REVIEW ARTICLE

Antibiotics for Common Respiratory Tract Infections in Adults

J. V. Hirschmann, MD

A thorough review of the published information indicates that antibiotics rarely benefit acute bronchitis, exacerbations of asthma and chronic bronchitis, acute pharyngitis, and acute sinusitis, although they are commonly prescribed for these illnesses. Rather than prescribing them for these conditions, practitioners should explain to their patients that antibiotics, which have numerous adverse effects, will not hasten resolution of their symptoms, which will often respond to other medications. Most patients will accept this approach if the clinician addresses their concerns, shows a personal interest in them, discusses the expected course of the ailment, and explains the treatment. *Arch Intern Med. 2002;162:256-264*

More than 100 years ago, William Osler[1] wrote, "A desire to take medicine is, perhaps, the great feature which distinguishes man from animals." Currently, people have an especial taste for antibiotics, which constitute about 1 of every 7 outpatient prescriptions in the United States.[2] Among adults nearly one half of prescriptions are for common respiratory tract infections—bronchitis, pharyngitis, sinusitis, and upper respiratory tract infections (otherwise unspecified).[3] When seeking medical care for conditions labeled as upper respiratory tract infections, bronchitis, and even the common cold,[3,4] 50% to 70% of adults receive an antibiotic prescription, especially if the clinician believes that the patient expects it.[5]

This prescriptive promiscuity, which increasingly involves newer agents with broader antimicrobial activity than the older preparations,[2] largely explains the escalating antibiotic resistance of common bacterial respiratory pathogens in the community.[6] In the selective pressure of indiscriminate antimicrobial use, susceptible bacteria succumb; with competition for nutrients and mucosal sites of residence diminished, resistant organisms thrive and proliferate. Consequently, *Haemophilus influenzae* and *Moraxella catarrhalis* are now widely resistant to ampicillin. In some areas, many infections with group A streptococci no longer respond to erythromycin and other macrolides, and penicillin is increasingly inactive against *Streptococcus pneumoniae*, a most worrisome development since few other effective agents exist. These bleak trends have led some infectious disease experts to the gloomy prediction of a "post-antibiotic" era; a return to conditions that prevailed before the discovery of antimicrobial agents, with no efficacious therapy for many serious bacterial infections.[7] Some hope emerges, however, from studies demonstrating that aggressive efforts to diminish the use of antibiotics to which organisms are insensitive may allow susceptible strains to reemerge as the dominant isolates.[8,9] In Finland, for example, a campaign to restrict macrolides led to a decrease in erythromycin resistance among group A streptococci.[8] A thoughtful approach to reducing the incidence of drug resistance is for clinicians not only to refrain from giving antibiotics for obvious viral diseases, such as the common cold, where they are clearly ineffectual, but also to examine their use in other respiratory tract infections for which they are commonly prescribed. In adults, such ailments include acute bronchitis, exacerbations of asthma and chronic bronchitis, pharyngitis, and acute sinusitis. This article derives data from a MEDLINE search of the English-language literature on topics of "acute bronchitis," "asthma," "chronic bronchitis," "acute pharyngitis," and "acute sinusitis" from 1966-2000, and a review of the pertinent material

From Puget Sound Veterans Affairs Medical Center, University of Washington School of Medicine, Seattle.

in the Cochrane Library as of 2001. It focuses primarily on the evidence from randomized, controlled trials, especially, when possible, on recent studies that reflect contemporary conditions.

ACUTE BRONCHITIS

Clinically, acute bronchitis is a recent, commonly productive cough without evident pneumonia. It lasts approximately 2 weeks in 20% of patients, 3 weeks in 30%, 4 weeks in 30%, and longer in 20%.[10] Typically, 3 to 4 weeks elapse from its onset until patients resume all usual daily activities.[11] Diverse viruses presumably cause most acute bronchitis.[12,13] *Mycoplasma pneumoniae*[14] and *Chlamydia pneumoniae*[15] are each present in about 5% of cases.[16-20]

Some have proposed that respiratory bacteria such as *Moraxella (Branhamella) catarrhalis*, *S pneumoniae*, and *H influenzae* produce acute bronchitis or superinfect an originally viral condition.[21] Since these organisms commonly inhabit upper airways of healthy adults,[22-24] their significance as isolates is unclear. No criteria for sputum culture findings distinguish innocent airway colonization from invasiveness, if, indeed, such a process occurs. Thus, the concept of "bacterial bronchitis" from these microbes remains unproven.

Eight placebo-controlled, double-blind trials have evaluated antimicrobial therapy.[10,25-31] The entry criterion was productive cough, with or without purulence, for less than 2 weeks. The average age was about 35 to 45 years, and all studies enrolled cigarette smokers unless they had chronic bronchitis. Fewer than 10% were febrile (temperatures >38°C).[26,27,31] Outcomes generally included duration of cough, feeling sick, time off work, and sputum production or purulence. In 4 studies, antibiotics conferred no significant advantage.[10,28-30] In the 4 trials favoring antimicrobials, the differences, though statistically significant, were typically small and clinically unimportant.

This overview is misleading because these studies vary considerably in quality and size. Defects include small numbers of participants,[25,26,28,29] high drop-out rates,[25] incomplete data collection,[25,26] clinically meaningless outcome criteria,[25] failure to enroll consecutive patients,[28] and inappropriate statistical evaluation, such as numerous analyses uncorrected for multiple comparisons.[26] Three investigations had numerous participants and reasonable methodological rigor. In one involving 91 patients, 25% with serologic evidence of *M pneumoniae* infection, erythromycin produced no advantage in duration of cough or chest congestion, improved well-being, and antitussive use, although the antibiotic recipients missed 1 day less of work.[27] In another, with 158 patients, doxycycline did not significantly shorten the duration of productive or nocturnal cough, feeling ill, or impaired daily activity.[31] With doxycycline, daytime cough disappeared 1.5 days faster, although it lasted at least 12 days in each group. In patients older than 55 years, cough lasted 4 days less in doxycycline recipients than in the placebo group, and those with frequent coughing who felt ill at entry returned to normal daily activities 2 days sooner with doxycycline administration. These differences, however, occurred in subgroups defined after the trial ended and emerged from numerous statistical analyses uncorrected for multiple comparisons. The largest trial investigated 212 patients with cough and purulent sputum; doxycycline did not reduce daytime or nocturnal cough, purulent sputum, and time "off-color" or off work.[30] Pneumonia was rare (2%), irrespective of the treatment.

