Rational Use of Antibiotics to Treat Respiratory Tract Infections

Thomas M. File, Jr, MD; and James A. Hadley, MD

Objectives: To foster the appropriate use of antimicrobial agents for respiratory tract infections and to review factors that should help achieve this objective.

Study Design: Review of evidence-based guidelines and recommendations for proper antibiotic drug use for respiratory tract infections.

Results and Conclusions: Antibiotic drug overuse and inappropriate antibiotic drug selection are associated with increased drug resistance among respiratory pathogens (most notably, *Streptococcus pneumoniae*), possible progression to chronic disease, and increased treatment costs. Awareness of clinical manifestations that help differentiate viral from bacterial infection and the use of guidelines can promote the appropriate management of respiratory tract infections. Community-acquired pneumonia, acute bacterial rhinosinusitis, and selected cases of acute exacerbations of chronic bronchitis (50%) warrant antimicrobial therapy, whereas otitis media with effusion, acute bronchitis, and most rhinosinusitis are viral and do not require antibiotic therapy.

(Am J Manag Care 2002;8:713-727)

Respiratory tract infections (RTIs) are the leading cause of acute morbidity and industrial and school absenteeism in the United States.[1] Data from the National Center for Health Statistics indicate that approximately three quarters of all antimicrobial drug use resulting from physician office visits is for RTIs.[2] Although many RTIs require antimicrobial drug therapy for optimal management (such as community-acquired pneumonia [CAP], acute bacterial rhinosinusitis [ABRS], and acute otitis media [AOM]), most "outpatient" RTIs (ie, acute bronchitis, nasal pharyngitis/common cold, and nonspecific upper RTIs) are caused by respiratory viruses for which antibiotic use is not warranted. Although RTIs are caused primarily by viral pathogens and therefore show little or no response to antibiotic treatment,[3-11] antibiotics are frequently prescribed.[4] For example, in 1992, of 57 million antibiotic prescriptions to adults in the United States, 12 million were written for colds, upper RTIs, and bronchitis. Patients receiving antibiotics included 51% of those diagnosed as having colds, 52% diagnosed as having upper RTIs, and 66% diagnosed as having bronchitis.[12] In 1994, 60% of outpatient and 48% of emergency department episodes of care for RTIs resulted in an antibiotic prescription being filled.[13]

Because as many as half of the adult patients with viral infections are inappropriately treated with antibiotics,[12] substantial overuse of antibiotics occurs, resulting in unnecessary additional cost. Furthermore, studies[14-16] suggest that inappropriate use of antibiotics contributes to the development of drug resistance, further increasing treatment costs. Scrutiny of these expenditures has been prompted by the fact that managed care organizations spend an average of 9% of their operating expenses on pharmaceuticals.[17] Promoting the appropriate use of antibiotics through the development and application of treatment guidelines and educational efforts aimed at clinicians as well as patients should help curb inappropriate prescribing and misuse of antibiotics, decrease treatment costs, and increase patient satisfaction.

This article considers issues that have contributed to the overuse of antibiotics and the development of antimicrobial resistance. It also emphasizes the need to foster the appropriate use of antimicrobial

From the Infectious Disease Service, Department of Medicine, Summa Health System, Akron, OH and the Northeastern Ohio Universities College of Medicine, Rootstown, OH (TMF) and the Division of Otolaryngology,University of Rochester, Rochester, NY (JAH).

Supported by an unrestricted educational grant from GlaxoSmithKline, Philadelphia, PA.

Address correspondence to: Thomas M. File, MD, 75 Arch Street, Suite 105, Akron, OH 44304. E-mail: filet@summa-health.org.

agents and reviews factors that should help achieve this objective.

FACTORS CONTRIBUTING TO ANTIBIOTIC DRUG OVERUSE

In addition to the prescription of antibiotics for viral infections, a variety of factors contribute to the inappropriate use of these agents, such as patient expectations, time constraints imposed on the clinician, and the practice of defensive medicine.[18-20] Many patients who consult clinicians expect an antibiotic to be prescribed; as a result, clinicians may feel pressured to write antibiotic drug prescriptions to satisfy patients and to maintain good physician-patient relationships. Receiving an antibiotic reinforces the patient's perception that antibiotics are warranted in similar situations. Thus, patients may continue to consult clinicians each time similar symptoms occur, expecting that antibiotics are again needed. Clinicians also may prescribe antibiotics as a rapid means of treating patients' symptoms rather than taking the time to educate patients that antibiotics are not always necessary, especially if a viral infection is suspected. Moreover, clinicians may prescribe antibiotics as part of a defensive approach to avoid the potential sequelae of not prescribing for patients with bacterial infection.

However, clinicians should recognize that patient satisfaction is not compromised by the absence of an antibiotic prescription[21] provided that patients understand the reasons. Hamm et al[21] demonstrated that patient satisfaction was affected by patient perceptions that the clinician spent enough time discussing the illness and by patient knowledge about the treatment choice. Decreasing excess antibiotic use is an important strategy for combating the increase in community-acquired antibiotic-resistant infections.[14]

DIFFERENTIATING VIRAL INFECTIONS FROM BACTERIAL INFECTIONS

According to Centers for Disease Control and Prevention estimates, as many as 50 million antibiotic prescriptions per year could be avoided if clinicians differentiated viral from true bacterial RTIs.[22] However, for the clinician faced with a patient exhibiting cough, nasal congestion, postnasal drip, nasal discharge, pressure or pain over the sinuses, and fever, differentiating viral from bacterial illness may present a challenge. Symptoms often overlap, and it is believed that bacterial infections may follow viral disease.[23] Although antibiotic treatment is effective for bacterial RTIs, such as OM, sinusitis, acute exacerbations of chronic bronchitis (AECBs), and CAP, antibiotics do not eradicate viruses and do not shorten the course of viral illness. In fact, when antibiotics are given for viral infections, the result may be subsequent infection with resistant bacteria, since previous antibiotic exposure may provide a selective advantage for resistant bacteria.[24] Furthermore, antibiotic use can affect others, fostering the carriage of resistant organisms among children in day care and to other family members.[25-27]

For OM, it is also important to differentiate between true AOM and OM with effusion because the latter does not warrant antibiotic use. Acute OM is diagnosed when fluid is present in the middle ear, accompanied by signs or symptoms of acute illness (eg, ear pain, otorrhea, or fever). Examination shows a reddened tympanic membrane or purulence behind a retracted tympanic membrane, and antimicrobial agents are prescribed to reduce infection and prevent complications. In contrast, OM with effusion, which also involves fluid in the middle ear (usually amber type or clear), is not accompanied by clinical signs or symptoms of infection (no fever or ear pain).[28]

Several factors may help clinicians distinguish between viral and bacterial rhinosinusitis. For example, viral illness is frequently self-limiting, lasting 2 to 7 days.[23] In contrast, bacterial infections typically worsen after a week or do not resolve after 7 to 10 days.[23,29] Although a thick, discolored nasal discharge is often seen in patients with RTIs, this sign is not a definitive indication that a bacterial infection is present. In these patients, it may be prudent to reserve antibiotic drug use unless the condition persists beyond 7 to 10 days. Acute bacterial rhinosinusitis is usually preceded by a viral upper RTI. Clinical judgment is used to distinguish between viral illness and ABRS. Some of the key clinical symptoms of viral and bacterial disease are listed in **Table 1**.[23,29,30]

Acute exacerbations of chronic bronchitis due to bacterial infection (which may account for up to 50% of AECBs[31] and warrants antibacterial therapy) are difficult to differentiate from nonbacterial exacerbations. However, it is important that the clinician try to distinguish AECBs from acute bronchitis, which does not require antimicrobial therapy. Acute exacerbations of chronic bronchitis are defined as illness in a patient with chronic bronchitis (defined

Table 1. Symptoms Associated With Viral and Bacterial Rhinosinusitis[23,29,30]

Viral Illness (Usually Lasting 2-7 d)	Acute Bacterial Rhinosinusitis (Persisting Beyond 5-7 d)
Sneezing	Purulent nasal drainage
Rhinorrhea	Fatigue
Nasal congestion	Nasal congestion
Hyposmia/anosmia	Hyposmia/anosmia
Sore throat	Maxillary facial pain
Postnasal drip	Postnasal drip
Fever	Fever
Cough	Cough
Ear fullness	Ear fullness/pressure
Facial pressure	Facial pain/pressure (especially unilateral and focused)
Myalgia	Note: worsening of symptoms after 7 d may indicate bacterial infection

