Appendix: Illustrated Case Studies

I. OVERVIEW

These extended case studies complement the basic information presented in Chapters 1 to 40. They reinforce basic principles of pharmacology, such as the role of patient factors in empiric antimicrobial therapy. Most of the cases provide clinical information obtained from a single patient; some cases describe a composite of typical features derived from several patients. These cases illustrate simple pharmacologic principles, such as consideration of kidney function in drug dosing—concepts useful in answering examination questions, and in the clinics.

CASE 1

A 53-year-old man was admitted into a hospital with fever, a cough that produced purulent sputum, and shortness of breath that had been present for several days.

Two years earlier he had developed Kaposi's sarcoma and was human immunodeficiency virus (HIV) positive. In the interim, therapy with anti-HIV drugs had been discontinued because of his inability to tolerate them. However, the Kaposi's sarcoma was treated with anticancer drugs, including *doxorubicin*. He was being maintained with *cotrimoxazole*, *fluconazole*, and *rifabutin* (a rifamycin antibiotic similar to *rifampin*) and receiving weekly treatments with *filgramstin* (*granulocyte stimulating factor*) and *erythropoietin*. At the time of admission for the cough his helper-induced T-cell (CD4) count was 13/μL.

A chest X-ray revealed a cavitary lesion of the right upper lobe. Cultures obtained from bronchoscopic biopsy and broncho-alveolar lavage specimens yielded methicillin-resistant Staphylococcus aureus (MRSA) with no evidence of fungal or acid-fast organisms. Treatment with the normal therapeutic dose of *vancomycin*, 1 gram intravenously (IV) every 12 hours, was begun. Because he insisted on receiving his treatment at home, he was discharged with a peripherally-inserted central venous catheter in place. Though his fevers abated initially, he again experienced frequent chills, fever, cough producing white-to-yellow sputum, and progressively disabling weakness 48 hours after the *vancomycin* had been started.

Several days later he was admitted to the hospital, where it was noted that he was alert, fully oriented, and extremely weak. His temperature was 103.6°F, his pulse 130 beats per minute (BPM), his blood pressure (BP) 80/60 mm Hg, and his respirations labored at a rate of 28 per minute. He was extremely cachetic at 6'4" in height and weighing 135 pounds (61 kg). There were purple tumorous plaques covering parts of his body. His chest revealed dullness and coarse crackles throughout the right upper and mid-lung fields, suggesting pneumonia. A chest X-ray confirmed the diagnosis (Figure A.1).

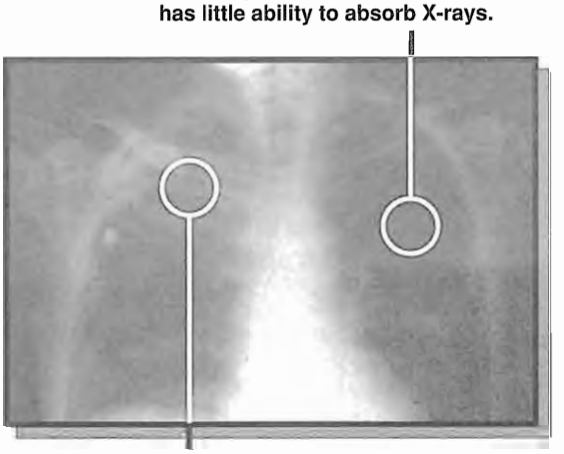


Figure A.1
Chest X-ray of patient.

Lippincott's Illustrated Reviews: Pharmacology, Second Edition.
by Mary J. Mycek, Richard A. Harvey and Pamela C. Champe.
Lippincott–Raven Publishers, Philadelphia, PA © 1997.

The patient was profoundly leukopenic with a white blood cell count of 700/μL–28% polymorphonuclear leukocytes (PMN's), 53% band forms, 3% metamyelocytes, 11% lymphocytes, 5% monocytes. [Normally, the total white blood cell count should be between about 4000 and 10,000 per mL.] The serum creatinine was 3.6 mg/dL (indicating significant renal dysfunction, normal creatinine ordinarily should not exceed about 1 mg/dL). A random plasma *vancomycin* level was 48.8 μg/mL. (Therapeutic range for "peak" level is 18 to 30 μg/mL.)

Question A.1: Was *vancomycin* the appropriate drug for treating this patient?

Answer: Yes. *Vancomycin* is the drug of choice (in fact, the only effective drug currently available) for the treatment of methicillin-resistant Staphylococcus aureus (MRSA) infections. It is bactericidal and thus important for treatment of a leukopenic individual.

Question A.2 : The best explanation for this extremely high plasma level of *vancomycin* is:

A. The very low CD4-positive lymphocyte count
B. The excessively high dose of *vancomycin* for this patient's weight
C. The impaired renal function
D. The leukopenia
E. Inhibition of *vancomycin* metabolism by *fluconazole*

The correct answer is **C** (impaired renal function). *Vancomycin* is excreted almost exclusively by the kidneys, with renal clearance linearly related to that of creatinine. Hence, even in patients with modest renal impairment, *vancomycin* regimens must be modified. This patient, presumably because of septic shock, developed renal failure while receiving vancomycin. Because his physicians were not aware of his clinical deterioration, his *vancomycin* regimen was not altered and he began to retain it significantly. **A** (very low CD4-positive lymphocyte count) is unrelated to *vancomycin* kinetics. **B** (excessive dose for weight) is not the best answer because, with a recommended dose of 15 mg/kg every 12 hours in adults with normal renal function, this patient's weight of 61 kg called for about 900 mg per dose, only slightly less than the dose that he was receiving. **D** (leukopenia) does not of itself result in changes in *vancomycin* kinetics. **E** (inhibition of *vancomycin* metabolism by *fluconzaole*).The azole antifungal agents interfere with the metabolism of many drugs, by inhibiting the hepatic microsomal enzymes. However, *vancomycin* is not one of the the drugs that is metabolized by microsomal enzymes.

The *vancomycin* regimen was suspended, and blood, sputum, and urine cultures were obtained. A gram stain of the patient's sputum revealed many polymorphonuclear leukocytes and many gram-negative rods (Figure A.2).

