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DIAGNOSIS AND MANAGEMENT OF RESPIRATORY TRACT INFECTIONS FOR THE PRIMARY CARE PHYSICIAN

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SINUSITIS

Background

Upper respiratory tract symptoms account for a majority of primary care physician office visits.[48] These symptoms may be caused by common colds or sinusitis. The term *rhinosinusitis* has been developed to include the full spectrum of the common cold and sinusitis.[31] Sinusitis is the inflammation or infection of the paranasal sinuses. Each year, there are 20 million cases of acute sinusitis and 31 million cases of chronic sinusitis in the United States.[37]

Sinusitis is categorized as acute or chronic based on the duration of symptoms. In acute sinusitis, symptoms may last up to 4 weeks. In chronic sinusitis, symptoms may persist up to 12 weeks despite optimal medical therapy.[56] The period of time between 4 and 12 weeks is less well defined. Some authorities classify symptoms for this period as subacute sinusitis.

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Cause

Most cases of rhinosinusitis are caused by viral upper respiratory tract infections. These infections lead to inflammation and edema causing obstruction of the sinus ostia and a decrease in mucociliary clearance of the sinuses. These effects create conditions that are favorable to bacterial growth. It is estimated that 0.5% to 2% of viral upper respiratory tract infections become secondarily infected with bacteria.[30] Other causes of rhinosinusitis include anatomic deformities such as septal deviation or polyps, foreign bodies such as nasogastric tubes, allergy, and immunodeficiency.[37, 56] Direct injury to the upper teeth can form fistulas that can lead to anaerobic growth within the sinuses. It is estimated that 10% of maxillary sinusitis is associated with dental disease.[21, 22]

Microbiology

Acute Sinusitis

The two most common bacterial causes of acute sinusitis are *Streptococcus pneumoniae* and nontypeable *Haemophilus influenzae.* These bacteria account for 50% to 75% of organisms causing acute bacterial sinusitis.[56] *Moraxella catarrhalis*, other streptococcal species, and anaerobes cause a smaller percentage of acute sinusitis.[30, 56] At least half of acute sinusitis is caused by viruses.[32] Rhinovirus, parainfluenza, and influenza are the most common viral causes of acute sinusitis.[30] Fungal etiologies of acute and chronic sinusitis are also increasingly recognized.[14]

Chronic Sinusitis

The most common organisms isolated in chronic sinusitis are *Staphylococcus epidermidis, Staphylococcus aureus, Streptococcus pneumoniae,* and anaerobes.[52] Sixteen percent of chronic sinusitis is caused by multiple organisms.[12, 52] Other organisms found in chronic sinusitis include *Streptococcus viridans, H. influenzae,* and gram-negative organisms.[12, 38]

Diagnosis

The diagnosis of sinusitis is usually based on clinical findings; however, other illnesses, such as allergic rhinitis, may present similarly. Common symptoms of acute rhinosinusitis include purulent nasal discharge, facial pain, congestion, cough, and fever. These symptoms are not specific to sinusitis.[69] The most specific symptom in sinusitis is maxillary toothache, but this symptom is limited to 11% of patients with sinusitis.[68] In a study by Williams and Simel,[68] findings of purulent or

colored nasal discharge, maxillary toothache, poor response to nasal decongestants, and abnormal transillumination were the best predictors of sinusitis. Physical examination usually reveals sinus mucosal edema, postnasal drainage, and sinus tenderness; however, none of these findings are specific to sinusitis.[68] It is often difficult to distinguish viral upper respiratory tract infection and bacterial sinusitis in the first 7 to 10 days of symptomatic illness. Worsening of symptoms after 5 days, persistence of symptoms after 10 days, and severe initial presentation may be more suggestive of bacterial illness.[56]

Laboratory studies such as nasal swab cultures are not usually recommended in the evaluation of acute sinusitis. Patients with chronic or recurrent sinusitis may need sinus endoscopy to evaluate sinus anatomy and to obtain bacteriologic cultures. An immunodeficiency evaluation should be considered in patients who do not respond to appropriate therapy.

Plain sinus films are often obtained in the evaluation of sinusitis. These films usually include four views of the sinus cavities.[56] One recent study suggests that a single Waters view (occipitomental view) may be substituted for the four-view series.[67] The three radiographic criteria used in the diagnosis of sinusitis are thickened mucosa greater than 6 mm, air-fluid levels, and opacification of the sinus cavities. Disadvantages of sinus films include poor visualization of the ethmoid air spaces and the inability to differentiate tumor, polyps, and infection.[56] Sinus CT scanning is the gold standard for radiographic imaging of the sinuses; however, these scans should not be used in the routine evaluation of acute sinusitis. Their main role is to help define the sinus anatomy before possible surgery.[56] Definitive diagnosis of acute sinusitis by piercing the sinuses and culturing extracted material is impractical for office use.[1]

Medical Management

Symptomatic therapy is often the initial therapy in sinusitis. Supportive therapy such as increased fluid intake and nasal saline sprays to enhance a moist environment are recommended. Decongestants such as topical phenylephrine (Neo-Synephrine) or oxymetazoline (Afrin) can be used to vasoconstrict local blood vessels and decrease edema; however, the use of topical decongestants for more than 3 days is not recommended because this practice can lead to rebound vasodilatation and rhinitis medicamentosa. Systemic decongestants provide symptomatic relief but have side effects such as nervousness, tachycardia, and hypertension.[23] Other common adjunctive therapies do not have proven efficacy but may be helpful in some patients. These therapies include mucolytics such as guaifenesin, antihistamines, and nasal steroid sprays. The latter two therapies may be helpful for patients with allergy symptoms.[37]

In mild cases of acute sinusitis, adjunctive therapy may be used alone because at least one third of patients have viral sinusitis. Studies

show a good response to placebo and antimicrobial regimens. Furthermore, antibiotics do not affect the duration and relapse rate of acute sinusitis.[66]