Table 2. Characteristics of Acute Bronchitis and Community-Acquired Pneumonia (CAP)[36-38]

Acute Bronchitis	CAP
Transient duration (<15 d) in patients without chronic lung disease	Cough
	Sputum production
Cough with or without sputum	Dyspnea
Substernal discomfort	Fever
With or without fever	Altered breath sounds
>90% viral	Rales
No chest radiographic evidence of pneumonia	Chest radiographic evidence of pneumonia

as a productive cough for at least 3 months for 2 consecutive years)[32,33] characterized by an increase in at least 1 of 3 cardinal symptoms: dyspnea, sputum volume, or sputum purulence. Acute bronchitis is generally used to describe a transient (usually <15 days) respiratory illness that occurs in patients without chronic lung inflammatory conditions and is characterized by cough (with or without sputum, fever, or substernal discomfort) and in the absence of radiographic findings of pneumonia.[34,35]

The challenge facing the clinician in establishing a diagnosis of CAP is to distinguish it from less serious RTIs such as acute bronchitis (**Table 2**).[36-38] Antibiotic therapy usually is not indicated for acute bronchitis but is warranted for patients with CAP.[37,38] A definitive diagnosis of CAP cannot be based on clinical symptoms alone; a chest radiograph is necessary to determine the presence of pneumonia.[38]

APPROPRIATE USE OF ANTIMICROBIAL AGENTS IN RTIS

Research has demonstrated that antibiotics, when used appropriately, are effective in eradicating pathogens that cause bacterial RTIs, leading to more rapid resolution of infection and improvement of symptoms.[23,39-41] For example, in patients with acute community-acquired bacterial sinusitis, Gwaltney and coinvestigators[42] showed that antibiotic drug use improved symptoms and decreased or eradicated bacteria from the maxillary sinus. Recovery also is more rapid in children with acute sinusitis who are treated with antimicrobial agents compared with those treated with placebo.[39] Antibiotics also can help avoid complications, such as in patients with bacterial AOM. Treatment of bacterial AOM with an antibiotic that provides coverage for the most common pathogens can help avoid the potential consequences of untreated or incorrectly treated disease, including hearing impairment and delayed speech development.[40,41] Antibiotic drug use also can help prevent progression of disease from acute to chronic manifestations. In addition, when sound principles are applied to select an appropriate empiric agent, the costs associated with incorrect prescribing and multiple courses of antibiotics can be avoided. Clinical practice guidelines can help outline appropriate empiric therapy.[43]

Inappropriate use of antibiotics has contributed to the development of drug resistance among the most common bacterial pathogens in RTIs—*Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*. For example, penicillin resistance (including intermediate and high levels) has risen among *S pneumoniae* over time, from when it was first identified in the 1960s to approximately 5% by 1979 to 23.6% in 1995.[44,45] The clinical relevance of penicillin-resistant *S pneumoniae* seems to vary depending on the level of

resistance and the site of infection. For CAP, intermediate resistance (minimum inhibitory concentration [MIC], 0.1-1.0 µg/mL) has not been shown to be associated with a detrimental outcome; however, this same level of resistance can be significant for otitis.[36] In 1997, resistance rates among *S pneumoniae* were reported to be 33.5% and 52.0%.[45,46] *Streptococcus pneumoniae* resistance to macrolide agents has also increased over time and, unlike resistance to the β-lactams, may not be overcome by raising the dose. Similarly, resistance among *H influenzae* and *M catarrhalis* has increased. Ampicillin resistance of *H influenzae* reached 50% in some areas by 1997[46] and is seen in >90% of *M catarrhalis* isolates.[45]

Antimicrobial therapy is intended to provide a concentration of the agent that exceeds the concentration needed to inhibit the infecting organism. Traditionally, the MIC, which defines the minimum amount of an antimicrobial agent necessary to inhibit the growth of a microbe, has been used to describe the in vitro activity of an agent against a specific organism. Microorganisms are identified as susceptible, intermediate, or resistant on the basis of specific MIC values, referred to as breakpoints. These breakpoints are generally determined by reference to levels of the drug achieved in human serum rather than the concentration of the drug attained at the infection site. These breakpoint values may not correlate with recent clinical data.[47,48] Data reported

Table 3. Agents Active Against Isolates at Pharmacokinetic/Pharmacodynamic (PK/PD) Breakpoints*

Antimicrobial Agent	PK/PD Breakpoints, µg/mL	Strains Susceptible at PK/PD Breakpoints, %		
		Streptococcus pneumoniae (n = 1760)	*Haemophilus* influenzae (n = 1919)	*Moraxella catarrhalis* (n = 204)
Amoxicillin	2	90	61	14
Amoxicillin (high dose)†	4	94	61	14
Amoxicillin-clavulanate	2	90	97	100
Azithromycin	0.12	67	0	100
Cefaclor	0.5	27	2	5
Cefixime	1	57	99.9	100
Cefpodoxime	0.5	63	99.9	64
Cefprozil	1	64	18	6
Cefuroxime	1	65	80	37
Clarithromycin	0.25	68	0	100
Clindamycin	0.25‡	89‡	NA	NA
Doxycycline	0.25	76	20	97
Erythromycin	0.25	68	0	100
Gatifloxacin	1	>99§	100	100
Levofloxacin	2	>99	100	100
Loracarbef	0.5	9	10	5
Moxifloxacin	2	>99§	100	100
TMP/SMX	0.5‡‖	57‡‖	76‡‖	10‡‖

NA = not available; TMP/SMX = trimethoprim/sulfamethoxazole.
*Data from the Sinus and Allergy Health Partnership[29] and Jacobs et al.[50]
†High-dose amoxicillin (80-90 mg/kg per day) currently is not approved by the Food and Drug Administration.
‡National Committee for Clinical Laboratory Standards breakpoint; PK/PD not available.
§Gatifloxacin and moxifloxacin values not included in references but should be at least as effective as levofloxacin.
‖Shown as TMP component.

in a number of studies, including those evaluating the bacteriologic efficacy of azithromycin and cefaclor in eradicating *H influenzae* from middle ear fluid,[47,48] demonstrate that many current breakpoints are inaccurate and need to be revised.

In contrast, pharmacodynamic breakpoints are based on the pharmacokinetic evaluation of antibiotic concentrations (usually using serum concentrations because they are readily measured), with consideration for how different antimicrobial agents exert their antibacterial action (ie, time- or concentration-dependent killing), and are correlated with clinical data on bacteriologic cure. Antibiotics that exhibit time-dependent pharmacodynamic effects are clinically successful (as measured by repeated tympanocentesis in therapy of AOM) in more than 80% of cases when the serum concentration exceeds the MIC for 40% to 50% of the dosing interval.[49] For the β-lactams and the macrolides clarithromycin and erythromycin, efficacy depends on the amount of time the serum drug concentration exceeds the MIC of the agent. In contrast, the efficacy of the fluoroquinolones is concentration dependent, with the pharmacodynamic breakpoint dependent on the ratio of the area under the concentration time curve to the MIC of the agent against the pathogen. Azithromycin is neither completely time dependent nor completely concentration dependent. This agent has a long postantibiotic effect that leads to the free-drug area under the concentration time curve/MIC as the pharmacodynamic indicator. The pharmacokinetic/pharmacodynamic breakpoints for agents that exhibit predominantly time-dependent activity against common respiratory pathogens (ie, *S pneumoniae*, *H influenzae*, and *M catarrhalis*) and the susceptibilities of these pathogens at these breakpoints are listed in **Table 3**.[29,50] The data demonstrate that 90% of the 1760 isolates of *S pneumoniae* tested were susceptible to amoxicillin and amoxicillin-clavulanate and 99% were susceptible to the new fluoroquinolones. *H influenzae* strains were highly susceptible to amoxicillin-clavulanate, cefixime, cefpodoxime, and the new fluoroquinolones.[50] All of the 204 *M catarrhalis* isolates remained susceptible to amoxicillin-clavulanate, cefixime, clarithromycin, and azithromycin. The pharmacokinetic/pharmacodynamic breakpoints referred to primarily rely on the drug concentration achieved in serum, which correlates well for infections such as otitis. For pneumonia, the pharmacokinetics of agents in the endothelial lining fluid may be a better marker of clinical effect. To date, however, clinical trial data have not supported or disproved this hypothesis.

