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Pulmonary Infections

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Acute Bronchitis

Acute bronchitis is a self-limited inflammation of the trachea and bronchi. It is common in smokers and occurs frequently during the winter months. In the United States bronchitis accounts for about 12 million physician visits a year and more than $300 million in physician visits and prescriptions. Work absences are common and probably run into millions of days each year. Much of this disability is due to acute flare-ups of chronic bronchitis, which is not discussed in this section.

Although a diagnosis of acute bronchitis is often made in patients without chronic lung diseases, there is an association between bronchitis and asthma. Adult patients with a diagnosis of acute bronchitis are significantly more likely to have a history of asthma or atopic disease and an increase in subsequent visits for asthma than patients without bronchitis. Indeed, the term "asthmatic bronchitis" may be appropriate to express the midrange of the spectrum that goes from acute bronchitis to asthma. In one study, 40% of patients with acute bronchitis but no history of lung disease or asthma had a forced expiratory volume in 1 second (FEV_1) of less than 80% of the predicted value; the FEV_1 returned to normal over a 5-week period.[1]

Wheezy bronchitis in children is a term used to describe a lower respiratory tract infection (LRI) in which wheezing is prominent. Boys with two or more episodes of a wheezing LRI before age 6 subsequently had a higher degree of small airway dysfunction than those with no visits, suggesting that wheezy bronchitis at a young age may help identify those who have increased bronchial reactivity.[2]

Clinical Presentation

The definition of bronchitis is a clinical one. Acute bronchitis (or tracheobronchitis) is defined as an acute cough, usually productive of purulent phlegm without evidence of pneumonia. The phlegm may be tenacious, clear, or discolored, increased in amount, and foul tasting. Bronchitis is the most common cause of hemoptysis. The temperature may be mildly elevated—usually not above 102°F—and night sweats or fatigue are common. Shortness of breath may be noticeable in those with underlying diminished pulmonary capacity. Occasionally there is pleuritic chest pain, usually induced by coughing. Wheezing is also frequently present, particularly in children or those with a history of respiratory allergies or obstructive airway disease.

Pulmonary signs may be absent; more commonly, though, there are harsh breath sounds, bibasilar crepitations, or variable amounts of expiratory wheezing. Auscultatory sounds in the chest can be divided into musical and nonmusical. Musical sounds are termed wheezes and nonmusical crepitations. Rhonchi are low-pitched wheezes. Synonyms for crepitations are rales and crackles. A deep breath that clears atelectasis or a cough that removes secretions in the large airways may clear the crepitations heard with bronchitis.

Diagnosis

The etiology of acute bronchitis is usually infectious. It is frequently impossible, and seldom necessary, to isolate the specific cause. Common infectious etiologies are listed in Table 86.1. By far the most common is viral, accounting for well over half of the diagnoses; more than 180 viruses have been identified as causing upper respiratory tract infections. As a guideline, a cough develops in 50% of patients who have such an infection; and in 50% of those patients, a productive cough characteristic of acute bronchitis occurs. The most common viral cause of acute bronchitis is probably the rhinovirus, followed by the adenovirus. Influenzavirus can cause extensive destruction of the respiratory epithelium, and up to 95% of patients infected have bronchitic symptoms. Respiratory syncytial virus is the usual cause of bronchiolitis in young children.

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Table 86.1. **Common Causes of Tracheobronchitis**

Bacteria
Haemophilus influenzae
Streptococcus pneumoniae
Moraxella catarrhalis
Bordetella pertussis
Viruses
Influenzas A and B
Parainfluenzae
Rhinoviruses
Respiratory syncytial virus
Adenoviruses
Coxsackieviruses
Coronavirus
Other infectious agents
Mycoplasma pneumoniae
Chlamydia pneumoniae

The second most common cause of bronchitis, at least in young adults, is *Mycoplasma pneumoniae,* accounting for 10% to 20% of diagnoses. *Chlamydia, Legionella,* and *Bordetella pertussis* can also cause bronchitis. *Chlamydia pneumoniae,* previously called the TWAR strain, has been found in 5% of cases of bronchitis in college students. It is also significantly associated with newly diagnosed asthma, developing after bronchitis.

A smaller portion of the cases of acute infections are due to bacteria. Sputum cultures from 80% to 95% of patients with acute bronchitis grow out only normal flora. Although it is generally accepted that normal bronchi are sterile, many bacteria, including *Haemophilus influenzae* and *Streptococcus pneumoniae,* are often found further up the upper respiratory tract, making interpretation of a sputum culture difficult. Nevertheless, *S. pneumoniae* and *H. influenzae* are thought to be causes of acute bronchitis, particularly in those with more systemic symptoms.

Moraxella catarrhalis (formerly called *Neisseria catarrhalis*) is a gram-negative diplococcus recently recognized as a pathogen in acute bronchitis and in acute exacerbations of chronic bronchitis. In one study, it was the third most common bacterial pathogen (after *S. pneumoniae* and *H. influenzae*). The diagnosis is suggested from a Gram stain, where it appears as a kidney bean-shaped, gram-negative diplococcus.

The chest roentgenogram often helps differentiate bronchitis from pneumonia in those with systemic symptoms and chest findings. There is no diagnostic radiographic finding characteristic of bronchitis, and usually the chest film is interpreted as normal. Findings consistent with bronchitis on chest roentgenograms include thickening of the adventitia or mucosa around large bronchi (peribronchial cuffing), increased pulmonary markings in the lower lobes, or overinflation.

Management

Dextromethorphan- or codeine-containing cough suppressants may be indicated in those with significant nighttime cough. Glycerol guaiacolate, potassium iodide, mucolytic agents, antihistamines, and decongestants are usually not helpful.

