TCAs) such as amitriptyline, desipramine, nortriptyline, imipramine, amoxapine, protriptyline, and trimipramine have more side effects and are dangerous in overdose.
- MAOIs such as phenylzine, tranylcypromine, and isocarboxazid require dietary restrictions and have many drug–drug interactions; selegiline is now available as a skin patch with better tolerability.
- Potential for withdrawal syndromes requires gradual tapering of most agents.
- Drug selection should be influenced by any history of prior responses.
- If response is inadequate, can either switch to a second agent or try augmenting the first agent.
- Augmentation agents include lithium, thyroid hormone, stimulants, or addition of a second antidepressant.

**Therapeutic Procedures**

- Electroconvulsive therapy (ECT) is the most effective (70%–85%) treatment for severe depression.
  - Most common side effects are headache and memory disturbances, which are usually short lived.
- Psychotherapy (specifically cognitive behavioral therapy) alone has similar efficacy to medication, but combining medication and psychotherapy is most effective.
A middle-aged man is transported to the emergency department accompanied by a hospital nurse. She states that the patient was in line in front of her in the hospital cafeteria when he suddenly fell to the floor. He then had a “generalized tonic-clonic seizure” and was then unconscious. With assistance, she brought him to the emergency department. No other history is available. On physical examination, the patient is drowsy, confused, and unresponsive to commands. He is breathing adequately. Vital signs are temperature, 38°C; blood pressure, 170/90 mm Hg; heart rate, 105 beats/min; respiratory rate, 18 breaths/min; and oxygen saturation, 99% (on 2 L of O₂). Neurologic examination is notable for reactive pupils of 3 mm, intact gag reflex, decreased movement of the left side of the body, and positive Babinski signs bilaterally. Examination is otherwise unremarkable.

What are the salient features of this patient’s problem? How do you think through his problem?
Salient features: Witnessed seizure activity; postictal confusion; immediate neurologic abnormalities

How to think through: Can a syncopal event include myoclonic seizure-like movements? (Yes. Syncope—lack of sufficient blood flow to the brain [definition that distinguishes it from seizure]—can be associated with myoclonic jerks.) What features help identify this event as a seizure? (Postictal confusion and drowsiness, transient neurologic abnormalities consistent with Todd paralysis. Tongue biting and incontinence are also common with seizure and not with syncope.)

Knowing nothing about this patient’s history, what are the primary causes of seizure to consider? (Hypoglycemia, hyponatremia, alcohol or benzodiazepine withdrawal, medication or illicit sympathomimetic toxicity [e.g., cocaine], and central nervous system [CNS] mass effect from tumor, trauma, stroke, or infection.) How should he be managed upon arrival in the emergency department? (First, review the ABCs [airway, breathing, circulation]. Establish intravenous access. Administer thiamine and glucose. Send a complete blood count [CBC] and serum electrolytes, glucose, and calcium. Pending history and clinical course, consider CNS imaging.) What defines epilepsy? (Recurrent seizures.) What features constitute a tonic-clonic seizure? Can a patient have a bilateral tonic-clonic seizure and remain conscious? (No. Both hemispheres are involved.) How are seizures classified? (Focal vs. generalized.) What are common anticonvulsants? (Phenytoin, carbamazepine, valproic acid, phenobarbital, others.)
What are the essentials of diagnosis and general considerations regarding epilepsy?
Essentials of Diagnosis

- Recurrent seizures (epilepsy should not be diagnosed on basis of a solitary seizure)
- Characteristic electroencephalographic (EEG) changes may occur
- Postictal confusion or focal neurologic deficits may follow and last hours

General Considerations

- Genetic epilepsy onset ranges from the neonatal period to adolescence or even later in life.
- Metabolic disorders such as hypoglycemia, hyperglycemia, uremia, hyponatremia, or withdrawal from CNS depressants such as alcohol may manifest as seizures.
- Tumors and other space-occupying lesions result in seizures that are often focal.
- Vascular disease and neurodegenerative disorders may cause seizures in later life.
- CNS infections (meningitis, encephalitis, or brain abscess) must be considered in all age groups as potentially reversible causes of seizures.
- Other important causes of seizures include trauma, febrile seizures in young children, and CNS vasculitis (e.g., systemic lupus erythematosus).
What are the symptoms and signs of epilepsy?
Symptoms and Signs

- Symptoms and signs are nonspecific prodrome in some (headache, mood alterations, lethargy, myoclonic jerking).
- Aura may precede a generalized seizure by a few seconds or minutes and is itself a part of the attack, arising locally from a restricted region of the brain.
- The type of aura depends on the cerebral site of origin of the seizure (e.g., gustatory or olfactory hallucinations or visual hallucinations with temporal or occipital lesions).
- In most patients, seizures occur unpredictably.
- Fever, sleep loss, alcohol, stress, or flashing lights may precipitate seizures.
- Clinical examination may be normal interictally unless there is a structural cause for the seizures.
- Immediately postictally, there may be a focal deficit (Todd paresis) or bilateral positive Babinski signs (extensor plantar responses).
- Focal signs postictally suggest a focal CNS abnormality.
What is the differential diagnosis of epilepsy?
Differential Diagnosis

- Syncope
- Cardiac arrhythmia
- Stroke or transient ischemic attack
- Pseudoseizure
- Panic attack
- Migraine
- Narcolepsy
What are the laboratory, imaging, and procedural findings in epilepsy?
Laboratory Tests
- Hematologic and biochemical screening tests should be done for possible causes including a CBC, serum glucose, electrolytes, creatinine, calcium, magnesium, and liver tests.
- Lumbar puncture may be necessary when any sign of infection is present or to evaluate new-onset seizures.

Imaging Studies
- All patients with a progressive underlying disorder and those with new onset of seizures should undergo CNS imaging; magnetic resonance imaging (MRI) is more sensitive than computed tomography.
- Obtain an immediate MRI if there are focal neurologic symptoms or signs, focal seizures, or a focal EEG disturbance.

Diagnostic Procedures
- History is key, including eyewitness accounts.
- EEG may support clinical diagnosis, classify the seizure disorder, and guide prognosis.
- Repeated Holter monitoring may be necessary to establish the diagnosis of cardiac arrhythmia with seizure-like movements related to hypotension.
What are the treatments for epilepsy?
Medications

- Choice of antiepileptic medication is based on seizure type and side effect profile.
- Lamotrigine, levetiracetam, topiramate, and valproic acid can be used to treat both generalized and partial seizures.
- Phenytoin and carbamazepine are used in partial or secondarily generalized seizures.
- Ethosuximide, valproic acid, and clonazepam are treatments for absence seizures.
- Anticonvulsant drug treatment is generally not required for alcohol withdrawal seizures or single seizures without underlying treatable pathology; benzodiazepine (e.g., diazepam) therapy may be useful.
- Anticonvulsant drug dose is gradually increased until seizures are controlled or side effects occur.

Surgery

- Surgical resection is most efficacious when there is a single well-defined seizure focus, particularly in the temporal lobe.

Therapeutic Procedures

- Advise patients to avoid situations that may be dangerous if they have a seizure; state laws may require clinicians to report patients with seizures to public health or motor vehicle departments.
A 19-year-old freshman living in a college dormitory presents to the emergency department with 1 day of fever and headache. On presentation, she complains of anorexia, lethargy, nausea, and vomiting, as well as muscle aches and neck stiffness. On physical examination, her temperature is 39.1°C and heart rate is 124 beats/min. She appears toxic. Her neck is stiff, and there are small, purple, nonblanching petechiae on both legs. She is slightly confused about the day’s events. Lumbar puncture is performed, and the opening pressure is elevated. Cerebrospinal fluid (CSF) examination shows elevated protein, pleocytosis, low glucose, and intracellular gram-negative diplococci on gram-stained smear.

What are the salient features of this patient’s problem? How do you think through her problem?
Salient features: Young adult living in a crowded situation; headache, confusion, muscle aches; meningismus; fever and tachycardia; toxic appearance; petechial rash; CSF with elevated opening pressure, pleocytosis, elevated protein, low glucose, and intracellular organisms consistent with meningococcus on smear

How to think through: Fever, headache, nausea, and myalgias are common nonspecific symptoms, usually caused by a viral infection. The challenge is to identify patients with a more serious infection, such as bacterial endocarditis or meningitis. Clinicians should always ask patients with acute headache about neck stiffness or pain and photophobia. On physical examination, the Kernig and Brudzinski signs are not sensitive tests; the jolt test, in which headache worsens with rapid horizontal rotation, may be more sensitive. This patient’s heart rate is commensurate with fever but could also indicate the onset of shock. Her petechial rash is a crucial physical finding. Where should the examiner search for petechiae? (The entire skin and mucosa of the soft palate.) Although there is a broad differential diagnosis for a petechial rash, meningococcal meningitis is an emergency, so this finding should spur rapid evaluation and treatment. She should be placed on isolation precautions. What complications could occur? (Shock, disseminated intravascular coagulation, altered mental status, seizures, coma, death.) How should she be managed? (Rapid initiation of antibiotics. Corticosteroids improve outcomes in pneumococcal meningitis, so dexamethasone is also often given in bacterial meningitis. But meningococcus is seen on Gram stain, so corticosteroid treatment is not indicated. Fluid resuscitation is important.)
What are the essentials of diagnosis and general considerations regarding meningitis?
**Essentials of Diagnosis**
- Fever, headache, vomiting, confusion, delirium, convulsions, neck and back stiffness (meningismus)
- Purulent spinal fluid with bacteria on Gram stain and cultures
- Meningococcal disease may cause petechial rash of skin and mucous membranes

**General Considerations**
- *Streptococcus pneumoniae* is the most common cause of meningitis in adults.
- *Neisseria meningitidis* (meningococcus) is transmitted by droplets and may take the form of meningococcemia (a fulminant form of septicemia) without meningitis, meningococcemia with meningitis, or predominantly meningitis.
What are the symptoms and signs of meningitis?
**Symptoms and Signs**

- High fever, chills, and headache; nuchal and back rigidity; back, abdominal, and extremity pains; and nausea and vomiting are typical.
- In severe cases, rapid development of confusion, delirium, seizures, and coma occurs.
- Petechial rash first appears on the lower extremities and at pressure points in meningococcemia.
- Compared with meningitis caused by meningococcus, pneumococcal meningitis lacks a rash and has more focal neurologic deficits, and there may be pneumonia (and sometimes endocarditis, the so-called “Osler triad”) simultaneously.
What is the differential diagnosis of meningitis?
Differential Diagnosis

- Meningitis may be caused by other bacteria (e.g., *Listeria monocytogenes*) or viruses (e.g., echovirus causing an “aseptic” meningitis)
- Subarachnoid hemorrhage
- Encephalitis
- Petechial rash may be attributable to other cause (e.g., infective endocarditis, thrombotic thrombocytopenic purpura, other infections)
- “Neighborhood reaction” causing abnormal CSF findings, such as brain or epidural abscess, vertebral osteomyelitis, or brain tumors
- Dural sinus thrombosis
- Noninfectious meningeal irritation from carcinomatous or lymphomatous meningitis, sarcoidosis, systemic lupus erythematosus, or drug reactions
What are the laboratory, imaging, and procedural findings in meningitis?
Laboratory Tests
- Smear and culture of the CSF, oropharynx, blood, or aspirated petechiae
- CSF findings: elevated opening pressure, elevated white blood cell count (typically >1000/mcL) with a predominance of polymorphonuclear leukocytes, low glucose concentration, and elevated protein
- CSF gram stain may show bacteria, but absence does rule out the diagnosis

Imaging Studies
- If there are any neurologic defects or signs of elevated intracranial pressure, magnetic resonance imaging or computed tomography imaging should be done to exclude a mass lesion before lumbar puncture to prevent herniation (although after blood cultures are obtained, antibiotic administration should not be delayed to obtain imaging studies).

Diagnostic Procedures
- Lumbar puncture and CSF examination are essential to the diagnosis.
What are the treatments for meningitis?
Medications

- Intravenous antimicrobial therapy should be started *immediately* when meningitis is suspected.
- Empiric high-dose ceftriaxone, plus the addition of vancomycin for resistant organisms (e.g., some strains of *Pneumococcus*), should be given.
- Ampicillin is added for empiric *Listeria* coverage in patients older than age 50 years or younger than age 2 years.
- Further antimicrobial therapy is guided by cultures and susceptibility testing.
- Dexamethasone may be given intravenously immediately before or with the first dose of antibiotics.
A 35-year-old woman presents to the clinic complaining of double vision (diplopia) intermittently with progressive worsening over 2 months. In addition, she has noted intermittent drooping of her eyelids (ptosis). She works as a computer programmer, and both the diplopia and ptosis seem to worsen with prolonged computer work. Both symptoms subside with rest. She is generally fatigued but has no other weakness or neurologic symptoms. Her medical history is unremarkable. Physical examination is notable only for impaired lateral movement of the right eye and bilateral ptosis, both of which worsen with repetitive eye movements. Motor, sensory, and reflex examinations are otherwise unremarkable.

What are the salient features of this patient’s problems? How do you think through her problems?
**Salient features:** Young woman with diplopia and ptosis; intermittent but progressive symptoms; bilateral eye muscle weakness, which worsens with repetitive eye movements and improves with rest.

**How to think through:** Diplopia should always be carefully evaluated. Although it has many possible etiologies, what serious causes should be considered on initial evaluation? (Intracranial structural lesion or bleeding, temporal arteritis, thyroid ophthalmopathy, botulism, and others.) What is the pattern of symptoms seen in myasthenia gravis (MG)? (Daily fatigability, fluctuation of severity over weeks.) In addition to young women, what other demographic group is most often diagnosed with MG? (Older men.) What other comorbid and familial diseases occur with MG? (Autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, Hashimoto thyroiditis, and Graves disease.) What muscle groups should be examined? (Ocular, bulbar [dysphagia, dysarthria], respiratory, and limb muscles.) Does MG affect the pupils? (No. This can help distinguish MG from botulism and third cranial nerve compression.) Does MG affect the sensory system? (No.) What causes muscle weakness in MG? (Autoantibodies to acetylcholine receptors or to muscle-specific receptor tyrosine kinase [MuSK].) How can we confirm the diagnosis? (Acetylcholine receptor antibody testing; electrophysiologic testing, including repetitive nerve stimulation and electromyography.) When MG is diagnosed, it is important to evaluate the thymus gland for thymic hyperplasia (present in 85% of patients with MG) and thymoma (in 15%). Thymoma resection can improve MG symptoms. What is the mainstay of MG treatment? (Anticholinesterase drugs.)
What are the essentials of diagnosis and general considerations regarding myasthenia gravis?
Essentials of Diagnosis

- Fluctuating weakness of voluntary muscles, producing symptoms such as diplopia, ptosis, and difficulty in swallowing
- Activity increases weakness of affected muscles
- Short-acting anticholinesterases transiently improve the weakness

General Considerations

- MG is most common in young women with HLA-DR3 and in older men with associated thymoma.
- MG is also associated with thyrotoxicosis, rheumatoid arthritis, or systemic lupus erythematosus.
- The onset is usually insidious but may be unmasked by a coincidental infection.
- Exacerbations may occur before the menstrual period and during or shortly after pregnancy.
- Symptoms are attributable to blockage of neuromuscular transmission caused by autoantibodies binding to acetylcholine receptors.
- The external ocular muscles and certain other cranial muscles, including the masticatory, facial, and pharyngeal muscles, are especially likely to be affected.
- The respiratory and limb muscles may also be involved.
What are the symptoms and signs of myasthenia gravis?
Symptoms and Signs

- Initial symptoms include ptosis, diplopia, difficulty chewing or swallowing, respiratory difficulty, or limb weakness.
- Weakness may be generalized or localized to a few muscle groups, especially the extraocular muscles.
- Symptoms often fluctuate in intensity during the day.
- This diurnal variation is superimposed on a tendency to longer-term spontaneous relapses and remissions that may last for weeks.
- Clinical examination confirms the weakness and fatigability of affected muscles.
- Extraocular palsies and ptosis, often asymmetric, are common.
- Pupillary responses are normal.
- The bulbar and limb muscles are often weak, but the pattern of involvement is variable.
- Sustained activity of affected muscles increases the weakness, which improves after a brief rest.
- Sensation is normal.
- Usually no reflex changes are present.
What is the differential diagnosis of myasthenia gravis?
Differential Diagnosis

- Lambert-Eaton myasthenic syndrome (usually paraneoplastic)
- Botulism
- Aminoglycoside-induced neuromuscular weakness
What are the laboratory, imaging, and procedural findings in myasthenia gravis?
Laboratory Tests
- Elevated level of serum acetylcholine receptor antibodies
  - Test has a sensitivity of 80% to 90%
- Certain patients have an elevated level of serum antibodies to MuSK
  - These patients are more likely to have facial, respiratory and proximal muscle weakness than those with antibodies to acetylcholine receptors.