THE VALUE OF GUIDELINES

The use of clinical practice guidelines can be an effective means of changing behavior,[51] such as promoting the appropriate use of antibiotics. Effective clinical guidelines should improve patient care while enhancing cost savings. However, cost savings should not be the primary motivating factor. A recent example reported by Beilby et al[52] described a government intervention in Australia intended to decrease costs by reducing the use of amoxicillin-clavulanate. As a result, costs increased through the occurrence of adverse outcomes in patients with OM, sinusitis, lower RTI, and AECBs.

To maximize effectiveness and applicability, antibiotic drug use guidelines should be evidence based.[53] The guidelines should also reflect data on resistance, recognizing that local patterns of resistance often differ across geographic regions. Hence, effective guidelines should be readily adaptable for implementation locally. Primary objectives of guidelines for treating RTIs should be to discourage antibiotic use to treat viral illness, to outline diagnostic criteria, and to avoid use of ineffective antimicrobial agents.

A meta-analysis of relevant studies has shown that there are numerous barriers to adherence to practice guidelines (**Table 4**).[54] For example, clinicians may not be aware of all of the available guidelines or may not be well versed in how to apply specific recommendations appropriately. In addition, clinicians may not agree with some or all of the recommendations made or, as a general principle, may resist the concept of guidelines. If clinicians are doubtful that they can perform the task called for in the guidelines or harbor a belief that the recommendations will be unsuccessful, they probably will not follow the guidelines. Time constraints or healthcare organization requirements may impose restrictions that hamper the clinician's ability to implement the guidelines. Furthermore, the clinician may not have control over some changes called for in guidelines, such as the acquisition of new resources to perform diagnostic tests. Patient preferences for alternatives not recommended in guidelines also may obstruct adherence to clinical practice guidelines. To be successful, educational efforts and interventions aimed at improving adherence to practice guidelines—such as use of

Table 4. Barriers to Clinician Adherence to Clinical Practice Guidelines*

Barrier	Explanation
Lack of awareness	Clinician unaware that the guidelines exist
Lack of familiarity	Clinician aware of guidelines but unfamiliar with specifics
Lack of agreement	Clinician does not agree with a specific recommendation made in guidelines or is averse to the concept of guidelines in general
Lack of self-efficacy	Clinician doubts whether he or she can perform the behavior
Lack of outcome expectancy	Clinician believes that the recommendations will be unsuccessful
Lack of motivation	Clinician is unable/unmotivated to change previous practices
Guideline-related barriers	Guidelines are not easy or convenient to use
Patient-related barriers	Clinician may be unable to reconcile guidelines with patient preferences
Environmental-related barriers	Clinician may not have control over some changes (eg, time, resources, organizational constraints)

*Adapted from Cabana et al.[54]

checklists and reminder systems—should address all of the identified barriers.

USE OF TREATMENT RECOMMENDATIONS/GUIDELINES IN RTIS

Acute Otitis Media

Treatment for bacterial AOM must take into account the pathogens most commonly implicated in this condition (ie, *S pneumoniae*, *H influenzae*, and *M catarrhalis*) (**Table 5**)[55-58] as well as their resistance patterns. Treatment recommendations for AOM have been developed in the context of increasing levels of drug-resistant bacteria and selecting the appropriate antibiotic agents.[59] After reviewing the data, the Drug-Resistant *Streptococcus pneumoniae* Therapeutic Working Group of the Centers for Disease Control and Prevention recommended that amoxicillin (standard dose, 40-45 mg/kg per day, or high dose, 80-90 mg/kg per day) should be used as first-line therapy in AOM (**Figure**).[59] If factors associated with the likelihood of resistance are present, the recommendations suggest using high-dose amoxicillin, high-dose amoxicillin-clavulanate, or cefuroxime aextil as first-line therapy.[59] These factors include day care attendance, age, and recent exposure to antibiotics (eg, within 4-6 weeks).[29,60-63] Amoxicillin-clavulanate, cefuroxime axetil, and intramuscular ceftriaxone are recommended for treatment if amoxicillin fails after 3 days of therapy (Figure). Although a single injection of intramuscular ceftriaxone achieves high concentrations in middle ear fluid for several days,[64] the clinical outcome is not improved compared with a 10-day course of amoxicillin-clavulanate.[65] Furthermore, a series of daily injections given for 3 days may be needed to improve the effectiveness of ceftriaxone against penicillin-resistant *S pneumoniae*.[59] Other agents, such as cefprozil, cefpodoxime, cefaclor, cefixime, ceftibuten, loracarbef, trimethoprim/sulfamethoxazole, and the macrolides, are not included in the list of preferred antimicrobial agents for a variety of reasons, including inadequate pharmacokinetic properties and decreased activity against β-lactamase enzymes and drug-resistant *S pneumoniae*.[59]

Patients who are allergic to penicillin may be treated with a newer macrolide or trimethoprim/sulfamethoxazole. However, these agents have limited utility against drug-resistant *S pneumoniae*. Fluoroquinolones, although effective against common respiratory pathogens, are not approved for use in children.

Cost and convenience issues also should be addressed when selecting an appropriate antimicrobial agent. Dosing frequency and adverse effects play a significant role in promoting or deterring patient adherence to therapy. Selecting agents that have more favorable adverse effect profiles and less-frequent dosing requirements can aid in achieving adherence. **Table 6** compares the coverage, dosing requirements, and adverse effect profiles of agents frequently used to treat RTIs.[29,50,66]

Acute Bacterial Rhinosinusitis

Similar to the Centers for Disease Control and

Prevention's recommendations for AOM, the guidelines issued by the Sinus and Allergy Health Partnership recommend empiric choices for treating ABRS.[29] Table 5 lists the most common bacterial pathogens observed in patients with ABRS.[55-58] As in AOM, *S pneumoniae* and *H influenzae* are frequently implicated in ABRS; however, *M catarrhalis* is less likely to be the infectious cause of this condition compared with its role in AOM (2% vs 12%).[55,56] The guidelines recognize that patients exposed to an antibiotic within 4 to 6 weeks of their current infection are likely to be infected with a resistant pathogen. The predicted bacterial efficacy rates of antibiotics used in children and adults as determined by mathematical modeling of in vitro efficacy data are listed in **Table 7**.[29] In developing its antimicrobial guidelines, the Panel of experts of the Sinus and Allergy Health Partnership Task Force used the Poole Therapeutic Outcome Model to predict the therapeutic effectiveness of various antimicrobial agents. Recognizing that resistance rates may change over time and may vary from community to community, the Panel intends to revise the guidelines as resistance rates change and as new antibiotics are introduced. The model is available at the Sinus and Allergy web site (http://www.allergysinus.org), where clinicians can input local resistance rates and develop their own optimal treatment recommendations.