If symptoms of sinusitis persist for more than 10 days, the cause is more likely bacterial infection.[22] Empiric antibiotic therapy should be active against common causative organisms such as *S. pneumoniae, H. influenzae,* and *M. catarrhalis.* The selection of antibiotics also depends on the antibiotic resistance pattern in the community. The rate of penicillin (PCN)-resistant *H. influenzae* infection may reach 40%, whereas the rate of PCN-resistant *M. catarrhalis* infection may reach 90%.[14, 56] There is an increasing rate of multidrug-resistant *S. pneumoniae.*[33]

Even with the increasing PCN resistance of common causative agents, many experts still recommend amoxicillin as first-line therapy for acute sinusitis owing to its narrow spectrum, few side effects, and low cost. Trimethoprim and sulfamethoxazole (TMP-SMX) can be used as first-line therapy for patients with PCN allergy. If the patient does not respond to first-line therapy in 2 to 3 days, the regimen should be changed to cover beta-lactamase–producing *H. influenzae* or PCN-resistant streptococcus. The recommendations for second-line agents in acute sinusitis are amoxicillin-clavulanate, second- or third-generation cephalosporins (cefuroxime axetil, cefpodoxime proxetil, loracarbef), newer macrolides such as azithromycin and clarithromycin, and fluoroquinolones such as gatifloxacin, moxifloxacin, and levofloxacin. Clindamycin also has activity against PCN-resistant *S. pneumoniae.* The duration of treatment for acute sinusitis is usually 10 to 14 days.[32] These recommendations have been supported by two sets of guidelines for the management of sinus disease.[1, 14] An additional set of guidelines recommended by the Sinus and Allergy Partnership advocates the use of amoxicillin/clavulanate, cefpodoxime praxetil, and cefuroxime axetil as initial agents and discourages the use of TMP-SMX.[64]

Antibiotics for chronic sinusitis should be active against staphylococcal species and beta-lactamase–producing organisms.[52] The second-line agents used in acute sinusitis are also affective in the treatment of chronic sinusitis. The first-line agents are not recommended owing to higher rates of bacterial resistance in chronic sinusitis. Metronidazole and clindamycin can be added if the initial agents are not active against anaerobes and the patient does not respond in 5 to 7 days. The total duration of antimicrobial therapy for chronic sinusitis should be 3 to 4 weeks. Endoscopic sinus cultures may be obtained in patients with chronic sinusitis because there is a higher incidence of multiple organisms or resistance to antibiotics.[52]

Surgical Management

Indications for surgical intervention include complications of sinusitis, such as local spread of infection to nearby structures (eye, brain), treatment failures after two courses of antibiotics, frequent recurrences

(more than three episodes per year), nosocomial infections, and sinusitis in the immunocompromised host.[3, 52]

PHARYNGITIS

Pharyngitis is the inflammation or infection of the nasopharynx or oropharynx.[13] It is primarily a childhood illness but also affects adults, especially during winter and early spring.[46] Most cases of pharyngitis are caused by viruses. One must differentiate between viral and bacterial causes of pharyngitis because bacterial pharyngitis caused by group A streptococcus can have serious complications if not treated appropriately.

Microbiology

Viruses cause at least 30% to 40% of pharyngitis.[13, 42] The most common virus causing pharyngitis is rhinovirus, followed by coronavirus, adenovirus, parainfluenza, and influenza virus.[13] Viral pharyngitis can also be caused by herpes simplex virus, Epstein-Barr virus (EBV), cytomegalovirus (CMV), and HIV. Group A streptococcus causes at least 30% of pharyngitis. Other bacterial causes of pharyngitis include group C streptococcus, mixed anaerobic infections, diphtheria, *Arcanobacterium haemolyticus*, *Chlamydia pneumoniae*, and *Mycoplasma pneumoniae*. Noninfectious causes of pharyngitis include bullous pemphigoid, systemic lupus erythematosus, Behçet's syndrome, and Kawasaki's syndrome.[42]

Clinical Presentation

It is often difficult to differentiate between viral and bacterial pharyngitis. Patients with viral pharyngitis usually have nonspecific flulike symptoms such as fever, malaise, and myalgia. Patients with pharyngitis owing to rhinovirus usually present with nasal symptoms as the primary complaint with mild-to-moderate sore throat.[42] Other viral agents, such as adenovirus, EBV, CMV, and herpes simplex virus, may cause more severe pharyngitis resembling group A streptococcal pharyngitis.[42] Most viruses cause self-limiting illnesses that resolve within a week. On physical examination, there may be varying degrees of pharyngeal erythema with or without exudates. Specific features of viral pharyngitis can be helpful when present. These findings include adenoviral conjunctivitis, herpetic vehicles, and lymphadenopathy or splenomegaly associated with EBV/mononucleosis.[42]

Patients with streptococcal pharyngitis may complain of pharyngeal pain, odynophagia, headaches, fever, and chills.[13] Physical examination may reveal erythema and exudate of the pharynx and tonsils, uvular edema, and tender lymphadenopathy. One may also find a maculopapular rash associated with scarlet fever or a red enlarged tongue known as

the "strawberry tongue." These findings are not specific for group A streptococcal pharyngitis.[13] Other bacterial causes such as group C streptococcus can present similarly. Anaerobic infections may present with purulent exudate, foul odor, and pharyngeal pain. Diphtheria has a characteristic pharyngeal gray membrane firmly attached to the pharynx or tonsils.[42] These findings may be helpful in the diagnosis of bacterial pharyngitis.