Imaging Studies
- Computed tomography of the chest with and without contrast to search for coexisting thymoma

Diagnostic Procedures
- Electrophysiology demonstrates decrementing muscle responses to repetitive stimulation.
- Needle electromyography shows marked variation in configuration and size of individual motor unit potentials in affected muscles.
What are the treatments for myasthenia gravis?
Medications

- Drugs, such as aminoglycosides, that may exacerbate MG should be avoided.
- Anticholinesterase drugs such as neostigmine or pyridostigmine provide symptomatic benefit without influencing the course of the disease.
- Corticosteroids are indicated in patients with a poor response to anticholinesterase drugs and a prior thymectomy, but weakness may be initially aggravated by corticosteroid treatment.
- Mycophenolate mofetil may provide symptomatic relief and allow for decreased corticosteroid dose.
- Azathioprine may also be effective.
- Plasmapheresis or intravenous immunoglobulin therapy is helpful in patient with major disability or acute crisis or for stabilization before thymectomy.

Surgery

- Thymectomy usually leads to symptomatic benefit or remission.
A 63-year-old man comes to the clinic with a several month history of difficulty with his gait and coordination. He finds walking difficult and has almost fallen on a number of occasions, especially when trying to change directions. He has also found that using his hands is difficult, and other people have noticed that his hands shake. Physical examination is notable for a resting tremor in the hands that disappears with intentional movement. He has a shuffling gait with difficulty turning. There is “cogwheeling” rigidity in his arms, a jerky sensation with passive flexion and extension of the arms.

What are the salient features of this patient’s problems? How do you think through his problems?
Salient features: Gait disturbance; difficulty in changing directions; resting tremor without intention tremor; shuffling gait; cogwheeling rigidity of limbs on physical examination

How to think through: This patient has several characteristic physical findings of parkinsonism. What other findings are commonly seen in Parkinson disease and should be explored here? (Name as many as possible, then see Symptoms and Signs.) Before concluding that this patient has idiopathic Parkinson disease, what other processes should be considered? (Extrapyramidal side effects of neuroleptic medications; multisystem atrophy, characterized in part by dysautonomia; normal-pressure hydrocephalus, characterized by difficulty initiating gait and incontinence; progressive supranuclear palsy.) What neurodegenerative process is associated with Parkinson disease? (Dementia with Lewy bodies, characterized by paranoia, visual hallucinations, waxing and waning mental status, sometimes resembling delirium.) After a diagnosis of idiopathic Parkinson disease is made, how should the patient be treated? What pharmacologic classes are used? (Anticholinergics, amantadine, carbidopa–levodopa and other dopaminergic agonists; see Treatment.) Why might we delay treatment with levodopa and use other agents initially? (Although levodopa is the most effective treatment for Parkinson disease, it can cause both dyskinesias as well as the “on–off” phenomenon in which bradykinesia alternates unpredictably with dyskinesias.) What nonpharmacologic interventions are available? (Deep brain stimulation. Additionally, all patients should have physical therapy, home safety evaluation, and mobility aids as needed.)
What are the essentials of diagnosis and general considerations regarding Parkinson disease?
Essentials of Diagnosis
- Any combination of tremor, rigidity, bradykinesia, and progressive postural instability
- Cognitive impairment is sometimes prominent

General Considerations
- Parkinson disease is a common disorder; idiopathic Parkinson disease often begins between ages 45 and 65 years.
- Dopamine depletion caused by degeneration of the dopaminergic nigrostriatal system leads to an imbalance of dopamine and acetylcholine.
- Exposure to toxins and certain medications can lead to parkinsonism, including manganese dust, carbon disulfide, severe carbon monoxide poisoning, 1-methyl-4-phenyl-1,2,5,6-tetrahydropyridine (MPTP) (a recreational drug), neuroleptic drugs, reserpine, and metoclopramide.
- Postencephalitic parkinsonism is becoming increasingly rare.
- Only rarely is hemiparkinsonism the presenting feature of a space-occupying lesion.
What are the symptoms and signs of Parkinson disease?
Symptoms and Signs

- Cardinal features are tremor, rigidity, bradykinesia, and postural instability
- Mild decline in intellectual function
- Tremor is most conspicuous at rest, four to six cycles per second, enhanced by stress, and is often absent or less severe during voluntary activity
- Rigidity causes the flexed posture
- Bradykinesia (i.e., a slowness of voluntary movement) is the most disabling symptom
- Immobility of the facial muscles with infrequent blinking and fixed facial expression (mask facies)
- Repetitive tapping (about twice per second) over the bridge of the nose producing a sustained blink response (Myerson sign)
- No muscle weakness and no alteration in the tendon reflexes or plantar responses
- Difficulty rising from a sitting position and beginning to walk
- Gait with small shuffling steps, loss of arm swing, and difficulty in turning or stopping
- Other findings include micrographia, a soft and poorly modulated voice, drooling, impairment of fine or rapidly alternating movements, slowed voluntary movements
What is the differential diagnosis of Parkinson disease?
Differential Diagnosis

- Essential tremor
- Depression
- Wilson disease
- Huntington disease
- Normal-pressure hydrocephalus
- Multisystem atrophy (previously called Shy-Drager syndrome)
- Progressive supranuclear palsy
- Corticobasal ganglionic degeneration
- Creutzfeldt-Jakob disease
- Other causes of parkinsonism: drugs causing parkinsonism such as antipsychotic agents, reserpine, metoclopramide
What are the procedural findings in Parkinson disease?
Diagnostic Procedures

- Primarily a clinical diagnosis
What are the treatments for Parkinson disease?
Medications

- Amantadine may improve all clinical features and combat dyskinesias from levodopa therapy.
- Anticholinergics are more helpful for tremor and rigidity than bradykinesia.
- Sinemet and Sinemet CR are combinations of carbidopa and levodopa in a fixed ratio.
- Entacapone and tolcapone, two catecholamine-\(O\)-methyltransferase inhibitors, may be used as an adjunct to Sinemet when there are response fluctuations or inadequate responses.
- Stalevo is a commercial preparation of levodopa combined with both carbidopa and entacapone.
- Pramipexole and ropinirole are newer dopamine agonists that are not ergot derivatives.
- Rasagiline slows disease progression, and selegiline improves levodopa response; both are selective monoamine oxidase B inhibitors.
- Confusion and psychotic symptoms often respond to atypical antipsychotic agents.

Surgery

- High-frequency bilateral stimulation of the subthalamic nuclei or globus pallidus internus may benefit all of the major features of the disease.

Therapeutic Procedures

- Physical and speech therapy and simple aids to daily living may help.
- Gene therapy trials are ongoing.
An 82-year-old woman with atrial fibrillation comes to the emergency department with 1 hour of difficulty moving her right arm and leg. Her medical history includes a transient ischemic attack (TIA), hypertension, and diabetes mellitus. She had been taking warfarin but discontinued it 3 months ago after a fall and now takes no medications. On physical examination, she has weakness in and sensory neglect of her right upper and lower extremities and a global aphasia with deficits in comprehension and object naming. Complete blood count, platelets, and coagulation panel findings are normal. Noncontrast computed tomography (CT) of the brain shows no intracranial bleeding. Intravenous recombinant tissue plasminogen activator is administered.

What are the salient features of this patient’s problem? How do you think through her problem?
**Salient features:** Elderly patient; acute onset of aphasia, right-sided hemiplegia and neglect; presentation within 4.5 hours of symptom onset; risk factors of atrial fibrillation, hypertension, diabetes mellitus, and previous TIA; on no anticoagulant medication; no intracranial bleeding

**How to think through:** Stroke is the second leading cause of death in the United States and is a major cause of morbidity. What are the likely mechanisms of this patient’s stroke? (Atrial fibrillation leading to cardioembolic stroke or hypertension and diabetes leading to carotid atherosclerosis or intracranial small vessel disease and thrombotic stroke.) What is her CHADS2 score? (Using this decision aid, she receives 1 point each for hypertension, age older than 75 years, and diabetes plus 2 points for prior TIA for a total of 5 points; without anticoagulation, this confers a 6.9% risk of stroke per year.) Based on her examination, what vascular territory is involved? (Left middle cerebral artery.) How does one differentiate aphasia from dysarthria? (Repetition of simple words is intact in most cases of aphasia and demonstrates intelligible speech production.) What factors must be assessed before thrombolysis? (Absence of hemorrhage on noncontrast CT scan; stroke or head trauma in prior 3 months; recent major surgery or major bleeding; duration of symptoms >4.5 hours; blood pressure >185/110 mm Hg; international normalized ratio >1.7; platelets >100,000/mcL.) If the patient is in atrial fibrillation the day after her stroke, should cardioversion be considered? (No! Given her atrial fibrillation, recent stroke, and lack of anticoagulation, cardioversion could precipitate an embolic stroke.)
What are the essentials of diagnosis and general considerations regarding stroke?
Essentials of Diagnosis

- Ischemic stroke is an occlusion of a major vessel leading to cerebral infarction.
- Intracerebral hemorrhage is usually caused by hypertension and occurs suddenly.
- With any stroke, the resulting deficit depends on the particular vessel involved and the extent of any collateral circulation.

General Considerations

- Ischemic and hemorrhagic strokes cannot be distinguished solely by clinical features.
- Brain imaging, usually starting with an immediate noncontrast head CT scan, is essential.
- Ischemic stroke is often caused by thromboembolism from atrial fibrillation or flutter.
- In elderly adults, cerebral amyloid angiopathy is a frequent cause of hemorrhage.
- The risk of both ischemic and hemorrhagic stroke increases with age.
What are the symptoms and signs of stroke?


**Symptoms and Signs**

- Symptoms and signs depend on the structures involved
- Ophthalmic artery occlusion: amaurosis fugax—sudden and brief monocular vision loss
- Anterior cerebral artery occlusion: weakness and sensory loss in contralateral leg, behavioral and memory disturbance, rigidity, confusion, urinary incontinence
- Middle cerebral artery occlusion: contralateral hemiplegia, hemisensory loss, homonymous hemianopia; language disturbance if dominant hemisphere (usually left) involved
- Posterior cerebral artery occlusion: ipsilateral facial, ninth and tenth cranial nerve lesions, limb ataxia and numbness, Horner syndrome
- Occlusion of both vertebral arteries or the basilar artery: coma, pinpoint pupils, quadriplegia
- Partial basilar artery occlusion: diplopia, visual loss, vertigo, dysarthria, ataxia
- Occlusion of any major cerebellar artery can cause vertigo, nausea, vomiting, nystagmus, ipsilateral limb ataxia; massive infarction can cause coma, herniation, and death
- Cerebral hemorrhage: focal neurologic signs, loss of consciousness (50% of patients), vomiting, headache, hemiplegia or hemiparesis
- Cerebellar hemorrhage: nausea, vomiting, dysequilibrium, headache, loss of consciousness
What is the differential diagnosis of stroke?
Differential Diagnosis

- Hypoglycemia
- Transient ischemic attack
- Focal seizure (Todd paralysis)
- Migraine
- Peripheral causes of vertigo (Ménière disease)
- Subarachnoid hemorrhage
- Space-occupying lesion (e.g., brain tumor)
- Subdural or epidural hemorrhage
What are the laboratory, imaging, and procedural findings in stroke?
Laboratory Tests

- Complete blood cell count, erythrocyte sedimentation rate, blood glucose, and serologic tests for syphilis
- Screening for hypercoagulable or bleeding disorders if suspected clinically
- Cerebrospinal fluid examination may be helpful for cerebral vasculitis or an inflammatory or infectious cause but only after imaging to exclude risk of herniation

Imaging Studies

- CT scan of the head (without contrast) immediately in all acute stroke to exclude hemorrhage
- Subsequent magnetic resonance imaging with diffusion-weighted sequences should be performed to define area of possible infarction
- Imaging of the cervical vasculature (e.g., MR angiography) may be warranted in selected patients

Diagnostic Procedures

- Electrocardiography or continuous cardiac monitoring and echocardiography if cardiac cause (arrhythmia, clot, vegetation, paradoxical embolus) is suspected
What are the treatments for stroke?
Medications
- Aspirin in ischemic stroke after hemorrhage has been excluded and if patient is not receiving thrombolysis
- Intravenous thrombolytic therapy with recombinant tissue plasminogen activator in ischemic stroke will reduce neurologic deficit without effect on mortality if given within 4.5 hours of symptom onset
- Contraindications to thrombolytic therapy include recent hemorrhage, risk of hemorrhage, or blood pressure greater than 185/110 mm Hg
- Anticoagulant drugs (warfarin or dabigatran) for ischemic stroke in the setting of atrial fibrillation

Surgery
- In cerebellar hemorrhage, prompt surgical evacuation of the hematoma may be indicated

Therapeutic Procedures
- Early management consists of general supportive measures
- Permissive hypertension allowed in ischemic stroke to avoid further ischemia
- Physical and occupational therapy helps with functional outcomes
A 33-year-old man visits his primary care clinician for advice about how to quit cigarette smoking. He started smoking a half pack daily at age 16 years but gradually increased over the next 6 years to 1 pack daily. He had one previous quit attempt at age 30 years but resumed smoking within several days. He has never used nicotine replacement or other medications to help quit. Currently, he smokes within a half hour of awakening, and when forced to go without cigarettes for more than a few hours (e.g., on coast-to-coast airplane flights), he begins to crave them, with restlessness and irritability. He says that smoking relaxes him, and he likes to smoke with coffee or alcohol and after meals. Over the past year, he has had several respiratory infections with prolonged cough. He and his wife have recently had their first child, and his wife and their pediatrician have asked him to avoid smoking around the infant and to try to quit.

What are the salient features of this patient’s problem? How do you think through his problem?
Salient features: ≥15 pack-year smoking history; previous quit attempt; no use of adjuvant therapies; addiction and withdrawal symptoms; using smoking to relax; cough as an adverse effect of smoking

How to think through: Tobacco is the most important of all modifiable disease risk factors. Although the approach must be tailored to each patient, smoking should be addressed by the clinician at every opportunity. The transtheoretical stages of change model provides a means of positioning a patient on the continuum of readiness to quit smoking. If this patient reports he is ready to quit, the clinician can facilitate development of a cessation plan. What are the elements of an effective, multidimensional plan? (Jointly choosing a quit date. Beginning preparation. Discussing risks and benefits of nicotine replacement, bupropion, and varenicline. Enlisting support from family, peers, groups, telephone quit lines, and behavioral medicine specialists. Avoiding activities associated with smoking and identifying smoking replacement rituals.) At the other end of the spectrum, are “precontemplators” with limited interest in quitting. What is an appropriate strategy in such cases? (Motivational interviewing. The birth of this patient’s first child and the patient’s respiratory infections are ideal anchors for such a discussion.)
What are the essentials of diagnosis and general considerations regarding smoking cessation?
Essentials of Diagnosis

- Tobacco use; dependence and withdrawal symptoms
- Assessment of willingness to quit and previous quit attempts
- History of use of nicotine replacement and other medications

General Considerations

- Smoking is the most important cause of preventable morbidity and mortality; responsible for one in four deaths in the United States; 4.8 million premature deaths worldwide attributed to smoking in 2000 alone.
- Smoking is the major cause of the leading causes of death: cardiovascular disease, chronic obstructive pulmonary disease (COPD), and lung cancer.
- It also increases risk of other cancers, stroke, peptic ulcers, pneumonia, and bone fractures.
- Second-hand smoke also has adverse effects on the cardiovascular and pulmonary systems.
- Smoking cessation reduces the risks of death and disease and increases life expectancy.
What are the symptoms and signs of smoking cessation?
Symptoms and Signs

- Nicotine withdrawal
  - Intense cravings for nicotine
  - Anxiety, frustration, irritability
  - Fatigue or insomnia
  - Depression
  - Increased caloric intake and weight gain
  - Difficulty concentrating
  - Headache
  - Nausea
- Weight gain occurs in 80% of patients; 10% to 15% have major weight gain (>13 kg)
What is the differential diagnosis of smoking cessation?
Differential Diagnosis

- Depression
- Anxiety disorder
- Other psychiatric illness
- Other or coexisting substance abuse disorder
What are the procedural findings in smoking cessation?
Diagnostic Procedures

- Clinician’s assessment of smoker’s willingness to quit and stage of change is important.
- Systems to identify smokers so that they can be targeted for intervention are essential.
- Tobacco use is undertreated; 70% of smokers see a physician each year, and only 20% receive advice or assistance about quitting.
- Patients whose clinicians advise them to quit are 1.6 times more likely to attempt quitting.
What are the treatments for smoking cessation?
Medications

- All patients without contraindications should be offered pharmacotherapy.
- Nicotine replacement with patch, gum, lozenges, nasal spray, or inhalers is effective.
- Bupropion is an effective agent for cessation; seizure disorder is a contraindication.
- Varenicline is a nicotinic acetylcholine-receptor agonist and is more effective than nicotine replacement or bupropion; increased thoughts of suicidality have been reported.