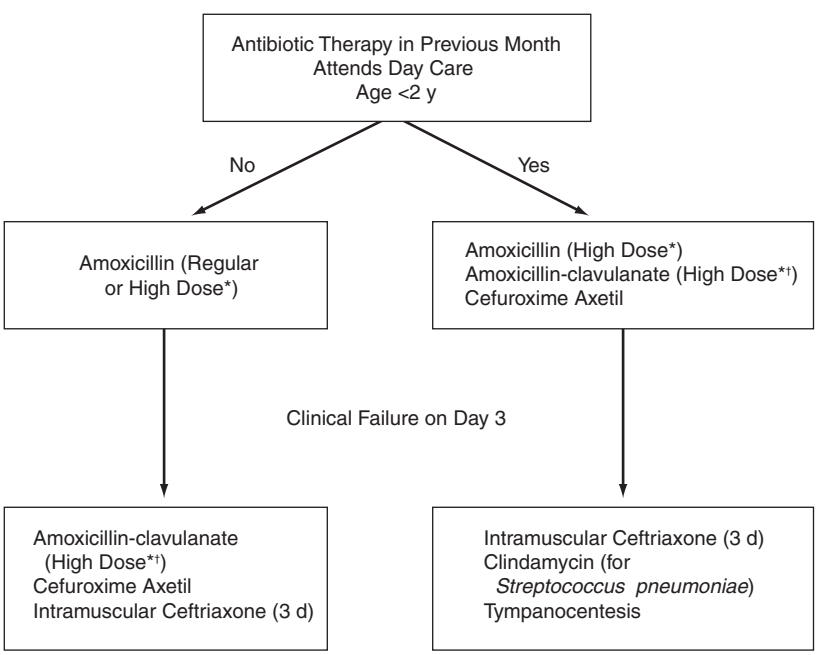
In adults, only amoxicillin-clavulanate and the new fluoroquinolones (ie, gatifloxacin, levofloxacin, and moxifloxacin) have expected efficacy rates exceeding 90%.[29] In children, amoxicillin-clavulanate and high-dose amoxicillin are the only agents expected to exceed a 90% efficacy rate. Although the Food and Drug Administration has not approved the use of high-dose amoxicillin, the general consensus is that this therapy seems to be safe, given its duration of use. Selection of the appropriate antibiotic agent can

Table 5. Most Common Bacterial Pathogens in AOM, ABRS, AECBs, and CAP*[14,55-58]

Pathogen	AOM (%)	ABRS (%)	AECBs (%)	CAP (%)†
Streptococcus pneumoniae	29	36	15-30	20-60
Haemophilus influenzae	26	26	40-60	3-10
Moraxella catarrhalis	12	2	15-30	1-2

AOM = acute otitis media; ABRS = acute bacterial rhinosinusitis; AECBs = acute exacerbations of chronic bronchitis; CAP = community-acquired pneumonia.
*Adapted from Jacobs[78].
†Atypical agents account for 20% to 30% of CAP cases.

Figure. Algorithm Outlining the Centers for Disease Control and Prevention Recommendations for Treating Acute Otitis Media[59]



*High-dose amoxicillin (80-90 mg/kg per day) is not yet approved by the Food and Drug Administration.
†Consists of 80 to 90 mg/kg per day of amoxicillin and 6.4 mg/kg per day of clavulanate.

Table 6. Coverage, Dosing, and Adverse Effects of Antibiotics Used to Treat Respiratory Tract Infections*[14,50,66]

Antibiotic	Dosage Regimen	Adverse Reactions	Advantages	Disadvantages
Amoxicillin (Amoxil)	Adults: 875 mg BID; 500-1000 mg TID Children: 45-90 mg/kg BID	Diarrhea, nausea, vomiting, penicillin-allergic reactions	Excellent activity against *Streptococcus pneumoniae*; pleasant-tasting suspension; generic availability; BID dosing	Increasing resistance of β-lactamase–producing organisms; not appropriate for penicillin-allergic patients
Amoxicillin-clavulanate (Augmentin)	Adults: 500-875 mg BID Children: 45 mg/kg BID	Diarrhea, nausea, rash, vomiting, penicillin-allergic reactions	Excellent activity against *S pneumoniae*, *Haemophilus influenzae* (including β-lactamase–producing strains), and *Moraxella catarrhalis*; BID dosing; pleasant-tasting suspension	Not appropriate for penicillin-allergic patients
Azithromycin (Zithromax)	Adults: 500 mg as a single dose, day 1; 250 mg as a single dose, days 2-5 Children: 10 mg/kg as a single dose, day 1; 5 mg/kg as a single dose, days 2-5	GI tract distress, abdominal pain, nausea, dizziness, headache	Activity against *M catarrhalis*; atypical coverage; QD dosing; 5-d duration; pleasant-tasting suspension	Increasing resistance of *S pneumoniae*; questionable activity against *H influenzae* based on pharmacokinetic/pharmacodynamic breakpoints for otitis media and sinusitis (see Table 3); demonstrates cross-resistance with erythromycin-resistant gram-positive strains
Cefaclor (Ceclor)	Adults: 250-500 mg TID Children: 20-40 mg/kg TID	Hypersensitivity reactions, diarrhea, serum-sicknesslike symptoms, vomiting	Generic availability; pleasant-tasting suspension	Demonstrates poor activity against *S pneumoniae*, *H influenzae*, and *M catarrhalis*; TID administration
Cefixime (Suprax)	Adults: 400 mg QD or 200 mg BID Children: 8 mg/kg QD or 4 mg/kg BID	Hypersensitivity reactions, GI tract distress, diarrhea, abdominal pain, nausea, rash	Excellent activity against *H influenzae* and *M catarrhalis*; QD dosing	Demonstrates moderate activity against *S pneumoniae*; high incidence of diarrhea; bitter taste
Cefdinir (Omnicef)	Adults: 300 mg BID (CAP) or 600 mg QD Children: 7 mg/kg BID or 14 mg/kg QD	Hypersensitivity reactions, GI tract distress, diarrhea, nausea	BID/QD dosing	
Cefprozil (Cefzil)	Adults: 500 mg QD, 250 mg BID Children: 7.5 mg/kg BID	GI tract distress, nausea, diarrhea, hypersensitivity	BID/QD dosing	Demonstrates moderate activity against *S pneumoniae* and poor activity against *H influenzae* and *M catarrhalis*; GI tract distress

BID = twice a day; TID = 3 times a day; GI = gastrointestinal; QD = once a day; TMP/SMX = trimethoprim/sulfamethoxazole.
Susceptibility: excellent = >90%; good = 90%-70%; moderate = 70%-50%; poor = <50%.
*Data are based on the faculty's clinical experience and may include unlabeled or unapproved uses of the drugs mentioned.

Table 6. Coverage, Dosing, and Adverse Effects of Antibiotics Used to Treat Respiratory Tract Infections*[14,50,66] *(continued)*

Antibiotic	Dosage Regimen	Adverse Reactions	Advantages	Disadvantages
Cefpodoxime (Vantin)	Adults: 100-200 mg BID Children: 5 mg/kg BID	Diarrhea, nausea, GI tract distress, vaginal infection, abdominal pain, headache	Excellent activity against *H influenzae*; BID dosing	Demonstrates moderate activity against *S pneumoniae* and *M catarrhalis*; bitter-tasting suspension; diarrhea; rash
Cefuroxime axetil (Ceftin)	Adults: 250-500 mg BID Children: 125-250 mg BID	GI tract symptoms, rash, diarrhea, nausea, vomiting, allergic reactions	Good activity against *H influenzae*; BID dosing; availability of parenteral form	Demonstrates moderate activity against *S pneumoniae* and poor activity against *M catarrhalis*; bitter taste
Clarithromycin (Biaxin)	Adults: 500 mg BID Children: 7.5 mg/kg BID; Biaxin XL, 1000 mg QD	GI tract symptoms, diarrhea, nausea, abnormal taste, headache, rash, abdominal pain	Activity against *M catarrhalis*; atypical coverage; BID dosing; QD dosing with XL	Increasing resistance of *S pneumoniae*; poor activity against *H influenzae* (see Table 3); demonstrates cross-resistance with erythromycin-resistant gram-positive strains
Doxycycline (Vibramycin, Doryx)	Adults: 100 mg every 12 h	GI tract symptoms, nausea, vomiting, diarrhea, hypersensitivity, photosensitivity	Atypical coverage, generic availability	*S pneumoniae* demonstrating increased resistance, phototoxicity
Gatifloxacin (Tequin)	Adults: 400 mg QD Children: not indicated	Nausea, diarrhea, headache, dizziness, abdominal pain, vomiting	Excellent activity against *S pneumoniae*, *H influenzae*, and *M catarrhalis*; atypical coverage; QD dosing; availability of parenteral form	Not approved for use in children; drug interactions with multivitamins; tendonitis
Levofloxacin (Levaquin)	Adults: 500 mg QD Children: not indicated	Diarrhea, nausea, headache, insomnia, dizziness, vaginitis	Excellent activity against *S pneumoniae* and excellent activity against *H influenzae* and *M catarrhalis*; QD dosing; availability of parenteral form	Not approved for use in children; drug interactions with multivitamins; tendonitis
Loracarbef (Lorabid)	Adults: 400 mg BID Children: 30 mg/kg BID	GI tract distress, headache, rash, diarrhea, nausea	BID dosing; pleasant-tasting suspension	Demonstrates poor activity against *S pneumoniae*, *H influenzae*, and *M catarrhalis*
Moxifloxacin (Avelox)	Adults: 400 mg QD Children: not indicated	Nausea, diarrhea, headache, dizziness, abdominal pain, vomiting	Excellent activity against *S pneumoniae*, *H influenzae*, and *M catarrhalis*; QD dosing	Not approved for use in children; drug interactions with multivitamins; tendonitis
TMP/SMX (Bactrim, Septra)	Adults: 160-800 mg BID Children: 8-40 mg/kg, divided, BID	GI tract distress, hypersensitivity reactions, rash, Stevens-Johnson syndrome, nausea, vomiting, anorexia	BID dosing; generic availability	Limited activity against *S pneumoniae* and *H influenzae*; little activity against *M catarrhalis*; increasing resistance will likely continue to diminish its utility; allergic reactions; phototoxicity

