AN OVERVIEW OF COMMUNITY-ACQUIRED RESPIRATORY TRACT INFECTIONS

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ABSTRACT

Community-acquired respiratory tract infections continue to be among the most common and important infections seen by practitioners. These infections typically involve the sinuses, the airways, and the lungs. Acute respiratory tract infections can be caused by a wide variety of microorganisms including viruses. This variety of respiratory pathogens is, in part, why the diagnosis and therapy of these infections remains a problem. The lack of rapid, accurate, and reliable methods for diagnosis makes it difficult to direct antimicrobial therapy at a specific pathogen. Thus, empirical therapy with broad-spectrum antimicrobial agents often is relied upon due to the absence of Gram's stain and culture results. As viruses can cause many of these community-acquired respiratory tract infections, overuse of empirical antimicrobial therapy frequently occurs. Empirical antimicrobial therapy is not only ineffective against viral respiratory tract infections, but overuse of such therapy can lead to microbial resistance. Indeed, resistance has occurred with many of the bacterial pathogens causing community-acquired respiratory tract infections. Yet, effective antimicrobial therapy of respiratory tract infections caused by bacterial pathogens is important in preventing hospitalization or decreasing length of hospitalization. As a rule, acute respiratory tract infections caused by viruses are self-limited and should not be treated. A notable and recent exception is influenza, which has become relatively easy to diagnose and treat. This overview will focus primarily on community-acquired respiratory tract infections that are caused by those pathogens, including the influenza virus, which can be treated. Community-acquired respiratory tract infections that are caused by such pathogens include acute bacterial sinusitis, influenza, Chlamydo philia pneumoniae respiratory tract syndrome, acute exacerbations of chronic bronchitis, and community-acquired pneumonia.

(C)ommunity-acquired respiratory tract infections continue to be among the most common and important infections seen by practitioners. These infections typically involve the sinuses, the airways, and the lungs and can be caused by a wide variety of microorganisms including viruses. As a rule, acute respiratory tract infections caused by viruses are self-limited and should not be treated. A notable and recent exception is influenza, which has become relatively easy to diagnose and to treat. This overview will focus primarily on community-acquired respiratory tract infections that are caused by those pathogens, including the influenza virus, which can be treated. Community-acquired respiratory tract infections that are caused by such pathogens include acute bacterial sinusitis, influenza, Chlamydo philia pneumoniae respiratory tract syndrome, acute exacerbations of chronic bronchitis, and community-acquired pneumonia.

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†Organisms in the Chlamydia order were grouped by DNA homology, which resulted in 2 distinct families of chlamydial organisms, the Chlamydo phila and Chlamydia families.
Epidemiology of Community-Acquired Respiratory Tract Infections

Community-acquired respiratory tract infections are the most common, and potentially most severe, of infections treated by clinicians. Risk factors for community-acquired respiratory tract infections include: extremes of age (young and elderly), smoking, alcoholism, immunosuppression, and comorbid conditions such as congestive heart disease and chronic obstructive pulmonary disease (COPD). Respiratory tract infections are the most common reason for office visits in the United States. There are approximately 112 million office visits per year for these respiratory tract infections, which is over twice that for the second most common reason, essential hypertension at 48 million office visits per year. A seasonal increase in the incidence of community-acquired respiratory tract infections is recognized with cold and rainy seasons being associated with increased respiratory tract infections due to crowding. For example, when viruses such as influenza and respiratory syncytial virus are circulating in the community, an increase in invasive pneumococcal disease has been documented. Although community-acquired respiratory tract infections are common and seasonal, the epidemiology of these infections can be confusing. This is because some acute respiratory tract infections such as influenza can be easily transmitted from one person to another. Accordingly, respiratory tract infections such as influenza have a known seasonal occurrence and may occur in epidemics. Other respiratory tract infections such as acute exacerbations of chronic bronchitis are related to colonization of the airways and thus involve the patient’s own flora. Yet other community-acquired respiratory tract infections may be multifactorial, perhaps beginning with a viral respiratory tract infection and then complicated by aspiration/colonization of the person’s own oral flora, which finally results in bacterial tracheobronchitis/pneumonia. It is actually easier to first consider the pathogenesis of community-acquired respiratory tract infections and then examine in more detail the epidemiological aspects of each of the common types of respiratory tract infections.