Urine gram stain showed no organisms. The patient was treated with IV fluids, and, based on the gram stain and other data, *ceftazidime* (one gram IV every 12 hours) was begun. In addition, the *granulocyte colony-stimulating factor* was increased to daily doses, in an effort to improve his quantitative leukocyte defenses. The patient's temperature came down and his renal function improved to nearly normal levels over the next 5 days, allowing resumption of regularly scheduled *vancomycin* doses. Cultures of sputum and blood yielded Pseudomonas aeruginosa.

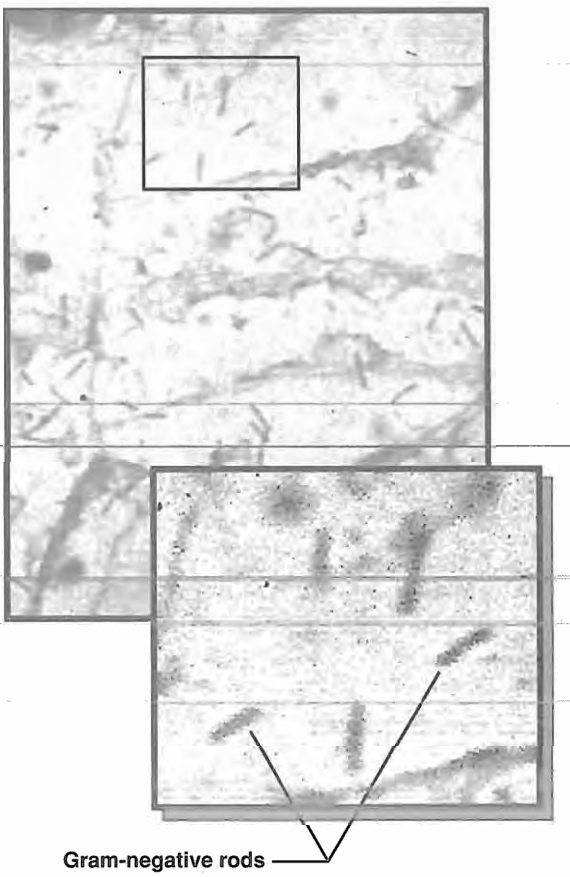


Figure A.2
Gram stain of patient's sputum.

Question A.3: Was the selection of *ceftazidime* a rational choice?

Answer: Yes. Patients with a profound leukopenia have very low numbers of neutrophils and are predisposed to severe infections with gram-negative rods, especially Pseudomonas aeruginosa. The patient's sputum gram stain is in accord with such an infection. *Ceftazidime* is a third generation cephalosporin, which covers many gram-negative organisms including Pseudomonas aeruginosa. It is also bactericidal.

Question A.4: Why was the patient not treated concurrently with an aminoglycoside, such as *tobramycin*?

Answer: The patient's high serum creatinine indicates compromised renal function. The aminoglycosides can be nephrotoxic and thus the drug was not employed. However, *tobramycin* might have been used together with *ceftazidime* if the dose were adjusted for renal function.

Question A.5: Which one of the following statements are true for *ceftazidime*?

A. Effective on oral administration.
B. Excretion depends on the kidney.
C. Interferes in vitamin K function to cause an anticoagulant effect.
D. Causes ototoxicity at high serum levels.
E. Ceftazidime is administered orally

The correct answer is **B** (excretion depends on the kidney). Most of the β-lactam antibiotics depend on the kidney for excretion. *Ceftazidime* is predominantly eliminated by glomerular filtration. Thus in this patient the dose of *ceftazidime* would have to be modified due to the patient's renal status. **A** (effective on oral administration) is incorrect. *Ceftazidime* is only given parenterally. **C** (interferes in vitamin K function to cause an anticoagulant effect) is incorrect. This property is peculiar to *cefoperazone* and *cefamandole*. **D** (causes ototoxicity at high serum levels) is not correct. **E**. *Ceftazidine* is administered IV or intramuscularly (IM).

This case illustrates the importance of considering patient-related information in selecting empiric antimicrobial therapy. Impaired renal function caused him to retain *vancomycin* to very high levels, requiring substantial modification of the dosage (that is, waiting while the drug was very slowly excreted). The renal failure also influenced on the dosage of *ceftazidime* that was initially given. An adult with normal renal function requires 2 grams of *ceftazidime* every 8 hours. The other important patient-related information that guided the antibiotic choice was his profound neutropenia, which led his physicians to suspect Pseudomonas on the first day. Had he not been treated with the right drug from the very beginning, the outcome would not have been good.

CASE 2

A 27-year-old woman with a history of asthma accidently inhaled a small nut from a candy bar she was eating. The presence of this foreign body in the airway triggered an explosive series of coughs, which ultimately expelled the food fragment from her lungs. After several minutes the airway was fully cleared, but she experienced progressive tightness in her chest. Her breathing became difficult and soon she was gasping for breath. She removed a canister from her purse and inhaled several puffs of medication. Her symptoms resolved over the next 20 minutes.

Question A.6: Which one of the following aerosolized medications would proved relief from the acute bonchoconstriction described for this woman?

A. *Salmeterol*
B. *Cromolyn*
C. *Beclomethasone*
D. *Albuterol*
E. *Nedocromil*

Correct answer is **D**. *Albuterol* is one of several of β_2 agonists available as an aerosol for treatment of bronchoconstrictive episodes associated with asthma. Its onset of action is rapid (5 to 10 minutes) and its effects on alveolar smooth muscle last several hours. **A** *Salmeterol*, also a β_2 agonist, has a slow onset of action and is not used in acute asthmatic attacks. **B**, **E** *Cromolyn* and *nedocromil* are used prophylacticlly, but are not effective in acute asthma. **C** *Beclomethasone* is an anti-inflamatory agent indicated for moderate to severe asthma. Inhaled *beclomethasone* reduces airway inflammation but its actions are not immediate; the drug is administered chronically, but it is not effective in the treatment of an acute asthmatic attack.

