Principles of Appropriate Antibiotic Use for Treatment of Acute Respiratory Tract Infections in Adults: Background, Specific Aims, and Methods

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The need to decrease excess antibiotic use in ambulatory practice has been fueled by the epidemic increase in antibiotic-resistant *Streptococcus pneumoniae*. The majority of antibiotics prescribed to adults in ambulatory practice in the United States are for acute sinusitis, acute pharyngitis, acute bronchitis, and nonspecific upper respiratory tract infections (including the common cold). For each of these conditions—especially colds, nonspecific upper respiratory tract infections, and acute bronchitis (for which routine antibiotic treatment is not recommended)—a large proportion of the antibiotics prescribed are unlikely to provide clinical benefit to patients. Because decreasing community use of antibiotics is an important strategy for combating the increase in community-acquired antibiotic-resistant infections, the Centers for Disease Control and Prevention convened a panel of physicians representing the disciplines of internal medicine, family medicine, emergency medicine, and infectious diseases to develop a series of "Principles of Appropriate Antibiotic Use for Treatment of Acute Respiratory Tract Infections in Adults." These principles provide evidence-based recommendations for evaluation and treatment of adults with acute respiratory illnesses.

This paper describes the background and specific aims of and methods used to develop these principles. The goal of the principles is to provide clinicians with practical strategies for limiting antibiotic use to the patients who are most likely to benefit from it. These principles should be used in conjunction with effective patient educational campaigns and enhancements to the health care delivery system that facilitate nonantibiotic treatment of the conditions in question.

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BACKGROUND

The Need To Improve Antibiotic Prescription for Acute Respiratory Infections

1. The epidemic increase in antibiotic-resistant Streptococcus pneumoniae *is an ambulatory care problem.*

Excessive use of antibiotics in ambulatory practice has contributed to the emergence and spread of antibiotic-resistant bacteria in the community (1–4). Penicillin resistance in *S. pneumoniae* has increased in an epidemic manner in the past 10 years (5, 6). Resistance to macrolides, doxycycline, trimethoprim–sulfamethoxazole, and second- and third-generation cephalosporins has also increased. Special attention to antibiotic-resistance profiles of *S. pneumoniae* is warranted, since this pathogen is the leading cause of community-acquired bacterial pneumonia, bacterial meningitis, bacterial sinusitis, and otitis media in the United States (7).

2. Previous antibiotic use is an important risk factor for carriage of and infection with antibiotic-resistant Streptococcus pneumoniae.

The major risk factors for carriage of and infection with antibiotic-resistant *S. pneumoniae* are geographic location, recent exposure to antibiotics, and exposure to young children. Carriage of *S. pneumoniae* (and antibiotic-resistant *S. pneumoniae*) primarily occurs in the nasopharynx and oropharynx of susceptible hosts (8, 9). Factors contributing to the spread of *S. pneumoniae* (such as close contact and viral respiratory infections) are also associated with the spread of antibiotic-resistant *S. pneumoniae* (10–12). For example, carriage and transmission of antibiotic-resistant *S. pneumoniae* are greatest during winter months and in environments that facilitate the transmission of respiratory secretions (8). The prevalence of carriage of *S. pneumoniae* and antibiotic-

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resistant *S. pneumoniae* appears to be greatest in young children; up to one third of children who visit health clinics are reported to be nasopharyngeal carriers of antibiotic-resistant *S. pneumoniae* (13–15). The prevalence of *S. pneumoniae* colonization in the upper airways in adults is about 5%; this value increases if children are present in the household (10). Although the risks for transmission of antibiotic-resistant *S. pneumoniae* mirror those for *S. pneumoniae*, numerous retrospective and prospective carriage studies have also identified previous antibiotic use, especially for a prolonged period (for example, as prophylaxis against recurrent acute otitis media), to be the most significant risk factor for carriage and subsequent spread of antibiotic-resistant *S. pneumoniae* (14–18). The risk for carriage of antibiotic-resistant *S. pneumoniae* is two to nine times greater in persons who have recently used antibiotics.

