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SUPPLEMENT

Treating Community-acquired Bacterial Respiratory Tract Infections:

Update on Etiology, Diagnosis, and Antimicrobial Therapy

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Acute bacterial sinusitis (ABS), acute bacterial exacerbations of chronic bronchitis (ABECB), and community-acquired pneumonia (CAP) are 3 respiratory tract infections (RTIs) in adults that pose a treatment challenge for clinicians in the primary care setting. Each of these conditions requires prompt initiation of therapy to achieve optimal patient outcomes, but diagnosis and selection of treatment typically are made without the benefit of diagnostic tests. Due to increasingly high levels of antibiotic resistance,[1,2] the decision to treat and the selection of therapy are critically important.[3-5]

This article briefly reviews the etiology of community-acquired bacterial RTIs, important diagnostic considerations, and current treatment options for patients who have these infections.

Practice recommendations

- Most community-acquired respiratory tract infections (RTIs) are not bacterial; therefore, patients do not require antibiotic treatment.
- Antibiotic therapy for community-acquired bacterial RTIs, including acute bacterial sinusitis (ABS), acute bacterial exacerbations of chronic bronchitis (ABECB), and community-acquired pneumonia (CAP), is typically empiric and requires careful evaluation of patients and antibiotics.
- Common respiratory tract pathogens, including *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*, are becoming increasingly resistant to currently used antibiotics.
- To reduce the development of drug-resistant bacteria and maintain their effectiveness, new-generation antimicrobials should be used only to treat infections that have been proven or are strongly suspected to be caused by bacteria.

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Community-acquired respiratory tract infections: Viral vs bacterial

The debate regarding whether to prescribe antibiotics for patients with community-acquired RTIs continues, since most of these infections are viral. Approximately 2% of patients with acute sinusitis have a bacterial infection.[4,6] The etiology of acute exacerbations of chronic bronchitis (AECB) is only about 50% bacterial; other causes for these exacerbations include viruses, allergens, and environmental pollutants.[3] Among ambulatory patients with CAP, even when diagnostic testing is performed, the causative pathogen cannot be identified in 40% to 50% of patients.[7] All of these findings support the view that many cases of acute sinusitis, AECB, or CAP are not caused by bacteria and patients with these types of infections will not benefit from antimicrobial therapy. A diagnostic challenge to primary care physicians is determining which patients have a bacterial infection.

TABLE 1

Signs and symptoms associated with community-acquired respiratory tract infections[3,13,14,17]

Acute sinusitis	
Major	*Minor*
• Facial pain/pressure/fullness*	• Headache
• Nasal obstruction/blockage	• Fever (other than acute disease)
• Nasal or postnasal discharge/ purulence (by history or physical examination)	• Halitosis
	• Fatigue
	• Dental pain
• Hyposmia/anosmia, fever (in acute disease only)†	• Cough
• Double-sickening	• Ear pain/pressure/fullness

Acute exacerbation of chronic bronchitis
Increased
• Dyspnea
• Sputum volume
• Sputum production

Community-acquired pneumonia
• Productive cough, pleuritic chest pain, or dyspnea
• Fever
• Tachypnea
• Tachycardia
• Altered breath sounds
• Rales
• Falls

*Facial pain/pressure alone does not constitute a suggestive history in the absence of another finding listed in the "major" category.
†Fever in acute sinusitis alone does not constitute a suggestive history in the absence of another finding listed in the "major" category.

Differential diagnosis of bacterial infection in patients with community-acquired respiratory tract infections

National and international guidelines have been developed to assist clinicians in the differential diagnosis of bacterial infections.[7-11]

Acute sinusitis

Clinical diagnosis of acute sinusitis is based primarily on medical history, symptoms, and physical findings.[4] A wide range of symptoms may occur in patients with acute sinusitis, as it does in patients with a common cold; **TABLE 1** shows the symptoms most likely to be associated with sinusitis.[12] No single clinical sign or symptom distinguishes between bacterial and viral causes of acute sinusitis; rather, it is the combination of these signs or symptoms that may lead to the diagnosis of bacterial sinusitis. A history of purulent secretions and symptoms that appear more severe than those typically associated with an upper RTI suggests ABS;[13] however, purulent discharge alone is not always indicative of a bacterial infection. "Double-sickening," in which the patient becomes ill and then gets worse, combined with elevation in C-reactive protein may indicate a bacterial infection.[14] Williams et al[15] recommended that clinical diagnosis emphasize key features such as maxillary toothache, poor response to over-the-counter decongestants or antihistamines, a history of colored nasal discharge, abnormal transillumination, and mucopurulent discharge on examination. A diagnosis of ABS may be made if symptoms persist for more than 10 days, worsen after 5 to 7 days, or are more severe than those normally associated with viral upper respiratory illness.[8,13]