Pathogenesis of Community-Acquired Respiratory Tract Infections

The pathogenesis of community-acquired respiratory tract infections is similar to and usually begins with impairment of the mucociliary defense mechanism. Such impairment may be due to an acute viral infection of the respiratory tract, but is also a chronic problem in persons who smoke tobacco or are exposed to second-hand tobacco smoke. The impairment of the mucociliary defense mechanism is due to damage/death of the ciliated epithelial cells lining the sinuses and airways. This is particularly a problem with infection of the respiratory tract caused by the influenza virus because influenza per se causes damage/death of cells lining the sinuses and airways. Interestingly, infection of these ciliated cells by another recently defined respiratory tract pathogen, *C. pneumoniae*, also interferes with the mucociliary defense mechanism by paralyzing the cilia. The paralysis of cilia accounts for the persistent cough seen in the characteristic tracheobronchitis caused by this atypical pathogen. The dominant respiratory tract pathogens seen in bacterial infections following impairment of the mucociliary defense mechanism are *Streptococcus pneumoniae*, *Haemophilus influenzae*, atypical pathogens such as *Mycoplasma pneumoniae*, *Legionella* species, and *C. pneumoniae*. Some of these pathogens such as *S. pneumoniae* and *H. influenzae* are present in the normal flora of the upper respiratory tract and may cause infection after aspiration. Others, such as *C. pneumoniae*, are initially acquired from droplet nuclei containing elementary bodies that have been aerosolized by the coughing of an infected person, but then can cause a low-grade chronic respiratory tract infection in which exacerbations can be triggered by viral infections. *Legionella* species are acquired from an external source such as dust, air conditioner mist, drinking water/aspiration, or showers. It is these multiple pathways for respiratory tract infections that make their epidemiology somewhat confusing.

Influenza

Influenza continues to be an important community-acquired respiratory disease and remains in the top 10 causes of death in the United States each year. This means that even in nonepidemic years, more than 20 000 Americans die annually from influenza. Influenza is an RNA virus with affinity only for cells of the respiratory tract. There are 2 important types of influenza virus, influenza A and B, with influenza A being more active in its antigenic drift and the only influenza type that undergoes antigenic shift. The diagnosis of acute influenza has for the most part been a clinical one, based in part on the knowledge that influenza is present in the local area. Generally, the acute onset of fever, chills, cough, malaise, and
severe myalgias are clinical findings that identify patients with influenza-like illness but are not particularly useful for confirming or excluding the diagnosis of influenza. These clinical findings are, however, sufficient to warrant the use of commercially available rapid assays for the identification of type A and B influenza viruses.13 There are a number of these assays available; they vary in complexity, specificity, sensitivity, test time, specimen analyzed, and cost. In general, these rapid influenza tests are more than 70% sensitive and 90% specific for influenza antigens.14 The results of these rapid influenza tests are quite useful in guiding treatment decisions and are changing the practice pattern of clinicians who care for patients with influenza.

Treatment of acute influenza may be symptomatic or specific. Antiviral pharmacotherapy has been shown to reduce the duration of disease, decrease viral shedding, relieve symptoms during disease, and enhance defervescence.15 The first antiviral agents, amantadine and rimantadine, were effective only against influenza A. Moreover, these agents can have neurological and gastrointestinal side effects, and resistant strains of influenza virus rapidly occur. However, with the advent of the neuraminidase inhibitors, zanamivir and oseltamivir, antiviral therapy effective against both influenza A and B is now available.16 These neuraminidase inhibitors have minimal side effects and far fewer problems with the development of resistant strains as infectivity of resistant strains is usually compromised. It must be remembered that antiviral therapy with any of these agents is effective only when initiated within 48 hours of the onset of symptoms.

**C. pneumoniae Respiratory Tract Syndrome**

*C. pneumoniae* is a recently recognized species of *Chlamydia*17 and is now known as a significant cause of both upper and lower respiratory tract infections.18 The *C. pneumoniae* respiratory tract syndrome is specifically covered in this overview because it is a relatively new syndrome and may be unappreciated by many physicians and pharmacists. *C. pneumoniae* infection has been described in otolaryngeal diseases such as pharyngitis, tonsillitis, laryngitis, sinusitis, and otitis media with an incidence ranging from 5% to 20%.18,19 Involvement of *C. pneumoniae* in these upper respiratory tract infections, particularly laryngitis in an adult, may herald lower respiratory tract infection, with upper respiratory tract symptoms fading as a persistent cough ensues.18,20 Lower respiratory tract infection with *C. pneumoniae* is characterized by a persistent cough that may initially mimic pertussis.18,20-23 The duration of this cough is usually greater than 2 weeks and may be as long as 3 months. Although low-grade fever may be present initially, these patients are generally afebrile by the time they seek medical assistance. The white blood count is usually not elevated in patients infected with *C. pneumoniae*. An important difference between the persistent cough caused by *C. pneumoniae* tracheobronchitis and that seen with pertussis is that within a week or two, the chlamydial cough becomes productive of grayish-green bronchial plugs in the morning only.