The role of antibiotics in the treatment of acute bronchitis is still debated. Unfortunately, most studies of bronchitis treatment were not done as randomized trials. Of five well designed studies, two reported moderate improvement, compared to placebo, for patients treated with erythromycin or trimethoprim-sulfamethoxazole (TMP/SMX).[3,4]

The oral antibiotics that might be reasonable choices for therapy are listed in Table 86.2 along with the pathogens they affect. The decision of whether to use an antibiotic and, if so, which one rests with clinical judgment. The authors' recommendation is not to treat those who are otherwise healthy and who have no significant systemic symptoms.[5] Acute bronchitis is a self-limiting condition usually caused by viruses with a course that is not dramatically changed by giving antibiotics. For those with preexisting conditions—such as diabetes mellitus or congestive heart failure—and those who have a produc-

Table 86.2. **Antibiotic Sensitivity of Common Causes of Bronchitis and/or Pneumonia**

Drug	*Streptococcus pneumoniae*	*Haemophilus influenzae*	*Moraxella catarrhalis*	*Legionella*	*Chlamydia pneumoniae*	*Mycoplasma pneumoniae*
Tetracycline/doxycycline	Equivocal	Equivocal	+	+	+	+
Ampicillin	+	Equivocal	Equivocal	–	–	–
Amoxicillin/clavulanate	+	+	+	–	–	–
Erythromycin	+	Equivocal	+	+	+	+
Azithromycin or clarithromycin	+	+	+	+	+	+
TMP/SMX	+	+	+	–	–	–
Cefaclor or cefuroxime	+	+	+	–	–	–
Ciprofloxacin	Equivocal	+	+	+	+	–

+ = organism usually sensitive; – = organism usually resistant or unknown; equivocal = organism may be resistant, sometimes depending on antibiotic dose.

tive cough along with systemic symptoms, most physicians lean toward treating for 1 to 2 weeks with one of the drugs listed in Table 86.2. The goal of the treatment is to decrease sputum production and perhaps prevent the occasional progression toward pneumonia or respiratory failure.

Although the appropriate length of treatment for each etiologic agent has not been investigated, 10 to 14 days of erythromycin administration would be the most logical choice for acute bronchitis, especially if one is considering a mycoplasmal or chlamydial origin. This antibiotic is inexpensive and has good penetration into sputum. For children, erythromycin estolate has greater bioavailability and fewer side effects, but its use should be avoided in adults because it may cause cholestatic jaundice. The most common side effects of erythromycin are gastrointestinal.

Azithromycin and clarithromycin are chemically related to erythromycin. Both are expensive but well tolerated, and neither causes the high incidence of nausea that occurs with erythromycin. They are good alternatives for the treatment of lower respiratory tract infections.

Tetracycline and doxycycline are not consistently effective against *H. influenzae* or *S. pneumoniae* but are choices for initial treatment because of their effectiveness against *Chlamydia* and *Mycoplasma.* TMP/SMX, the oral cephalosporins, amoxicillin, and ampicillin also lack specificity against *Chlamydia* and *Mycoplasma,* making these antibiotics second choices, unless one is more confidently dealing with a bacterial infection such as in the elderly or in those with underlying lung disease. Because of the increasing incidence of β-lactamase-producing *H. influenzae* and *M. catarrhalis* strains, amoxicillin–clavulanate potassium is used instead of ampicillin or amoxicillin when specific therapy against these pathogens is needed. The quinolones ciprofloxacin and ofloxacin are effective against most bacterial pathogens, but high doses are needed for *S. pneumoniae.* These antibiotics are good choices for patients in whom gram-negative bronchitis is a possibility (e.g., those with cystic fibrosis or bronchiectasis) or where the patient is not responding after initial treatment with erythromycin or doxycycline. Occasionally, chronic cough continues for up to 3 months following acute bronchitis.

There are no precise guidelines for monitoring therapy; a decrease in dyspnea, less sputum, and sputum that is more mucoid than purulent are reasonable indicators. Additional therapies to be considered in those who are not responding to antibiotic therapy include bronchodilators, inhaled steroids, and reemphasizing the importance of adequate hydration. Hospital admission in order to give parenteral therapy, fluid replacement, and supplemental oxygen is occasionally necessary.

Prevention and Family Issues

Obviously, if the patient smokes, this bronchitis episode provides an opportune time for counseling. Patients may be more motivated to quit if they are coughing and feeling poorly. Prophylactic antibiotics to prevent exacerbations of chronic bronchitis have not been shown to alter the natural progression of the disease. Only stopping smoking can do that. Immunizations against respiratory infection are discussed in the section on pneumonia.

Pneumonia

Pneumonia is an acute lower respiratory tract infection with fever and cough; it develops in persons who have new findings on chest examination and an abnormal chest roentgenogram. It is estimated that in the United States each year pneumonia develops in as many as 3 million persons, of whom about 500,000 are admitted to a hospital and about 50,000 die. Of more than 500,000 visits to family and general practitioners in Virginia, pneumonia was found to be the 25th most common problem seen and comprised 0.8% of all office visits. Although community-acquired pneumonia (CAP) is a common office problem, there has been little published about its incidence in the United States, and there are few controlled clinical trials of outpatient treatment. This section primarily discusses the diagnosis and management of bacterial-caused CAP. The "atypical" pneumonias, including that due to *Legionella,* are discussed in more detail in separate sections.

A probable order of frequency of the causes of CAP in otherwise healthy adults is *Streptococcus pneumoniae, Mycoplasma pneumoniae, Haemophilus influenzae,* influenza virus, and *Chlamydia pneumoniae.*[6] In the elderly, alcoholic, or debilitated patient, or those with chronic obstructive pulmonary disease (COPD), bacterial infections are more common; and pathogens such as *Mycobacterium tuberculosis,* the anaerobes and gram-negative pathogens, *Moraxella catarrhalis,* and *Staphylococcus aureus* must be considered. The latter is seen more commonly in times of influenza epidemics, especially among infants and the elderly. Aspiration (anaerobic) pneumonia is usually seen in the setting of major trauma, coma, stroke, or intoxication. *H. influenzae* is a more common cause in young children but still ranks after *S. pneumoniae.*

In patients with the acquired immunodeficiency syndrome (AIDS), a probable order of etiologic frequency (from most common to least common) of CAP is *Pneumocystis carinii,* pyogenic bacteria (especially pneumococci), *Mycobacterium avium* complex, fungi (especially *Cryptococcus neoformans*), *M. tuberculosis,* and cytomegalovirus.