Acute exacerbations of chronic bronchitis

There is no definitive agreement regarding what constitutes an AECB. Symptoms originally described by Anthonisen et al[16] are commonly used to define AECB: increased cough and sputum, increased sputum purulence, and increased dyspnea over baseline (**TABLE 1**).[17] A thorough physical and detailed medical history usually are sufficient to diagnose AECB while ruling out conditions such as pneumonia, congestive heart failure, myocardial ischemia, upper RTI, pulmonary embolism, and recurrent aspiration. A chest x-ray or an electrocardiogram may help with

TABLE 2

Treatment of acute exacerbations of chronic bronchitis[8]

Type	Symptoms*	Antimicrobial therapy
Type 1 — Severe exacerbation	3 of 3 symptoms	More benefit than when treated with placebo
Type 2 — Moderate exacerbation	2 of 3 symptoms	Less benefit than when treated with placebo
Type 3 — Mild exacerbation	1 of 3 symptoms	No benefit

* Increased dyspnea, increased sputum volume, and increased sputum purulence.

differential diagnosis in some patients.[17,18] Nevertheless, determination of whether an acute exacerbation is bacterial or viral may be difficult because many patients with this disease have persistent airway colonization with the same bacteria thought to be responsible for AECB. To help physicians decide if antibiotics are necessary, practice guidelines have stratified patients by type of exacerbation (mild, moderate, or severe) and risk factors (**TABLE 2**).

Community-acquired pneumonia

Patients with CAP usually present with acute onset of lower respiratory symptoms (**TABLE 1**). Older and immunosuppressed patients may present with non-respiratory symptoms, such as confusion, worsening of a chronic condition, or even falls. It is important to note that no combination of clinical signs and symptoms is a definitive diagnosis of CAP.[19] All patients with suspected CAP should have a chest radiograph with posteroanterior and lateral views, as radiographs are essential for confirming a diagnosis.[3] The Infectious Diseases Society of America (IDSA) and the American Thoracic Society support use of the Pneumonia PORT (Pneumonia Outcomes Research Team) Severity Index (PSI) as a means of risk stratification, combined with careful assessment of the patient and use of clinical judgment when determining whether a patient can be treated on an outpatient basis or should be hospitalized.[10]

Although it is important to attempt to identify the infecting organism, antimicrobial treatment for CAP is empiric because of the time it takes to get laboratory results and the potential for rapid deterioration of the patient's condition. Further, patients with CAP may not produce sputum for Gram stain and culture; or, if they do, it may be mixed with upper respiratory tract secretions. *Streptococcus pneumoniae* may not grow from sputum culture; or, if found, it may be unclear whether the patient is colonized or infected.[20] Bacteria cultures may not be helpful either, as blood cultures usually are sterile in patients with CAP.[20]

No single clinical sign or symptom distinguishes between bacterial and viral causes of acute sinusitis

Selection of antimicrobial therapy

Once a bacterial infection is suspected, antibiotic treatment should be initiated promptly. Antibiotic therapy for ABS, ABECB, and CAP is simplified somewhat because the distributions of bacterial pathogens associated with each infection overlap substantially. The pathogens encountered most often in patients with ABS are *S pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*. To a lesser extent, anaerobic bacteria, other streptococcal species (including *S pyogenes*, *S intermedius*, and a-hemolytic streptococci), and *Staphylococcus aureus* also have been shown to cause ABS.[21]

Bacteria are isolated from the sputum of 40% to 60% of patients with AECB, and the predominant species are consistent with those listed for ABS. Atypical respiratory pathogens, most notably *Chlamydophila* (previously *Chlamydia*) *pneumoniae*, account for about 5% to 10% of organisms isolated from patients with ABECB.[17] Patients with CAP also tend to be infected with the above-listed typical pathogens as well as the atypical *Mycoplasma pneumoniae*, *C pneumoniae*, and *Legionella pneumophila*. **TABLE 3** lists pathogens associated with community-

acquired bacterial RTIs and the effectiveness of commonly used antibiotics and telithromycin, a recently approved antimicrobial agent.

Resistance of bacterial pathogens

Although the common causative pathogens for community-acquired bacterial RTIs are few, selection of antibiotic therapy is becoming more complicated by the increasing rate of bacterial resistance to many of the antibiotics commonly used to treat these RTIs.

Resistance has been documented for all organisms associated with community-acquired RTIs.