Diagnosis

The diagnosis of group A streptococcal pharyngitis is usually confirmed by laboratory tests. Throat culture is the gold standard for identifying streptococcal infections.[53] With proper specimen collection, the sensitivity of this test is 95%.[15] Cultures can take up to 48 hours to confirm, which may result in an unnecessary delay in treatment.[42] Antibiotic administration before testing can result in a false-negative test.[13] The Rapid Antigen Detection Test (RADT) was developed to diagnose streptococcal pharyngitis in the outpatient clinic within minutes; however, the convenience of this test is offset by its higher cost and low sensitivity of 60% to 90%.[15] Because a negative RADT does not rule out streptococcal pharyngitis, it must be confirmed by streptococcal culture (Fig. 1). A positive RADT is highly correlative with streptococcal pharyngitis, with a specificity of more than 95%.[15] Antistreptococcal antibody titers do not have a role in the detection of acute streptococcal pharyngitis because these titers reflect past infections.[13]

Management

Treatment of viral pharyngitis is mainly supportive, with adequate hydration, antipyretics, analgesics, and saline gargles. Newer therapies, such as amantadine, rimantadine, and neuraminidase inhibitors, may be helpful if given early in the course of illness. PCN continues to be the mainstay therapy for streptococcal pharyngitis. There are no reported cases of PCN resistance among group A streptococcus.[18] A 10-day course of PCN V or a single injection of benzathine PCN is sufficient to treat and prevent complications of group A streptococcal pharyngitis.[62] Patients who are allergic to PCN can be treated with a 10-day course of erythromycin, although failure rates may be higher.[13, 62] The newer macrolides, second-generation cephalosporins such as cefuroxime, cefixime, and amoxillin/clavulanate can also be used. Other common causes of bacterial pharyngitis may be treated similarly with PCN.

Recurrences of group A streptococcal pharyngitis may occur owing to noncompliance, reinfection by close contacts, or viral infection in a streptococcus carrier.[13] A second course of antibiotics with benzathine PCN may be helpful to ensure compliance. Treating close contacts with

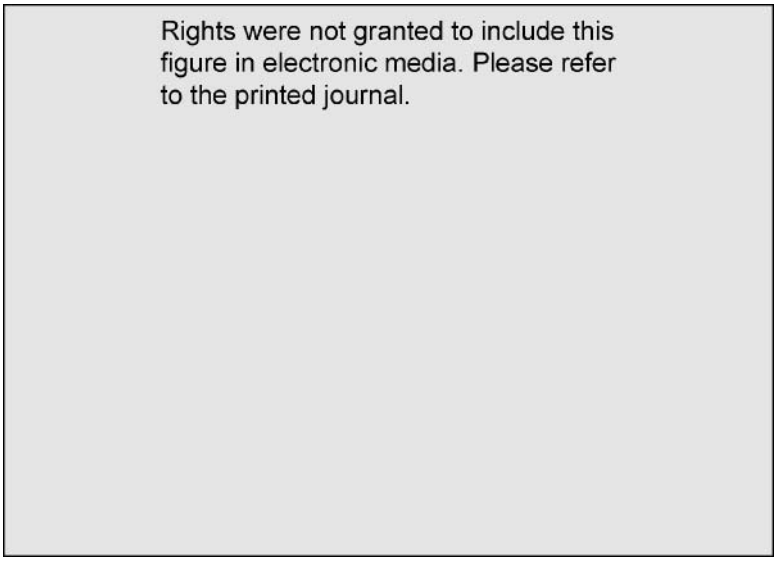

Figure 1. Diagnosis and management of acute pharyngitis. This applies to uncomplicated cases of acute pharyngitis; additional diagnostic and therapeutic measures may be necessary for patients with suppurative complications (e.g., peritonsillar abscess or cervical lymphadenitis) or when infection with uncommon pharyngeal bacterial pathogens (e.g., *Corynebacterium diphtheriae* or *Neisseria gonorrhoeae*) is suspected. (*From* Bisno AL, Gerber MA, Gwaltney JM, et al: Diagnosis and management of Group A streptococcal pharyngitis: A practice guideline. Clin Infect Dis 25: 574–583, 1997; with permission.)

positive streptococcal RADT and repeating the throat culture may be also be necessary in these patients.[13, 42, 62]

Complications

Complications of group A streptococcal pharyngitis can be severe and life-threatening. Direct complications such as peritonsillar abscess and scarlet fever require hospitalization and treatment with intravenous antibiotics. Immunologic consequences of group A streptococcal infection occur after resolution of the acute infection. These illnesses are immune complex–mediated and cannot be treated with antibiotics. The hallmark immune-mediated, post-streptococcal diseases are acute rheumatic fever and acute glomerulonephritis.

Acute rheumatic fever was a common complication of group A streptococcal pharyngitis before PCN therapy. A recent rise in incidence of this complication has alerted clinicians to diagnose group A streptococcal pharyngitis accurately.[15] Acute rheumatic fever typically occur 2 to 5 weeks after pharyngitis. It is diagnosed using the Jones criteria. These items include major criteria such as carditis, migratory polyarthri-

tis, Sydenham's chorea, subcutaneous nodules, and erythema marginatum. Minor criteria include arthralgia, fever, a prolonged P-R interval, and an elevated sedimentation rate or C-reactive protein. Acute glomerulonephritis occurs mostly in children about 10 days after the onset of pharyngitis.[46] Treatment of acute glomerulonephritis is mainly supportive.

ACUTE BRONCHITIS

Acute bronchitis affects 5% of the US population annually and is ranked fifth among the most common causes of outpatient office visits.[11, 41] Acute bronchitis is an inflammation of the tracheobronchial tree, causing bronchial edema and increased mucus secretion.[36] It is often precipitated by viral infections and usually occurs in the winter, when respiratory infections are most frequent.[42]

Epidemiology/Etiology

Most cases of acute bronchitis in healthy adults are caused by viral infections.[11] The ratio of viral to bacterial etiology is not known. The most common viruses that cause acute bronchitis are influenza, adenovirus, respiratory syncytial virus (RSV), and rhinovirus.[11, 41] Coxsackievirus, coronavirus, measles, and herpes virus can also cause acute bronchitis.[11, 41, 50] The bacterial pathogens known to be associated with acute bronchitis in otherwise healthy adults are *M. pneumoniae*, *C. pneumoniae*, and *Bordetella pertussis*.[36, 41, 50] *S. pneumoniae* and *H. influenzae* may also be causative agents, but this link is controversial.