Clinical Presentation

The signs and symptoms of pneumonia are well recognized. In a study of 453 patients with pneumonia, cough was present in 88%, dyspnea in 71%, sputum production in 69%, chest pain in 64%, hemoptysis in 17%, and confusion in 17%.[7] It is important to remember that pneumonia in the elderly can often present with confusion and a low grade fever. Another, not infrequent presentation of pneumonia in the very young and very old is upper quadrant abdominal pain, sometimes with guarding and ileus. An upper respiratory infection precedes pneumonia only about one-third of the time. Characteristic signs, symptoms, and findings of the two pneumonic "syndromes" (bacterial and atypical) are presented in Table 86.3.[8]

The rales and wheezes heard in the chest are nonspecific: They can also be heard with bronchitis and congestive heart failure. The more specific signs (e.g., bronchial breath sounds, egophony, and dullness to percussion) are often heard later in the course and so may not help with the initial diagnosis. A

Table 86.3. **Characteristic Findings in Community-Acquired Pneumonia**

Characteristic	Typical pneumonia	Atypical pneumonia
Onset	Often sudden	Usually gradual
Myalgia-headache-photophobia	Not prominent	Often prominent
Rigors	Common	Rare
Toxicity	Marked	Mild to moderate
Cough	Productive, purulent, or bloody sputum	Nonproductive paroxysms or only scant mucoid sputum
Pleuritic pain	Common	Rare
Fever	> 38.9°C (> 102°F)	< 38.9°C (< 102°F)
Physical findings	Dullness with bronchial signs of lung consolidation	Often minimal
Roentgenographic findings	Localized; findings correlate well with physical examination	Involvement in excess of physical findings
Leukocyte count	> 15,000/mm^3	< 15,000/mm^3
Pathogen	Bacteria, including *Legionella*	*Mycoplasma pneumoniae, Chlamydia pneumoniae,* viruses

normal chest examination excludes pneumonia 95% of the time.

Diagnosis

For an outpatient, only three diagnostic tests are needed: chest roentgenogram, leukocyte count, and Gram stain of sputum specimens.

The *chest film* is important for three reasons. First, it may help distinguish whether a pneumonia is viral or bacterial. Focal alveolar or lobar infiltrates on a chest roentgenogram strongly suggest a bacterial infection. Diffuse interstitial infiltrates are suggestive of a viral, mycoplasmal, or chlamydial infection. Second, a chest film shows if a pleural effusion is present. If the effusion is small (it does not layer out to more than 2 cm on a lateral decubitus film) and if the patient's condition does not appear toxic and responds well to initial antibiotic therapy, thoracentesis is probably not needed. If, however, there is a large effusion or the patient is toxic, thoracentesis is mandatory to exclude empyema. The most common cause of empyema is an anaerobic infection; such an empyema occurs more frequently in patients with alcoholism or impaired consciousness. Third, follow-up chest films are needed to see if the infiltrate clears completely. More than 75% of patients show resolution within 3 months. Follow-up films should be done within 3 to 6 months for all patients who smoke or who are over age 40. If an abnormality has not cleared on follow-up films, the patient should be evaluated for a possible cancer.

To help identify those patients who need hospitalization (Table 86.4), a *leukocyte count* should be done. The count may aid in differentiating between pneumonia of viral or of bacterial cause. There is no clear dividing line between viral and bacterial pneumonias, although total counts of more than 15×10^6 (> 15,000/μl) suggest a bacterial cause. The differential cell count is not a reliable indicator.

Finally, if the patient has a productive cough, a *sputum Gram stain* should be done. Patients with a productive cough are more likely to have a bacterial infection. The Gram-stained specimen should be searched for areas where there are more than 10 neutrophils per high power field and few squamous epithelial cells. The predominant bacteria in these areas should be identified. Unfortunately, a Gram stain has low sensitivity. For pneumococcal pneumonia, its sensitivity ranges from 15% to 60%. It does have a high positive predictive value (80–90%). Therefore if a predominant organism is found, it is likely the cause of pneumonia.

Table 86.4. **Factors Associated with Increased Mortality from Pneumonia**

Age
Male sex
Confusion
Underlying conditions, such as alcoholism, neurologic disease, COPD, congestive heart failure, diabetes, cancer, or immunodeficiency (especially due to HIV)
Fever (temperature > 38.3°C)
Tachypnea (respiratory rate > 30/min)
Hypotension (diastolic < 60 mm Hg)
Hypoxemia (O_2 saturation < 88%)
Leukopenia (< 4000 WBC/mm^3)
Pronounced leukocytosis (> 30,000 WBC/mm^3)
Bacteremia
Elevated BUN
Bilateral or multilobe densities or large pleural effusion on chest film
Staphylococcal or gram-negative infection
Steroids, cytotoxic drugs, or other immunosuppressive therapy

Because sputum is expectorated through the upper airway, which has many bacteria, sputum cultures are not usually helpful in patients with CAP who are not admitted to the hospital. If the patient does not have a productive cough, no further diagnostic studies are warranted as an outpatient.

Evaluation of Hospitalized Patients

Factors noted in the literature to be associated with an increased mortality from pneumonia are presented in Table 86.4.[7,9,10] In patients with these risk factors, hospital admission should be strongly considered, and a more detailed workup for the etiology should be undertaken. The following tests may be indicated.

1. *Blood culture.* Blood cultures are positive in 25% to 40% of patients with pneumococcal pneumonia. Blood culture has lower sensitivity for other types of bacterial pneumonia.
2. *Sputum bacterial culture.* A culture is often done more by habit than intention. If a patient is sick enough to be hospitalized, however, a positive culture, despite its false-positive and false-negative results, may confirm a bacterial cause in those patients who have negative blood cultures; moreover, the antibiotic sensitivity tests may be helpful. The culture results inspire more confidence if they correlate with a good Gram stain.
3. *Invasive diagnostic techniques.* Some invasive procedures, such as bronchoscopic brushing, transtracheal aspirates, transcutaneous needle aspiration, bronchoalveolar lavage, and open lung biopsy, are used in very ill patients who do not respond to empiric antibiotics, but they yield an etiology only about 50% of the time.

The following tests are discussed in more detail in other sections of the chapter.

Legionella culture or antibody titer
Mycoplasmal titer
Chlamydial titer
Viral culture or antibody titers
Tuberculosis sputum smear and skin test
Pneumocystis carinii smear

Management

Outpatient Treatment

If a patient is a "normal host," produces little or no sputum so a Gram stain cannot be done, and is not being admitted to the hospital, the antibiotic of choice is usually erythromycin or one of the newer macrolide antibiotics: azithromycin and clarithromycin. These agents all cover *S. pneumoniae,* as well as *M. pneumoniae* and *C. pneumoniae.* Azithromycin has greater activity against *H. influenzae* and needs to be given only once daily.