Therapeutic Procedures

- Advice to quit should be tailored to the patient’s level of readiness to change.
- Do not show disapproval of patients who have failed cessation or are not ready to quit.
- Individualized, group, or telephone counseling is effective.
A 32-year-old unemployed man presents to the emergency department with right lower quadrant (RLQ) abdominal pain of 17 hours’ duration. He has a fever of 38.9°C, rebound tenderness over MacBurney’s point, and a white blood cell (WBC) count of 18,900/mcL (with a left shift). He says he drinks alcohol “socially” (“a glass or two of wine with dinner”). He undergoes emergency appendectomy. On postoperative day 2, he becomes anxious, restless, and diaphoretic, with a heart rate of 125 beats/min and blood pressure of 164/95 mm Hg, and he begins to pick at his intravenous line. When he becomes tremulous and begins to hallucinate about “bugs,” his girlfriend admits that since losing his job 1.5 years ago, he has been depressed and drinking “almost continuously,” up to 3 to 4 bottles of wine daily. Over the next 72 hours, he develops mental confusion, sensory hyperacuity, and both hypokalemia and hypomagnesemia.

What are the salient features of this patient’s problem? How do you think through his problem?
Salient features: Unemployment; heavy alcohol use, then abstinence for 48 to 72 hours; tremulousness; visual hallucinations; abnormal vital signs; diaphoresis; anxiety, confusion; hypokalemia, hypomagnesemia

How to think through: Tachycardia and confusion in a postoperative patient warrants consideration of infection, pain, pulmonary embolism, a medication side effect, and delirium. Substance use disorders are stratified as “at risk,” “abuse,” and “dependence.” This man’s symptoms and signs of withdrawal suggest the diagnosis of alcohol dependence. The interval since the patient’s last alcohol intake can help us to anticipate the risks of its abrupt withdrawal. What are these risk? (Hallucinations [12–48 hr since last intake]; seizures [12–48 hr]; tremor, autonomic instability, delirium tremens [48–96 hr]; falls, danger to staff, need for restraints and, in rare cases, death.) Delirium tremens is characterized by a clouded sensorium and signs of autonomic instability. How should he be managed? (Benzodiazepine; thiamine; hydration; electrolyte repletion.) However, when dysautonomia is controlled by benzodiazepines but hallucinations and agitation are not, haloperidol is often used. Oversedation is a major management challenge because benzodiazepines accumulate, and it can result in endotracheal intubation to avoid aspiration.
What are the essentials of diagnosis and general considerations regarding substance abuse?
Essentials of Diagnosis

- Psychological dependence: craving and behavior involved in procurement of the drug
- Physiologic dependence: withdrawal symptoms on discontinuance of the drug
- Tolerance: the need to increase the dose to obtain the desired effects
- Addiction: impairment in social and occupational functioning

General Considerations

- Often coexists with other substance abuse and psychiatric disorders
- Underdiagnosis and treatment of substance abuse is substantial; clinician identification improves chances of recovery
- Alcohol and opioids are the most commonly abused substances
What are the symptoms and signs of substance abuse?
Symptoms and Signs

- Alcohol intoxication: drowsiness, psychomotor dysfunction, disinhibition, dysarthria, ataxia, nystagmus; severe overdosage leads to respiratory depression, stupor, coma
- Acute alcohol withdrawal: anxiety, decreased cognition, tremulousness, vital sign abnormalities, seizures
- Delirium tremens (usually 24–72 hr after last drink): mental confusion, tremor, sensory hyperacuity, visual hallucinations, diaphoresis, dehydration, seizures
- Stigmata of cirrhosis: spider angiomas, ascites, palmar erythema, gynecomastia, caput medusa
- Opioid intoxication: euphoria, drowsiness, nausea, meiosis
- Opioid overdosage: respiratory depression, peripheral vasodilatation, pinpoint pupils, pulmonary edema, coma, and death
- Opioid withdrawal: craving, anxiety; yawning, lacrimation, rhinorrhea, perspiration; mydriasis, piloerection, anorexia, tremors, hot and cold flashes, aching; vital sign abnormalities; nausea, vomiting, diarrhea
What is the differential diagnosis of substance abuse?
Differential Diagnosis

- Coexisting diseases with alcohol abuse
  - Anxiety disorders
  - Posttraumatic stress disorder
  - Depression or bipolar disorder
  - Personality disorders

- Alcohol withdrawal differential diagnosis
  - Paranoid schizophrenia
  - Hypoglycemia
  - Delirium or chronic brain disorder (e.g., dementia)
  - Acute intoxication with another substance (e.g., an amphetamine)
What are the laboratory and procedural findings in substance abuse?
Laboratory Tests

- Patients with alcoholism may have elevated liver test results, uric acid level, triglyceride level, decreased potassium and magnesium, low albumin, and coagulopathy.
- Urinalysis with toxicology screening can be valuable, although water-soluble drugs such as alcohol, stimulants, and opioids are quickly eliminated.

Diagnostic Procedures

- Evidence-based screening questionnaires such as CAGE or AUDIT (Alcohol Use Disorder Identification Test) can identify those patients with alcohol use disorders.
- May also use one-item screening: “How many times in the past year have you had X or more drinks in a day?” (X is 5 for men and 4 for women, and a response of >1 is considered positive.)
What are the treatments for substance abuse?
Medications

- Benzodiazepines such as diazepam, lorazepam, or chlordiazepoxide are used in acute alcohol withdrawal.
- Symptom-triggered benzodiazepine administration is superior to fixed dosage schedule.
- Alcohol dependence can be treated with disulfiram (aversive agent, poor compliance), naltrexone or acamprosate (reduces cravings and relapse), or topiramate (not approved for this indication by the Food and Drug Administration).
- Methadone therapy for opioid dependence given daily reduces relapses.
- Buprenorphine, a partial opiate agonist, treats opioid withdrawal with less risk than methadone and may assist in enabling patients in coming off methadone maintenance.
- Intravenous naloxone can reverse opioid overdosage but has a short duration of action.

Therapeutic Procedures

- Brief physician intervention methods; cognitive behavioral therapy
A 28-year-old man presents to the emergency department with a headache, stiff neck, and fever. After a lumbar puncture, he is admitted to the intensive care unit with meningococcal meningitis. On hospital day 3, despite antibiotic treatment, he continues to be hypotensive and in shock and complains of new abdominal pain when he is awake. On physical examination, he has multiple areas of purpura on his skin. Serum testing reveals hyponatremia, hyperkalemia, and hypoglycemia.

What are the salient features of this patient’s problem? How do you think through his problem?
**Salient features:** Meningococcal meningitis with purpura; hypotension and shock; abdominal pain; hyponatremia, hyperkalemia, hypoglycemia

**How to think through:** This case shows the importance of assessing the full differential diagnosis when treating a patient in shock. This patient has an infection, but what other causes of hypotension, beyond septic shock, could be at play? (Cardiogenic shock, anaphylactic shock, neurogenic shock, adrenal insufficiency.) How should adrenal function be evaluated? (Morning plasma cortisol level <3 mg/dL is diagnostic. Cosyntropin stimulation test indicates primary adrenal insufficiency if the rise in cortisol is <20 mcg/dL 30 to 60 minutes after administration of cosyntropin. The test is less reliable in the setting of acute illness, and thus empiric corticosteroid treatment is often warranted.) If adrenal insufficiency is suspected, what are the possible causes? (Bilateral hemorrhagic adrenal infarction; autoimmune adrenal insufficiency [Addison disease]; indolent adrenal infection such as tuberculosis; adrenal atrophy caused by chronic glucocorticoid use; secondary [pituitary level] or tertiary [hypothalamic] lesions are possible but rare.) What is the eponym for adrenal infarction in the setting of meningococcemia? (Waterhouse-Friderichsen syndrome.). How do hyponatremia and hyperkalemia help localize the problem? (Only primary adrenal disease impacts aldosterone production.) Is imaging indicated? (Yes. Computed tomography [CT] of the abdomen may show adrenal hemorrhage.) How should he be treated? (Draw a plasma cortisol level; then start intravenous hydrocortisone for hypocortisolism and 50% dextrose in water [D50W] for hypoglycemia.)
What are the essentials of diagnosis and general considerations regarding adrenocortical insufficiency?
Essentials of Diagnosis

- Weakness, anorexia, weight loss; abdominal pain, muscle and joint pains; amenorrhea
- Increased skin pigmentation in chronic disease, especially of creases, pressure areas, and nipples
- Hypotension, dehydration, hyponatremia, hyperkalemia, hypercalcemia
- Plasma cortisol levels low or fail to rise after administration of cosyntropin

General Considerations

- Adrenocortical insufficiency can be chronic or result from an acute deficiency of cortisol.
- Causes of chronic adrenocortical insufficiency include autoimmune destruction of adrenal glands; congenital; and infections such as HIV, cytomegalovirus, fungal, and tuberculosis.
- Acute adrenocortical insufficiency is an emergency condition caused by primary adrenal gland or pituitary dysfunction; it may be caused by withdrawal of cortisol replacement in patients with chronic insufficiency or by increased cortisol need in stress, trauma, surgery, or infection.
What are the symptoms and signs of adrenocortical insufficiency?
Symptoms and Signs

- Weakness and fatigability, weight loss, myalgias, anorexia, nausea and vomiting, fever
- Anxiety, mental irritability, and emotional changes common
- Skin with hyperpigmentation, especially over knuckles, elbows, knees, posterior neck, palmar creases
- Other autoimmune disease manifestations
- Hypoglycemia; in patients with diabetes, increased insulin sensitivity
- Hypotension and orthostasis are usual; systolic blood pressure above 130 mm Hg is rare
- Scant axillary and pubic hair (especially in women)
- Acute adrenal insufficiency: confusion, coma, high fever, hypotension and shock, abdominal pain, hypoglycemia
- Meningococcemia may cause purpura and adrenal insufficiency secondary to adrenal infarction (Waterhouse-Friderichsen syndrome)
What is the differential diagnosis of adrenocortical insufficiency?
Differential Diagnosis

- Other cause of shock or hypotension: medications, sepsis, hypovolemia, anaphylaxis, and cardiogenic shock
- Hyperkalemia from another cause: chronic kidney disease, rhabdomyolysis, medication effect
- Hyponatremia from another cause: hypothyroidism, diuretic use, heart failure, cirrhosis, vomiting
- Abdominal pain from another cause
- Hyperpigmentation from another cause (e.g., hemochromatosis)
- Isolated hypoaldosteronism
- Low serum cortisol-binding globulin in critical illness, causing low total serum cortisol; in these cases, serum free cortisol level is normal
What are the laboratory and imaging findings in adrenocortical insufficiency?
**Laboratory Tests**

- Moderate neutropenia, lymphocytosis, and total eosinophil count greater than 300/mcL
- Hyponatremia, hyperkalemia, hypercalcemia, hypoglycemia
- Blood, sputum, or urine culture results may be positive if bacterial infection is the precipitating cause of acute insufficiency
- Low plasma cortisol level (<3 mg/dL) at 8 AM is diagnostic, especially if accompanied by simultaneous elevated adrenocorticotropic hormone (ATCH; usually >200 pg/mL)
- Cosyntropin stimulation test is diagnostic standard synthetic ACTH 1 to 24 (cosyntropin) given; serum cortisol obtained 30 to 60 minutes later; normally, cortisol rises to ≥20 mcg/dL; hydrocortisone given before the test will interfere, but other corticosteroids such as dexamethasone will not

**Imaging Studies**

- Abdominal CT to assess adrenal glands for enlargement (neoplasm, granuloma) or calcification (tuberculosis, hemorrhage, fungal infection, pheochromocytoma, melanoma)
What are the treatments for adrenocortical insufficiency?
**Medications**
- Corticosteroid and mineralocorticoid replacement is required in most cases.
- The corticosteroid dose must be raised in case of infection, trauma, surgery, diagnostic procedures, or stress.
- Treat all infections immediately.
- If acute adrenocortical insufficiency is suspected, draw serum cortisol and ACTH levels and immediately treat with intravenous corticosteroids while waiting for results.
- Administer D50W to treat hypoglycemia with careful monitoring of serum electrolytes and creatinine, and blood urea nitrogen.

**Therapeutic Procedures**
- When an acute adrenocortical crisis is over, the clinician must assess the degree of permanent adrenal insufficiency.
A 35-year-old woman has hypertension of recent onset. Review of systems reveals several months of weight gain and menstrual irregularity. On examination, she is obese, with a plethoric appearance. The blood pressure is 165/98 mm Hg. There are prominent purplish striae over the abdomen and multiple bruises over both lower legs. The patient’s provider entertains a diagnosis of hypercortisolism (Cushing syndrome).