Simple spirometric testing with a bronchodilator challenge can identify patients with reversible airway obstruction, such as asthma (Figure A.3). The patient fills his or her lungs maximally and then expels the air as rapidly as possible. First a baseline reading is taken for this forced expiratory volume in the first second (FEV_1). Next, an aerosol bronchodilator, such as *albuterol*, is administered and the test is repeated after 15 minutes. Airway obstruction is considered to be reversible when the FEV_1 improves by more than

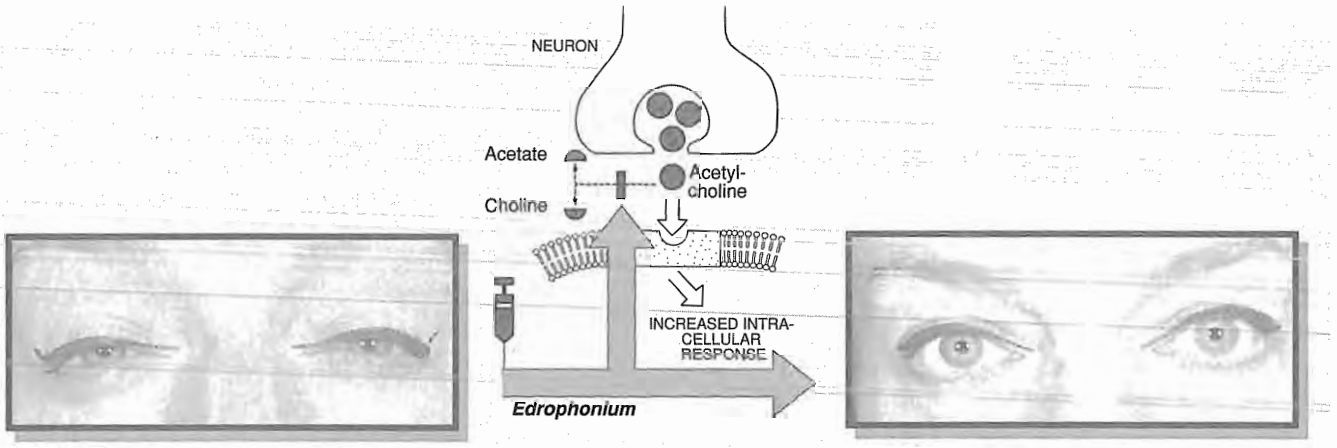


Figure A.5
Efffect of *edrophonium* in a patient showing symptoms of myasthenia gravis.

Question A.12: What antibiotic medication may have contributed to the unmasking of the myasthenia?

The aminoglycoside, *amikacin*. The aminoglycosides can inhibit Ca^{++} uptake which is required for the release of acetylcholine at the neuromuscular junction, and can cause neuromuscular blockade. This is rare at usual doses of the drug, but patients with myasthenia gravis are particularly susceptible.

CASE 5

A 36-year-old man was admitted to the hospital with fever and chills, which began 3 weeks earlier. Until that time he was well except for a heart murmur which was asymptomatic. Three months prior to admission, he developed a dental abscess which was treated with surgical drainage of the abscess and *erythromycin ethylsuccinate* (400 mg orally three times daily for 10 days). He felt well until 3 weeks prior to admission, when he began to have fever as high as 101°F every evening, sometimes accompanied by low back pain. He saw his physician ten days after the onset of the fever and was again given *erythromycin ethylsuccinate* (400 mg orally three times daily). When his symptoms did not improve, he was admitted to the hospital.

Upon admission, the patient's temperature was 100.4°F, his pulse 100 BPM, and his BP 135/70 mm Hg. An oral examination revealed several carious teeth. There was a soft systolic murmur consistent with mitral insufficiency. His spleen was palpable 2 centimeters below the left costal margin. The remainder of the physical examination was unremarkable. His past history included an episode of wheezing and shortness of breath when he had received *penicillin* for a sore throat at age 10.

Question A.13: What tentative diagnosis would you make?

Answer: Because of the patient's dental history, that is, an abscess and several carious teeth, and the presence of heart murmurs and low grade fever at night, the possibility of subacute bacterial endocarditis is likely. Streptococcus of the viridans group is a common etiological agent for this condition in patients with dental problems.

Question A.14: Assuming that the patient is suffering from endocarditis due to Streptococci, what antibiotic would be appropriate to employ empirically before the etiological organism was identified?

Answer: The patient's history suggests a hypersensitivity to *penicillin* (wheezing and shortness of breath indicative of bronchospasm). Therefore, ß-lactam antibiotics would carry a risk of a serious allergic attack and be inappropriate despite their known efficacy against this organism. *Vancomycin* is effective against this organism and has no cross-allergenicity with penicillin. In addition, like *penicillin*, it is bactericidal. Rapid treatment is indicated for this life-threatening condition .

This patient was treated empirically with *vancomycin* alone because his physicians suspected that he had endocarditis, caused by Streptococcus of the viridans group. The history indicated that the origin of the infection was the patient's mouth. Three days later the results from the clinical microbiology laboratory showed that three blood cultures, taken at the time of admission, grew Enterococcus faecalis, susceptible to *ampicillin*, *vancomycin*, *gentamicin*, and *streptomycin*.

Question A.15: The appropriate regimen for this patient's enterococcal endocarditis is:

A. *Ampicillin* and *gentamicin*
B. *Ceftriaxone* and *gentamicin*
C. *Vancomycin*
D. *Vancomycin* and *gentamicin*
E. *Clindamycin* and *gentamicin*

The correct answer is **D** . Ordinarily one would treat enterococcal endocarditis with regimen **A** (*ampicillin* and *gentamicin*), but this patient's history of bronchospasm (wheezing and shortness of breath) when he received *penicillin*, even many years before, makes any penicillin derivative unacceptable in him, unless there is no alternative. **B** is not a correct answer because the cephalosporins do not have activity against Enterococcus species and the fact that *ceftriaxone* is a β-lactam places the patient at risk of an allergic attack. **C** is incorrect specifically because the infection to be treated is endocarditis. *Vancomycin* is effective against most strains of Enterococcus, but in endocarditis it is adequately bactericidal only when it is used in combination with an aminoglycoside such as gentamicin. The combination is synergistic because vancomycin's effect on cell wall synthesis facilitates the entry of the aminoglycoside. Both drugs are bactericidal. **E** is incorrect for two reasons: *clindamycin* is ineffective against Enterococcus and, even in patients with endocarditis due to an organism susceptible to *clindamycin*, such as many strains of Staphylococcus aureus, *clindamycin* should not be used, because it is bacteriostatic. Endocarditis must be treated with a bactericidal drug, since the valvular lesion of endocarditis, called a "vegetation," contains only fibrin, platelets, and bacteria. Thus it has no cells that intrinsically kill bacteria. Cure requires that all the killing be done by antibiotics. The only correct answer, therefore, is **D**. Because the etiology turned out to be Enterococcus, a combination of *vancomycin* and *gentamicin* was employed with beneficial results.