An alternative to erythromycin is tetracycline or doxycycline; however, some pneumococci are resistant. Neither penicillin nor ampicillin is active against *Chlamydia* species or *M. pneumoniae.* TMP/SMX provides adequate coverage for three common bacterial pathogens—*S. pneumoniae, H. influenzae, M. catarrhalis*—but does not cover *M. pneumoniae* or *C. pneumoniae.* The newer, more expensive, oral, second generation cephalosporins, such as cefaclor or cefuroxime, cover a respiratory pathogen spectrum similar to that covered by TMP-SMX. Ciprofloxacin has some activity against *M. pneumoniae,* but high doses are needed for it to be bactericidal against the pneumococci. It is not recommended as the initial drug of choice for respiratory infections, except where gram-negative organisms are the suspected agents. Refer to Table 86.2 for antibiotic sensitivities of common pneumonia pathogens.[11]

If the patient is a "normal host" and produces a purulent sputum specimen, the Gram stain of sputum helps guide antibiotic selection. The use of Gram stain for initial antibiotic selection is depicted in Table 86.5.

Inpatient Treatment

If the Gram stain shows the classic picture of pneumococci in a hospitalized patient, penicillin is still the best choice. If the patient is penicillin-allergic, erythromycin is recommended. *H. influenzae* pneumonia is more common in the young and the old, and amoxicillin-clavulanate is an effective drug. Cefuroxime, another second generation cephalosporin, and

Table 86.5. **Use of Sputum Gram Stain to Select Initial Antibiotics for Treatment of Pneumonia**

Gram stain results	Pneumonia suspected	Initial treatment of pneumonia[a]
Few WBCs, no predominant organism	Viral, mycoplasmal, chlamydial	Erythromycin[b] (doxycycline)
WBCs and gram-positive lancet-shaped diplococci	Pneumococcal	Penicillin (erythromycin[b])
WBCs and small gram-negative rods	*Haemophilus influenzae*	Amoxicillin-clavulanate (cefuroxime or azithromycin)
WBCs and large grape-like gram-positive cocci	Staphylococcal	Admit for IV nafcillin therapy (vancomycin)
WBCs and gram-negative rods	Gram-negative	Admit for IV aminoglycoside and third generation cephalosporin (quinolone)
WBCs and mixed pleomorphic flora	Unclear	Amoxicillin-sulbactam (quinolone and metronidazole)

[a]Alternative drug in parentheses.

[b]If the patient is intolerant of erythromycin, consider the related antibiotics azithromycin and clarithromycin.

azithromycin are alternatives. For the sick nursing home patient or one with alcoholism in whom there is also concern about a gram-negative, anaerobic, or staphylococcal infection, initial treatment with a parenteral combination drug (e.g., amoxicillin–sulbactam sodium) is a reasonable choice. If the primary concern is a staphylococcal infection, nafcillin or vancomycin is the agent of choice. If there is a possible pseudomonal infection (unusual in CAP), gentamicin and ceftazidime are good initial choices. If the primary concern is anaerobic aspiration pneumonia, clindamycin or metronidazole is the best choice. In the case of an unclear cause where aspiration is a possibility, amoxicillin–sulbactam offers wide initial empiric coverage, as does a quinolone and metronidazole.

Criteria for hospital discharge include the resolution of fever, an ability to take medicines orally, no need for supplemental oxygen, no progression of a chest film infiltrate, a decrease in leukocyte count, and the presence of social and family support. After discharge from a hospital, 75% of patients return to normal activities within 6 weeks.

Prevention and Family Issues

Influenza vaccine is protective at a 70% to 80% level for the currently covered strains. Unfortunately, fewer than 20% of patients over age 65 or others at high risk (residents of long-term care facilities or those with chronic cardiac, renal, or hematologic illness) are immunized each year. If an influenza outbreak is relatively certain, amantadine is also protective at the 70% to 90% level. The usual dose is 200 mg/day, but in the elderly 100 mg/day is recommended to decrease the side effects of insomnia, dizziness, and personality changes. If amantadine is given within the first 48 hours of symptoms, it may also decrease the severity of the influenza.

The use of pneumococcal vaccine in the elderly or those with underlying conditions (e.g., COPD, transplants, splenectomy) probably reduces the chances of pneumococcal pneumonia by 60% to 80%. It is less effective in high risk populations (the very old and the institutionalized) where revaccination every 6 to 7 years is indicated. Lastly, *Haemophilus* B vaccine is now being used in children beginning at 2 months to protect against meningitis. The polysaccharide–diphtheria conjugate vaccine (PRP-CRM) may also decrease the incidence of *H. influenzae* respiratory infections and should be given to those with immunodeficiency who are at high risk.[12]

"Atypical" Pneumonias: *Mycoplasma* and *Chlamydia*

In the past, pneumonias were divided clinically and radiographically into two spectrums: bacterial "typical" pneumonias and "atypical" pneumonias (see Table 86.3). A variety of causes of an atypical syndrome have now been identified, including *Mycoplasma,* three types of *Chlamydia, Coxiella burnetii* (the cause of Q fever), and many types of virus. In the young adult without underlying medical conditions, pneumonia is more likely to be caused by the atypical pathogens than the typical ones.

Mycoplasma pneumoniae accounts for 10% to 35% of outpatient pneumonias. It is caused by one of a class of bacterial L-forms, which are the smallest free-living organisms. The incidence of infection is highest in children and in young men.[13] Infection is endemic in humans, although epidemics are seen on a 3- to 7-year frequency. Reinfections can occur, and serious ones are more likely in those over 45 years old.

The bacterial genus *Chlamydia* contains three species that infect man: *C. trachomatis, C. psittaci,* and *C. pneumoniae* *C. pneumoniae* was first identified as a cause of pneumonias in college students during the mid-1980s. Although not discussed further in this chapter, infants have a 10% to 20% risk of pneumonia when born to women with a genitourinary *C. trachomatis* infection. *C. pneumoniae* is now recognized as a worldwide infection, and antibodies have been found in 25% to 50% of adults.[14] Therefore subclinical infection is likely.