What are the salient features of this patient’s problem? How do you think through her problem?
Salient features: Hypertension; weight gain; menstrual irregularity (indicating pituitary dysfunction); purple striae on the abdomen

How to think through: Is a complete workup for secondary causes of hypertension appropriate in every new hypertension diagnosis? (No; 30% of U.S. adults have hypertension, and most have idiopathic “essential hypertension.” Also, tests such as endocrine assays have imperfect sensitivity and specificity. Look for symptoms and signs of secondary causes and then direct the diagnostic workup accordingly. Also, evaluate fully all cases of early onset and refractory hypertension.) In this case, evidence gathered by history and physical examination points to a possible secondary cause. In addition to her cushingoid appearance, weight gain, irregular menses, striae, and bruising, what other manifestations of cortisol excess should be sought in this patient? (Proximal muscle weakness, mood lability, elevated fasting glucose.) How do we establish that she has elevated cortisol levels or Cushing syndrome? (24-hour urine cortisol. Low-dose dexamethasone suppression test.) What test establishes the broad categories of possible causes of Cushing syndrome? (Plasma adrenocorticotropic hormone [ACTH] level. ACTH levels are abnormally high in ACTH-dependent processes such as hypothalamic cortisol-releasing hormone [CRH] hypersecretion, ACTH-producing pituitary adenoma, and ectopic ACTH-producing tumor. Plasma ACTH levels are low in ACTH-independent processes such as adrenal adenoma or exogenous corticosteroid use.) Which of these is the most common cause of Cushing disease? (Cushing disease implies an ACTH-producing pituitary adenoma.)
What are the essentials of diagnosis and general considerations regarding Cushing syndrome?
Essentials of Diagnosis

- Central obesity, muscle wasting, thin skin, psychological changes, hirsutism, purple striae
- Osteoporosis, hypertension, poor wound healing
- Hyperglycemia, leukocytosis, lymphocytopenia, hypokalemia, glycosuria
- Elevated serum cortisol and urinary free cortisol; lack of normal suppression by dexamethasone

General Considerations

- Cushing syndrome refers to manifestations of excessive corticosteroids, commonly caused by supraphysiologic doses of corticosteroid drugs.
- Cushing disease is caused by ACTH hypersecretion by the pituitary, often from an adenoma.
- ACTH-secreting pituitary adenoma (Cushing disease) is more than three times more common in women than men.
What are the symptoms and signs of Cushing syndrome?
Symptoms and Signs

- Central obesity with plethoric “moon face,” “buffalo hump,” supraclavicular fat pads, protuberant abdomen, and thin extremities
- Oligomenorrhea or amenorrhea in women (or erectile dysfunction in males)
- Hypertension, glaucoma, thirst, and polyuria
- Osteoporosis or avascular bone necrosis
- Acne, superficial skin infections, easy bruising, impaired wound healing, purple striae
- Hirsutism and virilization may occur with adrenal carcinomas
What is the differential diagnosis of Cushing syndrome?
Differential Diagnosis

- Chronic alcoholism (alcoholic pseudo-Cushing syndrome)
- Diabetes mellitus
- Depression (may have hypercortisolism)
- Osteoporosis or obesity due to other cause
- Primary hyperaldosteronism
- Anorexia nervosa (high urine free cortisol)
- Striae distensae ("stress marks") seen in adolescence and in pregnancy
- Lipodystrophy from antiretroviral agents
What are the laboratory, imaging, and procedural findings in Cushing syndrome?
Laboratory Tests
- Hyperglycemia, leukocytosis, hypokalemia without hypernatremia
- Low-dose dexamethasone suppression test: low serum cortisol level at 8 AM after dexamethasone is given at 11 PM the night before excludes Cushing syndrome
- 24-hour urine for free cortisol and creatinine can confirm hypercortisolism

Imaging Studies
- Pituitary magnetic resonance imaging shows an adenoma in about 50% of cases of ACTH-dependent Cushing syndrome.
- $^{111}$In-octreotide scanning is also useful in detecting occult tumors.

Diagnostic Procedures
- Inferior petrosal venous sampling can confirm a pituitary ACTH source.
What are the treatments for Cushing syndrome?
Medications
- Hydrocortisone replacement is required temporarily after resection of a pituitary adenoma
- Ketoconazole for patients with Cushing disease who are not surgical candidates
- Mitotane for adrenal carcinoma; treat osteoporosis with bisphosphonates

Surgery
- Selective transsphenoidal resection of a pituitary adenoma in Cushing disease
- Surgical resection of neoplasms; bilateral adrenalectomy if recurrence or no remission

Therapeutic Procedures
- Stereotactic pituitary radiosurgery (gamma knife) helpful in two-thirds of patients
- Conventional radiation therapy cures 23%
A 22-year-old woman with a history of poorly controlled type 1 diabetes mellitus presents to the emergency department with abdominal pain, nausea, and vomiting. She had been feeling ill with a cough, sore throat, and decreased appetite, so she has skipped several doses of insulin. On physical examination, she is tachypneic, and her abdomen is diffusely tender to palpation without rebound or guarding. Serum testing reveals a glucose level of 512 mg/dL and an anion gap of 23, and her arterial pH is 7.12. Her urine dipstick is positive for ketones as well as glucose. A serum β-hydroxybutyric acid level is elevated.

What are the salient features of this patient’s problem? How do you think through her problem?
Salient features: Young age; abdominal pain, nausea, vomiting; recent illness and insulin nonadherence; anion-gap metabolic acidosis with resulting tachypnea; elevated serum and urine glucose; urine and serum ketosis

How to think through: What clinical evidence helps distinguish between type 1 and type 2 diabetes at the time of initial diagnosis? (Weight loss rather than obesity; absence of acanthosis nigricans, dyslipidemia, hypertension, or polycystic ovaries. Onset of type 1 is typically in early childhood or early puberty. Autoantibody tests positive.) With what symptoms did this patient most likely present at the time of diagnosis? (Polyuria, polydipsia, lethargy, and weight loss.) She now presents with the defining features of diabetic ketoacidosis (DKA). In DKA, it is crucial to identify the precipitating factor. What likely precipitated DKA in this case? (Cough and pharyngitis suggest she has an infection along with nonadherence to insulin.) Is any additional testing warranted to establish the precipitating factor? (Chest radiography, if history or examination suggests pneumonia, urinalysis, and in older patients, consider electrocardiography.) DKA is best managed using a protocol. What are the key clinical and laboratory factors to monitor? (Volume status, serum glucose, bicarbonate, anion gap, potassium, and corrected sodium.) How much volume repletion is typically needed in DKA? (4–6 L.)
What are the essentials of diagnosis and general considerations regarding type 1 diabetes mellitus?
Essentials of Diagnosis

- Polyuria, polydipsia, and weight loss associated with random plasma glucose ≥200 mg/dL
- Plasma glucose ≥126 mg/dL after an overnight fast documented on more than one occasion
- Ketonemia, ketonuria, or both

General Considerations

- Caused by pancreatic islet β-cell destruction, usually immune-mediated
- Most type 1 patients possess either HLA-DR3 or HLA-DR4; HLA-DQB1*0302 is very specific
- Most patients have circulating antibodies to islet cells (ICA), insulin (IAA), glutamic acid decarboxylase (GAD65), and tyrosine phosphatase IA2 (ICA-512) and zinc transporter 8 (ZnT8) at diagnosis
- Prone to ketoacidosis
- Occurs at any age but most commonly arises in children and young adults
What are the symptoms and signs of type 1 diabetes mellitus?
Symptoms and Signs

- Increased thirst (polydipsia) and increased urination (polyuria)
- Increased appetite (polyphagia) with weight loss
- Ketoacidosis
- Paresthesias
- Recurrent blurred vision
- Vulvovaginitis or pruritus
- Nocturnal enuresis
- Postural hypotension from lowered plasma volume
What is the differential diagnosis of type 1 diabetes mellitus?
Differential Diagnosis

- Type 2 diabetes
- Hyperglycemia resulting from other causes
  - Medications (high-dose corticosteroids, pentamidine)
  - Other endocrine conditions (Cushing syndrome, glucagonoma, acromegaly, pheochromocytoma)
- Metabolic acidosis of other causes (e.g., alcoholic ketoacidosis)
- Nondiabetic glycosuria (renal glycosuria)
What are the laboratory findings in type 1 diabetes mellitus?
Laboratory Tests

- Fasting plasma glucose >126 mg/dL or >200 mg/dL 2 hr after glucose load
- Ketonemia, ketonuria, or both
- Glucosuria and ketonuria
- Glycated hemoglobin (hemoglobin A\textsubscript{1c}) reflects glycemic control over the preceding 8 to 12 weeks
- Serum fructosamine reflects control in preceding 2 weeks; helpful in abnormal hemoglobins
- Lipoprotein abnormalities (although less pronounced than in type 2 diabetes)
- Plasma glucagon is elevated
- C peptide levels do not reliably distinguish between type 1 and type 2 diabetes mellitus
What are the treatments for type 1 diabetes mellitus?
Medications
- Regular insulin and rapidly-acting insulin analogs: lispro, aspart, glulisine
- Intermediate-acting insulin purified: neutral protamine Hagedorn (NPH)
- Long-acting insulins purified: insulin glargine, insulin detemir
- Premixed combinations of insulins exist, such as 70/30 insulin (70% NPH, 30% regular)

Surgery
- Islet cell, solitary pancreas, or simultaneous pancreas and kidney transplant in select patients

Therapeutic Procedures
- Treat microalbuminuria with angiotensin-converting enzyme inhibitor to retard diabetic nephropathy
- Treat hypertension and hyperlipidemia
- Healthy diet
A 53-year-old man presents to his primary care provider for a routine checkup. He complains of increased thirst and frequent urination for the past few months. On physical examination, he is an obese man; his blood pressure is 152/87 mm Hg. His urinalysis is positive for glucose. A random fingerstick blood glucose reading in the office is 352 mg/dL. Serum hemoglobin A1c level is 10.2%.

What are the salient features of this patient’s problem? How do you think through his problem?
Salient features: Middle aged; obese; polyuria and polydipsia; associated hypertension; glycosuria; random blood sugar >200 mg/dL with symptoms; hemoglobin A₁c level >6.5%

How to think through: Factors that increase the risk of developing type 2 diabetes include obesity, as in this case. What other risk factors should be considered? (Family history, ethnicity; physical activity; fat distribution; smoking; and others, even sleep duration.) Besides polyuria and polydipsia, what other symptoms are often present when diabetes is first recognized? (Fatigue, weight loss, candidal vaginitis, blurred vision, peripheral neuropathy.) Do blurred vision and peripheral neuropathy necessarily indicate prolonged undetected diabetes? (Blurred vision may be caused by acute hyperglycemia rather than long-standing diabetic retinopathy, but neuropathy implies long-term hyperglycemia.) Glucosuria occurs above what serum glucose concentration? (Approximately 300 mg/dL.) How should this patient be evaluated? (Full physical examination, including ophthalmologic, neurologic, and foot examinations; complete blood count; serum electrolytes, creatinine, lipid panel; urine microalbumin test; and baseline electrocardiography.) What are the four treatment priorities to reduce his risk of macrovascular and microvascular complications? (Weight loss, blood pressure control, glucose control, and statin therapy aiming for a low-density lipoprotein cholesterol level of at least <100 mg/dL but ideally <70 mg/dL.) How should he be treated today? (If serum electrolytes and creatinine are normal and given the degree of glucose elevation, begin metformin and a long-acting insulin or sulfonylurea. Patient education. An antihypertensive should be initiated if hypertension is confirmed at the next visit, and statin therapy should follow.)
What are the essentials of diagnosis and general considerations regarding type 2 diabetes mellitus?
Essentials of Diagnosis

- Typically >40 years of age, obese, often with associated hypertension and dyslipidemia
- Polyuria and polydipsia; candidal vaginitis sometimes an initial manifestation
- Fasting plasma glucose ≥126 mg/dL or hemoglobin A₁c >6.5%

General Considerations

- Circulating endogenous insulin is sufficient to prevent ketoacidosis but inadequate to prevent hyperglycemia from tissue insensitivity
- Strong genetic influences; highly prevalent in Pima Indians and Pacific Islanders
What are the symptoms and signs of type 2 diabetes mellitus?
Symptoms and Signs

- Polyuria
- Increased thirst (polydipsia)
- Weakness or fatigue
- Recurrent blurred vision
- Vulvovaginitis or anogenital pruritus or balanoposthitis
- Peripheral neuropathy
- Obesity
- Often asymptomatic
What is the differential diagnosis of type 2 diabetes mellitus?
Differential Diagnosis

- Endocrinopathies: type 1 diabetes mellitus, Cushing syndrome, acromegaly, pheochromocytoma, glucagonoma, somatostatinoma
- Drugs: corticosteroids, thiazides, phenytoin, niacin, oral contraceptives, pentamidine
- Pancreatic insufficiency: subtotal pancreatectomy, chronic pancreatitis, hemochromatosis ("bronze diabetes"), hemosiderosis
- Other: gestational diabetes, cirrhosis, Schmidt syndrome from polyglandular failure
- Polyuria: diabetes insipidus
- Psychogenic polydipsia
- Nondiabetic glycosuria: genetic, Fanconi syndrome, chronic kidney disease, pregnancy
What are the laboratory findings in type 2 diabetes mellitus?
Laboratory Tests

- Fasting plasma glucose ≥126 mg/dL or ≥200 mg/dL 2 hr after glucose load
- Glucosuria (Clinistix, Diastix)
- Ketonuria on occasion without ketonemia (Acetest, Ketostix)
- Glycated hemoglobin (HbA1c) reflects glycemic control over preceding 8 to 12 weeks
- Serum fructosamine reflects glycemic control over preceding 2 weeks and is helpful in the presence of abnormal hemoglobins and in ascertaining glycemic control at time of conception among diabetic women
- Lipoprotein abnormalities include high serum triglycerides and low high-density lipoprotein cholesterol level
What are the treatments for type 2 diabetes mellitus?
Medications
- Drugs that stimulate insulin secretion: sulfonylureas, meglitinide analogs, D-phenylalanine derivative
- Drugs that primarily lower glucose levels by their actions on the liver, muscle, and adipose tissue: metformin, thiazolidinediones
- Drugs that principally affect glucose absorption: α-glucosidase inhibitors
- Drugs that mimic incretin effect: exenatide, sitagliptin, liraglutide
- Others: pramlintide (islet amyloid polypeptide analog)
- Insulin: indicated for hyperglycemia unresponsive to diet and oral hypoglycemic agents
- Preprandial rapid-acting insulin plus basal insulin replacement with an intermediate- or long-acting insulin can be used to attain acceptable control of blood glucose

Therapeutic Procedures
- Limitations to cholesterol and simple carbohydrate intake; increase in exercise
A 42-year-old man presents for evaluation of newly diagnosed hypertension. He is currently taking no medications and offers no complaints. A careful review of systems reveals symptoms of fatigue; loss of stamina; and frequent urination, particularly at night. Physical examination is normal except for a blood pressure of 168/100 mm Hg. Serum electrolytes are sodium, 152 mEq/L; potassium, 3.2 mEq/L; bicarbonate, 32 mEq/L; and chloride, 112 mEq/L.

What are the salient features of this patient’s problem? How do you think through his problem?
**Salient features:** Hypertension, including diastolic blood pressure elevation; fatigue; polyuria; hypernatremia; hypokalemia; elevated serum bicarbonate

**How to think through:** A complete diagnostic workup for secondary causes of hypertension is not necessary for every new diagnosis of high blood pressure, nor would it be feasible given the prevalence of hypertension in the population. At the same time, secondary causes of hypertension, such as hyperaldosteronism, are underrecognized. What are the major factors that should trigger a workup for secondary hypertension? (Onset at age <50 years; symptoms suggestive of pheochromocytoma, including headache, sweating, or palpitations; hypertension refractory to three medications, one of which is a diuretic; physical examination findings such as abdominal bruit or a cushingoid appearance.) This patient’s age, his systolic blood pressure of greater than 160 mm Hg, and his diastolic pressure of 100 mm Hg are indications for investigation. Serum sodium and potassium levels were appropriately checked and suggest a hyperactive renin–angiotensin–aldosterone axis. How can the problem be localized? (By obtaining an aldosterone-to-plasma renin activity ratio. If an elevated ratio is found, the next step is to document increased aldosterone secretion with a 24-hour urine collection.) Are his fatigue, poor stamina, and nocturia potentially attributable to this problem? (Yes. These may be caused by the associated hypokalemia.) What are the two most likely causes of hyperaldosteronism? (Bilateral adrenal hyperplasia and unilateral adrenal adenoma [Conn syndrome].) How should he be treated? (An aldosterone blocking agent such as spironolactone or eplerenone.)
What are the essentials of diagnosis and general considerations regarding hyperaldosteronism?
Essentials of Diagnosis

- Hypertension that may be severe or drug resistant
- Hypokalemia (in minority of patients) may cause polyuria, polydipsia, muscle weakness
- Elevated plasma and urine aldosterone levels and low plasma renin level

General Considerations

- Excessive aldosterone production which increases sodium retention and potassium excretion
- Cardiovascular events are more prevalent in patients with hyperaldosteronism
- Most commonly caused by bilateral adrenal hyperplasia and aldosterone-producing adrenal adenomas (Conn syndrome)
- Screen patients for hyperaldosteronism if they have blood pressure over 160/100 mm Hg; drug-resistant hypertension; hypertension with hypokalemia; adrenal incidentaloma; a family history of hyperaldosteronism, early-onset hypertension, or stroke
What are the symptoms and signs of hyperaldosteronism?
Symptoms and Signs
- Hypertension is typically moderate
- Some patients have only diastolic hypertension without other symptoms and signs
- Edema (rare)
- Muscular weakness (at times with paralysis simulating periodic paralysis), paresthesias with frank tetany, headache, polyuria, and polydipsia may be seen in patients with hypokalemia
What is the differential diagnosis of hyperaldosteronism?
Differential Diagnosis

- Essential hypertension
- Hypokalemic thyrotoxic periodic paralysis
- Renal vascular hypertension (hypertension and hypokalemia but plasma renin activity is high)
- Hypokalemia from another cause (e.g., diuretics)
- Secondary hyperaldosteronism (dehydration, heart failure)
- Congenital adrenal hyperplasia: 11 β-hydroxylase deficiency, 17 α-hydroxylase deficiency
- Cushing syndrome
- Excessive real licorice ingestion
- Syndrome of cortisol resistance
What are the laboratory, imaging and procedural findings in hyperaldosteronism?
Laboratory Tests

- Obtain plasma potassium level in all hypertensive individuals; hypokalemia may suggest the diagnosis.
- Serum bicarbonate (HCO\textsubscript{3}\textsuperscript{-}) concentration may be elevated.
- Perform plasma renin activity (PRA) and aldosterone to determine the aldosterone-to-renin ratio.
- A high aldosterone-to-renin ratio indicates primary hyperaldosteronism; elevated values without elevated ratio indicate secondary hyperaldosteronism.
- Serum aldosterone (ng/dL):PRA (ng/mL/h) ratios below 24 exclude primary hyperaldosteronism, ratios between 24 and 67 are suspicious, and ratios above 67 are very suggestive of the diagnosis.
- If an elevated ratio is found, the next step is to document increased aldosterone secretion with a 24-hour urine collection.
- Testing must be done holding all diuretics, angiotensin-converting enzyme inhibitors, β-blockers, and calcium channel blockers.