A precipitously rapid increase in antibiotic resistance has also been observed for strains of *S. pneumoniae* in blood, cerebrospinal fluid, and joint fluid in the United States since 1986, when invasive antibiotic-resistant *S. pneumoniae* isolates were rare or absent (5). Like carriage of antibiotic-resistant *S. pneumoniae*, invasive infection with antibiotic-resistant *S. pneumoniae* is associated with previous antibiotic use (6, 19–22). When invasive infection with antibiotic-resistant *S. pneumoniae* occurs, antibiotics with poor central nervous system penetration and bacteriostatic (instead of bactericidal) properties must sometimes be used. Treatment failures have been reported in patients with pneumococcal meningitis after therapy with penicillin, chloramphenicol, clarithromycin, ceftriaxone, and cefotaxime (12, 23–26).

The management of outpatient bacterial infections, such as acute otitis media, becomes substantially more difficult because of high rates of antibiotic-resistant *S. pneumoniae* in children with such infections (27, 28). However, few studies have quantified the clinical impact of antibiotic-resistant *S. pneumoniae* on morbidity, mortality, and health care costs in children or adults. In a study of hospitalized patients with severe pneumococcal pneumonia in Spain, where a high prevalence of antibiotic-resistant *S. pneumoniae* preceded the current increase in the United States, no association was seen between antibiotic resistance and mortality (29). However, most patients had intermediate-level penicillin resistance; in such patients, serum and lung interstitium concentrations of antibiotic are sufficiently high to overcome resistance. A recent study of U.S. adults hospitalized with community-acquired pneumonia due to *S. pneumoniae* found that mortality was significantly associated with high-level antibiotic-resistant *S. pneumoniae* (minimum inhibitory concentration ≥ 4 μg/mL), after exclusion of deaths that occurred within the first 2 to 4 days of hospitalization (30). Exclusion of early deaths is justified, since antibiotic therapy has not been shown to affect early mortality in adults with antibiotic-susceptible pneumococcal disease (31). Because of the current increase in antibiotic resistance in community bacterial pathogens, many experts are predicting an impending "postantibiotic era" (2–4).

3. Most antibiotic prescriptions in the ambulatory setting are for acute respiratory infections.

Intervention strategies aimed at reducing community use of antibiotics must address the management of acute respiratory infections. These illnesses are the most frequent reasons for seeking medical attention in the United States, and they are associated with up to 75% of total antibiotic prescriptions each year (32). Transmission of *S. pneumoniae* is enhanced during viral acute respiratory infection through increased respiratory and nasal secretions (10). As a result, antibiotic treatment of viral acute respiratory infections is particularly problematic, since it may selectively promote the acquisition and spread of antibiotic-resistant bacteria by patients.

Specific acute respiratory infections that must be targeted for reducing unnecessary antibiotic use in adults are uncomplicated acute bronchitis (not including acute exacerbations of chronic bronchitis), acute sinusitis, pharyngitis, and nonspecific upper respiratory tract infection (including the common cold). These diagnoses are usually made in the presence of a clinical syndrome with a predominant clinical feature, so that prominent acute cough is taken to mean acute bronchitis, prominent nasal and sinus symptoms are thought to signify sinusitis, and prominent acute sore throat is considered pharyngitis. Acute respiratory symptoms in the absence of a predominant symptom are typically diagnosed as "upper respiratory tract infection." Each of these syndromes can be caused by a multitude of different viruses and, on occasion, bacteria.

The degree of excess prescription of antibiotics varies for each diagnosis. Antibiotic treatment of a cold, an upper respiratory tract infection, or acute bronchitis is

almost always inappropriate because the vast majority of these syndromes have a nonbacterial cause. Antibiotic treatment of sinusitis and pharyngitis is sometimes justified but should be limited to appropriate subsets of patients.

Potential Benefit and Harm of Adherence to Principles of Appropriate Antibiotic Prescription

Potential Benefits of Indiscriminant Antibiotic Prescription

Some clinicians may prescribe antibiotics because they believe that a very small fraction of patients might benefit or they hope to prevent the remote case of a bad outcome (and a potential lawsuit). A theoretical clinical benefit of treating viral respiratory tract infections with antibiotics cannot be excluded. A truism for all clinical trials performed in medicine is that a benefit of treatment cannot be excluded for outcomes that occur less frequently than the sample size can detect (that is, there will always be specific outcomes that were not or cannot be measured). For example, invasive bacterial disease, such as sepsis or bacterial meningitis, is too rare an event to be evaluated in a randomized, controlled trial with enough power to exclude a potential benefit of antibiotic treatment. The incidence of bacterial meningitis in the United States is about 3 per 100 000 persons in the general population (1995) (33) or about 9 per 100 000 persons with an office visit for an acute respiratory illness (unpublished data based on the National Ambulatory Medical Care Survey, 1997). Indiscriminant use of antibiotics may also in theory prevent complications of other undiagnosed bacterial infections, such as acute rheumatic fever. While these hypothetical benefits are possible, no evidence supports their existence.