Many principles of antibiotic selection are illustrated by this patient. (1) His history of serious allergy to penicillin eliminated this entire family of antibiotics from consideration. Thus, when his dental abscess had to be treated, he had to be given a "second-line" drug, *erythromycin*, when his dentist really would have preferred to give him *penicillin*. [Note: *Erythromycin* has the benefit of being able to penetrate abscesses.] (2) A cephalosporin would not have been safe enough, because a small percentage of patients who are allergic to *penicillin* also manifest allergy to cephalosporins. The reaction (bronchospasm) that this patient had could be so life-threatening that the dentist correctly chose not to take the risk, however small, that this patient might be allergic to both β-lactam categories. (3) That the patient had endocarditis required that the drug(s) with which he was to be treated must be bactericidal. (4) Finally, the role of Enterococcus in his endocarditis made it necessary to treat him with two antibiotics which act synergistically on this organism. [Note: The treatment of Enterococcal faecalis is becoming a problem due to resistant strains.]

CASE 6

A 41-year-old female presented to her primary medical doctor with a chief complaint of insomnia and nervousness worsening over the past several months. Since her last gynocologic exam, which was normal, she has experienced irregular menstrual cycles. She described her job as stressful and attributed some of the nervousness to her job.

BP 135/80 (120/80); pulse 135 bpm (60-80) and regular; respiratory rate of 20(12-18) and temperature of 99.5°F.

Physical exam reveals exophthalmos (abnormal protrusion of the eyeball) with weakened extraocular muscles (Figure A.6). Her skin was warm and moist

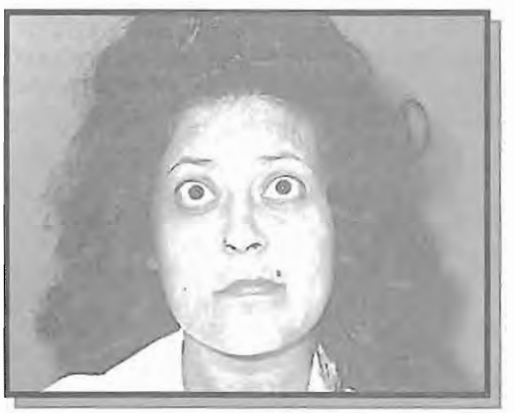


Figure A.6
Patient with exophthalmos.

and her hair was fine. Upon palpation the thyroid gland appeared slightly enlarged, uniform and without palpable nodules or masses. Pulses were strong bilaterally. Heart sounds were normal. Hand tremors presented as well as slight hyperreflexia.

Laboratory Tests reveal elevated thyroxine (T_4) and slightly decreased thyroid-stimulating hormone (TSH). All other tests were within normal limits.

The woman was treated with *propylthiouracil* 100mg every 8 hours, and *propranolol* 40 mg twice daily.

Question A.16: Which one of the following best describes the mechanism of action of *propylthiouracil*?

A. blocking the thyroid hormone receptor.
B. inhibiting the formation of thyroid hormone.
C. attenuation of the sympathetic excess seen in hyperthyroidism.
D. inhibition of iodine uptake into the thyroid gland.
E. inhibition of TSH release from pituitary

Correct answer is **B**. *Propylthiouracil* inhibits the formation of thyroid hormone.

Questions A.17: When using a thioamide, either *methimazole* or *propylthiouracil*, the most serious adverse drug reaction to monitor for is?

A. Agranulocytosis
B. Fatigue
C. Myalgias
D. Gastrointestinal (GI) upset
E. Edema

Correct a answer is **A**. The other side effects may occur, but the primary concern is agranulocytosis ,because this can be life threatening. The edema may be managed with diuretics and the diarrhea with antidiarrheal agents.

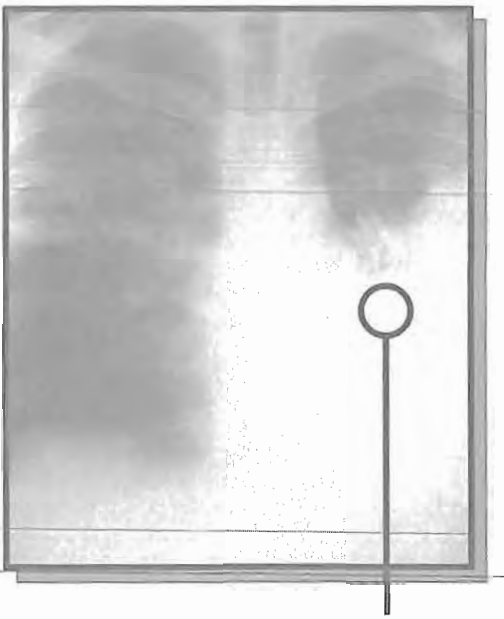
Question A.18: Why are β adrenergic blocking agents needed in addition to thioamides at the onset of treatment of hyperthyroidism?

Because thioamides inhibit the synthesis of new thyroid hormone and do little to inhibit the activity of circulating thyroid hormone, β blockers are needed to control the hypertension and tachycardia of hyperthyroidism in the first few weeks of therapy. In addition, adrenergic receptors are upregulated (there is a higher population in the vasculature) in the hyperthyroid patient, this it is important to block these β receptors and thereby reduce the blood pressure. With return to euthryroid condition, the receptor number decreases.

CASE 7

A 32 year-old homeless, HIV-negative man arrived at the clinic complaining of general malaise and a chronic productive cough.

The patient stated that he had been feeling poorly for about 5 weeks and thought he was losing weight. Upon physical examination, a slightly elevated temperature and chest congestion were noted; no other apparent irregularities were present. Lab tests were ordered, including a complete blood count (CBC), sputum culture, and an acid-fast bacilli (AFB) stain. A chest X-ray (Figure A.7) was obtained and a purified protein derivative (PPD) was administered. The patient was told to return in 2 days for a follow-up visit.



This lighter area in the lung is abnormal and shows the presence of cells and pus rather than air. This indicates the possible presence of infection.

Figure A.7
Chest X-ray of patient.