Clinical Presentation

Mycoplasma pneumoniae and *C. pneumoniae* infections have presentations that are similar and nonspecific. Infections usually begin with coryza, pharyngitis, headache, myalgias, malaise, and fever. The pharyngitis may be severe and confused with streptococcal disease. Sinusitis is often seen. A cough is usually present, either dry or productive of clear mucus, but dyspnea or pleuritic chest pain is uncommon. The lung examination of patients with either *Chlamydia* or *Mycoplasma* pneumonia is often less impressive than the chest roentgenogram. Crepitations (râles) are frequent, but signs of consolidation are usually absent. *M. pneumoniae* may rarely cause a bullous myringitis, and, if present, helps distinguish this etiology. Other rare extrapulmonary complications of *M. pneumoniae* include hepatitis, pericarditis, hemolysis, erythema multiformis, and neurologic abnormalities such as aseptic meningitis, transverse myelitis, or possibly, Guillain-Barré syndrome.[15]

Diagnosis

Routine laboratory tests are nonspecific. The white blood cell (WBC) count is usually normal. With *Mycoplasma* infection, many serologic abnormalities may be present, including false-positive rheumatoid factor and serologic tests for syphilis. The most common laboratory finding in *Mycoplasma* pneumonia patients is an elevated cold agglutinin test (> 50%). This test, however, also has many false-positives, and cold agglutinins are seen with up to 25% of viral pneumonias.

The chest roentgenogram is nondiagnostic. The infiltrates are often segmental but can be unilateral or bilateral, patchy or dense. Pleural effusions can be seen but are uncommon. As with other pneumonias, it may take up to 2 months for the infiltrates to resolve. The Gram stain of sputum, when present, shows few WBCs and no predominant organism. Cultures are difficult. *Mycoplasma* is fastidious and slow growing; *Chlamydia* is handled only in special laboratories. Therefore serology tests are used for diagnosis. A fourfold rise in specific complement fixation antibody titers in paired serum samples obtained 4 weeks apart of a single immunoglobulin M (IgM) titer greater than 1:64 is considered diagnostic for *Mycoplasma pneu-*

moniae. A fourfold rise in specific complement titers is considered diagnostic for *Chlamydia pneumoniae.* Because the results of these tests are not available when treatment decisions are made, they are used primarily for hospitalized patients or epidemiologic studies.

Management

Antibiotic treatment is similar for both diseases (which is another reason laboratory tests to distinguish the two are less important). Erythromycin, azithromycin, clarithromycin, tetracycline, and doxycycline are the drugs of choice.[16] Treatment should be continued for 1 week after defervescence has occurred or for at least 2 weeks. It is important to remember that tetracycline or doxycycline should not be given to pregnant women.

Preventive and Family Issues

Because both organisms are likely to spread by droplet infection, it is important to ask about symptoms in other household members and to recommend respiratory hygiene of covering one's mouth when coughing. In high risk populations, such as college students or military recruits, prevention is impossible. One hopes that as more is learned about the etiology, transmission, and diagnosis of these diseases, prevention strategies will develop.

Legionnaire's Disease

Legionnaire's disease got its name from an outbreak of pneumonia among those attending an American Legion convention in 1976. Many species and serotypes of the *Legionella* bacteria have now been found to cause disease, both endemically and in epidemics worldwide. There has been wide disparity in studies of legionnaire's disease incidence, ranging up to 3% of outpatient pneumonias to over 20% of inpatient pneumonias.

Legionnaire's disease can occur in any group, but middle-aged and elderly men are most commonly affected. Although the disease can strike healthy individuals, risk factors include immunosuppression, cigarette smoking, COPD, cardiac or renal disease, or diabetes.

Legionella bacteria are found in water, and institutional water systems (cooling towers, condensers, showers, nebulizers) are an important source for infection. Transmission seems to be exclusively from the environment, not person-to-person. Inhalation or ingestion of aerosolized particles is a likely means of lung infection.[17]

Clinical Presentation

Although often considered as an atypical pneumonia, the presentation of legionnaire's disease is distinctly similar to that of a bacterial pneumonia. It presents with high fever, shaking chills, and a minimally productive cough. Headache and myalgias sometimes briefly precede the fever. Pleuritic pain, hemoptysis, diarrhea, and confusion may be accompanying symptoms.

The physical examination is similar to that with other bacterial pneumonias, but lung findings usually do not show consolidation. The neurologic examination may show peripheral neuropathy or meningeal signs.

Diagnosis

A high index of suspicion is needed, as few findings are characteristic. Leukocytosis (up to 30,000/μl) is common, as is hyponatremia (seen in more than 50% of patients). The chest roentgenogram typically shows a patchy infiltrate, which rapidly progresses to involve contiguous lobes. Pleural effusions are common.

The Gram stain may show many WBCs, but few organisms are seen, as *Legionella* is only weakly gram-negative. No sign or symptom is characteristic of legionnaire's disease, so the definitive diagnosis depends on serology or culture. Detection of the *Legionella* antigen in the urine is a rapid test with good sensitivity and specificity. Direct immunofluorescent stains of tissue or bronchial washings has a high specificity but low sensitivity. In addition, indirect immunofluorescent antibody titers of more than 1:128 are highly suggestive. The organism is fastidious but can be cultured on selective media (charcoal-yeast) from sputum, pleural fluid, or blood.

Management

The key issue is prompt recognition and treatment. Among immunocompromised patients, mortality can reach 50%; overall mortality ranges from 5% to 25%. In the presence of pneumonia of unknown etiology, radiographic progression and the development of respiratory failure should alert one to make sure antibiotics cover *Legionella.*

Erythromycin, clarithromycin (Biaxin), and azithromycin (Zithromax) are the drugs of choice. Erythromycin 1.0 g IV q6h is typically used. Doxycycline has also been used with excellent success.[18] Ciprofloxacin (Cipro) also is active against the organism and is an alternative choice.

Prevention and Family Issues

Typically, outbreaks of legionnaire's disease lead to epidemiologic investigation and subsequent identification of the organism in water that has been aerosolized. The organism is then eradicated or controlled through careful cleaning, heating (to 160°F), or chlorination of the water system.

Histoplasmosis

Histoplasmosis is caused by a fungus found in moist soil throughout the temperate zones of the world (in the United States, especially in the Ohio and Mississippi River Valleys). Growth of the fungus is enhanced by bird droppings. Humans inhale mycelial fragments, which then convert to a yeast phase in the lung, followed by dissemination to regional lymph nodes. Dissemination to other organs, including the spleen, can occur. Subsequent calcifications are then seen on radiographs, which may have a characteristic concentric or target pattern.

Clinical Manifestations

The primary infection is usually asymptomatic. Flu-like symptoms (fever, malaise, and cough) may develop if there is a heavy inoculum of spores. Symptoms generally run a course of days to several weeks. Occasionally, rheumatologic syndromes (arthralgia, erythema nodosum) occur and may mimic sarcoidosis.