Potential Harms of Indiscriminant Antibiotic Prescription

In contrast to the theoretical clinical benefit of indiscriminant prescription of antibiotics, the potential harm of this practice is well established at the level of the patient and society. At the patient level, risks include allergic reactions (such as urticaria, rash, and anaphylaxis), adverse reactions (such as gastrointestinal discomfort or yeast infections), and drug–drug interactions (such as QT interval prolongation caused by warfarin and oral contraceptives), as well as the increased likelihood that a pneumococcal infection in the ensuing months will be due to an antibiotic-resistant strain. At the societal level, the adverse effects of indiscriminant antibiotic use on rates of antibiotic resistance are well established, and the effects on health care costs (for antibiotics and office visits) are straightforward. Finally, indiscriminant antibiotic use could serve to inappropriately medicalize viral illnesses. This tendency not only usurps the ability of individual persons to care for self-limited illnesses but also carries large associated costs in terms of unnecessary office visits and prescriptions.

Potential Benefits of Limiting Indiscriminant Antibiotic Prescription

Besides decreasing the risk for the harms noted above, the intended result of efforts to decrease indiscriminant antibiotic use in the ambulatory setting is to reduce (and preferably reverse) the increase in antibiotic-resistant *S. pneumoniae*. It is encouraging that in Finland, a 40% reduction in community use of macrolides was associated with a 48% decrease in the prevalence of erythromycin resistance among group A streptococcal isolates over 4 years (34).

Potential Harms of Limiting Indiscriminant Antibiotic Prescription

If a benefit of indiscriminant antibiotic use on rare clinical outcomes does exist, it is possible that limiting indiscriminant antibiotic prescribing will attenuate this benefit. A risk or harm voiced more frequently, however, is that not prescribing an antibiotic will lead to patient dissatisfaction with care or increased return visits. In a study of adults seeking care for acute respiratory illness, the quality of the clinician–patient interaction rather than receipt of an antibiotic was the most important determinant of patient satisfaction with care (35). A recent patient and clinician educational intervention that reduced antibiotic prescribing for adults with acute bronchitis did not lead to increased return visits (36) or dissatisfaction with care (37).

Strategies To Decrease Indiscriminant Antibiotic Use for Acute Respiratory Infections in the United States

The Centers for Disease Control and Prevention (CDC) has initiated activities for decreasing inappropriate antibiotic use, of which practice guidelines are one component. The goals of the campaign are to decrease

unnecessary antimicrobial use and thereby reduce the spread of antibiotic resistance. To this end, partnerships are being established with a wide variety of groups, including health departments, medical societies, managed care plans, pharmacy benefits managers, and industry, so that these sectors may work jointly to promote appropriate antibiotic use. Other components of the initiative include developing materials to educate physicians and the general public; developing and implementing interventions; assessing the impact of interventions on antibiotic use, resistance, and physician and patient satisfaction; and serving as a resource to groups undertaking campaigns.

The first set of broad-scale practice-oriented activities targeted the management of acute respiratory infections in children. These included the development of educational materials for patients and clinicians that promote appropriate antibiotic use and the development, publication, and dissemination of "Principles of Judicious Use of Antimicrobial Agents for Pediatric Upper Respiratory Tract Infections." This series was published as a supplement in the January 1998 issue of *Pediatrics*. The CDC has now turned its attention to the management of acute respiratory infections in adults and plans to develop and disseminate a set of patient and clinician materials tailored toward adults.

Although the development of evidence-based practice recommendations that help guide clinical decision making is an important component of quality improvement efforts (such as clinical practice guidelines or the principles of antibiotic use in adults in this issue), the implementation of practice recommendations appears to be critical for successfully changing physician behavior (38, 39). The factors that influence the decision to prescribe antibiotics for acute respiratory infections when they are unlikely to benefit are diverse. Patient expectations and demands for antibiotics have been singled out in multiple studies as having a strong association with excess antibiotic use (35, 40, 41). However, other studies have found that rates of antibiotic prescription for upper respiratory tract infections increase as patient volume increases (42), suggesting that limited time to discuss nonantibiotic treatment alternatives is a factor in busy practices. Thus, the decision to prescribe antibiotics for acute respiratory infections appears to be a result of complex interactions among patient, physician, and system factors, and effective strategies to improve antibiotic prescribing behavior will probably need to address each of these domains.