Noninfectious etiologies such as allergy and air pollution can also trigger acute bronchitis. These triggers cause inflammation of the tracheobronchial tree, resulting in increased secretions, impaired mucociliary clearance, and increased airway reactivity.[50]

Clinical Presentation

The main presenting symptom of acute bronchitis is cough with or without sputum production. Although the cough usually subsides after 10 days, it may persist for weeks.[36] Nonspecific flulike symptoms such as fever, chill, and malaise may also be present. These symptoms usually resolve within 5 days.[11] If the lower airways are involved, the patient may experience pleuritic chest pain or hemoptysis. Dyspnea is not usually associated with acute bronchitis unless the patient has underlying cardiopulmonary disease. On physical examination, findings consistent with reactive airway disease, such as wheezing, may be heard. Rales and rhonchi may also be present. There may be a localized decrease in breath sounds from focal atelectasis.[50] None of these findings are specific

for acute bronchitis; therefore, it may be difficult to differentiate acute bronchitis from more serious illnesses of the lower respiratory tract.

Diagnosis

A thorough history and physical examination can help differentiate acute bronchitis from other causes of cough, such as sinusitis, reflux, asthma, cardiovascular disease, or pulmonary disease such as pneumonia or embolism. Laboratory tests, such as sputum Gram stain, may be helpful if a predominant organism is seen. Sputum cultures are not usually helpful owing to contamination of nasopharyngeal flora and difficulty in interpreting the result.[50] Moreover, acute bronchitis is often caused by viral infections in which sputum cultures are negative.[36] Serologic studies for mycoplasma and chlamydia can be obtained if these agents are suspected. Patients with more severe or persistent symptoms should be evaluated further with chest radiography, complete blood count, pulse oximetry, or blood gas to rule out more serious causes of respiratory illness.

Treatment

Because most cases of acute bronchitis are caused by viral rather than bacterial infections, antibiotics are not usually recommended. Nevertheless, studies show that more than half of patients with acute bronchitis are treated with antibiotics.[48] This practice encourages the development of antimicrobial resistance and increases the risk of antimicrobial-related side effects. Most patients can be treated symptomatically with hydration, cough suppressants, antipyretics, and analgesics. Bronchodilators may be helpful in patients with bronchospasm.[34, 35] Amantadine, rimantadine, and the new neuraminidase inhibitors can shorten the duration and decrease the severity of symptoms of viral infections if given in the first 24 to 48 hours of symptomatic influenza illness. Influenza and pneumococcal vaccinations are also invaluable in the prevention of these illnesses.

Antibiotics should be considered in patients at extremes of age, with significant underlying medical disease, or presenting with severe or persistent symptoms.[50] Antibiotics should be active against predominant bacterial organisms, such as *C. pneumoniae*, *M. pneumoniae*, and *Bordetella pertussis*. Tetracycline, doxycycline, TMP/SMX, and macrolides should provide adequate coverage for these organisms.

Acute bronchitis is a common entity affecting many persons who are otherwise healthy. The appropriate diagnosis is based on clinical findings and the exclusion of more serious illnesses. Antibiotics are usually not necessary in the treatment of acute bronchitis; instead, symptomatic therapy is the mainstay treatment for this self-limiting illness.

ACUTE EXACERBATION OF CHRONIC BRONCHITIS

Acute exacerbation of chronic bronchitis (AECB) occurs when patients with chronic bronchitis present with an acute worsening of respiratory symptoms. Patients may present with an increase in cough, sputum production, wheezing, or dyspnea.[63] Unlike acute bronchitis, the treatment of AECB usually warrants antibiotics.[57] The antibiotic chosen should be active against common causative organisms, such as *H. influenzae*, *S. pneumoniae*, and *Moraxella catarrhalis*.[5] Viral agents and atypicals may also have a role in treating these exacerbations. Antibiotics recommended in the treatment of AECB include second-generation cephalosporins, such as cefuroxime or cefpodoxime, and newer macrolides, such as azithromycin or clarithromycin. Quinolones or amoxicillin/clavulanate may be more appropriate in patients with moderate-to-severe chronic obstructive pulmonary disease (COPD) or comorbid illnesses. Adjunctive therapy such as bronchodilators, anticholinergics, beta-agonists, and oxygen may be added for underlying pulmonary disease.

COMMUNITY-ACQUIRED PNEUMONIA

Overview

Community-acquired pneumonia (CAP) is the sixth most common cause of death in the United States.[43] A total of 45,000 deaths can be attributed to CAP annually in the United States.[16] Most of these deaths occur in patients with underlying diseases or in those requiring hospitalization for CAP. Several organizations have published guidelines to help primary care physicians in the management of CAP, such as the 1993 American Thoracic Society Guidelines and the 1998 Infectious Diseases Society of America Guidelines.

Diagnosis

Patients with pneumonia often present with cough, dyspnea, purulent sputum, or pleuritic chest pain. Systemic signs of infection include fever, chills, nightsweats, and fatigue. On physical examination, patients may have fever and increased respiratory rate. Signs of consolidation or pleural effusion may be present.

Chest radiography should be obtained to confirm the clinical findings of pneumonia. Respiratory symptoms are less likely caused by pneumonia in the absence of consolidation. False-negative chest films may be seen in early pneumonia, dehydration, and *Pneumocystis carinii* pneumonia (PCP).[51] False-positive findings may occur in atelectasis, pulmonary infarct, and bronchogenic carcinoma.[7] Chest radiographs are helpful in assessing the severity of disease[49]; however, it is not always possible to obtain a chest radiograph in outpatient settings.