Disseminated histoplasmosis usually reflects a defective immune system and is most common in infants or the elderly. Fever, weight loss, and splenomegaly are common manifestations. Two long-term problems may be seen: (1) erosions or compression due to calcified lymph nodes; and (2) chronic cavitary histoplasmosis, a disease of middle-aged men with COPD. The latter often resembles tuberculosis and probably represents reinfection.

Diagnosis

Skin test conversion occurs within 2 to 3 weeks after inhalation. Sputum cultures are usually negative. Complement-fixation (CF) tests are often used for diagnosis, and a fourfold rise in titer or a single titer above 1:32 is highly suggestive of recent infection. It is important to remember that CF titers rise in response to the skin-test antigen.

With primary disease, the chest roentgenograms frequently show a bilateral, patchy, lower lobe pneumonia, hilar adenopathy, and rarely a small pleural effusion. Nodular residua can remain that may resemble a metastatic neoplasm or "buckshot" calcification.

Management

No treatment is usually needed in a normal host.[19] Therapy of disseminated histoplasmosis requires high dose (> 2 g) intravenous amphotericin given over 8 to 12 weeks. In patients with human immunodeficiency virus (HIV), this regimen is usually followed by ketoconazole (400 mg/day) indefinitely.[20]

Coccidioidomycosis

The *Coccidioides* fungus is found in the soil of the semiarid southwestern United States. The primary infection is usually asymptomatic, but up to 40% of patients have symptoms of acute "valley fever" with cough, low grade fever, and often erythema nodosum. A few develop progressive pulmonary or disseminated disease, with African Americans, Native Americans, and Filipinos at higher risk. The chest roentgenogram is nonspecific with transient infiltrates and occasionally hilar adenopathy or pleural effusions. Multiple nodules or thin-walled cavities can develop. Sputum smears and cultures are sometimes positive in those with abnormal chest films.

There are two cocci skin tests: Spherulin is more sensitive (read at 24 hours) and Coccidioidin more specific. Early in the disease, the latex agglutination and precipitin serologies are positive. Eventually, the CF and immunodiffusion tests turn positive. High or rising CF titers may indicate pulmonary progression or dissemination. Therapeutic options for these patients include surgical resection or administration of amphotericin or ketoconazole.[21]

Tuberculosis

Tuberculosis (TB) incidence in the United States decreased from 80 per 100,000 in 1930 to about 10 per 100,000 in 1985; but it has now risen steadily in hand with the HIV epidemic.[22] The incidence of TB is disproportionately higher in younger African Americans and Hispanics. In the United States 25% of tuberculosis occurs in foreign-born persons. In the underdeveloped world, TB may still be the leading cause of death.

Tuberculosis is caused by a small bacterium with a thick lipid wall, making it particularly resistant to destruction from either macrophages or drugs. It multiplies slowly and can lay dormant for long periods. The infection usually starts after the organisms are inhaled in droplets from an infected person's cough; the mycobacteria are then deposited in the periphery of the new host's lung where they cause a local inflammatory reaction. There is usually some hematogenous spread: Kidneys, liver, and bone are the most common other organs seeded. Clinical disease rarely occurs at this stage, although occasionally foci irritate or rupture into the pleura causing a pleural effusion.

After this initial asymptomatic infection, most individuals are left only with a positive skin test and possibly a parenchymal calcification (Ghon lesion), which may be associated with calcified hilar lymph nodes (Ranke complex).

About 90% of active TB is reactivation, that is, a breakdown of these foci years later. Why this breakdown occurs is poorly understood. Risk factors for active TB include recent weight loss (associated with malnutrition or alcoholism), poorly controlled diabetes, and immunosuppression (from steroid therapy, HIV, or cancer). HIV has been called the most potent activator of TB ever detected.

Of the individuals infected with bacilli (i.e., those who convert their skin test), it is estimated that about 3% to 5% develop active TB within the first year after exposure. The risk is higher in infants and adolescents and those with immunodeficiency. On average, this risk falls to a baseline rate of reactivation variously estimated at 1 in 1500 to 1 in 4000 per year. Of all those with positive skin tests, no risk factors, a normal chest film, and not a recent tuberculin converter, one person in approximately 2000 develops active tuberculosis each year. Over a lifetime, then, most people who convert their skin tests have about a 3% to 5% chance of developing the disease initially, and another 3% to 5% chance over the rest of their lives.

Clinical Presentation

Active pulmonary tuberculosis most commonly presents as a progressive cough that is productive of a mucopurulent sputum. Hemoptysis is not common but, when present, can be massive. Malaise, low grade fever, and weight loss are often present. Dyspnea and chest pain are uncommon. The physical examination may include crepitations or decreased breath sounds and dullness from a pleural effusion.

Extrapulmonary tuberculosis can involve any system and is seen in up to 50% of those with immunodeficiency and tuberculosis. Extrapulmonary disease in HIV-positive patients can affect lymph nodes (including hilar adenopathy) bone marrow, liver, kidneys, meninges, pericardium, and the gastrointestinal tract.

Diagnosis

The chest roentgenogram in patients with active TB most frequently shows a fibronodular upper lobe infiltrate. Cavities may form; and hilar node adenopathy, pleural effusion, or upper lobe volume loss may be present.

The definite diagnosis is based on a smear and culture of the sputum or other infected material. Smears may be done using a Ziehl-Nielsen or an acid-fast technique causing the organisms to appear red ("red snappers"); but more frequently a fluorescent technique is used. Rapid culture techniques and identification using gene (DNA) probes have decreased the time required for laboratory identification to 2 to 3 weeks. All initial isolates should be tested for antimicrobial sensitivity.

The TB skin test is one of the oldest diagnostic tests still in use today, having been initially developed by Koch 100 years ago. The recommended test is the Mantoux, using 0.1 ml of PPD-T injected intracutaneously; and the result (induration, not erythema) is read within 48 to 72 hours (Table 86.6). The multiple puncture tests are not recommended.

A positive reaction indicates past exposure (at least 2–3 months previously). Unfortunately, it is often negative in the elderly and those with HIV. Up to 60% of patients with AIDS and TB may have a false-negative test. All patients with a positive test should have a chest roentgenogram to rule out active disease.