In conclusion, although about 70% to 90% of patients seen for acute bronchitis receive antibiotics,[16,32,33] published trials demonstrate no clinically important benefit, even in those with purulent sputum. Four systematic reviews,[34-37] one[37] including results from an unpublished trial, concur in concluding that antibiotics are not warranted for acute bronchitis. Instead of prescribing antibiotics, clinicians should explain that cough persists for 2 to 4 weeks, occasionally longer, and that sputum purulence is unimportant unless other features, such as high fever and chills, suggest pneumonia, which is a rare complication. An antitussive agent, such as dextromethorphan, may relieve symptoms,[38] and inhaled bronchodilators help some patients, especially with dyspnea, wheezing, or severe cough.[39,40]

ASTHMA EXACERBATIONS

Asthma denotes episodic, reversible airway obstruction, usually defined as reduced airflow improved by inhaled bronchodilators. Exacerbations are characterized by increased dyspnea, wheezing, and cough, which is often productive. Microorganisms provoke some attacks: viruses in at least 10% to 55% of patients,[41-44] *M pneumoniae* in less than 5%,[44,45] and *C pneumoniae* in 5% to 10%.[46-48] Investigations have not convincingly incriminated respiratory bacteria such as *S pneumoniae*.[44] One study examined putative "infective" asthma—exacerbations with features suggesting a bacterial process, including altered sputum volume or color, radiographically defined sinusitis, nasal congestion or drainage, pharyngitis, and fever.[49] Twenty-seven patients with asthma and 12 healthy controls underwent transtracheal aspirates to obtain uncontaminated lower respiratory tract secretions. Samples from both groups were sterile or yielded only sparse growth, primarily bacteria of low virulence, such as coagulase-negative staphylococci.

Despite no evidence for bacterial infections in exacerbations, 20% to 50% of patients receive antimicrobials,[41,50-52] a treatment examined in 1 double-blind trial.[53] All 60 hospitalized participants received systemic corticosteroids and bronchodilators for their 71 episodes and randomly received amoxicillin or placebo. This antibiotic improved no outcome measure, including cough severity, dyspnea, wheezing, spirometrically measured airflow, and hospital stay.

In conclusion, without pneumonia, a rare complication, neither obtaining sputum cultures nor prescribing antibiotics is appropriate. Instead, patients should receive bronchodilators and systemic corticosteroids to relieve airway inflammation and obstruction, as authoritative US and British guidelines recommend.[54,55] Neither endorses antibiotic use for uncomplicated exacerbations.

EXACERBATIONS OF CHRONIC BRONCHITIS

Clinically defined, chronic bronchitis is sputum production on most days for at least 3 months annually for 2 consecutive years.[56] Patients are usually current or prior cigarette smokers. Most studies characterize exacerbations by 1 or more of these features: purulent phlegm or increased dyspnea, cough, or sputum volume. Investigations implicate viruses in approximately 20% to 50% of attacks,[57] *C pneumoniae* in about 5%[58,59] (although by serologic examination rather than culture findings), and *M pneumoniae* in less than 1%.[60,61]

Whether respiratory tract bacteria, which chronically colonize many patients' airways, are pathogenic remains controversial. In most investigations, sputum cultures yield *S pneumoniae* and *H influenzae* from about 30% to 50% of patients during purulent exacerbations.[61,62-67] Two careful prospective studies discovered no significant increase in the number of patients whose sputum grew these organisms during exacerbations when compared with periods of remission,[60,61] and neither the presence nor density of these bacteria consistently correlates with sputum purulence or the development of exacerbations.[60,61,68,69] *M catarrhalis* is present in about 5% to 15% of exacerbations, but usually with *S pneumoniae* and *H influenzae*, not as a pure isolate.[65-67] *Haemophilus parainfluenzae*, common in chronic bronchitis, does not increase during attacks.[70] Other bacteria identifiable by routine culture findings could explain few, if any, episodes: protected brush samples from bronchoscopy during exacerbations in both outpatient and hospital settings yielded significant growth from the lower respiratory tract in only about 50% of cases, the isolates being primarily those already discussed.[66,67]

Studies on the serologic and pathologic changes that occur in exacerbations of chronic bronchitis also fail to provide convincing evidence of a bacterial cause.[71] Another approach to elucidate the role of bacteria is to examine the double-blind, placebo-controlled antibiotic trials in treating exacerbations. Of 11 such investigations,[62-64,72-79] 8 show no statistically significant benefit.[63,64,72-74,76,78,79] Unfortunately, these studies vary considerably in quality, size, and outcome criteria, including many subjective ones. A meta-analysis found 6 trials, 2 favoring antimicrobials, that used peak expiratory flow rate as an objective end point and discovered a 10.75 L/min greater improvement in the antibiotic group.[80] Since the patients' average peak expiratory flow rate was approximately 200 L/min, this result represents about a 5% difference, a finding that is clinically and physiologically inconsequential.[71]

The best study supporting antibiotic therapy investigated 173 patients with 362 exacerbations[77] defined by increased dyspnea, sputum volume, or sputum purulence. Overall, success was significantly greater in those receiving antibiotics (68%) than placebo (55%) and failures were fewer (10% vs 19%). For exacerbations with only 1 feature, antibiotics conferred no clinical advantage, and, with 2 features, it was marginal. With all 3 criteria present, about 40% of exacerbations, antibiotics recipients had greater success (63% vs 43%) and less deterioration (14% vs 30%), although whether these differences were statistically significant is unstated. Another large study, involving 278 patients, however, demonstrated no benefit for amoxicillin vs placebo.[78] Both trials concur that antimicrobials are not beneficial in mild attacks. Why these 2 studies otherwise disagree is unclear, but potential explanations include differing entry criteria, patient populations, disease severity, and outcome assessments. Another dissimilarity is that the latter study eliminated patients with fever or suspected pneumonia, while 29% of subjects in the study favoring antibiotics reported fever. If some of these patients had pneumonia, a point impossible to ascertain because chest radiographs were not obtained, the benefit for antibiotics is not surprising. The latter trial also excluded patients taking oral corticosteroids, while in the one favoring antibiotics, about 40% of participants received them, but in no systematic assignment, dose, or duration. A disproportionate number of patients receiving these agents in high doses in the various groups might account for some of the differences in outcome.

The issue of corticosteroids illuminates the crux of treating exacerbations: namely, the goal. Patients primarily seek therapy not for altered sputum volume or color but for diminished exercise capacity and increased dyspnea.[77] Treatment should relieve these symptoms and prevent severe respiratory compromise, the most common reason for hospitalization,[81] by reducing bronchial inflammation and airflow obstruction. Systemic corticosteroids achieve this goal by resolving bronchoconstriction and airway inflammation significantly faster than placebo, both in patients hospitalized with exacerbations[82-84] and in outpatients.[85] The outpatient study showed a striking advantage not only in improving oxygenation and peak expiratory flow rate, but also in preventing deterioration and hospital admission.[85] When patients take systemic corticosteroids for exacerbations, antimicrobials may provide no further benefit. In the large study that favored antibiotics overall,[77] there was no significant benefit for those concurrently receiving systemic corticosteroids. In another trial, among 71 patients treated with prednisolone, those randomly allocated to antibiotics in addition improved no faster than the placebo group.[78] This investigation was small, however, and included 10 patients with asthma.