Resistance may be overcome via an antibiotic with pharmacokinetic properties or a dosing regimen that achieves very high drug concentrations at sites of infection

Current estimates indicate that 25% to more than 50% of *S pneumoniae* strains are not completely susceptible to penicillin and that nearly one third of strains may be resistant to macrolides.[22] Penicillin-resistant *S pneumoniae* also may have reduced susceptibility to other antibiotics, including tetracycline, erythromycin, azithromycin, cephalosporins, clindamycin, trimethoprim/sulfamethoxazole (TMP/ SMX), and chloramphenicol.[23] *Streptococcus pneumoniae* have developed resistance to fluoroquinolones as well. This is of particular concern to the Centers for Disease Control and Prevention (CDC), having influenced its recommendations regarding empiric treatment of pneumonia.[10] Macrolides have been mainstays in empiric therapy of CAP because of their activity against both typical and atypical respiratory pathogens; however, their effectiveness has been compromised by a rapid rise in resistance by *S pneumoniae*. Recent evaluation of *S pneumoniae* isolates collected between 2000 and 2001 showed that resistance rates to erythromycin, clarithromycin, and azithromycin had increased to 31.0%, 30.7%, and 31.0%, respectively.[24] Further, results from 1 recent surveillance study that examined macrolide resistance among patients with community-acquired RTIs being treated by primary care physicians indicated that 23% to 33% of *S pneumoniae* isolates were resistant to macrolides.[24,25] Resistance also is becoming prevalent among other pathogens associated with community-acquired RTIs, including *H influenzae* and *M catarrhalis*.[25-27] This may complicate management of patients with community-acquired RTIs; infection with a treatment-resistant pathogen can increase risk for morbidity and mortality if treatment fails to eradicate the bacteria.[20,28] However, the clinical impact of resistance remains controversial. Resistance may be overcome with the use of an antibiotic with pharmacokinetic properties or a dosing regimen that achieves very high drug concentrations at sites of infection. Host defense mechanisms also may contribute to eradication of organisms with in vitro resistance to an antibiotic.[29,30] Further, since many infections are caused by viruses with high-resolution rates and since some bacterial infections resolve due to host response, the in vivo efficacy of an antibiotic may be much higher than its in vitro sensitivity.

Antibiotics currently prescribed for patients with community-acquired bacterial RTIs

Empiric antibiotic therapy for patients with community-acquired bacterial RTIs should provide coverage against clinically important pathogens likely to be associated with these infections, including resistant strains (**TABLE 3**). The antibiotic selected should specifically target respiratory pathogens. For example, broad-spectrum antibiotics are not the optimum choice, as they affect both respiratory and nonrespiratory pathogens (eg, gram-negative enterics; *Escherichia coli* and *Klebsiella pneumoniae*), which may result in resistance among these organisms.[1,31]

Antibiotics suitable for treatment of patients with ABS are summarized in **TABLE 4**. These agents vary widely in their spectra of activity as well as their ability to overcome pathogen resistance (**TABLE 3**). Amoxicillin, a very narrow-spectrum β-lactam, generally is considered to be first-line therapy for children and adults who have ABS[32] but may have little activity against resistant strains of *S pneumoniae*, *H influenzae*, and *M catarrhalis*.[2]

An analysis by the Agency for Healthcare Research and Quality concluded that amoxicillin or folate inhibitors (eg, TMP/SMX) are the most cost-

TABLE 3

Pathogens associated with ABS, CAP, and ABECB and in vitro effectiveness of commonly used antibiotics and telithromycin[40]

	Amoxicillin	Amoxicillin/ Clavulanate	Cefuroxime	Erythromycin	Clarithro-mycin	Azithro-mycin	Moxi-floxacin	Telithro-mycin
*Streptococcus pneumoniae**	+	+	+	+	+	+	+	+
Resistant	±†	–	–	–	–	–	+	+
Haemophilus influenzae								
β-lactamase–negative	+	+	+	±	±	±	+	+
β-lactamase–positive	–	+	+	±	±	±	+	+
Moraxella catarrhalis	+	+	+	+	+	+	+	+
Mycoplasma pneumoniae	–	–	–	+	+	+	+	+
Chlamydophila pneumoniae	–	–	–	+	+	+	+	+
Legionella sp	–	–	–	+	+	+	+	+

ABS = acute bacterial sinusitis
CAP = community-acquired pneumonia
ABECB = acute bacterial exacerbations of chronic bronchitis
+ = effective.
– = not active.
± = significant resistance, but active against most strains.
*Resistance is increasing; nationwide survey suggests 21% to 43% resistance to penicillin.
†Amoxicillin doses of 80 mg/kg/d may be effective against nonmeningeal, penicillin-resistant *S pneumoniae*.

effective choices for initial therapy in an otherwise healthy adult population with uncomplicated ABS.[33] For adults who fail to improve after 2 to 3 days, broad-spectrum and β-lactamase-resistant antibiotics for 7 to 14 days should be considered. A clinical practice guideline sponsored by the American Academy of Family Physicians, the American College of Physicians-Society of Internal Medicine, the CDC, and the IDSA recommends initiating treatment with narrow-spectrum agents, eg, amoxicillin, doxycycline, or TMP-SMX for patients with severe or persistent moderate symptoms of ABS.[34,35]