BID = twice a day; TID = 3 times a day; GI = gastrointestinal; QD = once a day; TMP/SMX = trimethoprim/sulfamethoxazole.
Susceptibility: excellent = >90%; good = 90%-70%; moderate = 70%-50%; poor = <50%.
*Data are based on the faculty's clinical experience and may include unlabeled or unapproved uses of the drugs mentioned.

Table 7. Expected Clinical Efficacy Rates of Antibiotics in Acute Bacterial Rhinosinusitis in Adults and Children[29]

	Antibiotics	
Efficacy Rate, %	**Adults**	**Children**
>90	Amoxicillin-clavulanate, gatifloxacin, levofloxacin, moxifloxacin	Amoxicillin-clavulanate, amoxicillin (high dose)*
80-90	Amoxicillin (high dose),* cefpodoxime proxetil, cefixime (based on *Haemophilus influenzae* and *Moraxella catarrhalis* coverage), cefuroxime axetil, TMP/SMX	Cefpodoxime proxetil, cefixime (based on *H influenzae* and *M catarrhalis* coverage), cefuroxime axetil, clindamycin (based on gram-positive coverage), azithromycin, clarithromycin, erythromycin, TMP/SMX
70-80	Clindamycin (based on gram-positive coverage), cefprozil, doxycycline, azithromycin, clarithromycin, erythromycin	Cefprozil
60-70		Cefaclor, loracarbef
50-60	Cefaclor, loracarbef	

TMP/SMX = trimethoprim/sulfamethoxazole.
*High-dose amoxicillin (80-90 mg/kg per day) is not yet approved by the Food and Drug Administration.

help prevent the development of chronic sinusitis, decrease costs associated with multiple treatment failures, and curtail the development of resistance.

The preferred agents recommended for the treatment of ABRS are those that are active against the pathogens commonly implicated in acute sinusitis—*S pneumoniae*, *H influenzae*, and *M catarrhalis*.[29] Switching to a second agent is suggested if, after 72 hours, the patient's condition does not clinically improve or worsens.

First-line therapy recommended for adults with mild disease and no antibiotic therapy during the previous 4 to 6 weeks is high-dose amoxicillin, amoxicillin-clavulanate, cefpodoxime proxetil, and cefuroxime axetil.[29] The guidelines note that cefprozil may have a bacterial failure rate of up to 25%. Similarly, although clarithromycin, trimethoprim/sulfamethoxazole, doxycycline, azithromycin, or erythromycin may be considered for patients with β-lactam allergies, they are generally less active for drug-resistant *S pneumoniae*. Use of trimethoprim/sulfamethoxazole also has been associated with potentially fatal toxic epidermal necrolysis. For adults with mild disease who have had recent antibiotic therapy or for those with moderate disease with no recent antibiotic therapy, first-line treatment recommendations include amoxicillin-clavulanate, high-dose amoxicillin, cefpodoxime proxetil, and cefuroxime axetil. Appropriate agents for β-lactam–allergic or β-lactam–intolerant patients include gatifloxacin, levofloxacin, and moxifloxacin. In adults with moderate disease and recent antibiotic use, the indicated agents are amoxicillin-clavulanate, gatifloxacin, levofloxacin, moxifloxacin, or combination therapy (amoxicillin or clindamycin for gram-positive coverage plus cefixime or cefpodoxime proxetil for gram-negative coverage).[29]

In children with mild disease and no antibiotic use in the previous 4 to 6 weeks, first-line therapy includes amoxicillin-clavulanate, high-dose amoxicillin, cefpodoxime proxetil, or cefuroxime axetil.[29] In patients with a history of immediate type I hypersensitivity to β-lactams, use of trimethoprim/sulfamethoxazole, azithromycin, clarithromycin, or erythromycin is recommended, although bacterial failure rates of 20% to 25% are possible with these agents. For children with moderate disease who have had no recent antibiotic therapy or for those with mild disease who have had recent antibiotic therapy, indicated treatment agents are high-dose amoxicillin, amoxicillin-clavulanate, cefpodoxime proxetil, and cefuroxime axetil. In children with moderate disease who have received recent antibiotic therapy, the recommended treatment is amoxicillin-clavulanate or combination therapy—amoxicillin or clindamycin for

gram-positive coverage plus cefixime or cefpodoxime proxetil for gram-negative coverage.[29]

Acute Exacerbations of Chronic Bronchitis

Timely and accurate diagnosis and treatment of AECBs remain challenging to clinicians because of the indefinite beginnings and uncertain treatment modalities of the condition. Because patients with AECBs have chronic bronchitis as an underlying disease and because the definition of AECBs is subjective, it is sometimes difficult to determine when an exacerbation has begun or ended.

The most common bacterial pathogens associated with AECBs are listed in Table 5.[55-58] Because as many as 50% of AECB episodes may be nonbacterial in origin[31] and because there is no reliable method of distinguishing bacterial episodes from nonbacterial episodes based on clinical criteria,[67] the appropriateness of antimicrobial therapy is controversial, particularly in light of current trends in resistance. However, since recurrent episodes of AECB can impair pulmonary function and can severely impact quality of life, many clinicians choose to treat the condition with antibiotics to address those cases that are bacterial in origin. To help decide whether antimicrobial therapy is warranted, clinicians may also stratify patients by the type of exacerbation and by the presence of risk factors associated with poor outcome. Several randomized, placebo-controlled trials have shown that antibiotic treatment is beneficial in selected patients with AECBs.[68] Specifically, studies show that patients with more severe exacerbations (type I) are more likely to experience benefit than those with less severe disease. Patients with type I exacerbations have all 3 cardinal symptoms—increased dyspnea, increased sputum volume, and increased sputum purulence—whereas patients with type II exacerbations have 2 symptoms and those with type III exacerbations have only 1.[69] In comparison, patients with moderate exacerbations (type II) experienced less benefit from antibiotic therapy compared with those who received placebo, and patients with mild episodes (type III) did not seem to benefit from antibiotic treatment compared with the placebo group. In the study by Anthonisen et al,[69] patients with AECBs who received antibiotic therapy had more rapid return of peak flow, were more likely to achieve clinical success, and experienced clinical failure less frequently than did patients given placebo. Other studies also have shown the benefit of antibiotic therapy in AECBs.[70] A clinical practice guideline for the management of AECBs formulated by the American College of Physicians–American Society of Internal Medicine and the American College of Chest Physicians was recently published; this position paper recommends use of antibiotics in patients with severe exacerbations (such as type I) of chronic obstructive pulmonary disease.[71]

In addition to stratification by type, patients at high risk for a poor AECB outcome have been identified, including individuals with a history of repeated infections (>4 per year), comorbid illnesses (such as diabetes mellitus, asthma, or coronary heart disease), or marked airway obstruction (<50% forced expiratory volume in 1 second).[72]

In patients with AECBs of bacterial origin, antibiotic therapy may have a long-term benefit of decreasing the amount of bacteria chronically colonizing the airway once the patient is clinically stable, thus helping to prevent progression to parenchymal lung infection.[57] Antibiotic drug treatment may also prevent progressive airway injury due to persistent infection and may prolong the duration between exacerbations.[57]

Agents with activity against the most commonly encountered pathogens in AECBs—*S pneumoniae*, *H influenzae*, and *M catarrhalis*—should be selected for treatment. An appropriate agent also should be resistant to β-lactamase destruction, should have good penetration into bronchial tissue and sputum, should promote patient adherence through convenient dosing, and should have a favorable adverse effect profile.[67] The specific choice of antibiotic for AECBs remains controversial. Most previously published trials have demonstrated a benefit of narrow-spectrum antibiotics (ie, amoxicillin, trimethoprim/sulfamethoxazole, and tetracycline) as initial treatment.[68] However, most of these studies were done before the emergence of multidrug-resistant pathogens. Many experts recommend stratifying antibiotics on the basis of severity of disease and on the presence of risk factors of outcome. **Table 8** lists agents recommended for AECB treatment according to one classification scheme.[72] Note that AECBs do not generally occur in children; also, we describe the drawbacks of several of the antibiotics in Table 6.