Imaging Studies

- Thin-section computed tomography can be used to screen for rare adrenal carcinoma.

Diagnostic Procedures

- Adrenal vein sampling can direct surgery to correct adrenal in unilateral aldosterone excess.
What are the treatments for hyperaldosteronism?
Medications

- Spironolactone and eplerenone are effective treatments; spironolactone can cause or gynecomastia, but eplerenone does not have antiandrogen effects.
- Low-dose dexamethasone will suppress glucocorticoid-remediable hyperaldosteronism (which is very rare).

Surgery

- Laparoscopic adrenalectomy may be done for Conn syndrome (unilateral aldosterone-secreting adrenal adenoma).
A 71-year-old woman with lung cancer presents to her primary care provider with complaints of constipation, nausea, and increased urination. She also has new depression and generalized weakness. Her only medication is calcium carbonate, which she takes for prevention of osteoporosis. On cardiac examination, she has frequent ectopy. Her serum calcium level is elevated at 13.5 mg/dL, her serum parathyroid hormone (PTH) level is low, and her serum PTH-related protein (PTHrP) level is elevated.

What are the salient features of this patient’s problem? How do you think through her problem?
Salient features: Constipation, nausea, polyuria, weakness, depression, ectopy; known malignancy; elevated serum calcium; elevated serum PTHrP and low serum PTH levels

How to think through: Rapid diagnosis of hypercalcemia requires recognition of a constellation of symptoms. What are the broad categories of symptoms caused by hypercalcemia? (Gastrointestinal, e.g., constipation, nausea; neuropsychiatric, e.g., fatigue, weakness and altered mental status; renal, e.g., nephrolithiasis and polyuria; and cardiac, e.g., shortened QT interval and ectopy.) The cause of hypercalcemia is determined by a differential diagnosis with several key branch points; it is helpful to recall that most cases are caused by primary hyperparathyroidism or malignancy. The PTH was likely the first laboratory result in this case, with her low value ruling out hyperparathyroidism. From there, what causes were likely next considered? (Malignancy, granulomatous disease, hypervitaminosis D, milk-alkali syndrome, thyrotoxicosis.) Malignancy, the most common cause of hypercalcemia with a suppressed PTH level, is a concern here given the degree of serum calcium elevation. The elevated PTH-rP confirms this suspicion. What three cancer types most frequently cause hypercalcemia? (Breast and lung carcinoma and multiple myeloma.) How should she be managed in the short term? (She should be admitted to the hospital for an expedited diagnostic workup and therapy to lower her serum calcium level, including aggressive intravenous saline hydration and, when well hydrated, treatment with a bisphosphonate.)
What are the essentials of diagnosis and general considerations regarding hypercalcemia?
Essentials of Diagnosis
- Serum calcium level is 10.5 mg/dL; serum ionized calcium is 5.3 mg/dL.
- Hypercalciuria usually precedes hypercalcemia.
- Symptomatic and severe disease is often caused by malignancy; asymptomatic and mild disease is often caused by primary hyperparathyroidism.

General Considerations
- Primary hyperparathyroidism and malignancy account for 90% of cases.
- The hypercalcemia related to PTHrP production is the most common paraneoplastic endocrine syndrome.
- Granulomatous diseases, such as sarcoidosis and tuberculosis, can cause hypercalcemia from production of active vitamin D₃ (1,25 dihydroxyvitamin D₃) by the granulomas.
What are the symptoms and signs of hypercalcemia?
Symptoms and Signs

- Mild hypercalcemia is often asymptomatic; serum calcium above 12 mg/dL or acute hypercalcemia produces more severe symptoms
- Gastrointestinal: constipation, nausea, vomiting, anorexia, peptic ulcer disease
- Renal: nephrolithiasis, polyuria
- Polyuria from hypercalciuria-induced nephrogenic diabetes insipidus can result in volume depletion and acute kidney injury
- Polyuria is absent in familial hypocalciuric hypercalcemia
- Neurologic manifestations may range from mild drowsiness to weakness, depression, lethargy, stupor, and coma in severe cases
- Cardiac: ventricular ectopy and idioventricular rhythm occur and can be accentuated by digitalis
What is the differential diagnosis of hypercalcemia?
Differential Diagnosis

- Increased intake or absorption: milk-alkali syndrome, vitamin D or A excess
- Endocrine disorders: primary and secondary hyperparathyroidism, acromegaly, adrenal insufficiency, pheochromocytoma, thyrotoxicosis
- Neoplastic diseases: tumor production of PTHrP (ovary, kidney, lung), multiple myeloma (osteoclast-activating factor), lymphoma
- Thiazide diuretics or lithium intake
- Granulomatous diseases
- Paget disease
- Hypophosphatasia
- Immobilization
- Familial hypocalciuric hypercalcemia
What are the laboratory, imaging, and procedural findings in hypercalcemia?
Laboratory Tests
- Serum calcium level is above 10.5 mg/dL; ionized calcium is above 5.3 mg/dL.
- High serum chloride and a low serum phosphate suggest primary hyperparathyroidism.
- Low serum chloride with high bicarbonate, blood urea nitrogen, and creatinine suggests milk-alkali syndrome.
- Measure urinary calcium excretion.
- PTH and PTHrP levels help distinguish between hyperparathyroidism (elevated PTH and absent PTHrP) and malignancy-associated hypercalcemia (suppressed PTH and elevated PTHrP).

Imaging Studies
- Chest radiography to exclude malignancy or granulomatous disease

Diagnostic Procedure
- Electrocardiography: shortened QT interval
What are the treatments for hypercalcemia?
Medications

- Establish euvolemia with intravenous fluids to induce renal excretion of $\text{Na}^+$ and $\text{Ca}^{2+}$.
- Furosemide intravenously may be useful, although its efficacy is unclear.
- Thiazides can worsen hypercalcemia.
- In the treatment of hypercalcemia of malignancy, bisphosphonates are the mainstay, although they have a delayed effect; calcitonin may be helpful in short term.

Therapeutic Procedures

- In emergency cases, dialysis with low or no calcium dialysate may be needed.
A 56-year-old woman presents to her primary care clinician complaining of progressive fatigue, weakness, and diffuse bony pain. She says that her symptoms have been getting worse over the past 2 months. Her medical history is notable for well-controlled hypertension and recurrent renal stones. Physical examination is unremarkable. A serum calcium level is elevated.

What are the salient features of this patient’s problem? How do you think through her problem?
Salient features: Female sex; fatigue; weakness; bone pain; renal stones; elevated serum calcium

How to think through: The diagnosis of hypercalcemia requires recognition of a constellation of common symptoms. In addition to her fatigue, weakness, diffuse bony pain, and nephrolithiasis, what other symptoms should be elicited? (Other neuromuscular or psychiatric symptoms, including depression; other renal symptoms, including polyuria; gastrointestinal symptoms, including anorexia.) Because the differential diagnosis of hypercalcemia is complex, it is useful to remember that two causes account for 90% of cases. What are these two causes? (Primary hyperparathyroidism and malignancy.) How should an elevated serum calcium level be confirmed? (Obtain a serum albumin level and correct the serum calcium value for a low albumin, if present, or obtain an ionized calcium level.) Often a serum phosphate level is available with the initial calcium value; how can this guide the differential diagnosis? (Primary hyperparathyroidism and malignancy with an elevated parathyroid hormone–related protein [PTHrP] both increase renal excretion of phosphate, leading to a low serum phosphate. Other causes of hypercalcemia generally lead to an elevated serum phosphate.) If the serum PTH level is found to be elevated in this case, what is the likelihood of malignant hypercalcemia? (Very low. Cancer leads to hypercalcemia by secretion of PTHrP or by bony metastasis; the serum PTH level is suppressed in almost all such cases. A PTH-secreting tumor is the rare exception.) What is the most likely diagnosis here, and how should this be confirmed? (Primary hyperparathyroidism is most likely. A 24-hour urinary calcium collection is needed. Low urine calcium indicates familial hypocalciuric hypercalcemia, a benign entity.) How should she be treated? (Symptomatic patients with primary hyperparathyroidism are best managed with parathyroidectomy.)
What are the essentials of diagnosis and general considerations regarding hyperparathyroidism?
Essentials of Diagnosis
- Renal stones, polyuria, hypertension, constipation, mental changes, bone pain
- Serum and urine calcium elevated; urine phosphate high with low or normal serum phosphate; alkaline phosphatase normal or elevated
- Elevated or high-normal serum parathyroid hormone (PTH) level
- More common at age older than 50 years and in females more often than males

General Considerations
- Primary hyperparathyroidism from PTH hypersecretion is usually caused by parathyroid adenoma
- Secondary or tertiary hyperparathyroidism occurs from chronic renal failure or renal osteodystrophy
- 10% of cases are familial, such as in multiple endocrine neoplasia (MEN) syndrome
What are the symptoms and signs of hyperparathyroidism?
Symptoms and Signs

- Frequently asymptomatic
- Symptoms include “bones, stones, abdominal groans, psychic moans, fatigue”
- Bone pain and arthralgias are common
- Osteitis fibrosa cystica: diffuse demineralization, pathologic fractures, and cystic bone lesions from severe, chronic disease
- Symptoms of severe hypercalcemia:
  - Paresthesias, muscular weakness, diminished reflexes
  - Malaise, fatigue, cognitive impairment, psychosis
  - Hypertension, prolonged P-R interval, shortened Q-T interval, bradyarrhythmias
  - Polyuria and polydipsia, nephrogenic diabetes insipidus
  - Anorexia, nausea, vomiting, abdominal pain, constipation
  - Band keratopathy
  - Calciphylaxis
What is the differential diagnosis of hyperparathyroidism?
Differential Diagnosis

- Hypercalcemia of malignancy
- Multiple myeloma
- Vitamin D intoxication
- Sarcoidosis, tuberculosis
- Immobilization
- Hypercalcemia
- Hyperthyroidism
- Vitamin D deficiency can cause high serum PTH with normal serum calcium
- High-dose corticosteroid therapy in patients taking thiazide diuretics
What are the laboratory and imaging findings in hyperparathyroidism?
Laboratory Tests
- Elevated serum calcium, elevated PTH; alkaline phosphatase elevated if bone disease is present
- Immunoradiometric assay (IRMA) is most specific and sensitive
- Serum phosphate is often low but high in secondary hyperparathyroidism (renal failure)
- Urine calcium excretion is high or normal but low for the degree of hypercalcemia
- Urine phosphate is high despite low to low normal serum phosphate
- 24-hour urine for calcium and creatinine screens for familial benign hypocalciuric hypercalcemia

Imaging Studies
- Imaging is not useful for the diagnosis of hyperparathyroidism but can locate parathyroid adenomas; sestamibi-iodine subtraction scanning and neck ultrasonography are the most sensitive tests.
- Bone radiographs are usually normal but may show demineralizations or pathologic fractures.
What are the treatments for hyperparathyroidism?
Medications
- Bisphosphonates for bone mineral density; oral preparations do not treat hypercalcemia
- Cinacalcet hydrochloride for severe hypercalcemia caused by parathyroid carcinoma
- Vitamin D replacement for patients with deficiency
- Calcitriol, doxercalciferol, or paracalcitol used in secondary and tertiary hyperparathyroidism associated with azotemia
- Propranolol may prevent adverse cardiac effects of hypercalcemia

Surgery
- Parathyroidectomy for symptomatic patients and asymptomatic patients if young, high urine calcium, low bone density, difficult medical follow-up, or pregnancy (second trimester)

Therapeutic Procedures
- Keep mobile; avoid thiazides and calcium supplements; drink fluids
A 25-year-old African American woman presents with a complaint of rapid weight loss despite a voracious appetite. Physical examination reveals tachycardia (pulse rate, 110 beats/min at rest), fine moist skin, symmetrically enlarged thyroid, mild bilateral quadriceps muscle weakness, and fine tremor.

What are the salient features of this patient’s problem? How do you think through her problem?
Salient features: Weight loss with increased appetite; tachycardia; moist skin; enlarged thyroid; muscle weakness; tremor

How to think through: Weight loss, weakness, and tachycardia indicate a systemic process. To avoid anchoring prematurely to thyroid disease as an explanation, what are the other major disease categories that could cause these findings? (Infection, malignancy, connective tissue diseases, vasculitis, medication toxicity.) What other symptoms of hyperthyroidism could you elicit to help confirm your suspicion? (Heat intolerance, restlessness, diarrhea, sleep disturbance, irregular menses.) What additional physical examination signs should be sought when considering hyperthyroidism? (Eyelid lag, exophthalmos, hyperdefecation, abnormally rapid relaxation phase to deep reflexes, pretibial myxedema.) In this case, examination of the thyroid gland shows asymmetry. What common etiologies of hyperthyroidism might present with an asymmetrical exam? (Toxic adenoma, toxic multinodular goiter.) What common etiologies are more likely to present as symmetrical processes? (Graves disease, viral thyroiditis, early autoimmune thyroid disease [“hashimotoxicosis”], thyroid-stimulating hormone [TSH]–producing pituitary adenoma.) How should her thyroid function be evaluated? (Serum TSH alone is the most sensitive initial test.) If the TSH suppressed, what would be the next diagnostic steps? (Serum triiodothyronine [T₃], thyroxine [T₄], thyroid-stimulating immunoglobulins; thyroid ultrasonography, and possibly a radioactive iodine scan; ophthalmology evaluation.) If the TSH in this patient is found to be suppressed, how should she be treated while awaiting the subsequent studies? (The nonspecific β-blocker propranolol is used to control tachycardia and to improve anxiety.) What are the complications of untreated hyperthyroidism? (Heart failure, osteoporosis, risk of thyroid storm.) What are the features of thyroid storm? (Fever, delirium, vomiting, diarrhea, tachycardia, heart failure.)
What are the essentials of diagnosis and general considerations regarding hyperthyroidism?
Essentials of Diagnosis

- Sweating, weight loss, anxiety, tachycardia and palpitations, heat intolerance, tremor
- Goiter and ophthalmopathy in Graves disease
- Suppressed TSH in primary hyperthyroidism; increased $T_4$, free thyroxine ($FT_4$), $T_3$, free triiodothyronine ($FT_3$)

General Considerations

- Causes include Graves disease, toxic adenomas, iodine-induced, subacute de Quervain thyroiditis, amiodarone-induced thyroiditis, Hashimoto thyroiditis, and exogenous thyroid hormone
What are the symptoms and signs of hyperthyroidism?
Symptoms and Signs