High-dose amoxicillin/clavulanate 2000/125 mg, twice daily, was shown to be effective in treating patients with ABS, ABECB, and CAP caused by *S pneumoniae*, including penicillin-resistant *S pneumoniae*.[29]

Amoxicillin or folate inhibitors (eg, trimethoprim-sulfamethoxazole) are the most cost-effective choices for initial therapy in an otherwise healthy adult with uncomplicated ABS

TABLE 4

Antibiotics currently being used for the treatment of community-acquired bacterial respiratory tract infections[41-44]

Generic	ABS*	CAP†	ABECB‡
β-Lactams			
Amoxicillin	500 mg every 8 hours	500 mg to 1 g every 8 hours	500 mg 3 times daily
Amoxicillin/clavulanate	500 mg every 8 hours	500 mg/125 mg every 8 hours or 875 mg/125 mg every 12 hours	875/125 mg bid
Cefuroxime	250 to 500 mg twice daily	500 mg twice daily	500 mg twice daily
Macrolides			
Clarithromycin	500 mg every 12 hours for 14 days	250–500 mg every 12 hours	500 or 750 mg every 12 hours for 7 to 14 days
Clarithromycin extended-release tablets	1000 mg once daily for 14 days	1000 mg once daily for 7 days	1000 mg once daily for 7 days
Azithromycin	500 mg once daily for 3 days	500 mg first day, then 250 mg/day for 2 to 5 days	500 mg once daily for 3 days or 500 mg first day, then 250 mg/day for 4 days
Erythromycin		250 to 500 mg twice daily	250 or 500 mg 3 or 4 times daily
Fluoroquinolone			
Moxifloxacin	400 mg once daily for 10 days	400 mg once daily for 7 to 14 days	400 mg once daily for 5 days
Ketolide			
Telithromycin	800 mg once daily for 5 days	800 mg once daily for 7 to 10 days	800 mg once daily for 5 days
Other Antibiotics			
Trimethoprim-Sulfamethoxazole			160 mg trimethoprim and 800 mg sulfamethoxale every 12 hours for 14 days

*Treatment is for 10 to 14 days unless otherwise indicated.
†Treatment ranges from 7 to 14 days unless otherwise noted.
‡Treatment is for 10 days unless otherwise noted.

The macrolides erythromycin, clarithromycin, and azithromycin are effective against susceptible strains of all organisms commonly associated with ABS, but many strains of *S pneumoniae* also are resistant to these drugs.[23,26] Respiratory fluoroquinolones are effective against all pathogens commonly associated with ABS, including resistant strains;[26] however, they also have significant activity against gram-negative enterobacteriaceae and thus may increase the potential for emergence of resistant strains of these organisms.[36] Ketolides are derived from the macrolide class and were designed to be effective against macrolide-resistant, gram-positive cocci.[10] The first ketolide, telithromycin, is an alternative to macrolides for the treatment of patients with ABS, ABECB, and CAP. It is highly active

against both common and atypical respiratory pathogens, including resistant strains, but has little activity against either enterobacteriaceae or anaerobes.[37]

All of the same considerations mentioned for the treatment of ABS also apply to the selection of therapy for patients with ABECB or CAP (**TABLE 4**). Empiric antimicrobial therapy for these 2 conditions, particularly CAP, also must cover atypical respiratory pathogens.[17,38] For a number of years, monotherapy with a macrolide provided coverage against all of the pathogens likely to be associated with CAP and ABECB. In light of the emergence of resistance to these drugs by *S pneumoniae*, physicians should consider local and regional resistance rates before prescribing. In fact, File and colleagues[39] have suggested that current recommendations favoring the use of macrolides in patients with CAP may have to be reconsidered if clinical failure continues to be observed with these agents. Cunha[38] has taken an even stronger position, stating that macrolide monotherapy should be avoided in patients with CAP because of the high prevalence of *S pneumoniae* resistance to this class of antibiotics. These authors' conclusions should be carefully weighed against the CDC's and IDSA's recommendations. The CDC previously recommended combination of macrolides and ceftriaxone for hospitalized patients to avoid emergence of fluoroquinolone resistance. The IDSA recommended empiric use of fluoroquinolones with conversion based on culture sensitivities when available.

Conclusions

Appropriate prescribing of antibiotics can effectively slow the development of bacterial resistance. Before selecting an antibiotic for a patient with a community-acquired RTI, primary care clinicians should first evaluate whether such treatment is even necessary. Treatment of ABS, ABECB, or CAP is compromised by increasing pathogen resistance to the currently used antibiotics. Use of high-dose amoxicillin and the other "older" antibiotics may delay the emergence of resistance to "newer" drugs, making newer drugs useful for treatment of more difficult cases. New agents to the antibiotic armamentarium give primary care physicians additional therapeutic options for patients who present with bacterial RTIs. ■

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