Laboratory studies, such as sputum Gram stain or culture, may be obtained to look for a predominant organism.[24, 26] Contamination of upper respiratory tract organisms may lower the yield of these studies.[55] Sputum studies are invaluable in stains for acid-fast bacilli, fungi, and PCP in selected patient populations.[49] Invasive procedures such as bronchoscopy are not usually necessary unless the patient is severely ill. Serologic studies for atypical pneumonias are not recommended in the initial evaluation of patients with CAP but may be helpful for epidemiologic purposes.[9, 49]

Ancillary laboratory tests, including pulse oximetry, complete blood count, and chemistry, can help assess the severity of pneumonia. Patients who require hospitalization should undergo additional tests, such as arterial blood gas, blood cultures, and HIV testing if the patient is 15 to 54 years old with severe pneumonia. Thoracentesis can be performed to rule out empyema if pleural effusion is present.[9]

Microbiology

Even with extensive diagnostic testing, a pathogen is not found in at least one third of patients with CAP.[9, 26, 43] This observation reflects the difficulty in obtaining a good respiratory specimen and isolating the organism. The most common cause of CAP is *S. pneumoniae,* followed by *H. influenzae,* atypical organisms, gram-negative organisms, and *S. aureus.*[24] Viral agents account for 2% to 15% of CAP.[7] Influenza is the most common cause of viral pneumonia, but other viruses such as parainfluenza, RSV, and adenovirus are also associated with CAP.[61] Tuberculosis and PCP are common causes of CAP, especially in immunocompromised patients.

Management

Because the causative agents are not often identified immediately, most cases of CAP are treated empirically. The selection of antibiotics depends on the patient population and the need for hospitalization. Outpatients who are younger than 60 years and without comorbid illnesses are more likely to have pneumonia caused by *S. pneumoniae, H. influenzae, M. pneumoniae,* or *C. pneumoniae.* The antibiotics of choice in these patients include macrolides, such as azithromycin and clarithromycin, or the newer fluoroquinolones, such as levofloxacin, sparfloxacin, and grepafloxacin. Doxycycline and amoxicillin/clavulanate are also recommended.[9] In communities where PCN resistance is not prevalent, amoxicillin or second-generation cephalosporins (cefpodoxime, cefprozil, cefuroxime) can be used as initial therapy.

Patients who are older than 60 years, who have comorbid illnesses, or who require hospitalization are more likely to have pneumonia caused by *S. pneumoniae, H. influenzae,* gram-negative organisms, or *S. aureus.*

The recommended antibiotics in this group of patients include second- or third-generation cephalosporins or a beta-lactam with a beta-lactamase inhibitor in combination with a macrolide. Alternatively, the newer quinolones can be used alone because they have good activity against all of these organisms (Table 1). Patients with underlying structural lung disease should have additional antipseudomonal coverage with agents such as ciprofloxacin. Patients with aspiration pneumonia should also be treated with antianaerobic agents.

The decision to admit a patient to the hospital is one of the most important steps in the evaluation of CAP. Approximately 15% of patients with CAP are hospitalized.[4] The mortality rate for outpatients is approximately 1% to 5%, whereas patients requiring hospitalization have mortality rates reaching 25%.[27, 45]

Patients with certain risk factors are prone to complications. These risk factors include age greater than 65 years; comorbid illnesses such as COPD, diabetes mellitus, renal and liver disease; and congestive heart failure; alcohol abuse or malnutrition; and immunocompromised states.[49] Many clinical findings are associated with poor outcomes, including a respiratory rate greater than 30 breaths per minute, diastolic blood pressure less than 60 mm Hg or systolic blood pressure less than 90 mm Hg, temperature greater than 101°F, or mental status changes. Laboratory findings associated with a worse prognosis include a white blood count less than $4 \times 109/L$ or greater than $30 \times 109/L$, neutropenia, a PaO_2 less than 60 mm Hg or greater than 50 mm Hg on room air, a hematocrit less than 30%, abnormal renal functions, multiple lobe involvement or pleural effusion on chest radiography, and evidence of sepsis, such as disseminated intravascular coagulation.[9, 49]

Table 1. EMPIRIC ANTIMICROBIAL THERAPY FOR COMMUNITY-ACQUIRED PNEUMONIA

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Adapted from Bartlett JG, Breiman RF, Mandell LA, et al: Community-acquired pneumonia in adults: Guidelines for management. Clin Infect Dis 26:811–838, 1998; with permission.

Duration of Therapy

There are no specific recommendations regarding the duration of therapy in CAP. Generally, patients with bacterial CAP should be treated for 1 to 2 weeks. Atypical causes of CAP may require a longer course of therapy lasting 10 to 21 days.[9] Immunocompromised patients may also need longer courses of therapy.

Response to Therapy

In otherwise healthy patients, fever and leukocytosis usually resolve within 2 to 4 days. Abnormal physical findings usually resolve within 7 to 10 days. Chest radiographs may take longer to normalize but generally resolve in 6 weeks.[49]

Failure of Response to Therapy

There are many reasons for therapeutic failure. The patient may have a noninfectious illness, such as pulmonary infarct or granulomatous disease; the organism may be resistant to the antibiotic chosen; or the patient may have complications of pneumonia, such as empyema or metastatic abscesses, that fail to respond to antibiotic therapy.[26] These patients may need further evaluation with thoracentesis or bronchoscopy.

Community-acquired pneumonia is a common infectious illness that can lead to significant morbidity and mortality. Prompt diagnosis and appropriate treatment can greatly improve patient outcome.