Community-Acquired Pneumonia

A complete consideration of pneumonia treatment is beyond the scope of this article. However, principles of rational therapeutic decision making also apply to the selection of appropriate antibiotic agents for CAP. After distinguishing between acute bronchitis and CAP (see Table 2)[36-38] and after establishing a diagnosis of CAP, the clinician must choose

Table 8. Proposed Classification of and Therapy for Acute Bronchitis and Acute Exacerbations of Chronic Bronchitis*

Clinical Status	Criteria/Risk Factors	Pathogens	Antimicrobial Treatment
Acute bronchitis	No underlying chronic inflammatory lung disease	Viral	None
Simple chronic bronchitis	FEV_1 >50%, increased sputum volume and purulence	*Haemophilus influenzae*, *Moraxella catarrhalis*, and *Streptococcus pneumoniae*	Amoxicillin, doxycycline, newer macrolides (azithromycin or clarithromycin), cephalosporin
Complicated chronic bronchitis	As for class 2 + any of the following: FEV_1 <50%, advanced age, >4 exacerbations/year, significant comorbidity	*H influenzae*, *M catarrhalis*, and *S pneumoniae*; concern for resistant strains	Quinolone, amoxicillin/clavulanate
Chronic bronchial infection	Class 3, continuous sputum through year	*H influenzae*, *M catarrhalis*, and *S pneumoniae*; *Enterobacteriaceae*; *Pseudomonas aeruginosa*	Ciprofloxacin

FEV_1 = forced expiratory volume in 1 second.
*Modified from Adams and Anzueto[72] and Grossman.[79]

antibiotics with activity against the pathogens most commonly encountered in this condition. Similar to other RTIs, *S pneumoniae* is the most common pathogen associated with CAP, accounting for 20% to 60% of cases in North America (Table 5[14,55-58]) and approximately two thirds of bacteremic pneumonia cases.[37] Rising resistance among *S pneumoniae* is of particular concern in the treatment of CAP and is an important consideration in the rational use of antibiotics for the treatment of this condition.

Guidelines for the treatment of CAP recently issued by the Infectious Diseases Society of America note that selection of appropriate agents is easier if the infecting pathogens have been identified. In most cases, though, pathogens are not isolated; therefore, treatment usually is based on empiric decision making.[37] Antimicrobial agents generally considered effective for the most common (key) pathogens (ie, *S pneumoniae*, *H influenzae*, and the atypical organisms) include the macrolides, newer fluoroquinolones, and doxycycline.[37] Note that penicillin-resistant pneumococci may be resistant to macrolides or doxycycline. The choice among these agents should be determined in part by regional antibiotic susceptibility patterns for *S pneumoniae* and the presence of potential risk factors for drug-resistant *S pneumoniae* (use of antimicrobial agents within the past 3 months, hospitalization within 1 month, and presence within the household of a child who attends day care). The Infectious Diseases Society of America statement further indicates that "for older patients or those with underlying disease, a fluoroquinolone may be a preferred choice; some authorities prefer to reserve fluoroquinolones for such patients." The rationale to reserve the fluoroquinolones is that the fear of widespread use may lead to the development of fluoroquinolone resistance among the respiratory pathogens (as well as other pathogens colonizing treated patients).[73]

Although the recommended β-lactam antibiotics are effective against most isolates of *S pneumoniae* and *H influenzae*, they are not clinically effective for the atypical organisms. Penicillins combined with β-lactamase inhibitors (amoxicillin-clavulanate) and most cephalosporins (ie, cefuroxime, cefpodoxime, and cefprozil) are active against β-lactamase–producing organisms, such as *H influenze* and *M catarrhalis*, and can be considered appropriate in settings where the atypical organisms may be less likely (ie, smokers with purulent sputum). Regarding macrolides, the newer agents (clarithromycin and azithromycin) are better tolerated and have better activity against *H influenzae* than does erythromycin. Of increasing concern is the emergence of resistance of *S pneumoniae* to macrolides. In the United States, most macrolide

resistance is a result of increased drug efflux encoded by *mef* and with a MIC less than 32 µg/mL. It is possible that this resistance may be overcome by achievable levels of the newer macrolides in the lung or endothelial lining fluid.[74] Of note, however, are recent reports describing patients treated with oral macrolides who failed therapy and required admission to the hospital for therapy of macrolide-resistant *S pneumoniae* bacteremia.[75,76] To date, these reports are relatively few in light of the millions of doses of macrolides used in this country; however, these reports are the basis for future concern.

EDUCATIONAL STRATEGIES PROMOTE RATIONAL ANTIBIOTIC USE

Issuing guidelines on appropriate antibiotic drug use for treatment of different types of infections is only the first step in ensuring that rational principles are adopted and followed in clinical practice. Educational strategies aimed at enhancing clinician awareness of guidelines and encouraging their implementation are necessary. Educational materials promoting the implementation of practice guidelines and emphasizing their benefits could be developed and provided to clinicians. Translation of guidelines into practice also must involve educational efforts geared toward patients. Patients need to understand that antibiotics are not appropriate for the treatment of viral infections. They also must be educated about the need to take antibiotics as directed and for the entire duration prescribed. Public health campaigns can help spread the word, and traditional print and audiovisual patient education materials also may be useful.

Educational efforts aimed at providers and patients already have proved to be successful in promoting the rational use of antibiotics in upper RTIs. In a study[77] in rural Alaska, the education of healthcare workers and the community concerning appropriate antimicrobial drug use in children with upper RTIs was associated with a 22% reduction in the number of antibiotic prescriptions in children younger than 5 years and with a 28% decrease in penicillin-resistant pneumococcal nasopharyngeal isolates compared with the 2 control regions not provided with the educational intervention.

In addition to educational campaigns, there is no substitute for the few moments taken by the treating clinician to explain fully why antibiotics are not necessary or why they are being prescribed. This approach helps patients realize that their condition is being taken seriously. The investment in time and personal attention can increase patient satisfaction with the selected treatment and can help ensure that patients comply with therapy.

CONCLUSIONS

The widespread morbidity caused by RTIs is a serious problem for society in general and clinicians in particular. The appropriate management of RTIs poses multiple challenges for the clinician. Determining the bacterial or viral cause of an RTI is critical to deciding whether patients require antibiotic therapy. Bacterial infections warrant antimicrobial therapy, whereas viral infections do not. Viral illness generally resolves within a week, whereas bacterial infections typically worsen and can be accompanied by clinical signs of infection (eg, ear pain, otorrhea, or fever).

Inappropriate prescribing practices (eg, selecting agents with insufficient antimicrobial activity and treating viral infections with antibiotics) have contributed to the development of drug resistance among common respiratory pathogens (eg, *S pneumoniae*, *H influenzae*, and *M catarrhalis*). For example, among *S pneumoniae* isolates, penicillin resistance has risen to more than 50% in some areas of the United States. Factors contributing to inappropriate antimicrobial use include patient expectations, clinician time constraints, and the practice of defensive medicine. Antibiotic therapy with the appropriate agent shortens the course of the illness, lowers the risk of complications due to untreated disease, helps prevent disease progression and airway impairment, and avoids the added cost of multiple courses of antibiotics.

Although evidence-based recommendations and guidelines for treatment have been developed to assist clinicians in selecting appropriate antibiotics for empiric therapy, a variety of barriers and obstacles must be overcome in clinician and patient attitudes.