- Heat intolerance, sweating, nervousness, fine resting tremor, pruritus
- Frequent bowel movements (hyperdefecation), weight loss (or gain), menstrual irregularities
- Fatigue, weakness, muscle cramps, hyperreflexia
- Goiter (often with a bruit) in Graves disease; enlarged, tender thyroid in subacute thyroiditis
- Upper eyelid retraction, stare and eyelid lag with downward gaze, ophthalmopathy (chemosis, conjunctivitis, and mild proptosis) in Graves disease; diplopia if coexistent myasthenia gravis
- Moist, warm skin; fine hair; onycholysis; dermopathy (myxedema) in Graves disease
- Sinus tachycardia, palpitations, angina pectoris, arrhythmias
- Cardiomyopathy, thyroid storm, hypokalemic paralysis
What is the differential diagnosis of hyperthyroidism?
Differential Diagnosis

- General anxiety, panic disorder, mania
- Other hypermetabolic state (e.g., cancer, pheochromocytoma)
- Exophthalmos from another cause (e.g., orbital tumor)
- Atrial fibrillation from another cause
- Acute psychiatric disorders (may falsely increase serum thyroxine)
- High estrogen states (e.g., pregnancy)
- Hypopituitarism
- Subclinical hyperthyroidism
What are the laboratory and imaging findings in hyperthyroidism?
Laboratory Tests

- Serum TSH is suppressed; T₄, FT₄, T₃, FT₃, thyroid resin uptake and FT₄ index increased
- FT₄ sometimes normal but serum T₃ elevated
- Hypercalcemia, anemia, increased alkaline phosphatase
- Antibodies in Graves disease: thyrotropin receptor antibody (TRAb), antinuclear antibody (ANA), thyroperoxidase or thyroglobulin antibodies
- Erythrocyte sedimentation rate often elevated in subacute thyroiditis
- TSH elevated or normal despite thyrotoxicosis in TSH-secreting pituitary tumor

Imaging Studies

- High ¹²³I uptake in Graves disease and toxic nodular goiter, low uptake characteristic of subacute thyroiditis and amiodarone-induced hyperthyroidism
- Thyroid ultrasonography helpful in patients with hyperthyroidism and palpable thyroid nodules
What are the treatments for hyperthyroidism?
Medications
- Propranolol (extended-release formulation) controls symptoms
- Thioureas: methimazole or propylthiouracil (PTU)
- Iodinated contrast agents: iopanoic acid (Telepaque) or ipodate sodium (Bilivist, Oragrafin)
- Amiodarone-induced thyrotoxicosis and Graves ophthalmopathy treated with corticosteroids

Surgery
- Methimazole and propranolol used pre- and perioperatively
- Thyroidectomy preferred over radioiodine for patients with pregnancy, large goiters, suspected malignancy, solitary toxic thyroid nodules in patients younger than age 40 years

Therapeutic Procedures
- Radioactive iodine ($^{131}$I) therapy for Graves disease and toxic multinodular goiter
A 55-year-old woman complains of fatigue, 30 lb of weight gain despite dieting, constipation, thinning hair, and menorrhagia. On physical examination, the thyroid gland is not palpable; the skin is cool, dry, and rough; the heart sounds are quiet; the pulse rate is 50 beats/min; and the deep tendon reflexes show delayed relaxation. The rectal and pelvic examinations are normal, and the stool is guaiac negative.

What are the salient features of this patient’s problem? How do you think through her problem?
Salient features: Middle-aged woman; weight gain; constipation; menorrhagia; thinning hair; dry skin; bradycardia; delayed relaxation of reflexes

How to think through: What major disease categories might present with fatigue and weight gain? (Depression, Cushing syndrome, hypothyroidism.) In addition to the fatigue, constipation, weight gain, alopecia, and menorrhagia, what other symptoms should be sought in this case? (Cold intolerance, mental clouding, muscle weakness, or cramping.)

What are common causes of hypothyroidism? (Autoimmune [Hashimoto] thyroiditis is most common; drug toxicity, including amiodarone and lithium; iodine deficiency; surgical resection or radioablation of the thyroid gland.) If the thyroid-stimulating hormone [TSH] value in this case proves to be low normal, what diagnosis should we consider? (Secondary hypothyroidism caused by a pituitary process such as a mass effect from a prolactin-producing pituitary tumor.) Is this patient at risk for autoimmune hypothyroidism? (Yes, given her age and sex.) How should she be evaluated? (A serum TSH alone is the appropriate initial test; an abnormal TSH level should be followed by a free thyroxine ($T_4$). Tests for thyroperoxidase and thyroglobulin antibodies are positive in most cases of autoimmune thyroiditis but are nonspecific and may be positive in the setting of acute illness.) If this patient’s TSH value is elevated, and her free $T_4$ is low, how should thyroid replacement therapy be initiated? (Start low; go slow. The primary concern is that coronary artery disease can be “unmasked” if the metabolic rate accelerates too quickly.) What are other risks of overtreatment? (Osteoporosis, atrial fibrillation.)
What are the essentials of diagnosis and general considerations regarding hypothyroidism?
Essentials of Diagnosis

- Weakness, cold intolerance, constipation, depression, menorrhagia, hoarseness
- Dry skin, bradycardia, delayed return of deep tendon reflexes
- TSH is elevated and free thyroxine (FT$_4$) low

General Considerations

- Primary hypothyroidism is caused by thyroid gland disease, and secondary hypothyroidism is caused by a lack of pituitary TSH; TSH may be mildly elevated in euthyroid individuals.
- Maternal hypothyroidism during pregnancy results in cognitive impairment in the child.
- Amiodarone, caused by high iodine content, causes clinical hypothyroidism in 15% to 20%.
- High iodine intake from other sources may also cause hypothyroidism.
- Myxedema is caused by interstitial accumulation of hydrophilic mucopolysaccharides, leading to fluid retention and lymphedema.
What are the symptoms and signs of hypothyroidism?
Symptoms and Signs
- Weight gain, fatigue, lethargy, depression, weakness, dyspnea on exertion
- Arthralgias or myalgias, muscle cramps, paresthesias, carpal tunnel syndrome
- Cold intolerance, dry skin, thin nails and hair, headache, constipation
- Menorrhagia
- Bradycardia; diastolic hypertension
- Skin pallor or yellowing (carotenemia), peripheral edema, puffy face and eyelids
- Delayed relaxation of deep tendon reflexes
- Palpably enlarged thyroid (goiter), thickened tongue, thinning of outer half of eyebrows
- Cardiac enlargement (“myxedema heart”) and pericardial effusion
- Psychosis (“myxedema madness”)
What is the differential diagnosis of hypothyroidism?
Differential Diagnosis

- Causes of hypothyroidism with goiter
  - Hashimoto thyroiditis, Riedel thyroiditis, subacute (de Quervain) thyroiditis
  - Iodine deficiency, peripheral resistance to thyroid hormone
  - Hepatitis C, infiltrating diseases, genetic thyroid enzyme defects
  - Drugs: lithium, amiodarone, propylthiouracil, methimazole, sulfonamides

- Causes of hypothyroidism without goiter
  - Thyroid surgery, irradiation, or radiiodine treatment
  - Deficient pituitary TSH
  - Severe illness
What are the laboratory findings in hypothyroidism?
Laboratory Tests

- Serum TSH is increased in primary hypothyroidism but low or normal in secondary hypothyroidism (pituitary insufficiency).
- FT₄ may be low or low normal.
- Serum T₃ is not a good test for hypothyroidism.
- Increased serum cholesterol, hypoglycemia, and anemia are present.
- Hyponatremia occurs because of impaired renal tubular sodium reabsorption.
- Thyroperoxidase or thyroglobulin antibody titers are usually high in autoimmune thyroiditis.
- During pregnancy in women with hypothyroidism taking replacement thyroxine, check serum TSH frequently to ensure adequate replacement.
What are the treatments for hypothyroidism?
Medications

- $T_4$ is the treatment of choice, titrated based on TSH level; assess for angina, diarrhea, or malabsorption with treatment.
- $T_4$ dosage requirements can rise with metabolism inductions by other medications.
- Avoid administration concurrently with binding substances (e.g., iron, aluminum hydroxide antacids, calcium supplements, or soy milk) or with bile acid–binding resins (e.g., cholestyramine).
- Addition of $T_3$ (Cytomel) is controversial.
- Amiodarone-induced hypothyroidism is treated with enough $T_4$ to relieve symptoms.
- Myxedema crisis requires levothyroxine intravenously (IV).
- Myxedema coma treated with IV liothyronine ($T_3$, Triostat) and supportive care.
A 53-year-old woman came to the clinic to get help managing her weight. She has been overweight since childhood and has continued to gain weight throughout her adult life. She has tried numerous diets without lasting success. She initially loses weight but then regains it after a few months. She is otherwise healthy and is not taking any medications. Other family members are also overweight or obese. She does not do any regular exercise and has a sedentary office job. On examination, she is 5 feet, 3 inches tall and 260 lb, with a body mass index (BMI) of 46.2 (normal <25).

What are the salient features of this patient’s problem? How do you think through her problem?
**Salient features:** Long-standing obesity; multiple failed diets; family history; sedentary lifestyle; elevated BMI

**How to think through:** A BMI of 46 places her into which class of obesity? In addition to excess caloric intake and inadequate exercise, what are the important causes of obesity to consider in your evaluation of this patient? What are the potential endocrine causes? What medications cause weight gain? Psychiatric causes? (Depression.) What are the major medical complications of obesity, and how would you screen for each? (Hypertension, dyslipidemia, diabetes mellitus, coronary artery disease, degenerative joint disease, cholelithiasis.) Does obesity increase her risk of any cancers? What are the elements of a comprehensive treatment strategy? (Nutrition education, exercise program, and weight loss counseling, including a diet log, an exercise log, motivational interviewing, and changes to environmental cues.) Is there a difference between the success of low-fat or low-carbohydrate diets over time? If she makes limited progress after 6 months of the above, what are possible next steps? (Medically managed very low-calorie diets and gastric bypass surgery.) Are there pharmacologic agents for weight loss? (Yes, but of limited utility. Orlistat is modestly effective but has frequent gastrointestinal [GI] side effects. Catecholaminergic agents have high abuse and dependence potential.)
What are the essentials of diagnosis and general considerations regarding obesity?
Essentials of Diagnosis

- Excess adipose tissue; BMI >30, where BMI = Weight (in kg)/Height (in m)^2
- Upper body obesity (abdomen and flank) of greater health consequence than lower body obesity (buttocks and thighs)
- Associated with health consequences, including diabetes mellitus, hypertension, and hyperlipidemia, coronary artery disease, and early death

General Considerations

- BMI: normal = 18.5 to 24.9, overweight = 25 to 29.9, class I obesity = 30 to 34.9, class II obesity = 35 to 39.9, class III (extreme) obesity >40
- 68% of Americans are overweight; 33.8% are obese
- The relative risk associated with obesity decreases with age, and excess weight is no longer a risk factor in adults aged older than 75 years of age
What are the symptoms and signs of obesity?
Symptoms and Signs

- Assess BMI.
- Assess the degree and distribution of body fat.
- Assess overall nutritional status.
- Signs of secondary causes of obesity (hypothyroidism and Cushing syndrome) are found in fewer than 1% of individuals.
What is the differential diagnosis of obesity?
Differential Diagnosis

- Increased caloric intake
- Fluid retention: heart failure, cirrhosis, nephrotic syndrome
- Cushing syndrome
- Hypothyroidism
- Diabetes mellitus (type 2)
- Drugs (e.g., antipsychotics, antidepressants, corticosteroids)
- Insulinoma
- Depression
- Binge-eating disorder
What are the laboratory and procedural findings in obesity?
**Laboratory Tests**

- Endocrinologic evaluation, including serum thyroid-stimulating hormone and dexamethasone suppression test in obese patients with unexplained recent weight gain or clinical features of endocrinopathy or both
- Assessment for medical consequences and metabolic syndrome: blood pressure and fasting glucose, triglycerides, and low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol levels

**Diagnostic Procedures**

- Calculation of BMI
- Measurement of waist circumference
What are the treatments for obesity?
Medications

- Catecholaminergic or serotonergic medications may produce more short-term weight loss than placebo but not long-term benefits; amphetamines have high abuse potential.
- Orlistat reduces fat absorption, so it can cause GI side effects.
- Sibutramine has been removed by the Food and Drug Administration (FDA) from the U.S. market.
- Phentermine plus topiramate extended-release (Qsymia, formerly Qnexa) is FDA approved for use only with strict supervision by trained clinicians.

Surgery

- Consider for patients with BMI above 40 or BMI above 35 if obesity-related comorbidities are present.
- Surgical procedures (each can be done laparoscopically): roux-en-Y gastric bypass, vertical banded gastroplasty, gastric banding; surgical mortality rate is 0% to 1%.

Therapeutic Procedures

- Multidisciplinary approach: hypocaloric diets, behavior modification, exercise, social support.
- No special advantage to carbohydrate-restricted or high-protein diets.
A 72-year-old woman presents to the emergency department after falling in her home. She slipped on spilled water in her kitchen. She was unable to get up after her fall and was found on the floor in her kitchen by her son who stopped by after work. She complains of severe right hip pain. Her medical history includes giant cell arteritis, for which she has taken daily prednisone for more than 1 year. On examination, she has bruising over her right hip. Range of motion in her right hip is markedly decreased, with pain on both internal and external rotation. Radiography reveals a hip fracture and probable low bone mass.

What are the salient features of this patient’s problem? How do you think through her problem?
Salient features: Elderly; female sex; long-term glucocorticoid use; fall with fracture of hip; radiograph with low bone mass

How to think through: Osteoporosis is a common underdiagnosed problem. In the absence of screening for osteoporosis, the loss of bone density goes untreated and, as in this case, can lead to fracture. Fractures, in turn, precipitate significant morbidity in elderly adults. This patient is an older woman with a history of chronic corticosteroid use. What are the other major risk factors for osteoporosis that should be explored in her history? (Tobacco use, hyperthyroidism, inflammatory bowel and celiac disease, and premenopausal estrogen deficiency [e.g., eating disorders, hypopituitarism, and premature ovarian failure].) What is the screening test for osteoporosis? (Dual-energy x-ray absorptiometry [DEXA].) Can osteoporosis be diagnosed without DEXA testing? (Yes. An older woman, such the patient in this case, with a “fragility” or “low-trauma” fracture can be considered to have osteoporosis and should be so treated.) How should this patient be treated? (Bisphosphonates are the mainstay. Selective estrogen receptor modulators and parathyroid hormone [PTH] are considered in severe cases or with intolerance to bisphosphonate.) When the decision to treat is unclear, consider the many risk factors for fracture. These include age, prior fracture, family history of fracture, low body mass index, and alcohol use. Clinical formulas such as the FRAX algorithm incorporate these factors, along with the DEXA, to determine the risk of major osteoporotic fracture.
What are the essentials of diagnosis and general considerations regarding osteoporosis?
Essentials of Diagnosis

- Fracture propensity of the spine, hip, pelvis, and wrist from demineralization
- Serum PTH, calcium, phosphorus, and alkaline phosphatase usually normal
- Serum 25-hydroxyvitamin D levels often low as a comorbid condition

General Considerations

- Causes approximately 2 million fractures, mainly of the spine and hip, annually in the United States
- Morbidity and indirect mortality rates very high
- Rate of bone formation is often normal, but the rate of bone resorption is increased
- Most common causes include aging, high-dose corticosteroid administration, alcoholism, and sex hormone deficiency; occurs more often in women than men
- Osteogenesis imperfecta is caused by a mutation in the gene encoding for type I collagen
What are the symptoms and signs of osteoporosis?
Symptoms and Signs

- Usually asymptomatic until fractures occur
- May present as back pain of varying degrees of severity or as spontaneous fracture or collapse of a vertebra
- Loss of height common
- Fractures of femoral neck and distal radius also common
- After osteoporosis has been identified, careful history and physical examination are required to determine its cause
What is the differential diagnosis of osteoporosis?
Differential Diagnosis

- Osteomalacia or rickets
- Inadequate mineralization of existing bone matrix (osteoid)
- Multiple myeloma
- Metastatic cancer
- Paget disease of bone
- Renal osteodystrophy
What are the laboratory and imaging findings in osteoporosis?
Laboratory Tests
- Serum calcium, phosphate, alkaline phosphatase, and PTH: usually normal
- Vitamin D deficiency is very common
- Testing for thyrotoxicosis and hypogonadism may be required
- Screen for celiac disease with serum IgA anti-tissue transglutaminase

Imaging Studies
- Radiographs of spine and pelvis may show demineralization or compression of vertebrae
- DEXA is accurate and delivers negligible radiation
- Osteoporosis: bone densitometry T score ≤−2.5; osteopenia: T score ≤−1.0 to −2.5
- Quantitative computed tomography delivers more radiation than DEXA but is highly accurate
What are the treatments for osteoporosis?
Medications

- Calcium and vitamin D are used to prevent or treat osteoporosis.
- Bisphosphonates such as oral alendronate, risedronate and ibandronate or intravenous zoledronic acid increase bone density, reduce fracture risk, and prevent corticosteroid-induced osteoporosis.
- Consider estrogen or raloxifene for women with hypogonadism.
- Teriparatide stimulates production of new collagenous bone matrix that must be mineralized.
- Nasal calcitonin–salmon or subcutaneous denosumab useful if unable to tolerate bisphosphonates.