ATYPICAL PNEUMONIA

Pneumonias caused by *M. pneumoniae*, *Legionella pneumoniae*, and *C. pneumoniae* are often referred to as atypical. This classification stems from the early observation that patients with these pneumonias presented differently from patients with pneumococcal pneumonia.[49, 58] It is now established that there are often no distinguishing clinical or radiologic features differentiating atypical pneumonia from other bacterial pneumonia.[40, 44, 49] Furthermore, diagnostic laboratory tests are not always readily available; therefore, it is often difficult to diagnose atypical pneumonia.

Mycoplasmal Pneumonia

Mycoplasmal pneumonia is often considered the classic atypical pneumonia. Clinically, patients present with a prolonged cough lasting 3 to 4 weeks.[9] Constitutional symptoms, such as headache, malaise, myalgia, and sore throat, are often present. Extrapulmonary manifesta-

tions, such as rash and gastrointestinal and neurologic symptoms, can also be seen.[25] The onset of symptoms is usually insidious and self-limiting. Physical examination may be normal or may reveal scattered rales. Definitive laboratory diagnosis is often difficult owing to the delay of antibody production and slow growth of mycoplasma in culture. An increase in cold agglutinin titers may be suggestive but not specific for mycoplasma. Radiographic findings are variable but may show peribronchial infiltrates. Patients who present with signs and symptoms suggestive of mycoplasmal pneumonia can be treated with tetracycline, macrolides, or fluoroquinolones for 2 to 3 weeks to prevent recurrence.[25]

Legionella Pneumonia

Legionella is an intracellular organism causing approximately 6% of CAP and 20% to 40% of pneumonia in hospitalized patients.[60] Legionnaire's disease became well recognized after the outbreak of pneumonia in the 1976 Legionnaire's convention in Philadelphia.[65] Since then, most cases of legionellosis have been reported in the Northeast and Great Lakes area.[9, 25] Risk factors for legionnaire's disease include increased age; smoking; pulmonary, renal, or liver dysfunction; transplant recipients; and patients with impaired cell-mediated immunity.[25, 60, 65] Clinically, patients present in a similar fashion to patients with other bacterial pneumonias. Symptoms may range from mild-to-severe respiratory disease and usually include high fever, headache, myalgia, mildly productive cough, pleuritic chest pain, and hemoptysis. Diarrhea may be present in 20% to 40% of cases.[8, 65] Chest radiography usually shows lobar infiltrates with pleural effusion in one third of patients.[60, 65] Laboratory findings suggestive of legionella include hyponatremia less than 130 mmol/L and lactate dehydrogenase (LDH) greater than 700 U/mL.[58] A rapid diagnostic test for legionella is available. The diagnostic study of choice is the urinary antigen assay for legionella serogroup 1, which accounts for 70% of legionnaire's disease.[8] Testing for legionella should be considered in endemic areas or in patients with severe respiratory illness, immunocompromised state, lack of response to appropriate antibiotics, or with a clinical presentation suggestive of legionnaire's disease.[9] Testing should also be considered in patients who have recently traveled or who have an occupational exposure to water.[20]

Erythromycin has been the drug of choice for the treatment of legionnaire's disease; however, newer macrolides such as clarithromycin and azithromycin have fewer side effects and better in vitro results. Quinolones are also effective against legionella. Critically ill patients in the intensive care unit should be started on these therapies empirically because they have a higher incidence of legionnaire's disease. The duration of therapy for legionnaire's disease is 14 days, except in immunocompromised patients, in whom therapy should be extended to 21 days. Alternatively, azithromycin can be given for 5 to 10 days owing to its prolonged half-life.[65]

Chlamydial Pneumonia

Chlamydial pneumoniae was identified as a cause of CAP in 1985. Since then, the incidence of *C. pneumoniae* causing CAP is estimated to be about 10%.[39] Most primary infections occur in childhood or young adulthood, with recurrent infections in the elderly.[39] There are no distinguishing clinical or radiologic features of chlamydial pneumonia. Patients usually present with a mild respiratory illness that follows a subacute course. Symptoms are nonspecific and may include sore throat, hoarseness, headache, or low-grade fever.[25] Cough may be prominent, but sputum production is usually nonpurulent or absent. Radiologic studies may be normal or may show interstitial infiltrates.[39] There is no rapid diagnostic test available for *C. pneumoniae*; therefore, therapy with the newer macrolides, fluoroquinolones, or tetracycline is usually empiric in patients suspected of having chlamydial pneumonia.

VIRAL PNEUMONIA

Viruses can cause pneumonia in all age groups. The most common cause of viral pneumonia is influenza, followed by RSV and parainfluenza virus. Viral pneumonia can progress to secondary bacterial pneumonia and cause significant morbidity. When associated with severe pandemics, influenza can cause 40,000 deaths in the United States.[17]

Patients with influenza usually have symptoms of cough, sore throat, headache, and myalgia lasting 3 to 5 days. Secondary bacterial infection may be associated with recurrent fever and worsening of symptoms after 5 days.[19] Laboratory studies, such as viral culture and ELISA, are not useful for the immediate diagnosis of viral pneumonia. Treatment of viral pneumonia is mainly supportive. Antiviral agents, such as amantadine and rimantadine, inhibit viral replication and may decrease the severity and duration of symptoms. These drugs are only active against influenza A and must be administered within the first 48 hours of illness. Newer agents, such as the neuraminidase inhibitors, are active against influenza A and B. Zanamivir (Relenza) and oseltamivir (Tamiflu) are examples of neuraminidase inhibitors that have recently become available for commercial use. As is true for amantadine and rimantadine, the neuraminidase inhibitors must be given within the first 48 hours of illness to be effective. Annual flu vaccination of the elderly, immunocompromised, and health care workers is important to prevent influenza.