Not surprisingly, interventions that focus on clinician education and profiling in an attempt to decrease total antibiotic use in acute respiratory infections have been ineffective (43–45). In contrast, an intervention strategy that combined clinician education with patient education at the household and office levels successfully decreased prescription of antibiotics for acute bronchitis (36), and the effect of this intervention has been sustained in subsequent years with minimal reinforcement (37, 46). We propose that the "Principles of Appropriate Antibiotic Use for Acute Respiratory Tract Infections in Adults" will be most useful if they are incorporated into comprehensive quality improvement efforts that include patient education and delivery system improvements (47). These principles apply to immunocompetent adults who do not have significant comorbid conditions or clinical features that would affect the clinical presentation or potential response to antibiotic treatment (for example, acute bronchitis in adults with chronic obstructive pulmonary disease, chronic or recurrent pharyngitis, or sinusitis). Specific exclusions are detailed in each paper. The principles should be applied with caution to elderly patients because many of the diagnosis and treatment trials specifically excluded or underrepresented persons older than 65 years of age.

SPECIFIC AIMS

A panel consisting of clinicians who routinely care for adults with acute respiratory infections and of experts in infectious diseases was assembled to develop a series of Principles of Appropriate Antibiotic Use for Acute Respiratory Tract Infections in Adults. Representatives from the disciplines of internal medicine, family practice, emergency medicine, and infectious diseases and from the CDC were included.

Principles were developed for acute bronchitis, acute sinusitis, pharyngitis, and upper respiratory tract infections. Evidence-based elements of practice guideline development were used, such as 1) explicit identification and selection of evidence; 2) explicit identification of management options and outcomes; 3) evaluation and rating of the quality of the evidence; and 4) incorporation of practice guideline elements that are important to practicing clinicians (endorsement by

professional societies and provision of a simple message) (48).

Endorsement or recognition of the principles was obtained from the American Academy of Family Physicians, American College of Physicians–American Society of Internal Medicine, CDC, and Infectious Diseases Society of America (excluding pharyngitis).

The principles are being disseminated through publication (in whole or in part) in professional society journals (*American Family Physician, Annals of Emergency Medicine, Annals of Internal Medicine)*, presentation at annual meetings of professional societies, and established channels at the CDC.

The Web site on antimicrobial resistance of the CDC Respiratory Diseases Branch (www.cdc.gov/ncidod/dbmd/antibioticresistance/) will be used to provide updates and obtain feedback from clinicians.

Strategic Plan and Methods

Conceptual Framework

To provide some uniformity across specific acute respiratory tract infections and to enhance transfer of the principles from the literature to practice, each article focuses on the major decisions or issues that clinicians face during routine evaluation of patients with symptoms of an acute respiratory illness. The major decisions about the management of acute respiratory infections tend to cluster around establishing a diagnosis; estimating the likelihood of a bacterial cause; and determining whether, and in whom, antibiotic therapy is indicated.

Each recommendation or Principle within each article was approached as a distinct unit (that is, as a starting point for initiating review of the literature and evidence). A considerable number of articles and recommendations on appropriate methods for developing and reporting on clinical practice guidelines shaped the development of each article (48–53). The guideline development process (model II) recommended by the American College of Physicians–American Society of Internal Medicine Clinical Efficacy Analysis Subcommittee and a recent article by Shaneyfelt and colleagues (49) outlining a comprehensive list of "standards for reporting" on clinical practice guidelines were incorporated to the fullest extent possible in each article.

For example, for each condition, an evidence model was developed to frame specific questions to be addressed. Specifically, it was assumed that determining which, if any, patients with bronchitis, sinusitis, pharyngitis, or nonspecific upper respiratory tract infection are likely to benefit from antibiotic treatment depends on accurate diagnosis and accurate assessment of the likelihood of a bacterial cause. Diagnostic and treatment options were discussed when appropriate and were specifically linked to the evidence model; for example, we asked such questions as, "On the basis of clinical presentation or test results, are there patients who are more likely to have a bacterial infection or more likely to benefit from antibiotic treatment?" When antibiotic treatment was recommended, we intentionally avoided detailed discussions on antibiotic selection, since this information is covered in numerous other publications, must take into account local resistance patterns, and will continue to evolve more quickly than the inherent message in these principles (that is, when to diagnose and when to treat).