Lower respiratory tract infections caused by *C. pneumoniae* may involve an acute tracheobronchitis accompanied by laryngitis and sinusitis, chronic bronchitis, or community-acquired pneumonia. Although the name *C. pneumoniae* suggests its role as a cause of community-acquired pneumonia, where studies have demonstrated that it accounts for 6% to 20% of these pneumonias, it is more likely to cause acute tracheobronchitis or chronic bronchitis than pneumonia.18,20 Indeed, chronic infection by *C. pneumoniae* has been found to be common in chronic bronchitis.18,20 This chronic infection may contribute to the pathogenesis of chronic bronchitis, with cilostasis4 and chronic inflammation. Over time, this chronic chlamydial infection of the bronchi may contribute to the development of both small airway disease and emphysema. In fact, chronic *C. pneumoniae* infection is now a recognized risk factor for the development of COPD.25 In addition to its role in chronic bronchitis and COPD, *C. pneumoniae* has also been associated with both child-onset and adult-onset asthma.26,27 The exact role(s) of *C. pneumoniae* infection in asthma is currently being determined. It is known that acute respiratory tract infections, including those caused by *C. pneumoniae*, cause exacerbations of asthma in children.28 Chronic *C. pneumoniae* infection also may play a role in asthma by contributing to the chronic inflammatory derangements of the airways and could even play a role in new-onset asthma.29 Clearly, chronic *C. pneumoniae* infection may lead to an increase in the severity of asthma; prolonged antichlamydial therapy appears to result in an improvement in asthma control.30

**Acute Exacerbations of Chronic Bronchitis**

Acute exacerbations of chronic bronchitis are important because the incidence of chronic bronchitis
is rising, especially in persons aged 18 to 44 years and in the elderly. Chronic bronchitis comprises 90% of all cases of COPD. The major risk factors for COPD are smoking tobacco; a family history of obstructive lung disease; exposure to tobacco smoke and atmospheric, domestic, and occupational pollutants; and recurrent respiratory tract infections, particularly with *C. pneumoniae* and during infancy. COPD accounts for more than 14 million office visits to family physicians and 500,000 hospital admissions annually. COPD is the fourth leading cause of death in the United States and the second most important cause of work disability. Patients with COPD and chronic bronchitis are prone to acute exacerbations, which frequently are caused by bacterial pathogens; antimicrobial therapy of these acute exacerbations appears warranted. The most common bacterial pathogens are *H. influenzae* and *S. pneumoniae* with *C. pneumoniae* becoming increasingly recognized as both a common and important pathogen in COPD and chronic bronchitis. Infection with *S. pneumoniae* and other gram-positive cocci tend to cause a less severe bronchitis than infection with *Enterobacteriaceae* and *Pseudomonas*. Nontypeable *H. influenzae* is an important pathogen in chronic bronchitis that can be difficult to eradicate due to its intracellular location; therefore, the ability of an antimicrobial agent to penetrate human cells is an important factor in treating this microorganism.

**Community-Acquired Pneumonia**

Community-acquired pneumonia remains an important therapeutic problem in medical practice. In the United States, approximately 4 million cases of pneumonia are reported annually. Including influenza, pneumonia is the sixth leading cause of death in the United States. The mortality rate for community-acquired pneumonia continues to be approximately 14%. It is the possibility of community-acquired pneumonia that causes concern when a patient presents with a community-acquired respiratory tract infection. Even a relatively benign viral respiratory tract infection can lead to a secondary bacterial pneumonia. This consideration is, in part, what the clinician uses to determine whether antibiotics should be given to a patient with a community-acquired respiratory tract infection. The annual direct and indirect costs of community-acquired pneumonia total $23 billion. Although the influenza virus can cause community-acquired pneumonia, *S. pneumoniae*, *H. influenzae*, and the atypical pathogens *M. pneumoniae*, *Legionella* species, and *C. pneumoniae* cause the majority of these infections. Empirical antimicrobial therapy should cover each of these bacterial pathogens, including resistant strains.

**Acute Bacterial Sinusitis**

Acute bacterial sinusitis is a major problem today with approximately 31 million cases of acute and chronic sinusitis being reported annually in the United States. The annual direct and indirect costs of acute bacterial sinusitis in the United States are more than $3.4 billion. The diagnosis of acute bacterial sinusitis can be difficult and involves localized maxillary facial pain, poor response to decongestants, history of purulent nasal secretions/discharge, and abnormal transillumination result. Antimicrobial therapy of acute bacterial sinusitis is important because the complications of these sinus infections include chronic sinusitis; orbital complications, especially in children; and intracranial complications such as meningitis, epidural abscess, subdural empyema, venous sinus thrombosis, and cerebral abscess. Acute bacterial sinusitis is the fifth most common diagnosis for which antimicrobial agents are prescribed. The dominant bacterial pathogens in acute bacterial sinusitis are *S. pneumoniae* and *H. influenzae*.