Educational efforts targeted toward clinicians as well as patients are necessary to encourage implementation of guidelines, to avoid misuse of antibiotics for viral infections, and to prevent prescription of antibiotics that are ineffective for treating the most likely respiratory pathogens. The judicious and rational use of appropriate antibiotic agents in the treatment of RTIs can help reduce the complexities, costs, and disease complications that currently burden the management of these common conditions.

REFERENCES

1. Slavin RG. Nasal polyps and sinusitis. JAMA 1997;278:1849-1854.

2. McCaig LF, Hughes JM. Trends in antimicrobial drug prescribing among office-based physicians in the United States. JAMA 1995;273:214-219.

3. Verheij TJM, Hermans J, Mulder JD. Effects of doxycycline in patients with acute cough and purulent sputum: A double blind, placebo controlled trial. Br J Gen Pract 1994;44:400-404.

4. Dunlay J, Reinhardt R, Roi LD. A placebo-controlled, double-blind trial of erythromycin in adults with acute bronchitis. J Fam Pract 1987;25:137-141.

5. Brickfield FX, Carter WH, Johnson RE. Erythromycin in the treatment of acute bronchitis in a community practice. J Fam Pract 1986;23:119-122.

6. Franks P, Gleiner JA. The treatment of acute bronchitis with trimethoprim and sulfamethoxazole. J Fam Pract 1984;19:185-190.

7. Williamson HA Jr. A randomized, controlled trial of doxycycline in the treatment of acute bronchitis. J Fam Pract 1984;19:481-486.

8. Stott NCH, West RR. Randomised controlled trial of antibiotics in patients with cough and purulent sputum. BMJ 1976;2:556-559.

9. Howie JGR, Clark GA. Double-blind trial of early demethylchlortetracycline in minor respiratory illness in general practice. Lancet 1970;2:1099-1102.

10. King DE, Williams WC, Bishop L, Shechter A. Effectiveness of erythromycin in the treatment of acute bronchitis. J Fam Pract 1996;42:601-605.

11. Kaiser L, Lew D, Hirschel B, et al. Effects of antibiotic treatment in the subset of common-cold patients who have bacteria in nasopharyngeal secretions. Lancet 1996;347:1507-1510.

12. Gonzales R, Steiner JF, Sande MA. Antibiotic prescribing for adults with colds, upper respiratory tract infections, and bronchitis by ambulatory care physicians. JAMA 1997;278:901-904.

13. Mainous AG III, Hueston WJ. The cost of antibiotics in treating upper respiratory tract infections in a Medicaid population. Arch Fam Med 1998;7:45-49.

14. Guillemot D, Courvalin P, and the Working Party to Promote Research to Control Bacterial Resistance. Better control of antibiotic resistance. Clin Infect Dis 2001;33:542-547.

15. Guillemot D, Carbon C, Balkau B, et al. Low dosage and long treatment duration of β-lactam: Risk factors for carriage of penicillin-resistant *Streptococcus pneumoniae*. JAMA 1998;279:365-370.

16. Diekema DJ, Brueggemann AB, Doern GV. Antimicrobial-drug use and changes in resistance in *Streptococcus pneumoniae*. Emerg Infect Dis 2000;6:552-556.

17. Marion Merrell Dow Inc. Marion Merrell Dow Managed Care Digest, HMO Edition. Kansas City, MO: Marion Merrell Dow Inc; 1993.

18. Audit Commission. A Prescription for Improvement: Towards More Rational Prescribing in General Practice. London, England: HMSO; 1994.

19. Schwartz B, Bell DM, Hughes JM. Preventing the emergence of antimicrobial resistance: A call for action by clinicians, public health officials, and patients. JAMA 1997;278:944-945.

20. Bradley CP. Uncomfortable prescribing decisions: A critical incident study. BMJ 1992;304:294-296.

21. Hamm RM, Hicks RJ, Bemben DA. Antibiotics and respiratory infections: Are patients more satisfied when expectations are met? J Fam Pract 1996;43:56-62.

22. Dowell SF, Schwartz B, Phillips WR, and The Pediatric URI Consensus Team. Appropriate use of antibiotics for URIs in children, part II: Cough, pharyngitis and the common cold. Am Fam Physician 1998;58:1335-1342.

23. Gwaltney JM Jr. Acute community-acquired sinusitis. Clin Infect Dis 1996;23:1209-1223.

24. Dowell SF, Schwartz B. Resistant pneumococci: Protecting patients through judicious use of antibiotics. Am Fam Physician 1997;55:1647-1654.

25. Miller YW, Eady EA, Lacey RW, Cove JH, Joanes DN, Cunliffe WJ. Sequential antibiotic therapy for acne promotes the carriage of resistant staphylococci on the skin of contacts. J Antimicrob Chemother 1996;38:829-837.

26. Mainous AG III, Evans ME, Hueston WJ, Titlow WB, McCown LJ. Patterns of antibiotic-resistant *Streptococcus pneumoniae* in children in a day-care setting. J Fam Pract 1998;46:142-146.

27. Cherian T, Steinhoff MC, Harrison LH, Rohn D, McDougal LK, Dick J. A cluster of invasive pneumococcal disease in young children in child care. JAMA 1994;271:695-697.

28. Dowell SF, Marcy SM, Phillips WR, Gerber MA, Schwartz B. Otitis media—principles of judicious use of antimicrobial agents. Pediatrics 1998;101(suppl):165-171.

29. Sinus and Allergy Health Partnership. Antimicrobial treatment guidelines for acute bacterial rhinosinusitis. Otolaryngol Head Neck Surg 2000;123(suppl):S1-S32.

30. Lanza DC, Kennedy DW. Adult rhinosinusitis defined. Otolaryngol Head Neck Surg 1997;117:S1-S7.

31. Fish JE. Bacterial infection in acute exacerbations of chronic bronchitis: How to detect—how to manage. Consultant 1993;33(suppl):10-16.

32. Sethi S. Infectious exacerbations of chronic bronchitis: Diagnosis and management. J Antimicrob Chemother 1999;43(suppl A):97-105.

33. American Thoracic Society. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease (COPD) and asthma. Am Rev Respir Dis 1987;138:225-244.

34. Hueston WJ, Mainous AG III. Acute bronchitis. Am Fam Physician 1998;57:1270-1276, 1281-1282.

35. Gwaltney JM Jr. Acute bronchitis. In: Mandell GL, Bennett JE, Dolin R, eds. Principles and Practice of Infectious Diseases. 4th ed. New York, NY: Churchill Livingstone Inc; 1995:606-608.

36. File TM Jr. Treating CAP caused by penicillin-resistant *S pneumoniae*. J Respir Dis 1999;20:833-842.

37. Bartlett JG, Dowell SF, Mandell LA, File TM Jr, Musher DM, Fine MJ. Community-acquired pneumonia in adults. Clin Infect Dis 2000;31:347-382.

38. Metlay JP, Kapoor WN, Fine MJ. Does this patient have community-acquired pneumonia? Diagnosing pneumonia by history and physical examination. JAMA 1997;278:1440-1445.

39. Wald ER, Chiponis D, Ledesma-Medina J. Comparative effectiveness of amoxicillin and amoxicillin-clavulanate potassium in acute paranasal sinus infections in children: A double-blind, placebo-controlled trial. Pediatrics 1986;77:795-800.

40. Bluestone CD, Klein JO. Otitis Media in Infants and Children. 2nd ed. Philadelphia, PA: WB Saunders Co; 1995:145-240.

41. Teele DW, Klein JO, Rosner B, and the Greater Boston Otitis Media Study Group. Epidemiology of otitis media during the first seven years of life in children in greater Boston: A prospective, cohort study. J Infect Dis 1989;160:83-94.

42. Gwaltney JM Jr, Scheld WM, Sande MA, Sydnor A. The microbial etiology and antimicrobial therapy of adults with acute community-acquired sinusitis: A fifteen-year experience at the University of Virginia and review of other selected studies. J Allergy Clin Immunol 1992;90:457-462.