Question A.19: Based on these findings, the patient is suspected of having:

A. Streptococcal pneumonia
B. Mycobacterium infection
C. Pneumocystis carinii pneumonia (PCP)
D. Pseudomonas infection
E. Autoimmune deficiency syndrome (AIDS)

The correct answer is **B**. The chest X-ray with lung infiltrates could indicate lung cancer, pneumonia or other lung diseases. However, in conjunction with a positive AFB stain, the tests indicate a mycobacterium infection. [Note: A positive AFB stain does not identify the species of mycobacterium, only the genus. A diagnosis of Mycobacterium tuberculosis at this time is not confirmed but should be suspected.] **A** is incorrect. Streptococcal pneumonia might have been a possibility given the appearance of the chest X-ray, but this diagnosis is not definitive without an identification of the microbe in the sputum or blood cultures. The presence of AFB bacteria points strongly toward tuberculosis (TB). **C** is incorrect. PCP is seen primarily in individuals with AIDS who have a CD4 count (a measure of cell-mediated immunity) less than 200. This patient has no history of HIV or AIDS and therefore this diagnosis is unlikely. **D** is incorrect because Pseudomonas was not observed in the sputum. **C** is incorrect because the patient has no history of HIV infection.

Two days later the patient returned to the clinic for a follow-up examination. The lab results indicated that his sputum culture was negative for growth, and the CBC showed a slight leukocytosis (increase in white blood cells).

[Note: The PPD is a purified protein derivative of Mycobacterium tuberculosis that is injected subcutaneously into the volar surface of the forearm to stimulate a hypersensitivity reaction. If, within 24 to 48 hours there is an area of induration greater than 10 mm in diameter, it is a positive PPD test and indicates that the patient had been exposed to and infected with Mycobacterium tuberculosis.] The patient's test was positive. Due to his homeless status, it is likely that he came in contact with TB-infected individuals.

Based on the patient's history and lab information, he was started on a regimen of isoniazid, rifampin, pyrazinamide, and ethambutol while waiting for definitive cultures. (Six weeks later, definitive culture results demonstrated growth of Mycobacterium tuberculosis.) The patient returned to the clinic complaining of blurred vision and an inability to differentiate between green and red colors.

Question A.20: Which of the drugs he is taking could be causing these adverse visual symptoms?

A. *Isoniazid*
B. *Rifampin*
C. *Ethambutol*
D. *Pyrazinamide*

The correct answer is **C**. *Ethambutol* is a bacteriostatic agent used in conjunction with other drugs to treat Mycobacterium tuberculosis infections. A major side effect of *ethambutol* therapy is optic neuritis, which could be the cause of the patient's blurred vision and red/green color blindness. A baseline vision test is recommended prior to starting *ethambutol* therapy and should be conducted periodically throughout the regimen. **A** is incorrect. *Isoniazid* is a bactericidal agent used to treat TB, but its side-effects profile does not include visual disturbances. **B** is incorrect. Side effects of *rifampin* therapy include hepatitis, thrombocytopenia, acute renal failure, and a red/orange discoloration of body fluids, but does not affect the vision. **D** is incorrect. *Pyrazinamide* has been known to cause hepatotoxicity and hyperuricemia, but it does not cause visual disturbances.

CASE 8

A 47-year-old woman complained of recurrent headaches. She described the pain as unilateral, located in the temple, and having a rhythmic or pulsating quality. The headaches arise spontaneously—often awakening her in the middle of the night. The headaches are accompanied by nausea, abdominal pain, and spots before the eyes.

Question A.21: Which one of the following agents is most likely to provide symptomatic relief for this patient?

A. Oral *sumatriptan*
B. Oral *acetaminophen* plus *butalbital*
C. *Propranolol*
D. Oral *ergotamine*
E. *Sumatriptan* subcutaneously

Correct answer is **E**; *Sumatriptan* administered subcutaneously is rapidly absorbed and provides pain relief within 20 minutes. However, the half-life of the the drug administered subcutaneoulsy is only about 2 hours, so that the headache my be of longer duration than the drug's effect. The drug is approved for two doses per 24 hours. **A** Oral *sumatriptan* is appropriate in patients whose headaches slowly increase in severity. Taken at the start of the headache, oral *sumatripan* provides relief within 1 to 2 hours. The headaches described by this patient peak rapidly and *sumatriptan* administered orally would not act rapidly enough to provide relief for the acute pain of her migraine attacks. The bioavailability of the oral form is only about 15% due to poor absorption and presystemic metabolism. **B** Oral *acetominophen* plus *butalbital* has a slow onset of action and is unlikely to be effective in treating headaches that develop so rapidly as to awaken a sleeping patient. These moderately effective agents are used in mild to moderate headaches. **C** *Propranolol* is used as a prophylactic agent. **D** Oral

ergotamine is a possible treatment option. However, the agent is most effective when give before the headache is established.

CASE 9

A 9 year-old boy was brought to the clinic by his mother. He was complaining of severe pruritus (itching) and bubbles on his arm.

Viewing the child's arm, the doctor noticed erythema (a red rash) and small vesicles (fluid-filled sacs) arranged linearly on the child's arm (Figure A.8). The doctor checked the child's profile and noticed no prior history of allergies to medication or foods, and no prior history of skin eruptions. The mother stated her son had not been wearing new clothing or taking any over the-counter-medications (OTC).

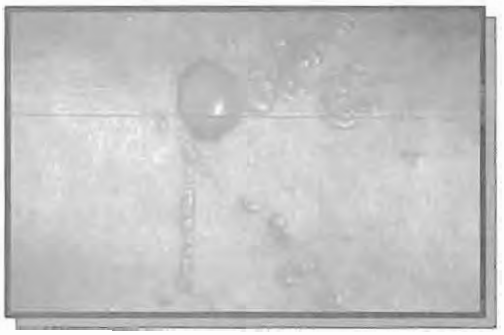


Figure A.8
Rash and vesicles on patient's arm.

The boy had recently been playing more outside in the yard, due to the hot weather, and his mother asked if the rash could have been caused by chiggers (larvae of mites that attached to the skin). With the patient's history of playing outdoors, and the characteristic linear vesicles, the doctor believed that the child had an allergic contact hypersensitivity reaction to poison ivy, and instructed the mother to apply cloths soaked in Burow's solution (aluminum acetate) until the vesicles crusted over. The mother was also told to thinly apply1% hydrocortisone cream (a low potency steroid) twice per day.