**Management of Community-Acquired Respiratory Tract Infections**

There are important factors to consider with the therapeutic options for bacterial community-acquired respiratory tract infections. The choice of initial antimicrobial therapy is usually empirical because of the serious nature of many of these respiratory tract infections. If purulent nasal discharge or purulent expectorated sputum specimens are available, a Gram's stain is often quite useful in guiding the initial choice of antimicrobial agents. Often a precise microbiological diagnosis is difficult, if not impossible, because the specialized and invasive procedures needed to obtain a specimen are out of proportion to the course of infection in the normal host. Even when specimens from the sinuses, airways, or lungs can be collected, the differentiation of infection from colonization or contamination is a problem. Moreover, mixed infections occur frequently. In mixed infections, one of the pathogens (e.g., *C. pneumoniae*) may be difficult to detect with normal microbiological diagnostic procedures. A number of newly identified respi-
atory tract pathogens such as *C pneumoniae* and *Simkania* are difficult to detect and are still being assessed in terms of their pathogenic potential. Finally, resistance of the most common bacterial pathogens has emerged and is increasing. This was first seen in *H influenzae* and more recently in *S pneumoniae*. Clinical management of respiratory tract infections has been complicated over the past decade by the emergence and spread of resistance in *S pneumoniae* to beta-lactam agents and to macrolides both worldwide and in the United States. Three-year data from the Prospective Resistant Organism Tracking and Epidemiology for the Ketolide Telithromycin-United States (PROTEKT US) longitudinal surveillance study initiated in 2000 have recently been published. The latest results from PROTEKT US showed that the prevalence of pneumococcal penicillin nonsusceptibility in the United States is either remaining the same or decreasing slightly. Overall pneumococcal macrolide (erythromycin) resistance rates have been at approximately 30% over 2000 to 2003, a level which is consistently higher than penicillin resistance. Importantly, the proportion of *S pneumoniae* isolated demonstrating multidrug resistance has been static over 2000 to 2003, and has an overall prevalence of approximately 31%. Multidrug-resistant *S pneumoniae* will most likely make the treatment of community-acquired respiratory tract infections more difficult.

Given the broad spectrum of respiratory tract pathogens and the problem of resistance, it becomes very clear that currently there are few, if any, ideal antimicrobial agents for respiratory tract infections. The characteristics of the ideal antimicrobial agent for community-acquired respiratory tract infections are listed in the Table. Clearly, the ideal antibiotic should have excellent activity against a targeted spectrum of respiratory tract infections with a low potential for the development of resistance. Ideally, the agent should not have significant activity against enteric bacteria occurring in other parts of the body as such activity may lead to increased resistance in these enteric bacteria. The model agent should have a high clinical success rate with empirical therapy. A favorable safety profile is also important for the ideal antimicrobial. Ideal therapy should have convenient dosing and oral as well as intravenous dosing should be available. Finally, a short treatment duration would be useful to address compliance issues.

**CONCLUSIONS**

Older classes of antimicrobial agents such as beta-lactam agents, macrolides, azolides, and fluoroquinolones all have members that have proven useful for the therapy of bacterial respiratory tract infections. Unfortunately, the emergence of newer pathogens as well as the emergence of resistance has lowered the clinical efficacy of these older agents. Newer classes of antimicrobial agents may provide additional agents that will prove useful for respiratory tract infections. These include the streptogramin class with quinupristin/dalfopristin, the oxazolidinone class with linezolid, and the ketolide class with telithromycin. Some of these newer classes such as the streptogramin class and oxazolidinone class are directed primarily against resistant gram-positive bacteria and should prove useful for respiratory tract infections caused by multidrug-resistant *S pneumoniae*. The ketolide class has the broadest spectrum of the newer classes of antimicrobial agents and is active against the important respiratory pathogens, including multidrug-resistant pneumococci. Moreover, ketolides such as telithromycin are bactericidal as well as chlamydicidal. Such bactericidal activity is important for eradication as well as decreasing resistance. Time will tell how useful these agents will be for the therapy of community-acquired respiratory tract infections.

**REFERENCES**


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**Table. Characteristics of the Ideal Antibiotic for Community-Acquired Respiratory Tract Infections**

- Activity against broad spectrum of pathogens causing respiratory tract infections, but not against enteric bacteria occurring in other parts of the body
- Low potential for resistance
- Empirical therapy associated with high clinical success rate
- Good tolerability
- Convenient dosing schedule (including both oral and intravenous formulations)
- Short treatment duration


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