In conclusion, microbiologic studies provide no conclusive evidence that bacteria cause exacerbations, and in most investigations, antibiotics provide no significant benefit. Overall, the preponderance of information indicates that obtaining sputum cultures and prescribing antimicrobials are unnecessary both in mild exacerbations and in the more severe episodes, which should be treated with systemic corticosteroids. This topic warrants further placebo-controlled, randomized trials, however, to clarify the microbiologic characteristics of exacerbations and determine whether any subgroups, particularly with severe disease, benefit from antimicrobial therapy when receiving concurrent systemic corticosteroids.

ACUTE PHARYNGITIS

Infection with *Streptococcus pyogenes* causes about 5% to 10% of adult pharyngitis in general practice[86-88] and 35% to 40% in emergency departments.[87,89] Other common causes include other streptococci, viruses, *M pneumoniae*, and *C pneumoniae*.[88] Infection with *Neisseria gonorrhoeae*, although usually asymptomatic,[90] constitutes 1% or less of cases.[91]

Discussions of pharyngitis have focused on treating *S pyogenes*. Identifying streptococcal pharyngitis by clinical features[89,92,93] is inaccurate; even when adjusted for disease prevalence,[94] the criteria are insufficiently reliable for confident management decisions.[95] Techniques to detect *S pyogenes* include obtaining pharyngeal culture specimens for everyone or only those with negative rapid test results that demonstrate group A antigen in throat swab findings.[96] Several strategies for treating acute pharyngitis have emerged. One is to prescribe penicillin for all cases, without obtaining any studies.[97] Trials examining this approach demonstrate no significant clinical benefit. In one, involving 528 patients, symptoms resolved no more quickly with penicillin than placebo.[98] Another study randomly assigned 716 patients to 1 of 3 approaches: immediate penicillin, no antibiotics, or delayed therapy—penicillin if symptoms were unimproved after 3 days.[99] No significant difference emerged for resolution of sore throat, time off school or work, or duration of any symptom, except fever, which abated 1 day sooner with antibiotics.

A second strategy is to treat only those cases of acute pharyngitis whose cultures are positive for *S pyogenes*. Several studies have shown that in this group antibiotics alter the clinical course little. Sore throat, fever, and cervical lymph node tenderness resolve only about 1 day sooner than with placebo.[100-102] Furthermore, in the trial reporting these outcomes,[103] patients receiving antimicrobials did not return to school or work more rapidly and had no reduction in respiratory tract infections over the subsequent 6 months.

A third approach is to treat patients whose clinical features suggest streptococcal infection. One double-blind study[104] included 561 adult patients with sore throat for less than 7 days who met at least 3 of the following 4 criteria[89]: history of fever, absence of cough, pharyngeal exudate, and swollen anterior cervical lymph nodes. Symptoms resolved 1.7 days sooner with 7 days of penicillin therapy than with placebo, and patients resumed usual activities 2 days sooner, but they did not return to school or work more rapidly. Nausea (40%) and abdominal pain (25%) were significantly more frequent in the penicillin recipients than in those receiving placebo (15%), although few discontinued the medications because of these adverse effects. The more rapid resolution of symptoms occurred in those with cultures positive for *S pyogenes* or when other streptococci were present in at least 3+ growth specimens (into the third inoculation area on the culture plate).

Although penicillin is unhelpful for patients whose cultures specifically fail to grow streptococci,[100,103,105] some pathogens, such as *M pneumoniae* and *C pneumoniae*, are susceptible to macrolides but not penicillin. Two trials testing erythromycin when throat cultures grew no *S pyogenes*, however, showed no important clinical advantage over placebo.[86,106]

An argument for detecting and treating streptococcal pharyngitis is to prevent its complications, including the immunologic sequelae of acute rheumatic fever (ARF), especially carditis, acute poststreptococcal glomerulonephritis, and the suppurative disorders, primarily peritonsillar abscesses. The efficacy of treating streptococcal pharyngitis to prevent acute poststreptococcal glomerulonephritis is unknown,[107] although some observations suggest a benefit in epidemics of streptococcal pyoderma.[108] In industrialized countries, acute poststreptococcal glomerulonephritis is quite uncommon following streptococcal pharyngitis: a study among Scottish children in the 1970s estimated that it occurred in about 1 of 17 000 cases of untreated patients.[109] It is even rarer in adults, its frequency and severity are declining,[110] and, even if antibiotics were effective, enormous numbers of patients would require treatment to prevent 1 case.

The role of antibiotics in averting peritonsillar abscesses is also uncertain. In a study of 434 untreated patients with sore throat, 1 occurred (0.2%).[111,112] In the trial that used clinical criteria for treatment,[104] 3 (1.7%) of 177 patients given placebo developed this complication. Fortunately, the implications of this infection are currently considerably less alarming than before; nearly all cases satisfactorily respond to outpatient therapy—needle aspiration of the abscess under local anesthesia and antibiotics. Hospitalization and tonsillectomy are rarely necessary.[113]

Studies from the mid 20th century, mostly in military personnel, demonstrated that antibiotics prevent ARF,[114] providing the rationale for the strategy of detecting and treating streptococcal pharyngitis that has prevailed for decades. Authoritative recommendations from prestigious organizations[95,115] and most experts still endorse this approach, based on the conviction that continued adherence to it remains necessary to control ARF. Some investigators,[114,116] however, have argued that in nations, such as the United States, Great Britain, and Australia, where it is rare, this policy is no longer appropriate, considering its costs (eg, time spent seeing patients with pharyngitis, tests to detect streptococci, antibiotics) and the potential therapeutic complications, ranging from minor adverse effects to fatal anaphylaxis, estimated to occur in about 1 to 2 of 100 000 penicillin recipients.[117] Certainly, ARF is very rare in many countries. Outbreaks in the United States during the mid 1980s occasioned concern about a resurgence of the disease[96]; although focal increases occurred; however, no nationwide rise developed. Instead its frequency continued a decline[118,119] that began before the antibiotic era, presumably attributable to 3 factors: better public health, especially reduced household size, which diminishes spread of streptococci; antibiotic administration; and, probably the most important factor in recent decades, decreased prevalence of "rheumatogenic" streptococcal strains likely to cause ARF.[120]

The current risk of adult ARF following untreated streptococcal pharyngitis is unknown, but the es-

timated incidence among Scottish children during the late 1970s, when its frequency equaled that in US children, was about 1 in 40 000.[121] Since the rate among adults even when the disease was more common was about one fifth of that in children[122,123] and its occurrence is now lower than 2 decades ago, the current probability is considerably less. Whatever the actual risk, enormous numbers of adults with streptococcal pharyngitis would require antibiotics to prevent a single case of ARF, and 3 times as many to prevent carditis, which occurs in about one third of adults with ARF.[124]

In conclusion, controlled trials do not support the policy of prescribing antibiotics to all adults with pharyngitis. Instead, most patients should receive antipyretics, reassurance, and information about the disease's natural history: it lasts about 5 days after consultation, and in almost 40% of patients, symptoms persist even longer.[111] For those who fulfill at least 3 of 4 clinical criteria, it is unclear whether the modest clinical benefits outweigh the adverse effects for most patients, but 1 reasonable approach is to offer a 7-day course of oral penicillin to those with more severe symptoms. Using antibiotics to prevent acute poststreptococcal glomerulonephritis and peritonsillar abscesses following streptococcal pharyngitis is unjustified because these complications are rare and the benefit of therapy is uncertain.