43. Gonzales R, Bartlett JG, Besser RE, et al. Principles of appropriate antibiotic use for treatment of acute respiratory tract infec-

tions in adults: Background, specific aims, and methods. Ann Intern Med 2001;134:479-486.

44. Spika JS, Facklam RR, Plikaytis BD, Oxtoby MJ, and the Pneumococcal Surveillance Working Group. Antimicrobial resistance to *Streptococcus pneumoniae* in the United States, 1979-1987. J Infect Dis 1991;163:1273-1278.

45. Thornsberry C, Ogilvie P, Kahn J, Mauriz Y, and the Laboratory Investigator Group. Surveillance of antimicrobial resistance in *Streptococcus pneumoniae*, Haemophilus influenzae, and Moraxella catarrhalis in the United States in 1996-1997 respiratory season. Diagn Microbiol Infect Dis 1997;29:249-257.

46. Jacobs MR, Bajaksouzian S, Lin G, Appelbaum PC. Susceptibility of *Streptococcus pneumoniae* and Haemophilus influenzae to oral agents: Results of a 1997 epidemiological study [abstract]. Presented at: 98th General Meeting of the American Society for Microbiology; May 17-21, 1998; Atlanta, GA. Abstract A-31.

47. Dagan R, Leibovitz E, Fliss DM, et al. Bacteriologic efficacies of oral azithromycin and oral cefaclor in treatment of acute otitis media in infants and young children. Antimicrob Agents Chemother 2000;44:43-50.

48. Dagan R, Johnson CE, McLinn S, et al. Bacteriologic and clinical efficacy of amoxicillin/clavulanate vs. azithromycin in acute otitis media. Pediatr Infect Dis J 2000;19:95-104.

49. Craig WA. Pharmacokinetic/pharmacodynamic parameters: Rationale for antibacterial dosing of mice and men. Clin Infect Dis 1998;26:1-12.

50. Jacobs MR, Bajaksouzian S, Lin G, Zilles A, Pankuch GA, Appelbaum PC. Susceptibility of *Streptococcus pneumoniae, Haemophilus influenzae,* and *Moraxella catarrhalis* to oral agents: Results of a 1998 US outpatient surveillance study. Poster presented at: Annual Meeting of Interscience Conference on Antimicrobial Agents and Chemotherapy; September 26-29, 1999; San Francisco, CA.

51. Grimshaw JM, Russell IT. Effect of clinical guidelines on medical practice: A systematic review of rigorous evaluations. Lancet 1993;342:1317-1322.

52. Beilby J, Marley J, Walker D, et al. The impact of changes in antibiotic prescribing on patient outcomes in a community setting: A natural experiment in Australia [abstract]. Presented at: 37th Annual Meeting of the Infectious Diseases Society of America (IDSA); November 18-21, 1999; Philadelphia, PA. Abstract 534.

53. Dowell SF, Marcy SM, Phillips WR, Gerber MA, Schwartz B. Principles of judicious use of antimicrobial agents for pediatric upper respiratory tract infections. Pediatrics 1998;101(suppl):163-165.

54. Cabana MD, Rand CS, Powe NR, et al. Why don't physicians follow clinical practice guidelines? A framework for improvement. JAMA 1999;282:1458-1465.

55. Hoberman A, Paradise JL, Block S, Burch DJ, Jacobs MR, Balanescu MI. Efficacy of amoxicillin/clavulanate for acute otitis media. Relation to *Streptococcus pneumoniae* susceptibility. Pediatr Infect Dis J 1996;15:955-962.

56. Gwaltney JM Jr. Sinusitis. In: Mandell GL, Bennett JE, Dolin R, eds. Mandell, Douglas and Bennett's Principles and Practices of Infectious Diseases. 3rd ed. New York, NY: Churchill Livingstone Inc; 1995;585-590.

57. Sethi S. Etiology and management of infections in chronic obstructive pulmonary disease. Clin Pulm Med 1999;6:327-332.

58. Bartlett JG, Mundy LM. Community-acquired pneumonia. N Engl J Med 1995;333:1618-1624.

59. Dowell SF, Butler JC, Giebink GS, et al. Acute otitis media: Management and surveillance in an era of pneumococcal resistance: A report from the Drug-Resistant *Streptococcus pneumoniae* Therapeutic Working Group. Pediatr Infect Dis J 1999;18:1-9.

60. Dowell SF, Whitney CH, Schwartz B. Regional characteristics of drug-resistant respiratory pathogens. Am J Med (Continuing Ed Ser) 1997;2:9-16.

61. Zenni MK, Cheatham SH, Thompson JM, et al. *Streptococcus pneumoniae* colonization in the young child: Association with otitis media and resistance to penicillin. J Pediatr 1995;127: 533-537.

62. Nava JM, Bella F, Garau J, et al. Predictive factors for invasive disease due to penicillin resistant *Streptococcus pneumoniae*: A population-based study. Clin Infect Dis 1994;19:884-890.

63. Reichler MR, Allphin AA, Breiman RF, et al. The spread of multiple resistant *Streptococcus pneumoniae* at a day care center in Ohio. J Infect Dis 1992;166:1346-1353.

64. Gudnason T, Gudbrandsson F, Barsanti F, Kristinsson KG. Penetration of ceftriaxone into the middle ear fluid of children. Pediatr Infect Dis J 1998;17:258-260.

65. Varsano I, Volovitz B, Horev Z, et al. Intramuscular ceftriaxone compared with oral amoxicillin-clavulanate for treatment of acute otitis media in children. Eur J Pediatr 1997;156:858-863.

66. Medical Economics Co. Physicians' Desk Reference. 54th ed. Montvale, NJ: Medical Economics Co; 2000.

67. Niederman MS. Acute exacerbations of chronic bronchitis: The role of infection and the selection of appropriate therapy. Pulm Crit Care Update 1996;11:2-7.

68. Bach PB, Brown C, Gelfand SE, McGory DC. Management of acute exacerbations of chronic obstructive pulmonary disease: A summary and appraisal of published evidence. Ann Intern Med 2001;134:600-620.

69. Anthonisen NR, Manfreda J, Warren CPW, Hershfield ES, Harding GKM, Nelson NA. Antibiotic therapy in exacerbations of chronic obstructive pulmonary disease. Ann Intern Med 1987;106:196-204.

70. Saint S, Bent S, Vittinghoff E, Grady D. Antibiotics in chronic obstructive pulmonary disease exacerbations: A meta-analysis. JAMA 1995;273:957-960.

71. Snow V, Lascher S, Mottur-Pilson C, for the Joint Expert Panel on Chronic Obstructive Pulmonary Disease of the American College of Chest Physicians and the American College of Physicians–American Society of Internal Medicine. Evidence base for management of acute exacerbations of chronic obstructive pulmonary disease. Ann Intern Med 2001;134:595-599.

72. Adams SG, Anzueto A. Antibiotic therapy in acute exacerbations of chronic bronchitis. Semin Respir Infect 2000;15:234-247.

73. Heffelfinger JD, Dowell SF, Jorgensen JH, et al, and Drug-Resistant Streptococcus pneumoniae Therapeutic Working Group. Management of community-acquired pneumonia in the era of pneumococcal resistance: A report from the Drug-Resistant *Streptococcus pneumoniae* Therapeutic Working Group. Arch Intern Med 2000;160:1399-1408.

74. Amsden GW. Pneumococcal macrolide resistance: Myth or reality? J Antimicrobial Chemother 1999;44:1-6.

75. Fogarty C, Goldschmidt R, Bush K. Bacteremic pneumonia due to multi-drug resistant pneumococci in 3 patients treated unsuccessfully with azithromycin and successfully with levofloxacin. Clin Infect Dis 2000;31:612-615.

76. Kelley MA, Weber DJ, Gilligan P, Cohen MS. Breakthrough pneumococcal bacteremia in patients being treated with azithromycin and clarithromycin. Clin Infect Dis 2000;31: 1008-1011.

77. Petersen K, Hennessy TW, Parkinson AJ, et al. Provider and community education decreases antimicrobial use and carriage of penicillin-resistant Streptococcus pneumoniae (PRSP) in rural Alaska communities [abstract]. Presented at: 37th Annual Meeting of the Infectious Diseases Society of America (IDSA); November 18-21, 1999; Philadelphia, PA. Abstract 62.