The skin test usually remains positive for years, but waning occurs with age. Repeated skin testings enhances reactivity (booster phenomenon). BCG vaccination, often given in underdeveloped countries, may cause a positive skin test for many years. HIV testing should be performed on all patients with newly diagnosed TB.

Table 86.6. **Interpretation of Tuberculin Skin Testing**

Diameter of induration (mm)	Positive result
> 5	Persons with HIV infection; persons who recently were exposed to clinically active tuberculosis; persons with chest films that indicate old healed tuberculosis
> 10	Persons with an increased risk for TB; those born in Africa, Asia, Latin America; Hispanics; Native Americans; African Americans; intravenous drug users; residents of long-term care facilities (nursing homes, prisons, mental institutions); those with certain medical conditions (diabetes, renal failure or silicosis)
> 15	All other persons

Management

The increased incidence of TB has been accompanied by an increase in drug resistance. The current recommendation for antituberculosis therapy for active disease is isoniazid (INH) 300 mg qd and rifampin (RIF) 600 mg qd for 6 months, with pyrazinamide (PZA) 15 to 30 mg/kg/day added for the first 2 months.[23] See Table 86.7 for dosage and side effects of commonly used anti-TB drugs.

For disseminated TB, TB meningitis, TB in HIV-positive patients and where drug resistance is possible, a regimen using four drugs (INH, RIF, PZA, ethambutol) is given initially. Once the drug sensitivities of the infecting organism are known, treatment should be continued with at least four drugs to which the mycobacteria is sensitive. Short course chemotherapy, i.e.,

Table 86.7. **Antibiotics for Tuberculosis**

Drug	Usual adult daily dose	Common side effects
Isoniazid	300 mg	Hepatitis (see text) Peripheral neuritis Increases phenytoin level CNS reactions
Rifampin	600 mg	Colors urine and stool orange Accelerates metabolism of certain drugs: oral contraceptives, coumarin anticoagulants, methadone Thrombocytopenia Hepatitis Febrile reactions
Ethambutol	15–25 mg/kg	Optic neuritis (rare at dose of 15 mg/kg) Skin rash
Pyrazinamide	15–30 mg/kg (max. 2 g)	Hepatitis Hyperuricemia Gastrointestinal disturbance

6 to 9 months, can only be used if the bacteria is sensitive to both INH and RIF. Immunocompromised patients, even if sensitive, should be treated for 9 to 12 months.[24] Alternative regimens, which do not contain both INH and RIF, should be given for 12 to 18 months. Occasionally, intramuscular streptomycin is used initially in the noncompliant patient. Secondary oral agents, including ethionamide, cycloserine, or paraaminosalicylic sodium are used in patients with multiple drug resistance.

Those who are smear-positive should be in respiratory isolation. After 2 to 3 weeks of therapy, most patients, even those remaining smear-positive, are noninfectious. Monthly follow-up sputum cultures are used to monitor compliance or resistance. The cultures should be negative after 3 to 4 months. Treatment is successful in essentially all compliant patients, even those with HIV infection.

Preventive and Family Issues

Because active pulmonary TB usually is a result of an infection that took place months to years before, this episode affords the opportunity for prevention. There is at least 80% efficacy in preventing future active disease with INH chemoprophylaxis in those who are skin-test-positive.[22] The definition of a positive skin test has recently changed (Table 86.6).[25] It is important to remember that an induration of 5 mm or more is now considered positive in HIV patients and in those with indications 1 and 2 below. The indications for INH chemoprophylaxis include the following.

1. Household members and other close contacts of newly diagnosed, sputum-positive (infectious) patients
2. Significant tuberculin skin test reactors with an abnormal chest roentgenogram (more than a calcified node or pleural thickening)
3. Newly infected persons, e.g., conversion of the skin test within a 2-year period
4. Tuberculin reactors in special clinical situations, such as those on steroids (> 15 mg of prednisone qd) or with silicosis, chronic renal insufficiency, poorly controlled diabetes, and conditions associated with nutritional deficiency and weight loss, including gastrectomy and intestinal bypass
5. Tuberculin-positive persons, age 35 and under, with no other risk factors

In those with normal chest roentgenograms and immune systems, 6 months of INH 300 mg qd is adequate. Vitamin B_6 does not need to be added routinely. A duration of 9 to 12 months is indicated for those with abnormal (but presumably) stable chest films or who are immunosuppressed.

The most common concern about INH is drug-induced hepatitis. The overall incidence is about 1%, although it is age-related. Hepatitis is rare in persons under age 20, whereas it occurs in more than 2% of those over age 50. Prodromal symptoms, such as tiredness and anorexia, may occur weeks to months before clinical toxicity. Seventy percent of hepatitis occurs during the first 3 months of therapy. The best way to follow patients on INH is regularly (monthly) and ask about prodromal symptoms of hepatitis, such as fatigue. Biochemical monitoring of those over age 35, heavy drinkers, and those with other liver disease is reasonable. Up to 20% may show a mild, asymptomatic rise in liver enzymes (less than five times normal). INH does not need to be discontinued in those individuals, but they should be followed more closely.

Vaccination with BCG is performed in many undeveloped countries, where TB is prevalent. Its efficacy is questionable, but the consensus is that it may prevent extrapulmonary disease (e.g., TB meningitis) in children. BCG vaccination usually leaves a keloid or scar where given (often on the left shoulder).

Mycobacterium Avium Complex

Mycobacterium avium intracellulare complex (MAC) disease is seen as a late-stage infection in 20% to 50% of AIDS patients. The organism is found in soil and water; it is not thought to be transmitted human-to-human. Before AIDS, MAC disease was uncommon and was seen primarily in older patients with COPD or prior tuberculosis.

The symptoms of infection are nonspecific: fever, anorexia, weight loss, severe fatigue, diarrhea, and abdominal pain. In AIDS patients, pulmonary symptoms are uncommon. Blood cultures are frequently positive. The organism can also be found in sputum, stool, and tissue biopsy specimens. When found on a sputum smear, treatment for active TB should be initiated until the culture results are known. Treatment for MAC decreases symptoms, but is unclear if it increases survival in AIDS patients. Because of high resistance, multiple drugs are used; rifampin, ethambutol, clarithromycin, clofazimine, and ciprofloxacin are often included.[26]

Pneumocystis Carinii

With the emergence of HIV, *Pneumocystis carinii* pneumonia (PCP) has become a common disease. Indeed, it is the most common pulmonary infections seen in AIDS patients. *P. carinii,* a widespread fungus, colonizes the lung at an early age, as most children show serologic evidence of exposure before age 5. Most infections, then, are exacerbations of an underlying opportunist when T-cell immunity is impaired. The HIV virus, high dose corticosteroids, or organ transplantation with immunosuppressive therapy set the stage for *P. carinii* infection (see Chapter 36).