Question A.22: The hypersensitivity reaction was not serious enough to warrant stronger pharmacologic therapy, but the patient requests some remedy to stop the pruritus (itching). Which of the following drugs should be recommended?

A. *Ranitidine*
B. *Alprazolam*
C. *Diphenhydramine* (oral)
D. *Scopolamine*
E. *Phenobarbital*

The correct answer is **C**. *Diphenhydramine* is an antihistamine that is a competitive inhibitor of the H_1 receptor. It is used to treat various hypersensitivity reactions that are mediated by histamine such as allergic contact dermatitis. It will decrease the pruritus (itching) and some of the erythema produced by the release of histamine. [Note: Topical *diphenhydramine* should be used with caution in treating allergic contact dermatitis because it can act as an allergen itself and stimulate further irritation.] **A** is incorrect. *Ranitidine* is an H_2 histamine antagonist that is used to treat gastric ulcers. H_2 antagonists are not effective against hypersensitivity reactions except in rare instances when they are used in combination with H_1 antagonists. **B** is incorrect. *Alprazolam* is a benzodiazepine drug that is used in the treatment of anxiety and panic attacks. It is not indicated for the treatment of pruritus. **D** is incorrect. *Scopolamine* is a cholinergic antagonist used primarily to treat motion sickness, and has no antipruritic effect. **E** is incorrect. *Phenobarbital* is a sedative without antihistaminic (and thus without antipruritic) activity.

Five days later the child returned to the clinic. His hands, forearms, and chest are erythematous, swollen, and covered with blisters. His mother explained the poison ivy was starting to clear up, but then her son disobeyed her and went into the woods to play.

Question A.23: Which one of the following pharmacologic therapies should have been prescribed next to attenuate the inflammatory response.?

A. Apply the *hydrocortisone* cream more frequently
B. Oral *prednisone* therapy, tapered down over 2 weeks
C. Hospitalization
D. *Betamethasone* ointment with occlusion
E. Apply ice frequently

The correct answer is **B**. Due to the increased severity of this allergic reaction secondary to re-exposure, the next step in therapy is oral steroids. *Prednisone*, a glucocorticoid, is commonly used to treat conditions such as skin inflammation, asthma, and arthritis. *Prednisone* acts by decreasing the production of the mediators of inflammation, thereby resulting in its antiinflammatory action. **A** is incorrect. *Hydrocortisone* is a low potency glucocorticoid that is indicated for mild inflammation and irritation of the skin. The child's inflammation is severe enough to require systemic steroid therapy.

Spreading a cream over such a large area is not very practical and may lead to a decrease in patient compliance. **C** is incorrect. Hospitalization might be required if the child's inflammation compromised respiration in some way or if it were severely debilitating. This child is ambulatory and in no severe distress, and so can be treated on an outpatient basis. **D** is incorrect. *Betamethasone* is a strong topical steroid that should be avoided in this patient. Applying this steroid over large areas and possibly broken skin could lead to excessive absorption and thus toxicity. **E** is incorrect. Ice may decrease some of the itching but it has limited use in such a severe skin eruption.

Question A.24: What are some of the problems associated with glucocorticoid therapy?

Answer: *Prednisone* therapy given over a long period is associated with a multitude of side effects which include hyperglycemia, increased susceptibility to infection, osteoporosis, Cushing's syndrome, central nervous systme (CNS) effects, electrolyte disturbances and adrenal insufficiency. To avoid these adverse effects, prednisone is given for a short period and is tapered down throughout the regimen.

CASE 10

A 50-year-old female visited the clinic for the first time. Her chief complaint was stomach pain and recent swelling in her legs.

The woman described her pain as sharp and localized, and stated that it had occurred frequently during the previous 2 weeks. One week prior to the clinic visit she had started taking MAALOX (aluminum/magnesium hydroxide antacid) and it seemed to help at first, but the pain persisted and shortly thereafter the leg swelling appeared. Her past medical history included a prior diagnosis of congestive heart failure (CHF) and rheumatoid arthritis. A physical examination of the patient was insignificant except for noted arthritic joints in the hands and obvious ankle edema (Figure A.9). Further questioning revealed recent episodes of shortness of breath and increased fatigue. Her current medications included digoxin, ibuprofen, Maalox, and furosemide (LASIX). She also stated that she had heard on the news that aspirin might be good for the heart, so she had begun to take two tablets a day for her heart condition. The physician ordered a CBC, electrolyte panel, digoxin level, and a hemoccult test (to test the stool for signs of gastrointestinal bleeding).

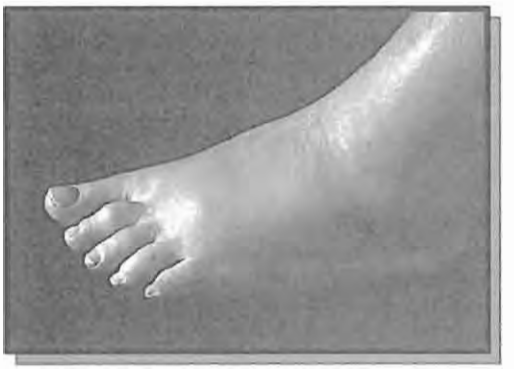


Figure A.9
Patient's ankle showing edema.

Question A.25: Based on the information presented above, what could be precipitating the stomach pain?