The RSV and parainfluenza virus usually cause self-limiting, mild respiratory infections in adults that can be treated supportively. In elderly and immunocompromised patients, these viruses can cause more severe lower respiratory tract infections associated with fever, cough, and dyspnea. Rapid antigen testing of nasal swabs can be performed for RSV and most serotypes of parainfluenza.[17, 19]

PNEUMOCYSTIS CARINII PNEUMONIA

Pneumocystis carinii pneumonia is the most common acquired immunodeficiency syndrome (AIDS) illness in HIV-positive patients.[7] Patients with CD4 cell counts below 200 are at higher risk for PCP; therefore, they should be placed on PCP prophylaxis with TMP/SMX. Alternative agents such as dapsone, atovaquone, or aerosolized pentamidine can be used if the patient is allergic to sulfa agents.

Patients with PCP usually present with fever, dyspnea, and nonproductive cough. Laboratory features suggestive of PCP include oxygen desaturation after exercise and elevated LDH[42]; however, an elevated LDH is neither sensitive nor specific for PCP. Chest radiography usually reveals an interstitial pattern resembling a ground glass appearance but may be normal in at least 30% of cases.[8] A definitive diagnosis of PCP can be made with a stain of induced sputum bronchoalveolar specimens. The most effective therapy for PCP is TMP/SMX. Alternative agents, such as atovaquone, pentamidine, or primaquine-clindamycin, can be used if the patient is sulfa allergic or if intolerance develops to TMP/SMX. Steroids should be added if the patient's PaO_2 is less than 70 mm Hg on room air. The duration of therapy is usually 21 days. The mortality rate for PCP ranges from 15% to 30% in varying studies.[8, 42]

TUBERCULOSIS

A detailed discussion of tuberculosis is beyond the scope of this article. Recently, there has been a rise in incidence and an increase in multidrug-resistant disease. Tuberculosis should be suspected in high-risk populations, such as HIV-positive patients, close contacts of patients with tuberculosis, or immunosuppressed patients who present with a cough lasting more than 1 month, nightsweats, or weight loss. The typical radiographic finding of tuberculosis includes upper lobe infiltrates or cavitary lesions; however, HIV-positive patients may not have all of these findings.[8] Confirmatory diagnostic studies include induced sputum for acid-fast bacillus stains and culture. DNA probes and polymerase chain reaction of mycobacterium tuberculosis has allowed a more rapid diagnosis.[6]

The treatment of tuberculosis depends on local resistance patterns. In areas where the incidence of resistant tuberculosis is less than 4%, treatment can be started with isoniazid, rifampin, and pyrazinamide for 8 weeks, followed by isoniazid and rifampin for 16 weeks. In areas of higher drug resistance, ethambutol should be added to the initial three-drug therapy for 8 weeks or until final sensitivities are known. Isoniazid and rifampin are then continued for additional 16 weeks if organisms are sensitive. Vitamin B_6 (pyridoxine) is usually administered with isoniazid to prevent peripheral neuropathies. HIV-positive patients with tuberculosis should be treated for 9 to 12 months. Patients who present with clinical and radiographic features of tuberculosis but who have

negative acid-fast bacillus smears should be treated until final cultures are negative, which can take up to 6 weeks.[10]

PREGNANCY ISSUES IN PNEUMONIA

Pneumonia may occur in as many as 1% of pregnancies.[2] The clinical presentation and diagnostic evaluation of pneumonia in pregnant and nonpregnant patients do not differ; however, the complications of pneumonia may be higher during pregnancy. There is a need for prompt diagnosis to prevent such complications. There is also the potential fetal risk of therapeutic agents (Table 2). The drugs of choice for pneumonia in the pregnant patient are second- or third-generation cephalosporins with erythromycin if atypical coverage is needed.

Two common causes of viral pneumonia in pregnancy are influenza and varicella pneumonia. Antiviral agents, such as amantadine, have been used in pregnancy, but their safety is not well defined. In contrast, the neuraminidase inhibitors seem to be safe for use in pregnancy.[29] The influenza vaccination is usually not necessary during normal pregnancy.[59] Varicella affects less than 2% of the adult population; however, there is an increased risk of varicella pneumonia if primary varicella infection develops during pregnancy.[59] Symptoms of varicella pneumonia include rash, pleuritic chest pain, dyspnea, and cough. Treatment with acyclovir should be initiated immediately. Although acyclovir is not usually administered during pregnancy, its use has not been associated with an increase in fetal abnormalities.[59] Without treatment, the mortality of varicella pneumonia in pregnancy may reach 35%.[2]

The incidence of tuberculosis during pregnancy may be as high as 0.1% in endemic areas.[2] Treatment of tuberculosis in pregnant and nonpregnant patients is slightly different. Isoniazid, rifampin, and ethambutol all cross the placenta but have not been shown to cause teratogenic effects. Pyrazinamide is not usually recommended during pregnancy owing to the lack of data regarding its teratogenic effects. Pregnant patients with tuberculosis should be treated for 9 months. Pyridoxine supplementation to prevent neuropathy is also essential in pregnant patients.[2] Drugs for tuberculosis are safe in patients who are breastfeeding; however, infants who are also taking these medications should not be breastfed to avoid supratherapeutic concentrations of the drugs.[2, 47] Pregnant patients who have a positive PPD skin test without active disease can receive prophylaxis with isoniazid but preferably after the first trimester.