Most authorities continue to recommend detecting and treating streptococcal pharyngitis to prevent ARF, but in industrialized nations this policy seems outdated. Certainly, however, it remains warranted in those with prior ARF, along with secondary prophylaxis, to prevent recurrent attacks; in epidemics of ARF or in locales where it remains endemic; and in scarlet fever, for which antibiotics provide substantial benefit.[125]

ACUTE SINUSITIS

Diagnosing bacterial sinusitis is unreliable without sampling sinus contents by surgery or needle aspiration. Computed tomography demonstrates that nearly 90% of patients with the common cold have radiological evidence of sinus disease that usually resolves or markedly improves in 2 to 3 weeks.[126] It is thus an acute rhinosinusitis, and many patients with presumed bacterial infection actually have uncomplicated viral disorders. Most cases of bacterial sinusitis, however, probably follow such infections, which obstruct sinus ostia and impair mucociliary clearance. Bacteria colonizing the nasopharynx apparently enter the normally sterile sinuses and, entrapped, provoke inflammation.[127] The most frequent isolates from needle aspirations, constituting about 60% to 90% of bacteria recovered, are *S pneumoniae* and *H influenzae*.[127,128] Viruses are detectable by culture findings in about 15%,[127] rhinoviruses by reverse transcription polymerase chain reaction in 40%.[129]

Clinicians suspect acute sinusitis when colds or influenza-like illnesses persist for several days, accompanied by nasal congestion, maxillary toothache, sinus discomfort or tenderness, purulent nasal discharge, fever, and headache or facial pain, often worsened on bending forward.[127,130-133] In 1 study, clinical findings independently associated with abnormalities, suggesting sinusitis on plain radiographs, included maxillary toothache, visible purulent nasal secretions, history of colored nasal discharge, poor response to decongestants, and altered transillumination.[130] Predicting the presence or absence of radiographic changes by clinical criteria was excellent at the extremes: sinus radiograph findings were abnormal in 9% of patients with no criterion present, 81% with 4, and 92% with all 5 criteria. With 1, 2, or 3 predictors, however, the probabilities were 21%, 40%, and 63%, respectively, making clinical diagnosis more difficult in these common settings. Moreover, radiographic changes do not reliably identify bacterial sinusitis: only about 60% of patients with abnormal radiograph results have positive culture findings from sinus needle aspiration.[127]

Other studies find no consistently reliable clinical criteria to identify acute sinusitis, including fever, which occurs in 10% to 15% of cases.[130,132,134] Several investigations[131-134] have also shown that only 45% to 70% of patients with clinically suspected sinusitis have radiographic or needle aspiration evidence of it, and only 30% to 40% have a bacterial infection.

For the 60% to 70% of patients having no bacteria in suspected acute sinusitis, antimicrobials presumably confer no benefit. Moreover, given the pathogenesis, promoting sinus drainage by relieving ostial obstruction may be more important than antibacterial therapy. Six double-blind, placebo-controlled trials evaluated antibiotics in acute sinusitis.[131,135-139] Four showed no benefit.[131,135,138,139] The studies conflict for unclear reasons, but examining the 3 best trials—those with numerous participants and clearly delineated entry and outcome criteria—is illuminating. One supported antibiotics,[131] 2 did not.[135,137] One, using computed tomographic criteria of fluid levels or total sinus opacification, randomly gave 130 patients amoxicillin, penicillin, or placebo.[131] Those receiving antibiotics recovered significantly faster: symptoms lasted a median of 9 days for amoxicillin, 11 days for penicillin, and 17 days for placebo. (In 70 patients with identical clinical features, but with only mucosal thickening on computed tomographic scan, antibiotics were no better than placebo, but the numbers in each group were small.[139]) Another trial randomized 214 patients with abnormal plain radiograph results to amoxicillin or placebo.[135] No benefit for antibiotic therapy emerged. The third study used clinical criteria: 3 major symptoms (preceding cold or influenza, purulent nasal discharge, maxillary sinus pain on bending forward) or 2 major symptoms plus 1 other complaint (predominant unilateral maxillary pain, toothache, or pain when chewing).[137] The trial randomized 192 patients to placebo or doxycycline; the antibiotic provided no advantage.

One possible explanation for these discrepant results is that computed tomographic criteria in the first study identified patients more likely to have bacterial infection than the radiographic or clinical criteria of the other 2 trials. Another difference, however, is that the latter studies explicitly prescribed xylometazoline na-

sal drops (which cause vasoconstriction, reducing mucosal edema) and steam inhalation, while the first neither required nasal decongestants nor specified their type or frequency of use. Since relief of ostial obstruction probably hastens improvement, antibiotics may add nothing to aggressive therapy that decreases mucosal edema.

In all studies, symptoms resolved slowly. On average, they began about 2 weeks before entry into the trials, and, however treated, at least 20% to 30% of patients had significant complaints 7 to 10 days later, some persisting for at least 2 to 3 weeks. In these studies placebo recipients developed no serious complications, such as subdural empyema or chronic sinusitis.

In conclusion, most patients with putative acute sinusitis have no bacterial infection, and antibiotics are unhelpful for most patients with suggestive symptoms, even when suspicious abnormal findings appear on radiographs or computed tomographic scans. Ordinarily, such tests are unnecessary, impractical, and expensive. Instead of antibiotics, most patients should receive nasal drops or sprays (xylometazoline or oxymetazoline), analgesics, and, possibly, steam inhalations 3 times daily. They should understand that symptoms abate slowly; complete resolution may require several weeks, but some improvement usually occurs within a few days. Currently, no clinical criteria reliably define patients who might benefit from antibiotics, but treatment is certainly reasonable for those with high fever, systemic toxicity, immune defects, or features suggesting intracranial or orbital involvement.