Literature Review

The principles are intended to be practice recommendations based on an evidence-based analysis and interpretation of the current scientific literature on diagnosis and treatment of acute respiratory tract infections in adults. They do not represent original systematic reviews of the literature, since up-to-date, high-quality systematic reviews of antibiotic treatment of upper respiratory tract infections, acute bronchitis, sinusitis, and sore throat have been conducted by such expert groups as the Cochrane Collaboration and the Agency for Healthcare Research and Quality. However, the literature review process for each of these areas was updated through March 2000. All studies were analyzed and interpreted by the Panel, and its conclusions do not necessarily reflect those of the original publications from which the studies were identified. For example, the Cochrane Collaboration's review and meta-analysis of sore throat did not stratify by age or etiology and concluded that antibiotic treatment of sore throat was not justified (54). However, the Panel was interested in the benefit of antibiotic treatment of group A streptococcal pharyngitis in adults (not in all cases of sore throat) and based its practice recommendations only on trials that stratified patients by etiology.

The Panel conducted comprehensive literature re-

Table. **Levels of Evidence***

Rating	Etiology or Diagnosis Studies	Treatment or Efficacy Studies
A	Independent, blinded comparison with reference standard in appropriate spectrum of patients, all of whom have undergone both the diagnostic test in question and testing with the current gold standard; or validated prediction rule	Randomized, placebo-controlled trials with little or no heterogeneity
B	Independent, blinded comparison in patients not enrolled consecutively or in a narrow spectrum of patients; or nonvalidated prediction rule	Randomized, placebo-controlled trials with some heterogeneity; or well-designed cohort studies
C	Independent, blinded comparison, but reference standard not applied to all patients	Case series or poor cohort studies
D	Reference standard not applied independently or not applied in a blinded manner; or expert opinion	Expert opinion

* Modified from reference 56.

views for areas not addressed in published systematic reviews, particularly those relating to etiology and diagnosis. Whenever possible, only studies that enrolled consecutive, nonreferral ambulatory patient populations were considered. Etiologic studies used to estimate incidence or prevalence of bacterial infections were also excluded if they were conducted during known outbreaks or epidemics of a pathogen (for example, a *Chlamydia pneumoniae* outbreak in a university setting). Studies were excluded if they included large numbers of patients with comorbid conditions such as chronic cardiopulmonary disease, end-organ failure, or immunosuppression, especially when such conditions were thought likely to affect antibiotic efficacy; for example, antibiotics appear to have a modest benefit for treatment of acute bronchitis in patients with chronic obstructive pulmonary disease (55). Although there may be reasons to decrease antibiotic use in these subgroups, such patients represent a small fraction of the total number of those receiving antibiotics for acute respiratory infections. Microbiological studies and randomized, controlled trials of antibiotic treatment for acute respiratory tract infections in these subgroups, with the exception of chronic obstructive pulmonary disease, are frequently lacking, and addressing the special issues relevant to each of these subgroups would lead to a much more dense and complicated product.

Rating the Evidence

Where appropriate, each recommendation is accompanied by a rating of the strength or level of the evidence. For these purposes, we have modified the classification of level of evidence advocated by Sackett and colleagues (56) (**Table**).

Development Process

Under the direction of Drs. Besser and Gonzales, the Panel was completed in August 1999. Two rounds of conference calls and drafts occurred between October 1999 and January 2000. Comments on the second drafts were solicited from the American College of Physicians–American Society of Internal Medicine Clinical Efficacy Analysis Subcommittee; the Respiratory Diseases Branch of the National Center for Infectious Diseases, CDC; and selected individuals. In response to this feedback, a third draft was completed by March 2000. Comments and endorsement of the third drafts were solicited from the American College of Physicians–American Society of Internal Medicine, the American College of Emergency Physicians, the American Academy of Family Physicians, and the Infectious Diseases Society of America. Further modifications were incorporated, and specific endorsement or recognition by each organization appears as a footnote in each article.

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Disclaimer: The Centers for Disease Control and Prevention sponsored the development of these principles and has approved all final products. As such, these documents do not necessarily reflect consensus of interpretation or opinion by all members of the Panel.

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