A. *Digoxin*
B. H. pylori
C. Nonsteroidal anti-inflammatory drugs (NSAIDs)
D. *Furosemide*
E. *Aluminum/magnesium hydroxide* combination antacid (Maalox®)

The correct answer is **C**. NSAIDs are used to decrease pain, inflammation, and fever. NSAIDs work by inhibiting the enzyme cyclooxygenase, which is responsible for producing prostaglandins, the body's mediators of pain and inflammation. Certain prostaglandins also have a protective effect on the stomach, causing a reduction in the production of stomach acid and maintaining the protective mucous barrier of the GI wall. Prolonged NSAID therapy leads to decreased quantities of prostaglandins and thus can result in GI erosion. The patient was prescribed the NSAID, *ibuprofen*, to decrease the symptoms associated with her rheumatoid arthritis. She was also taking a second NSAID, *aspirin*, which could result in additive stomach irritation and possible ulceration. This combination is probably responsible for the pain. **A** is incorrect. *Digoxin* belongs to the class of drugs called the cardiac glycosides, used to treat CHF by increasing the strength of the heart contraction and improving cardiac output. Side effects include nausea and vomiting, arrhythmias, and CNS effects including blurred vision and headache, but not sharp stomach pain. **B** is incorrect. Helicobacter pylori has been shown to be associated with stomach ulcers. From the patient history, there is no way to know without further investigation if she was colonized with H. pylori. **D** is incorrect. *Furosemide* is a loop diuretic used to eliminate fluid in patients with fluid overload such as in CHF or patients experiencing pulmonary edema. *Furosemide* is a fast acting diuretic with side effects that include: hypokalemia (low potassium), ototoxicity , and hypovolemia (dehydration). Side effects do not include excessive stomach pain. **E** is incorrect.

MAALOX is an *aluminum/magnesium hydroxide* combination antacid that is used to treat heartburn and sour stomach. The combination antacid has been known to cause constipation, diarrhea, and even CNS effects when used in renally compromised patients for extended periods, but does not cause sharp stomach pain.

The doctor hypothesized that the woman might have gastric or duodenal ulcers from NSAID therapy, and told her to collect three stool samples to be analyzed for the presence of blood. The doctor instructed the patient to discontinue using *ibuprofen* and *aspirin* until the actual reason for her pain could be diagnosed. She was to return for a follow-up visit in a few days. The doctor started treatment with an H_2 receptor antagonist to prevent any further GI irritation.

Question A.26: Why has the doctor prescribed the H_2 receptor antagonist?

Answer: All H_2 receptor antagonists work by preventing histamine from interacting with the H_2 receptor, thus decreasing the production of hydrochloric acid by the stomach. This decrease in acid production allows the stomach ulcer to heal. They also interfere in gastrin-mediated acid secretion. Basal and nocturnal acid secretion is also reduced. In addition, pepsin output also declines. Figure A.10 shows data obtained in a 24-week, double-blind, comparison of placebo with the H_2 receptor antagonist, *famotidine*. *Famotidine* significantly reduces the cumulative incidence of both gastric and duodenal ulcers in patients with arthritis receiving long-term NSAID therapy.

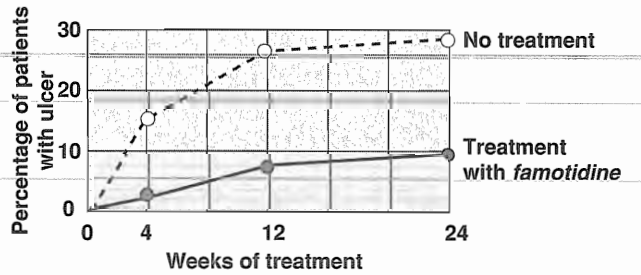


Figure A.10
Cumulative incidence of gastric or duodenal ulcers in patients receiving long-term NSAID therapy.

Question A.27: Which of the following drugs is NOT an H_2 receptor antagonist?

A. *Cimetidine*
B. *Famotidine*
C. *Omeprazole*
D. *Nizatidine*
E. *Ranitidine*

The correct answer is **C**. *Omeprazole* is an irreversible inhibitor of the H^+,K^+-ATPase (the "proton pump" of the parietal cell). It is used as an alternative to the H_2 receptor antagonists when the latter agents cannot control peptic ulcers. All of the other drugs are H_2 receptor antagonists. They vary in their side effect profile and to some extent in their pharmacokinetics. *Cimetidine* has the most side effects, which include confusion, dizziness, diarrhea, muscle pain, and gynecomastia (breast enlargement). In addition, *cimetidine* is a cytochrome P-450 enzyme inhibitor that decreases the metabolism of other drugs and can lead to drug toxicity. *Famotidine* has few side effects associated with its use.

Question A.28: Would you have recommended that she continue to take the MAALOX?

Answer: Probably not since she was placed on the H_2 receptor antagonist therapy and the antacid could have caused problems such as constipation and diarrhea.

The doctor next addressed the problem of edema. The patient's blood *digoxin* level was found to be in a subtherapeutic range, probably accounting for the ankle edema. The patient was questioned about being noncompliant (not taking her medication), but she insisted that she took her *digoxin* every day and that the swelling in the ankles appeared after she started taking MAALOX.

Question A.29: If the patient was being truthful about taking her medication every day, what could have caused the subtherapeutic blood levels of digoxin?

A. The *furosemide* was increasing her urine output and thereby increasing the elimination of digoxin from the blood.
B. *Aspirin* was competing for protein binding with *digoxin*, leading to increased concentrations of free *digoxin* and thus more free *digoxin* eliminated by the kidneys.
C. The patient is simply forgetful, and believes she takes her medication regularly, but frequently misses a dose.

D. The antacid she had been taking had been binding the *digoxin* in the GI tract and decreasing its absorption into systemic circulation.

E. The CHF is progressing and the patient is starting to deteriorate.

The correct answer is **D**. Combination *aluminum/magnesium hydroxide* antacids have been known to bind certain drugs such as *digoxin* in the GI tract and prevent them from being absorbed and distributed into systemic circulation. The patient had no edema prior to taking MAALOX, but developed it shortly after she started taking it. It is very likely that much of her *digoxin* dose was never absorbed by the body. If this is true then suspension of antacid intake should restore digoxin levels to the therapeutic range. If it does not, then the dose of digoxin must be increased. **A** is incorrect. *Furosemide* is a loop diuretic that increases urine output by inhibiting a carrier system in the ascending loop of Henle. It does not increase blood clearance of drugs by the kidney. **B** is incorrect. *Aspirin* is approximately 80% protein-bound. *Digoxin* is less than 25% protein-bound. Even if aspirin did displace *digoxin* from blood proteins, the increase in the free fraction of *digoxin* would not be significant and it is unlikely that there would be any increase in elimination of *digoxin* from the body. **C** is incorrect. It is certainly possible that the patient was noncompliant. However, the leg edema developed shortly after the stomach pain, but was absent prior to taking the antacid. This suggests possible drug interactions with concurrent patient medications. **E** is incorrect. It is a possibility that the patient's CHF was becoming worse and the disease was progressing. However, it would be wise to rule out the smaller problems (such as drug interactions) as a cause of edema before increasing the dose of *digoxin* or taking any drastic therapeutic measures.