ADVERSE EFFECTS

In many trials, drug-related complications were much more common with antibiotics, as 3 recent studies of acute sinusitis demonstrate. In 1, doxycycline recipients had a 17% incidence of adverse effects, with 4 (4%) of 98 patients discontinuing the medication, while only 2% reported complications in the placebo group, none stopping the agent for that reason.[137] In the second trial, adverse effects occurred in 9% in the placebo group vs 28% in the amoxicillin recipients,[135] and in the third study, they developed in 36% of the placebo group compared with 56% receiving amoxicillin and 59% receiving penicillin.[133] Recent investigations of pharyngitis, acute bronchitis, and exacerbations of chronic bronchitis also demonstrated substantially more adverse effects in those receiving antimicrobials.[22,31,78,104] Determining the overall benefits of treating respiratory tract infections, therefore, requires considering symptoms that antibiotics cause, which may be less palatable than those from the original disorder. One study, for example, queried patients about the additional duration of pharyngitis that they would accept compared with the therapeutic risks.[140] They preferred 1.5 to 2.5 days of symptoms to even a 5% chance of a mild penicillin rash (hives).

ANTIBIOTIC THERAPY AND PATIENT EXPECTATIONS

In a survey, the most common prescribing situation by far that disquieted English practitioners was respiratory tract infections, and the most troubling medicines were antibiotics.[141] In these difficult circumstances, patient expectation predominantly dictated whether practitioners provided medications. Indeed, several studies confirm that people expecting prescriptions receive them far more frequently than those who do not,[5,142-145] even when clinicians consider medications unjustified.[145] The strongest predictor is not the patients' actual attitude, but the practitioners' judgment of their attitude.[5,144,146] Physicians often err,[5,144,146] prescribing medications more often than patients desire[142,144-148] or consider appropriate.[142] Moreover, when patients state that they want antibiotics for respiratory tract infections, what they often really want is a medicine to relieve their symptoms.[149] Indeed, they are frequently mistaken about which medications are actually antibiotics.[149]

Clinicians may assume that providing antibiotics makes patients happier. Satisfaction, however, usually depends not on whether patients receive antibiotics for respiratory tract infections, even when they expect them,[5,99,150] but on whether practitioners deal with their concerns,[99] show personal interest in them,[151] provide and discuss the diagnosis,[5,151] reassure them that their disease is not serious,[152] and explain the treatment.[5] Contentment appears therapeutic: patients with pharyngitis improved faster when satisfied, which most closely related to feeling that clinicians addressed their concerns.[99]

Some practitioners may believe that prescribing antimicrobials is quicker than fulfilling these expectations, although no investigations evaluated the time involved with these different strategies or the patients' assessment of such behavior. Two studies of pharyngitis, however, showed that those not receiving antibiotics were less likely to return for subsequent episodes than those who did, although both groups were equally satisfied.[111,153] These trials occurred where patients were unlikely to seek other medical care; rather, they managed their illness by themselves. Physicians who educate patients in this way may actually reduce their workload.

CONCLUSIONS

Promiscuous prescribing of antibiotics substantially increases the cost of medical care, but it has a more pernicious effect. Antimicrobials are unique among medicines in that their excessive use, especially of those with a broad spectrum of antibacterial activity, can lead to decreased efficacy, as bacteria become resistant throughout the community. Unsurprisingly, the widespread indiscriminate administration of antibiotics that is common now has diminished the susceptibility of respiratory flora.[6] To help alleviate this problem, clinicians should avoid prescribing antibiotics for conditions for which they are ineffective, marginal, or unimpressive, reserving them instead for conditions for which they exert substantial clinical impact. Except where noted, the available information indicates that antibiotics provide little or no benefit for disorders reviewed here, which account for nearly half of adult outpatient antibiotic use. Rather than prescribing antimicro-

bials, practitioners should explain that these ailments are rarely serious; they spontaneously abate, albeit sometimes slowly; antibiotics do not hasten resolution, but often make patients decidedly worse; and treating symptoms by other means frequently helps. For nasal and sinus complaints, vasoconstricting nasal sprays or drops such as oxymetazoline are reasonable, and, in acute bronchitis, antitussives may diminish coughing. Inhaled bronchodilators are often beneficial for dyspnea, wheezing, or severe cough in acute bronchitis and are indicated, along with oral corticosteroids, for exacerbations of asthma and chronic obstructive lung disease.

Using terminology that suggests a viral cause may also help,[154] since many patients understand that antibiotics are ineffective for viral infections: practitioners should use diagnoses such as "viral sore throat" and "chest cold" rather than "acute bronchitis," and "sinus cold" rather than "acute sinusitis." As indicated at the beginning of this article, William Osler[155] acknowledged that humans enjoy taking drugs, but he also said, in a statement remarkably appropriate for antibiotics, "One of the first duties of the physician is to educate the masses not to take medicine."

Accepted for publication July 2, 2001.

Corresponding author and reprints: J. V. Hirschmann, MD, Medical Service (111), Puget Sound VA Medical Center, 1660 S Columbian Way, Seattle, WA 98108 (e-mail: pepsi@u.washington.edu).