Clinical Presentation

A chronic, progressive, nonproductive cough, low grade fever, and dyspnea in a susceptible patient are the usual presenting symptoms. The physical examination shows tachypnea and nonspecific diffuse basilar crackles, but there are no pathognomonic clues. The T-cell count is usually less than 200 per μL in HIV-infected patients.

Diagnosis

The chest roentgenogram usually shows diffuse bilateral interstitial infiltrates, spreading out from the hilar regions. Effusions and hilar adenopathy are unusual. However, a *P. carinii* infection can be present in those with a normal chest film as well. In

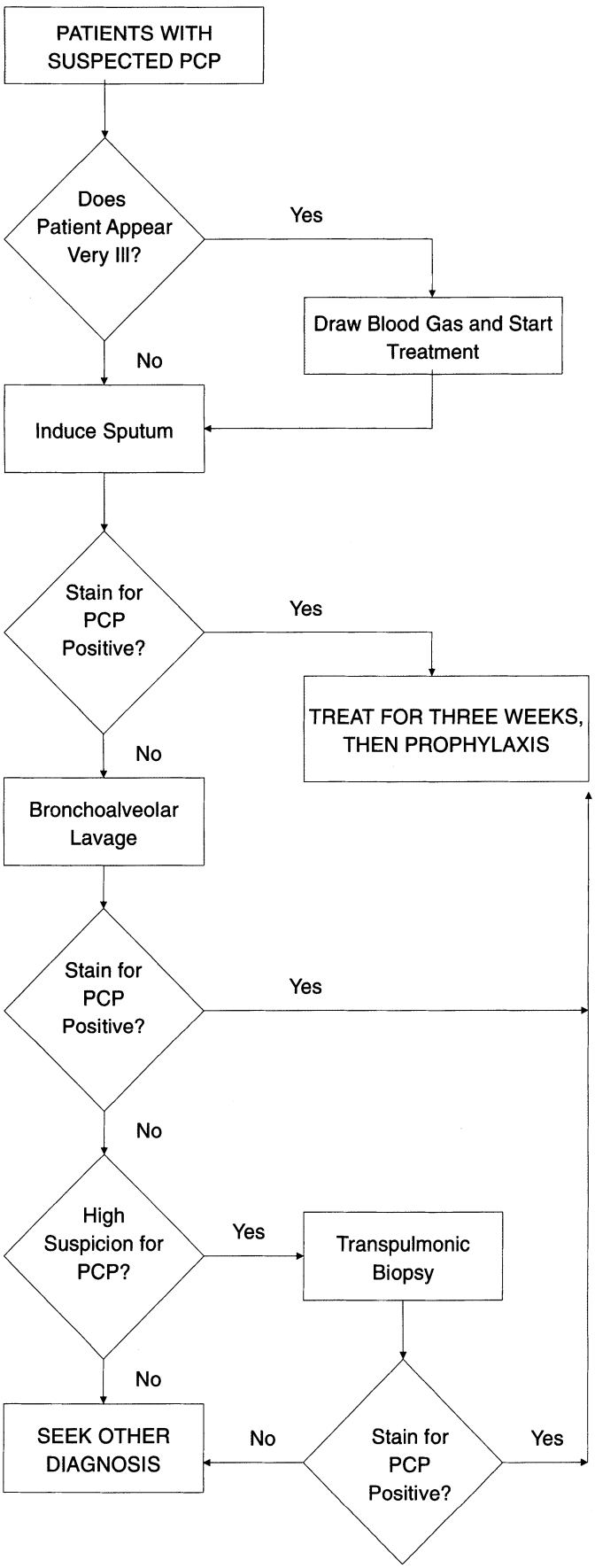

Fig. 86.1. Approach to the patient with suspected *Pneumocystis carinii* pneumonia (PCP).

these cases a gallium lung scan is positive and the carbon monoxide diffusion capacity is less than 80% of the predicted value (usually it is much lower). Arterial blood gases are sensitive measures of lung involvement and should be measured in anyone suspected of having PCP.

The diagnosis of PCP is usually confirmed by finding the organism on an induced sputum sample or in bronchoalveolar lavage fluid. A wide variety of staining techniques are used, depending on the laboratory's experience. An algorithm for diagnosis is presented in Figure 86.1.

Management

Hospitalization is usually recommended to monitor the clinical course and drug toxicities. If the arterial oxygen tension is less than 70 mm Hg, corticosteroids (40 mg prednisone qd, tapering over 10 days) are often added to help prevent respiratory failure.

Trimethoprim-sulfamethoxazole is the drug of choice. It can be given orally or intravenously, but the latter route is usually chosen for the first episode because of the potential for acute deterioration. The dose is calculated based on 12 to 15 mg/kg/day of the TMP component. Side effects are common and include skin rashes (even Stevens-Johnson syndrome), neutropenia, hepatitis, hyponatremia, azotemia, and drug fever. Side effects occur in more than 50% of patients and are more commonly seen between 7 and 14 days of therapy. Treatment should continue for 21 days. Alternatives for TMP/SMX (Septra, Bactrim) include intravenous pentamidine (Lomidine, Pentam) (4 mg/kg/day), dapsone plus trimethoprim (Proloprim, Trimpex), or clindamycin (Cleocin) plus primaquine.[26] All regimens have significant side effects. The presence of glucose-6-phosphate deficiency should be ruled out before starting dapsone or primaquine (Primachin) therapy.

Prevention and Family Issues

After treatment, or in patients with HIV and CD_4 T cell counts of less than 200 cells/μL, prophylaxis should be given. The usual choice is TMP/SMX, one DS tablet a day; however, one DS tablet three times per week (e.g., M–W–F) may be effective.[27] Alternatives to TMP/SMX include dapsone 50 to 100 mg/day or inhaled pentamidine 300 mg once every 4 weeks or 150 mg every 2 weeks. Without prophylaxis, up to 80% of HIV patients contract PCP, and its recurrence rate in 1 year is more than 50%. Because of the progressive nature of HIV infection, patients who are started on prophylaxis should consider having a durable power of attorney or a living will.

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