CASE 11

A 57-year-old obese male with a history of mild asthma and hypertension arrived at the clinic for a flu shot and annual physical examination.

The doctor noticed that the patient had been placed on hydrochlorothiazide 8 months earlier for treatment of his high blood pressure. Through the course of the examination, the patient complained of cramps and fatigue that had been continuous over the previous month. The patient's baseline lab tests, performed 8 months prior to this visit, had all been within the normal ranges.

The doctor performed a physical examination that revealed a BP of 143/92 mm Hg with no other abnormal signs. The patient was questioned about his diet and any other medications he had been taking, and he responded that he usually ate a lot of meat and potatoes, but few vegetables. His other medications included an *albuterol* inhaler, metamucil, and a daily multivitamin tablet. The doctor ordered serum electrolyte levels and a CBC with differential from the lab. Recognizing that the patient had a couple of problems, the doctor decided to deal first with the cramps and fatigue.

Question A.30: What could be causing the patient's fatigue and muscle cramps?

A. He has come down with the flu, which is responsible for the fatigue and cramps.

B. The *albuterol* is responsible for the symptoms, commonly seen in asthmatics on *albuterol* therapy.

C. Continued high blood pressure is responsible for the symptoms (that is, the patient's blood pressure is not controlled with the thiazide therapy).

D. Thiazide therapy is causing potassium depletion and resulting in the cramps and fatigue.

E. *Metamucil*, a bulk forming laxative, is leading to dehydration, which gives rise to fatigue and cramps.

The correct answer is **D**. *Hydrochlorothiazide* is a thiazide diuretic that exerts its action at the distal tubule of the kidney. It works by inhibiting a sodium/chloride transporter, which leads to increased sodium and water excretion into the urine and diuresis. When the elimination of sodium is increased, the kidney exchanges potassium for sodium in the transporter (both are monovalent cations), which over an extended period can lead to potassium depletion. If sufficient quantities of potassium are not obtained through the diet or by exogenous supplements, an individual may experience cramps, fatigue, and possibly arrhythmias. **A** is incorrect. The patient does not have a fever, chills or the muscle aches and pains that are characteristic of the flu. Also, the flu usually lasts no more than 2 weeks, whereas the patient had been having these symptoms for over a month with no fever. **B** is incorrect. *Albuterol* is a β_2-specific agonist that is used in the treatment of mild asthma. *Albuterol* promotes bronchodilation that counteracts the bronchoconstriction experienced by asthma sufferers during an attack. The most common side effects of *albuterol* therapy are tachycardia, tremor, and increased blood pressure. The patient had presumably been on this medication for quite a while, with no previous symptoms of cramps and fatigue. **C** is incorrect. Symptoms of high blood pressure are usually only seen when the pressure is extremely high. Under these circumstances, the patient will be in obvious distress, and rapid medical treatment is imperative. The patient's continued hypertension might result in future disease, but his current symptoms are not indicators of hypertension. **E** is incorrect. *Metamucil* is an OTC bulk forming laxative which, when taken with water, forms a bulky mass that stimulates GI motility. It has been known to adhere to some medications in the GI tract and prevent them from being absorbed into sys-

temic circulation. Adverse side effects include nausea, vomiting and stomach pain. *Metamucil* does not cause dehydration, and it is doubtful that this agent was causing the patient's symptoms of cramping and fatigue.

The lab test results were returned, and the doctor noted that there were no leukocytosis or abnormalities on the CBC, but that the serum electrolyte results showed a marked hypokalemia, as was expected. This provided an explanation for the patient's cramping and the fatigue. The doctor prescribed a potassium supplement for the patient, due to the extent of his hypokalemia.

Next, the doctor began to address the patient's uncontrolled hypertension. Believing him to be reasonably dependable and compliant with his diuretic therapy, the doctor realized that the patient's current hypertension medication was not working. Instead of increasing the dose of hydrochlorothiazide, he felt that the patient would benefit from an additional antihypertensive medication in combination with his present therapy.

Question A.31: Which additional antihypertensive medication will most benefit the patient?

A. An angiotensin converting enzyme (ACE) inhibitor
B. *Nitroglycerin*
C. A β-blocker
D. *Clonidine*
E. *Hydralazine*

The correct answer is **A**. ACE inhibitors are an effective group of antihypertension medications with a favorable side-effect profile. In addition to preventing vasoconstriction, ACE inhibitors also decrease aldosterone secretion, resulting in less sodium and water reabsorption and less potassium wasting. ACE inhibitors also decrease the breakdown of bradykinins, which are potent vasodilators. Since ACE inhibitors do not block β-receptors, they are a good choice for the treatment of asthma patients. ACE inhibitors are generally well tolerated, and are the best choice for this patient. **B** is incorrect. *Nitroglycerin* is an organic nitrate used for its vasodilator action to treat angina. It is not indicated for the treatment of hypertension. **C** is incorrect. β-Blockers are a group of medications used to treat hypertension, angina, glaucoma, and refractory migraine headaches. Although many β-blockers are β_1-specific blockers, they may also have β_2 blocking action. Use of β-blockers should be avoided in asthma patients, because they may experience bronchoconstriction and an asthma attack if their β_2 receptors are blocked. Also, β-blockers may complicate treatment of bronchospasm by decreasing the effectiveness of β_2 agonists such as *albuterol*. The patient suffered from mild asthma and, therefore, β-blockers are a poor choice for treating his hypertension. **D** is incorrect. *Clonidine* is a central-acting α_2 receptor agonist used to treat moderate hypertension. *Clonidine* works by decreasing sympathetic outflow to the periphery and thus decreases cardiac output. *Clonidine* does not decrease renal blood flow like other antihypertensive agents, which makes it a good agent for treatment of hypertensive patients with renal disease. The patient is suffering from mild hypertension. *Clonidine* could be used, but it has a larger side-effect profile and should probably be reserved for patients with more severe hypertension. **E** is incorrect. *Hydralazine* is a direct acting vasodilator used to treat moderately severe hypertension. *Hydralazine* is not a first line agent, due to its many side effects, and is used in combination with other agents. Since the patient suffers only from mild hypertension, strong antihypertensive therapy with *hydralazine* is not warranted.