REFERENCES

1. Osler W. Recent advances in medicine. *Science.* 1891;17:170-171.
2. McCaig LF, Hughes JM. Trends in antimicrobial drug prescribing among office-based physicians in the United States. *JAMA.* 1995;273:214-219.
3. 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.
4. Mainous AG III, Hueston WJ, Clark JR. Antibiotics and upper respiratory infection: do some folks think there is a cure for the common cold? *J Fam Pract.* 1996;42:357-361.
5. 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.
6. Jacoby GA. Prevalence and resistance mechanisms of common bacterial respiratory pathogens. *Clin Infect Dis.* 1994;18:951-957.
7. Cohen ML. Epidemiology of drug resistance: implications for a post-antimicrobial era. *Science.* 1992;257:1050-1055.
8. Seppala H, Klaukka T, Vuopio-Varkila J, et al. The effect of changes in the consumption of macrolide antibiotics on erythromycin resistance in group A streptococci in Finland. *N Engl J Med.* 1997;337:441-446.
9. Kristinsson KG. Effect of antimicrobial use and other risk factors on antimicrobial resistance in pneumococci. *Microb Drug Resist.* 1997;3:117-123.
10. Williamson HA. A randomized, controlled trial of doxycycline in the treatment of acute bronchitis. *J Fam Pract.* 1984;19:481-486.
11. Verheij T, Hermans J, Kaptein A, Mulder J. Acute bronchitis: course of symptoms and restrictions in patients' daily activities. *Scand J Prim Health Care.* 1995;13:8-12.
12. Cate TR, Couch RB, Fleet WF, Griffith WR, Gerone PJ, Knight V. Production of tracheobronchitis in volunteers with rhinovirus in a small-particle aerosol. *Am J Epidemiol.* 1965;81:95-105.
13. Monto AS, Cavallaro JJ. The Tecumseh study of respiratory illness, II: patterns of occurrence of infection with respiratory pathogens, 1965-1969. *Am J Epidemiol.* 1971;94:280-289.
14. Foy HM. Infections caused by *Mycoplasma pneumoniae* and possible carrier state in different populations of patients. *Clin Infect Dis.* 1993;17 (suppl 1):S37-S46.
15. Grayston JT, Aldous MB, Easton A, et al. Evidence that *Chlamydia pneumoniae* causes pneumonia and bronchitis. *J Infect Dis.* 1993;168:1231-1235.
16. Boldy DAR, Skidmore SJ, Ayres JG. Acute bronchitis in the community: clinical features, infective factors, changes in pulmonary function and bronchial reactivity to histamine. *Respir Med.* 1990;84:377-385.
17. Evans AS, Allen V, Sueltmann S. *Mycoplasma pneumoniae* infections in University of Wisconsin students. *Am Rev Respir Dis.* 1967;96:237-244.
18. Thom DH, Grayston JT, Wang SP, Kuo CC, Altman J. *Chlamydia pneumoniae* strain TWAR, *Mycoplasma pneumoniae*, and viral infections in acute respiratory disease in a university student health clinic population. *Am J Epidemiol.* 1990;132:248-256.
19. Thom DH, Grayston JT, Campbell LA, Kuo CC, Diwan VK, Wang SP. Respiratory infection with *Chlamydia pneumoniae* in middle-aged and older adult outpatients. *Eur J Clin Microbiol Infect Dis.* 1994;13:785-792.
20. Jonsson JS, Sigurdsson JA, Kristinsson KG, Guonadottir M, Magnusson S. Acute bronchitis in adults: how close do we come to its ætiology in general practice? *Scand J Prim Health Care.* 1997;15:156-160.
21. Henry D, Ruoff GE, Rhudy J, et al. Effectiveness of short-course therapy (5 days) with cefuroxime axetil in treatment of secondary bacterial infections of acute bronchitis. *Antimicrob Agents Chemother.* 1995;39:2528-2534.
22. Vaneechoutte M, Verschraegen G, Claeys G, Weise B, van den Abeele AM. Respiratory tract carrier rates of *Moraxella (Branhamella) catarrhalis* in adults and children and interpretation of the isolation of *M catarrhalis* from sputum. *J Clin Microbiol.* 1990;28:2674-2680.
23. Hendley JO, Sande MA, Stewart PM, Gwaltney JM Jr. Spread of *Streptococcus pneumoniae* in families, I: carriage rates and distribution of types. *J Infect Dis.* 1975;132:55-61.
24. Hirschmann JV, Everett ED. *Haemophilus influenzae* infections in adults: report of nine cases and review of the literature. *Medicine (Baltimore).* 1979;58:80-94.
25. Franks P, Gleiner JA. The treatment of acute bronchitis with trimethoprim and sulfamethoxazole. *J Fam Pract.* 1984;19:185-190.
26. 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.
27. King DE, Williams WC, Bishop L, Shechter A. Effectiveness of erythromycin in the treatment of acute bronchitis. *J Fam Pract.* 1996;42:601-605.
28. Brickfield FX, Carter WH, Johnson RE. Erythromycin in the treatment of acute bronchitis in a community practice. *J Fam Pract.* 1986;23:119-122.
29. Scherl ER, Riegler SL, Cooper JK. Doxycycline in acute bronchitis: a randomized double-blind trial. *J Ky Med Assoc.* 1987;85:539-541.
30. Stott NCH, West RR. Randomised controlled trial of antibiotics in patients with cough and purulent sputum. *BMJ.* 1976;2:556-559.
31. 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.
32. Hueston WJ, Mainous AG III, Brauer N, Mercuri J. Evaluation and treatment of respiratory infections: does managed care make a difference? *J Fam Pract.* 1997;44:572-577.
33. Mainous AG III, Zoorob RJ, Hueston WJ. Current management of acute bronchitis in ambulatory care: the use of antibiotics and bronchodilators. *Arch Fam Med.* 1996;5:79-83.
34. Orr PH, Scherer K, Macdonald A, Moffatt MEK. Randomized placebo-controlled trials of antibiotics for acute bronchitis: a critical review of the literature. *J Fam Pract.* 1993;36:507-512.
35. MacKay DN. Treatment of acute bronchitis in adults without underlying lung disease. *J Gen Intern Med.* 1996;11:557-562.
36. Bent S, Saint S, Vittinghoff E, Grady D. Antibiotics in acute bronchitis: a meta-analysis. *Am J Med.* 1999;107:62-67.
37. Fahey T, Stocks N, Thomas T. Quantitative systematic review of randomised controlled trials comparing antibiotic with placebo for acute cough in adults. *BMJ.* 1998;316:906-910.
38. Irwin RS, Curley FJ. The treatment of cough: a comprehensive review. *Chest.* 1991;99:1477-1484.
39. Hueston WJ. Albuterol delivered by metered-dose inhaler to treat acute bronchitis. *J Fam Pract.* 1994;39:437-440.
40. Melbye H, Aasebø U, Straume B. Symptomatic effect of inhaled fenoterol in acute bronchitis: a placebo-controlled double-blind study. *Fam Pract.* 1991;8:216-222.
41. Nicholson KG, Kent J, Ireland DC. Respiratory viruses and exacerbations of asthma in adults. *BMJ.* 1993;307:982-986.
42. Atmar RL, Guy E, Guntupalli KK, et al. Respiratory tract viral infections in inner-city asthmatic adults. *Arch Intern Med.* 1998;158:2453-2459.
43. Clarke CW. Relationship of bacterial and viral infections to exacerbations of asthma. *Thorax.* 1979;34:344-347.
44. Hudgel DW, Langston L Jr, Selner JC, McIntosh K. Viral and bacterial infections in adults with chronic asthma. *Am Rev Respir Dis.* 1979;120:393-397.
45. Huhti E, Mokka T, Nikoskelainen J, Halonen P.