Therapy for PCP during pregnancy is the same as in nonpregnant patients. There is a theoretical risk of kernicterus in the neonate when the pregnant patient is treated with TMP/SMX, but this complication has not been reported.[59] Folic acid should be administered to patients taking TMP/SMX. There are insufficient data regarding the safety of dapsone for use in pregnancy; however, the risk:benefit ratio usually justifies its use in pregnant patients with PCP who are intolerant of or

Table 2. COMMONLY USED ANTIBIOTICS IN PNEUMONIA AND RISK CATEGORY IN PREGNANCY

Antibiotics in Pneumonia	Risk Category in Pregnancy
Penicillin (PCN) and cephalosporins	
PCN V, 250–500 mg po q6–8h	B
PCN G, 0.5–0.2 mU IV q6h	B
Amoxicillin, 500 mg po tid	B
Ampicillin, 0.5–0.2 g mg IV q6h	B
Amoxicillin/clavulanate (Augmentin) 500 mg po tid or 875 po bid	B
Ampicillin/sulbactam (Unasyn), 1.5-3 g IV q6h	B
Ticarcillin/clavulanate (Timentin), 3.1 g IV q6h	B
Piperacillin/tazobactam (Zosyn), 3.375 g IV q6h	B
Cephalexin (Keflex), 500 mg po qid	B
Cehradine (Velosef), 500 mg po qid	B
Cefaclor (Ceclor), 500 mg po tid	B
Cefuroxime (Kefurox, Zinace), 1.5 g IV q8h	B
Cefpodoxime (Vantin), 400 mg po bid	B
Cefotaxime (Claforan), 1–2 g IV q8h	B
Ceftriaxone (Rocephin), 1–2 g IV q24h	B
Ceftazidime (Fortaz), 2 g IV q8h	B
Cefepime (Maxipime), 2 g IV q12h	B
Macrolides	
Erythromycin, 250–500 mg po qid or 1 g IV q6h	B
Clarithromycin (Biaxin), 500 mg po bid	C
Azithromycin (Zithromax), 500 mg po × 1 d, then 250 mg po qd × 4 d or 500 mg IV q24	B
Fluoroquinolones	
Ciprofloxacin (Cipro), 500–750 mg po q12h or 200–400 mg IV q12h	C
Levofloxacin (Levaquin), 500 mg po or IV q4h	C
Sparfloxacin (Zagam), 200–400 mg po q24h	C
Grepafloxacin (Raxar), 600 mg po q24 h	C
Miscellaneous	
Doxycycline, 100 mg po bid	D
TMP/SMX, 2–4 mg/kg of TMP IV q6h or DS po bid	C
Metronidazole, 250–500 mg po or IV q 12h (not first trimester)	B
Clindamycin, 300–450 mg po q6h or 600 mg IV q6h	B
Antivirals	
Amantadine (Symmetrel, Symadine), 100 mg po bid	C
Rimantadine (Flumadine), 100 mg po bid	C
Zanamivir (Relenza) nasal inhaler, 10 mg bid	B
Oseltamivir (Tamiflu), 75 mg po qd × 6 weeks for prophylaxis or bid × 5 days for treatment	C
Antituberculous agents	
Isoniazid, 300 mg po qd	C
Rifampin, 600 mg po qd	C
Pyrazinamide, 15–30 mg/kg po qd (max, 2 g)	Unsafe*
Ethambutol, 15–25 mg/kg po qd (max, 2.5 g)	Safe*
Anti-PCP agents	
Prophylaxis	
TMP/SMX DS, qd or q MWF or SS qd po	
Dapsone, 100 mg qd po	C
Atovaquone, 750 mg po bid	?
Aerosolized pentamidine, 300 mg q monthly	?

Table 2. COMMONLY USED ANTIBIOTICS IN PNEUMONIA AND RISK CATEGORY IN PREGNANCY *Continued*

Antibiotics in Pneumonia	Risk Category in Pregnancy
Treatment	
TMP, 15 mg/kg/d, plus SMX, 75 mg/kg/d IV (divided into three to four doses)	
TMP/SMX DS, 2 tabs po tid	
TMP, 15 mg/kg/d IV divided into three to four doses, plus Dapsone, 100 mg po bid	
Clindamycin, 600 mg IV q8h or 300–450 mg po q6h, plus primaquine, 30 mg po qd	
Atovaquone, 750 mg po bid	
Pentamidine, 4 mg/kg/d IV	

PCP = *Pneumocystis carinii* pneumonia.

A = studies in pregnant women, no risk; B = animal studies no risk, but human studies not adequate or animal toxicity but human studies no risk; C = animal studies show toxicity, human studies inadequate but benefit may exceed risk; D = evidence of human risk, but benefits may outweight; ? = unknown.

Data from Barnes PF, Barrows SA: Tuberculosis in the 1990s. Ann Intern Med 119:400–410, 1993; Bartlett JG: Management of Respiratory Tract Infections, ed 2. Philadelphia, Lippincott Williams and Wilkins, 1999; Bartlett JG: Pneumonia in the patient with HIV infection. Infect Dis Clin North Am 12:807–820, 1998; Chien JW, Johnson JL: Viral pneumonias: Epidemic respiratory viruses. Postgrad Med 107:41–52, 2000; Finch RG, Woodhead MA: Practical considerations and guidelines for the management of community-acquired pneumonia. Drugs 55:31–45, 1998; Gilbert DN, Moellering RC, Sande MA: Sanford Guide to Antimicrobial Therapy, ed 30. Hyde Park, NY, Jeb C. Sanford, 2000, p 56; Gubareva LV, Kaiser L, Hayden FG: Influenza virus neuroaminidase inhibitors. Lancet 355:827–835, 2000; and Rubins JB, Janoff EN: Community-acquired pneumonia: Tailoring management of adult patients according to risk category. Postgrad Med 102:45–62, 1997.

allergic to TMP/SMX. Parenteral pentamidine has several undesirable toxicities, including rash, neutropenia, and thrombocytopenia. Its use should be restricted to severe cases of PCP. Aerosolized pentamidine for prophylaxis is safe to use in pregnancy.

SUMMARY

Respiratory tract infections cause nearly half of deaths owing to infectious disease in the United States.[54] This article has discussed the management of several common respiratory tract infections, with an emphasis on appropriate diagnosis and use of antimicrobial agents. Understanding the cause of various respiratory tract infections enables primary care physicians to avoid unnecessary antibiotic use, decreasing adverse effects owing to medications and preventing the rise in antimicrobial resistance.

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