Therapeutic Procedures

- Diet adequate in protein, total calories, calcium, and vitamin D; avoid tobacco and alcohol
- Discontinue or reduce doses of corticosteroids, if possible
- High-impact physical activity (e.g., jogging), stair climbing, and weight training
- Fall-avoidance measures
A 28-year-old woman presents to her primary care clinician because of intermittent fevers for the past 3 days, reaching 39°C. She reports a sore throat, myalgias, and stomach upset. She had unprotected sex with a new partner 2 weeks prior. On physical examination, there is diffuse, nontender lymphadenopathy in the axillary, cervical, and occipital regions and an erythematous throat without tonsillar exudates. HIV enzyme-linked immunosorbent assay (ELISA) test results negative, but HIV viral load shows 150,000 copies/mL.

What are the salient features of this patient’s problem? How do you think through her problem?
**Salient features:** Young woman; fever; myalgias; sore throat without tonsillar exudates; unprotected sex; lymphadenopathy; negative HIV ELISA result but positive viral load indicating acute HIV infection

**How to think through:** Although most acute febrile illnesses are self-limiting, many serious illnesses present with fever. What broad categories of disease could account for the initial presentation of—fever, this patient’s pharyngitis, myalgias, gastrointestinal upset, and lymphadenopathy? (Infection, such as infectious mononucleosis, cytomegalovirus, streptococcal pharyngitis, or acute HIV infections; malignancy, such as lymphoma; inflammatory disease, such as lupus or sarcoidosis.) Most patients with acute fever can be managed with supportive care but only after assessment of risk factors and “red flag” symptoms. What exposures and social risk factors should be assessed? (High-risk sexual activity; injection drug use; substance use; new medications; travel; occupational exposures; contact with ill persons.) Physical examination is important for localizing the source of fever and for refining the differential diagnosis. What examination elements should be included? (Mental status; neck range of motion; cardiac, lung, abdominal, skin, and joint examinations.) At this patient’s initial presentation, what diagnostic testing would be appropriate in addition to the HIV antibody test? (Complete blood count [CBC], rapid strep test, heterophile test. Blood cultures and liver tests should also be considered in febrile patients.) Here, the diagnosis is acute HIV infection. What initial testing is needed to begin planning her care? (CBC, CD4 T-cell lymphocyte count, HIV genotype, serum creatinine, liver tests, hepatitis B serologies, hepatitis C antibody, toxoplasmosis IgG, G6PD level, and tuberculin skin test.)
What are the essentials of diagnosis and general considerations regarding fever?
Essentials of Diagnosis
- Age, localizing symptoms, weight loss, joint pain, injection drug use, immunosuppression, history of cancer, medications, and travel history

General Considerations
- Most febrile illnesses are caused by common infections, are short-lived, and are relatively easy to diagnose.
- The term FUO (“fever of undetermined origin”) refers to cases of unexplained fever exceeding 38.3°C on several occasions for at least 3 weeks in patients without neutropenia or immunosuppression.
- In HIV-infected individuals, fever may be caused by lymphoma or infections such as disseminated *Mycobacterium avium*, *Pneumocystis jiroveci*, cytomegalovirus, or disseminated histoplasmosis.
- In a returned traveler, consider malaria, dysentery, hepatitis, or dengue fever.
What are the symptoms and signs of fever?
Symptoms and Signs

- Fever is defined as an elevated body temperature above 38.3°C.
- The average normal oral body temperature taken in midmorning is 36.7°C (range, 36.0°–37.4°C).
- The normal diurnal temperature variation is 0.5° to 1.0°C (lowest in the early morning and highest in the evening).
- The normal rectal or vaginal temperature is 0.5°C higher; the axillary temperature is 0.5°C lower.
- Rectal is more reliable than oral temperature, particularly in tachypneic states.
What is the differential diagnosis of fever?
Differential Diagnosis

- Infections: bacterial (including tuberculosis), viral, rickettsial, fungal, parasitic
- Autoimmune diseases
- Central nervous system diseases: head trauma, mass lesions
- Malignant disease: renal cell carcinoma, liver cancer, leukemia, lymphoma
- Cardiovascular diseases: myocardial infarction, pulmonary embolism, thrombophlebitis
- Gastrointestinal diseases: inflammatory bowel disease, alcoholic or granulomatous hepatitis
- Drug fever
- Sarcoidosis
- Familial Mediterranean fever
- Tissue injury or hematoma
- Peripheral thermoregulatory disorders: heat stroke, malignant hyperthermia of anesthesia, malignant neuroleptic syndrome
What are the laboratory, imaging, and procedural findings in fever?
Laboratory Tests
- CBC with differential, urinalysis, liver function tests
- Erythrocyte sedimentation rate (ESR) or C-reactive protein level
- Blood and urine cultures

Imaging Studies
- Chest radiography
- Abdominal ultrasound and computed tomography
- Radionuclide-labeled leukocyte, gallium-67, and radiolabeled human immunoglobulin tests

Diagnostic Procedures
- Temporal artery biopsy in patients 60 years of age or older with elevated ESR
What are the treatments for fever?
Medications

- Antipyretic therapy with aspirin or acetaminophen
- After blood and urine cultures, empiric broad-spectrum antibiotics are indicated in patients who are unstable, neutropenic, immunosuppressed, or likely to have significant infection
- If a fungal infection is suspected, add fluconazole or amphotericin B

Therapeutic Procedures

- When temperature is above 41°C: alcohol or cold sponges, ice bags and baths, ice-water enemas
A 31-year-old man who is an injection drug user presents to the emergency department with a chief complaint of shortness of breath. He describes a 1-month history of intermittent fevers and night sweats associated with a nonproductive cough. He has become progressively more short of breath and now he feels dyspneic at rest. He appears to be in moderate respiratory distress. His vital signs are abnormal, with fever to 39°C, heart rate of 112 beats/min, respiratory rate of 20 breaths/min, and oxygen saturation of 88% on room air. Physical examination is otherwise unremarkable. Notably, the lung examination is normal. Chest radiography reveals a diffuse interstitial infiltrate in a “bat’s wing” or “butterfly” pattern.

What are the salient features of this patient’s problem? How do you think through his problem?
**Salient features:** Injection drug use; 1-month duration of intermittent fevers and night sweats; pneumonia symptoms (slowly progressive dyspnea, fever, tachycardia, hypoxia); abnormal chest radiograph findings suggesting an opportunistic infection.

**How to think through:** What are the broad categories in the differential diagnosis for this presentation? (One month of fevers, night sweats, cough, dyspnea, and hypoxia.) Among infections, what are possible causes? Could this be a typical bacterial pneumonia? (Unlikely, given the duration.) How about tuberculosis or a fungal infection (e.g., coccidioidomycosis)? What elements of the case strongly suggest pneumocystis? (The radiography pattern; hypoxia despite normal lung sounds.) At what CD4+ T cell count does pneumocystis become more likely? (<200 cells/mcL.) How is the diagnosis of pneumocystis definitively made? (Sputum induction or bronchoscopy.) What percent of HIV-positive patients in the United States are unaware of their diagnosis? (25%.) When unusual infections enter the differential diagnosis, one **must** think of HIV even in the absence of known risk factors. Which test is used to diagnose HIV and which to confirm the diagnosis? When, after exposure, is HIV antibody detectable? At what CD4+ T cell count is the diagnosis of AIDS made? (<200/mcL). If this patient’s CD4 count is 50 cells/mcL, what other infectious and noninfectious complications might he develop?
What are essentials of diagnosis and general considerations regarding HIV?
Essentials of Diagnosis
- Risk factors: sexual contact, needle sharing, transfusion, or perinatal exposure
- Prominent systemic complaints such as sweats, diarrhea, weight loss, and wasting
- Opportunistic infections caused by diminished cellular immunity
- Aggressive cancers, particularly Kaposi sarcoma and extranodal lymphoma
- Neurologic manifestations, including dementia, neuropathy, and aseptic meningitis

General Considerations
- Etiology: HIV-1, a retrovirus
- Diagnosis of AIDS generally requires evidence of HIV infection plus the presence of an “AIDS-defining” opportunistic infection or a CD4 count <200 cells/mcL
What are the symptoms and signs of HIV?
Symptoms and Signs

- HIV-related infections and neoplasms can affect virtually every organ.
- Many HIV-infected persons remain asymptomatic for years even without antiretroviral therapy; there is a mean of about 10 years between infection with HIV and development of AIDS.
- Symptoms protean and nonspecific, e.g., fever, night sweats, and weight loss.
- Shortness of breath, cough, and fever from pneumonia.
- Anorexia, nausea and vomiting, and increased metabolic rate contribute to weight loss.
- Diarrhea from bacterial, viral, or parasitic infections.
- Physical examination findings may be normal or reveal generalized lymphadenopathy.
- Conditions highly suggestive of HIV infection: hairy leukoplakia of the tongue, oral and esophageal candidiasis; Kaposi sarcoma, cutaneous bacillary angiomatosis; cytomegalovirus retinitis; tuberculosis and *Pneumocystis jiroveci* lung infections; many gastrointestinal infections, including *Cryptosporidium*; central nervous system (CNS) disease, including HIV encephalopathy, progressive multifocal leukoencephalopathy (PML), non-Hodgkin lymphoma, and toxoplasmosis; increased risk of malignancy, including lymphoma and cervical and anal carcinomas.
What is the differential diagnosis of HIV?
Differential Diagnosis

- Depends on mode of presentation
- Constitutional symptoms may be cancer, tuberculosis, endocarditis, or endocrinologic diseases such as hyperthyroidism
- Pulmonary processes may be acute or chronic lung infection, noninfectious pulmonary diseases
- Neurologic disease may be any other cause of mental status changes or neuropathy
- Diarrhea may be infectious or antibiotic-associated colitis, inflammatory bowel disease, or malabsorption syndromes
What are the laboratory and procedural findings in HIV?
Laboratory Tests
- HIV antibody by enzyme-linked immunosorbent assay, confirmed by Western blot (sensitivity >99.5%; specificity ∼100%)
- ∼95% of persons develop antibodies within 6 weeks after infection
- Absolute CD4 lymphocyte count: as count decreases, risk of serious opportunistic infection increases

Diagnostic Procedures
- For *P. jiroveci* pneumonia: chest radiography, Wright-Giemsa stain of induced sputum, bronchoalveolar lavage
- For CNS toxoplasmosis: head computed tomography scan, stereotactic brain biopsy
- For cryptococcal meningitis: cerebrospinal fluid (CSF) culture, CSF and serum cryptococcal antigen (CRAG)
- For HIV meningitis or myelopathy: CSF cell count, lumbar puncture, head magnetic resonance imaging or CT scan
- For AIDS dementia complex, depression: neuropsychiatric testing
- For enterocolitis: stool culture and ova and parasite examinations, colonoscopy and biopsy
What are the treatments for HIV?
Antiretroviral treatment should begin in most patients when the CD4 count is below 500 cells/µL. Antiretrovirals should never be used alone as a single agent, and at least three active agents should be used at all times; protease inhibitors are often “boosted” with ritonavir.

Major classes are nucleoside reverse transcriptase inhibitors (NRTIs, e.g., AZT, 3TC, ddI), non-nucleoside reverse transcriptase inhibitors (NNRTIs, e.g., efavirenz, nevirapine), protease inhibitors (PIs, e.g., atazanavir, darunavir), entry inhibitors (maraviroc), and integrase inhibitors (raltegravir).

Starting regimen usually includes two NRTIs plus an NNRTI, a PI, an entry inhibitor, or an integrase inhibitor.

Treat fever, anorexia, weight loss, and nausea symptomatically; treat opportunistic infections as indicated.

Treat *P. jiroveci* pneumonia with trimethoprim–sulfamethoxazole (TMP-SMX).

For *P. jiroveci* pneumonia prevention when CD4 counts are below 200 cells/µL: TMP-SMX, dapsone, or atovaquone.

For *Mycobacterium avium-intracellularare* complex (MAC) infection prevention when CD4 counts below 75–100 cells/µL, give azithromycin weekly.

For toxoplasmosis prevention when CD4 counts are below 100 cells/µL, give TMP-SMX.
A 71-year-old man is admitted to the intensive care unit for pneumonia, sepsis, and acute respiratory distress syndrome. He is treated with intravenous (IV) ceftriaxone. An initial improvement occurs in his sepsis symptoms and lung function, but on hospital day 6, he develops fever (39°C), tachycardia, and hypotension. His femoral central venous catheter site is noted to be erythematous and draining pus. The catheter is removed and IV vancomycin is administered with resolution of his fever, tachycardia, and hypotension. Blood cultures drawn from the catheter grow methicillin-resistant Staphylococcus aureus (MRSA).