Association of viral and mycoplasma infections with exacerbations of asthma. *Ann Allergy*. 1974; 33:145-149.
46. Allegra L, Blasi F, Centanni S, et al. Acute exacerbations of asthma in adults: role of *Chlamydia pneumoniae* infection. *Eur Respir J*. 1994; 7:2165-2168.
47. Cook PJ, Davies P, Tunnicliffe W, Ayres JG, Honeybourne D, Wise R. *Chlamydia pneumoniae* and asthma. *Thorax*. 1998;53:254-259.
48. Miyashita N, Kubota Y, Nakajima M, Niki Y, Kawane H, Matsushima T. *Chlamydia pneumoniae* and exacerbations of asthma in adults. *Ann Allergy Asthma Immunol*. 1998;80:405-409.
49. Berman SZ, Mathison DA, Stevenson DD, Tan EM, Vaughan JH. Transtracheal aspiration studies in asthmatic patients in relapse with "infective" asthma and in subjects without respiratory disease. *J Allergy Clin Immunol*. 1975;56: 206-214.
50. Neville RG, Hoskins G, Smith B, Clark RA. How general practitioners manage acute asthma attacks. *Thorax*. 1997;52:153-156.
51. Lahdensuo A, Haahtela T, Herrala J, et al. Randomised comparison of guided self management and traditional treatment of asthma over one year. *BMJ*. 1996;312:748-752.
52. Fitzgerald JM, Hargreave FE. Acute asthma: emergency department management and prospective evaluation of outcome. *CMAJ*. 1990;142: 591-595.
53. Graham VAL, Milton AF, Knowles GK, Davies RJ. Routine antibiotics in hospital management of acute asthma. *Lancet*. 1982;1;418-421.
54. National Institutes of Health. *Highlights of the Expert Panel Report 2: Guidelines for the Diagnosis and Management of Asthma*. Bethesda, Md: National Institutes of Health; 1997:1-50. NIH publication 97-4051A.
55. British Thoracic Society, British Paediatric Association, Research Unit of the Royal College of Physicians of London, et al. Guidelines for the management of asthma. *Thorax*. 1993;48 (suppl 2):S1-S24.
56. American Thoracic Society. Definitions and classification of chronic bronchitis, asthma, and pulmonary emphysema. *Am Rev Respir Dis*. 1962; 85:762-768.
57. Buscho RO, Saxtan D, Shultz PS, Finch E, Mufson MA. Infections with viruses and *Mycoplasma pneumoniae* during exacerbations of chronic bronchitis. *J Infect Dis*. 1978;137:377-383.
58. Beaty CD, Grayston JT, Wang SP, Kuo CC, Reto CS, Martin TR. *Chlamydia pneumoniae*, strain TWAR, infection in patients with chronic obstructive pulmonary disease. *Am Rev Respir Dis*. 1991;144:1408-1410.
59. Blasi F, Legnani D, Lombardo VM, et al. *Chlamydia pneumoniae* infection in acute exacerbations of COPD. *Eur Respir J*. 1993;6:19-22.
60. Gump DW, Phillips CA, Forsyth BR, McIntosh K, Lamborn KR, Stouch WH. Role of infection in chronic bronchitis. *Am Rev Respir Dis*. 1976; 113:465-474.
61. McHardy VU, Inglis JM, Calder MA, et al. A study of infective and other factors in exacerbations of chronic bronchitis. *Br J Dis Chest*. 1980;74:228-238.
62. Pines A, Raafat H, Greenfield JSB, Linsell WD, Solari ME. Antibiotic regimens in moderately ill patients with purulent exacerbations of chronic bronchitis. *Br J Dis Chest*. 1972;66:107-115.
63. Berry DG, Fry J, Hindley CP, et al. Exacerbations of chronic bronchitis: treatment with oxytetracycline. *Lancet*. 1960;1:137-139.
64. Elmes PC, King TKC, Langlands JHM, et al. Value of ampicillin in the hospital treatment of exacerbations of chronic bronchitis. *BMJ*. 1965;2: 904-908.
65. Schreiner A, Bjerkestrand G, Digranes A, Halvorsen FJ, Kommedal TM. Bacteriological findings in the transtracheal aspirate from patients with acute exacerbation of chronic bronchitis. *Infection*. 1978; 6:54-56.
66. Monsó E, Ruiz J, Rosell A, et al. Bacterial infection in chronic obstructive pulmonary disease: a study of stable and exacerbated outpatients using the protected specimen brush. *Am J Respir Crit Care Med*. 1995;152:1316-1320.
67. Fagon JY, Chastre J, Trouillet JL, et al. Characterization of distal bronchial microflora during acute exacerbation of chronic bronchitis: use of the protected specimen brush technique in 54 mechanically ventilated patients. *Am Rev Respir Dis*. 1990;142:1004-1008.
68. Fisher M, Akhtar AJ, Calder MA, et al. Pilot study of factors associated with exacerbations in chronic bronchitis. *BMJ*. 1969;4:187-192.
69. Storey PB, Morgan WKC, Diaz AJ, Klaff JL, Spicer WS Jr. Chronic obstructive airway disease: bacterial and cellular content of the sputum. *Am Rev Respir Dis*. 1964;90:730-735.
70. Smith CB, Golden CA, Kanner RE, Renzetti AD. *Haemophilus influenzae* and *Haemophilus parainfluenzae* in chronic obstructive pulmonary disease. *Lancet*. 1976;1:1253-1255.
71. Hirschmann JV. Do bacteria cause exacerbations of COPD? *Chest*. 2000;118:193-203.
72. Elmes PC, Fletcher CM, Dutton AAC. Prophylactic use of oxytetracycline for exacerbations of chronic bronchitis. *BMJ*. 1957;2:1272-1275.
73. Fear EC, Edwards G. Antibiotic regimes in chronic bronchitis. *Br J Dis Chest*. 1962;56:153-162.
74. Petersen ES, Esmann V, Høncke P, Munkner C. A controlled study of the effect of treatment on chronic bronchitis: an evaluation using pulmonary function tests. *Acta Med Scand*. 1967;182: 293-305.
75. Pines A, Raafat H, Plucinski K, Greenfield JSB, Solari M. Antibiotic regimens in severe and acute purulent exacerbations of chronic bronchitis. *BMJ*. 1968;2:735-738.
76. Nicotra MB, Rivera M, Awe RJ. Antibiotic therapy of acute exacerbations of chronic bronchitis: a controlled study using tetracycline. *Ann Intern Med*. 1982;97:18-21.
77. 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.
78. Jørgensen AF, Coolidge J, Pedersen PA, Petersen KP, Waldorff S, Widding E. Amoxicillin in treatment of acute uncomplicated exacerbations of chronic bronchitis: a double-blind, placebo-controlled multicentre study in general practice. *Scand J Prim Health Care*. 1992;10:7-11.
79. Sachs APE, Koëter GH, Groenier KH, van der Waaij D, Schiphuis J, Meyboom-de Jong B. Changes in symptoms, peak expiratory flow, and sputum flora during treatment with antibiotics of exacerbations in patients with chronic obstructive pulmonary disease in general practice. *Thorax*. 1995;50:758-763.
80. Saint S, Bent S, Vittinghoff E, Grady D. Antibiotics in chronic obstructive pulmonary disease exacerbations: a meta-analysis. *JAMA*. 1995; 273:957-960.
81. American Thoracic Society. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 1995;152(suppl):S77-S120.
82. Albert RK, Martin TR, Lewis SW. Controlled clinical trial of methylprednisolone in patients with chronic bronchitis and acute respiratory insufficiency. *Ann Intern Med*. 1980;92:753-758.
83. Niewoehner DE, Erbland ML, Deupree RH, et al. Effect of systemic glucocorticoids on exacerbations of chronic obstructive pulmonary disease. *N Engl J Med*. 1999;340:1941-1947.
84. Davies L, Angus RM, Calverley PMA. Oral corticosteroids in patients admitted to hospital with exacerbations of chronic obstructive pulmonary disease: a prospective randomised controlled trial. *Lancet*. 1999;354:456-460.
85. Thompson WH, Nielson CP, Carvalho P, Charan NB, Crowley JJ. Controlled trial of oral prednisone in outpatients with acute COPD exacerbation. *Am J Respir Crit Care Med*. 1996;154: 407-412.
86. Petersen K, Phillips RS, Soukup J, Komaroff AL, Aronson M. The effect of erythromycin on resolution of symptoms among adults with pharyngitis not caused by group A streptococcus. *J Gen Intern Med*. 1997;12:95-101.
87. Clancy CM, Centor RM, Campbell MS, Dalton HP. Rational decision making based on history: adult sore throats. *J Gen Intern Med*. 1988;3:213-217.
88. Huovinen P, Lahtonen R, Ziegler T, et al. Pharyngitis in adults: the presence and coexistence of viruses and bacterial organisms. *Ann Intern Med*. 1989;110:612-616.
89. Wigton RS, Connor JL, Centor RM. Transportability of a decision rule for the diagnosis of streptococcal pharyngitis. *Arch Intern Med*. 1986; 146:81-83.
90. Weisner PJ, Tronca E, Bonin P, Pedersen AHB, Holmes KK. Clinical spectrum of pharyngeal gonococcal infection. *N Engl J Med*. 1973;288: 181-185.
91. Komaroff AL, Aronson MD, Pass TM, Ervin CT. Prevalence of pharyngeal gonorrhea in general medical patients with sore throats. *Sex Transm Dis*. 1980;7:116-169.
92. Walsh BT, Bookheim WW, Johnson RC, Tompkins RK. Recognition of streptococcal pharyngitis in adults. *Arch Intern Med*. 1975;135:1493-1497.
93. Dagnelie CF, Touw-Otten FWMM, Kuyvenhoven MM, Rozenberg-Arska M, De Melker RA. Bacterial flora in patients presenting with sore throat in Dutch general practice. *Fam Pract*. 1993; 10:371-377.
94. Poses RM, Cebul RD, Collins M, Fager SS. The importance of disease prevalence in transporting clinical prediction rules: the case of streptococcal pharyngitis. *Ann Intern Med*. 1986;105: 586-591.
95. Dajani A, Taubert K, Ferrieri P, et al. Treatment of acute streptococcal pharyngitis and prevention of acute rheumatic fever: a statement for health professionals. *Pediatrics*. 1995;96:758-764.
96. Bisno AL. Group A streptococcal infections and acute rheumatic fever. *N Engl J Med*. 1991;325: 783-793.
97. Tompkins RK, Burnes DC, Cable WE. An analysis of the cost-effectiveness of pharyngitis management and acute rheumatic fever prevention. *Ann Intern Med*. 1977;86:481-492.
98. Whitfield MJ, Hughes AO. Penicillin in sore throat. *Practitioner*. 1981;225:234-239.
99. Little P, Williamson I, Warner G, Gould C, Gantley M, Kinmouth AL. Open randomised trial of prescribing strategies in managing sore throat. *BMJ*. 1997;314:722-727.