What are the salient features of this patient’s problem? How do you think through his problem?
Salient features: New sepsis in hospital despite initial improvement; fever, tachycardia, hypotension; central venous catheter with erythema and drainage; blood cultures showing MRSA; resolution with vancomycin

How to think through: What major causes of new fever, tachycardia and hypotension should be considered in this case besides the purulent femoral line? (Medication toxicity, pulmonary embolism, and infection. Within the category of infection, treatment of the pneumonia may be inadequate because of an improper antibiotic choice, dosing, or penetration of the infected tissue [e.g., with development of an empyema].) The patient may have also developed a new health care–associated infection; possibilities include ventilator-associated pneumonia, infection spread by contact such as Clostridium difficile, Foley catheter–associated urinary tract infection, and IV catheter–associated bloodstream infection. In this case, the latter (a femoral venous catheter infection) is the leading possibility. Line placement at a femoral site has a higher infection risk than one at a subclavian or internal jugular site. Removal of a central line is not a trivial consideration; venous access may be difficult to obtain, and it may be essential for treatment. When should a central line be removed? (If there is purulence at the exit site; if the organism is Staphylococcus aureus, a gram-negative rod, or a Candida species; if there is persistent bacteremia; or if septic thrombophlebitis, endocarditis, or metastatic abscesses occur.)
What are the essentials of diagnosis and general considerations regarding health care–associated infections?
Essentials of Diagnosis

- Acquired during the course of receiving treatment for other conditions more than 48 hours after admission
- Most health care–associated infections are preventable; hand washing is most effective

General Considerations

- Often result from devices for monitoring or therapy such as IV catheters, Foley catheters, drainage catheters, orotracheal tubes for ventilation; early removal reduces infection
- Often occur in critically ill patients with long hospitalizations and broad-spectrum antibiotic therapy
- Causative organisms are often multidrug resistant and different from those in community-acquired infections: MRSA, *Staphylococcus epidermidis*, *Enterococcus faecium* resistant to ampicillin and vancomycin; resistant gram-negative infections caused by *Pseudomonas*, *Citrobacter*, *Enterobacter*, *Acinetobacter*, and *Stenotrophomonas* spp.
What are the symptoms and signs of health care–associated infections?
Symptoms and Signs

- Those of the underlying disease
- All infections: fever, tachycardia, tachypnea, systemic inflammatory response syndrome (SIRS)/sepsis, hypotension
- Ventilator-associated pneumonia: increasing ventilator requirements, focal lung consolidation
- Central venous catheter infections: erythema, warmth, drainage at catheter site
- *C. difficile* infection: diarrhea
What is the differential diagnosis of health care–associated infections?
Differential Diagnosis

- Noninfectious
  - Drug fever
  - Nonspecific postoperative fevers (tissue damage or necrosis)
  - Hematoma
  - Pancreatitis
  - Pulmonary embolism
  - Myocardial infarction
  - Ischemic bowel
- Urinary tract infections
- Pneumonia
- Other source of bacteremia (e.g., abscess, genitourinary or gastrointestinal tract)
- Wound infection (e.g., pressure ulcer)
What are the laboratory and imaging findings in health care–associated infections?
Laboratory Tests

- Blood cultures are universally recommended; sputum Gram stain and cultures for pneumonia
- A positive wound culture without signs of inflammation or infection, a positive sputum culture without pulmonary infiltrates on chest radiograph, or a positive urine culture in a catheterized patient without symptoms or signs of pyelonephritis are all likely to represent colonization, not infection

Imaging Studies

- Chest radiographs frequently obtained
What are the treatments for health care–associated infections?
Medications
- Empiric therapy with vancomycin
- Empiric gram-negative coverage in patients who are immunocompromised or critically ill
- Antibiotic lock therapy for catheter lumens to salvage the catheter

Therapeutic Procedures
- Remove catheters if
  - There is purulence at the exit site.
  - The organism is *S. aureus*, gram-negative rods, or *Candida* spp.
  - There is persistent bacteremia (>48 hours while receiving antibiotics).
  - Complications, such as septic thrombophlebitis, endocarditis, or metastatic abscesses, occur.
- Central venous catheters may be exchanged over a guidewire provided there is no erythema or purulence at the exit site and the patient does not appear to be septic.
A 55-year-old man who recently emigrated from China presents to the emergency department with a fever. He has had recurring fevers over the past 3 weeks associated with chills, night sweats, and malaise. His medical history is remarkable for “being very sick as a child after a sore throat.” He recently had several teeth extracted for severe dental caries. He is taking no medications. On physical examination, he has a temperature of 38.5°C, blood pressure of 120/80 mm Hg, heart rate of 108 beats/min, respiratory rate of 16 breaths/min, and oxygen saturation of 97% on room air. Skin examination is remarkable for painful nodules on the pads of several fingers and toes. He has multiple splinter hemorrhages in the nail beds and painless hemorrhagic macules on the palms of the hands. Ophthalmoscopic examination is remarkable for retinal hemorrhages. Chest examination is clear. Cardiac examination reveals a grade 3 of 6 holosystolic murmur heard loudest at the left lower sternal border, with radiation to the axilla.

**What are the salient features of this patient’s problem? How do you think through his problem?**
Salient features: Constitutional symptoms (fever, chills, night sweats, malaise); likely prior rheumatic fever; poor dentition; tachycardia; painful Osler nodes, splinter hemorrhages, painless Janeway lesions; Roth spots on ophthalmoscopy; cardiac murmur

How to think through: Mortality from infective endocarditis (IE) is high, depending on the valve affected and organism. Often, only nonspecific symptoms and signs are apparent at presentation, but delay in diagnosis can be catastrophic. On presentation, this patient had the cardinal constitutional symptoms of fever, chills, night sweats, and malaise. What historical risk factors raise the likelihood of IE? (History of rheumatic fever, prosthetic valve, injection drug use.) What signs are associated with IE? (Fever, murmur, embolic lesions, peripheral stigmata.) What else should you look for in your initial evaluation? (Altered mental status, inflammatory arthritis, hematuria, embolic infarctions on chest radiograph.) What are the key tests for diagnosis and treatment? (Blood cultures and echocardiogram.) What are the most common organisms in IE? (Viridians strains of streptococci, Staphylococcus aureus, enterococci, coagulase-negative staphylococci.)
What are essentials of diagnosis and general considerations regarding infective endocarditis?
Essentials of Diagnosis

- Risk factors: preexisting organic heart lesion, prosthetic valve, injection drug use
- Fever, new or changing heart murmur, evidence of systemic emboli, positive blood culture findings
- Evidence of vegetation on echocardiography

General Considerations

- Clinical presentation is dictated by the infecting organism, valve infected, and route of infection.
- More virulent organisms, particularly *S. aureus*, cause rapidly progressive infections with acute valvular regurgitation and myocardial abscess.
- Subacute presentation is more common from viridians strains of streptococci and enterococci, but it can also be from other gram-positive and gram-negative bacilli, yeasts, and fungi.
- The initiating event is infection of the valve during bacteremia.
- Native valve endocarditis is most commonly caused by *S. aureus* (~40%), viridans streptococci (~30%), and enterococci (5%–10%).
- Prosthetic valve endocarditis early after implantation is more likely to be caused by gram-negative organisms, fungi, and both coagulase-positive and coagulase-negative staphylococci.
- Injection drug users are more likely to have *S. aureus* and tricuspid valve infection.
What are the symptoms and signs of infective endocarditis?
Symptoms and Signs

- Most present with a febrile illness that has lasted several days to 2 weeks
- Heart murmurs
  - In most cases, heart murmurs are stable.
  - A changing murmur is significant diagnostically but is the exception rather than the rule.
- Characteristic peripheral lesions occur in up to 20% to 25% of patients.
  - Petechiae (on the palate or conjunctiva or beneath the fingernails)
  - Subungual ("splinter") hemorrhages
  - Osler nodes (painful, violaceous raised lesions of the fingers, toes, or feet)
  - Janeway lesions (painless erythematous lesions of the palms or soles)
- Roth spots (exudative, hemorrhagic lesions of the retinas)
What is the differential diagnosis of infective endocarditis?
Differential Diagnosis

- Valvular abnormality without endocarditis
  - Rheumatic heart disease
  - Mitral valve prolapse
  - Bicuspid or calcific aortic valve
- Flow murmur (anemia, pregnancy, hyperthyroidism, sepsis)
- Atrial myxoma
- Noninfective endocarditis, such as systemic lupus erythematosus (Libman-Saks endocarditis), marantic endocarditis (nonbacterial thrombotic endocarditis)
- Acute rheumatic fever
- Vasculitis
- Hematuria from other causes, such as glomerulonephritis or renal cell carcinoma
What are the laboratory, imaging, and procedural findings in infective endocarditis?
Laboratory Tests

- Blood culture is the most important diagnostic tool; three sets from different sites before antibiotics maximizes yield
- Leukocytosis in acute endocarditis, anemia of chronic disease in subacute cases
- Hematuria, proteinuria, or renal dysfunction from emboli or glomerulonephritis
- Duke criteria for the diagnosis:
  - Major criteria: two positive blood cultures with typical microorganism, positive echocardiography findings, and new regurgitant murmur
  - Minor criteria: predisposing condition, fever $>38^\circ\text{C}$, embolic disease, immune phenomena (Osler nodes, Janeway lesions, Roth spots, glomerulonephritis, rheumatoid factor), positive blood cultures not meeting major criteria or active infection with typical organism
  - 80% accuracy with two major, one major and three minor criteria, or five minor criteria
  - Possible endocarditis with one major and one minor or three minor criteria
  - Endocarditis unlikely if criteria are not met and fever abates within 4 days or alternative explanation for illness is found

Imaging Studies

- Transthoracic echocardiography has only a 55% to 65% sensitivity, so it cannot rule out endocarditis.
- Transesophageal echocardiography has a 90% sensitivity and can detect myocardial abscess.
- Chest radiography may show an underlying cardiac abnormality or embolic infiltrates in right-sided endocarditis.

Diagnostic Procedures

- Conduction abnormalities on electrocardiography may suggest myocardial abscess formation.
What are the treatments for infective endocarditis?
Medications

- Antibiotic therapy should be targeted to causative organism and susceptibilities.
- Antibiotics are usually continued for at least 2 to 6 weeks.
- Penicillin-resistant organisms may be treated with vancomycin.
- Groups B, C, and G streptococci and enterococcal infections may require addition of gentamicin to antibiotic regimens.
- For methicillin-susceptible *S. aureus*, nafcillin or oxacillin is preferred.
- For HACEK (*Haemophilus aphrophilus* (now *Aggregatibacter aphrophilus*), *Actinobacillus actinomycetemcomitans* (now *Aggregatibacter actinomycetemcomitans*), *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella* spp.) organisms, high-dose ceftriaxone is preferred.

Surgery

- Indications for valve replacement include valvular regurgitation with acute heart failure, infections that do not respond to appropriate antimicrobial therapy, infection of sinus of Valsalva or septal abscesses, fungal or gram-negative bacilli infections, and continued embolization despite antibiotic treatment.

Therapeutic Procedures

- Colonoscopy should be done to exclude colon cancer in patients with *Streptococcus bovis* endocarditis.
A 65-year-old woman is admitted to the hospital with community-acquired pneumonia. She is treated with intravenous (IV) antibiotics and oxygen. A Foley catheter is inserted. On hospital day 3, she is switched to oral antibiotics. However, she then develops fever and tachycardia. Blood and urine cultures are ordered. The following morning, she is difficult to arouse. Her temperature is 35°C, blood pressure 85/40 mm Hg, heart rate 110 beats/min, and respiratory rate 25 breaths/min. Lung examination is unchanged from admission, with rales at the left base. Cardiac examination reveals a rapid but regular rhythm without murmurs, gallops, or rubs. Abdominal examination is normal. Extremities are warm. Neurologic examination is nonfocal. The patient is transferred to the intensive care unit with presumed sepsis and given IV fluids and broad-spectrum antibiotics. Blood and urine cultures are positive for gram-negative rods.

What are the salient features of this patient’s problem? How do you think through her problem?
**Salient features:** Foley catheter; hypotension; hypothermia, tachycardia, tachypnea; warm extremities (suggest decreased systemic vascular resistance [SVR]); positive blood and urine cultures

**How to think through:** First, consider other causes of shock (hypovolemic, cardiogenic, obstructive, other distributive). What physical finding makes blood loss or cardiogenic shock less likely? (These are states of increased SVR, but her skin is warm.) A high suspicion for sepsis is important since early intervention improves outcomes. What are the key components of management of septic shock? (Restore perfusion; ensure adequate oxygenation; identify and treat the infection [use broad-spectrum antibiotics initially and then narrow coverage based on blood cultures].) Replete intravascular fluids aggressively. If the patient remains hypotensive, use vasopressors. What end-organ effects of poor perfusion can one monitor? (Mental status; urine output; lactic acidemia, cardiac ischemia or arrhythmia; peripheral perfusion [pulses, capillary refill].) What are important complications of sepsis? (Disseminated intravascular coagulation; renal and hepatic hypoperfusion; acute respiratory distress syndrome.)
What are the essentials of diagnosis and general considerations regarding sepsis?
Essentials of Diagnosis

- Fever, tachycardia, elevated white blood cell (WBC) count, or increased respiratory rate
- Proven or probable source of infection; bacteremia with positive blood cultures
- Elevated lactate or end-organ dysfunction in severe disease; hypotension in septic shock

General Considerations

- Sepsis is defined as meeting SIRS criteria with a known source of infection
- SIRS is two or more of the four following criteria: temperature <36°C or >38°C; heart rate >90 beats/min; respiratory rate >20 beats/min or PaCO₂ <32 mm Hg; WBC count <4000/mcL or >12,000/mcL or differential with >10% bands
- Gram-negative bacteremia usually originates from the genitourinary system, hepatobiliary tract, gastrointestinal tract, and lungs but may also be from wounds and decubitus ulcers
What are the symptoms and signs of sepsis?
Symptoms and Signs

- Fevers and chills, often with an abrupt onset
- Hyperventilation with respiratory alkalosis
- Altered mental status
- Hypotension and shock are late findings and poor prognostic signs
- Symptoms and signs of infectious source (e.g., abdominal or urinary symptoms, pneumonia)
What is the differential diagnosis of sepsis?
Differential Diagnosis

- Gram-positive sepsis
- Fungal or acid-fast bacillus infection
- SIRS from another cause: trauma, burns, pancreatitis, myocardial or bowel ischemia, adrenal insufficiency, pulmonary embolism, aortic aneurysm rupture, anaphylaxis, toxin ingestion
- Shock from another cause: cardiogenic, neurogenic, hypovolemic, anaphylactic
What are the laboratory, imaging, and procedural findings in sepsis?
Laboratory Tests
- Complete blood count may show neutropenia or neutrophilia and immature polymorphonuclear leukocytes
- Thrombocytopenia; elevated lactic acid; coagulation dysfunction with or without disseminated intravascular coagulation (DIC)
- Three blood cultures should be obtained before starting antimicrobials if possible

Imaging Studies
- Chest radiography to look for pulmonary infection

Diagnostic Procedures
- Urinalysis with culture, which may show positive leukocyte esterase, elevated WBCs, and positive nitrite
- Culture of fluid from abscess if applicable
What are the treatments for sepsis?
Medications

- Antibiotic therapy should be given as soon as the diagnosis is suspected because delayed antibiotic therapy leads to increased mortality rates.
- Initially, give broad-spectrum antibiotic therapy; narrow antibiotics based on culture and sensitivity data.
- Give aggressive IV fluids and vasopressors to maintain blood pressure if needed.

Surgery

- May be required to control source of bacteremia, depending on the etiology

Therapeutic Procedures

- Drainage or removal of source of bacteremia (e.g., central venous catheter removal, abscess or empyema drainage)
The numbers listed are the card numbers for each entry.

**Acute Myocardial Infarction** 13
**Adrenocortical Insufficiency** 65
**Altered Mental Status** 55
**Aortic Regurgitation** 14
**Aortic Stenosis** 15
**Asthma** 4
**Atopic Dermatitis** 1

**Back Pain, Low** 42
**Benign Prostatic Hyperplasia** 39
**Breast Cancer, Female** 38

**Chest Pain** 16
**Cholecystitis, Acute** 27
**Chronic Obstructive Pulmonary Disease** 5
**Cirrhosis** 28
**Colorectal Cancer** 29
**Contact Dermatitis** 2
**Cough** 6
**Crohn Disease** 30
**Cushing Syndrome** 66

**Deep Venous Thrombosis and Thromboembolism** 25
**Dementia** 56
**Depression** 57
**Diabetes Mellitus, Type 1** 67
**Diabetes Mellitus, Type 2** 68
**Diarrhea** 31
**Dyslipidemia** 17
**Dysmenorrhea** 40
**Dyspnea** 7

**Epilepsy** 58
Fever 76
Gastrointestinal Bleeding, Lower 32
Gastrointestinal Bleeding, Upper 33
Glomerulonephritis 47
Gout 43

Healthcare-Associated Infections 78
Heart Failure 18
Hepatitis, Viral 34
HIV-AIDS 77
Hyperaldosteronism, Primary 69
Hypercalcemia 70
Hypercoagulable States 23
Hyperparathyroidism, Primary 71
Hypertension 19
Hyperthyroidism 72
Hypokalemia 48
Hyponatremia 49
Hypothyroidism 73

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Kidney Stone Disease 52
Knee Pain 44

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Meningitis, Bacterial 59
Metabolic Acidosis 53
Mitral Regurgitation 20
Mitral Stenosis 21
Myasthenia Gravis 60

Nephrotic Syndrome 54

Obesity 74
Osteoporosis 75
Pancreatitis, Acute 35
Pancreatitis, Chronic 36
Parkinson Disease 61
Pharyngitis 9
Pneumonia 10
Prostate Cancer 41
Psoriasis 3
Pulmonary Embolism 11
Rheumatoid Arthritis 45
Sepsis 80
Shock 22
Sinusitis 12
Smoking Cessation 63
Stroke 62
Substance Abuse 64
Systemic Lupus Erythematosus 46
Ulcerative Colitis 37
Vitamin B\textsubscript{12} Deficiency Anemia 26