100. Brumfitt W, Slater JDH. Treatment of acute sore throat with penicillin: a controlled trial in young soldiers. *Lancet*. 1957;1:8-11.
101. Denny FW, Wannamaker LW, Hahn EO. Comparative effects of penicillin, aureomycin and terramycin on streptococcal tonsillitis and pharyngitis. *Pediatrics*. 1953;11:7-13.
102. Brink WR, Rammelkamp CH Jr, Denny FW, Wannamaker LW. Effect of penicillin and aureomycin on the natural course of streptococcal tonsillitis and pharyngitis. *Am J Med*. 1951;10:300-308.
103. Dagnelie CF, van der Graaf Y, De Melker RA, Touw-Otten FWMM. Do patients with sore throat benefit from penicillin? a randomized double-blind placebo-controlled clinical trial with penicillin V in general practice. *Br J Gen Pract*. 1996; 46:589-593.
104. Zwart S, Sachs APE, Ruijs GJHM, Gubbels JW, Hoes AW, de Melder RA. Penicillin for acute sore throat: randomised double blind trial of seven days versus three days treatment or placebo in adults. *BMJ*. 2000;320:150-154.
105. Bennike T, Brøchner-Mortensen K, Kjaer E, Skadhauge K, Trolle E. Penicillin in acute tonsillitis, phlegmonous tonsillitis and ulcerative tonsillitis. *Acta Med Scand*. 1951;139:253-274.
106. McDonald CJ, Tierney WM, Hui SL, French MLV, Leland DS, Jones RB. A controlled trial of erythromycin in adults with nonstreptococcal pharyngitis. *J Infect Dis*. 1985;152:1093-1094.
107. Weinstein L, Le Frock J. Does antimicrobial therapy of streptococcal pharyngitis or pyoderma alter the risk of glomerulonephritis? *J Infect Dis*. 1971;124:229-231.
108. Johnston F, Carapetis J, Patel MS, Wallace T, Spillane P. Evaluating the use of penicillin to control outbreaks of acute poststreptococcal glomerulonephritis. *Pediatr Infect Dis*. 1999;18: 327-332.
109. Taylor JL, Howie JGR. Antibiotics, sore throats and acute nephritis. *J R Coll Gen Pract*. 1983; 33:783-786.
110. Tejani A, Ingulli E. Poststreptococcal glomerulonephritis: current clinical and pathologic concepts. *Nephron*. 1990;55:1-5.
111. Little P, Gould C, Williamson I, Warner G, Gantley M, Kinmouth AL. Reattendance and complications in a randomised trial of prescribing strategies for sore throat: the medicalising effect of prescribing antibiotics. *BMJ*. 1997;315:350-352.
112. Little P, Williamson I, Warner G, Moore M. Care must be taken when extrapolating data [letter]. *BMJ*. 2000;320:1666.
113. Stringer SP, Schaefer SD, Close LG. A randomized trial for outpatient management of peritonsillar abscess. *Arch Otolaryngol Head Neck Surg*. 1988;114:296-298.
114. Del Mar C. Managing sore throat: a literature review, II: do antibiotics confer benefit? *Med J Aust*. 1992;156:644-649.
115. Bisno AL, Gerber MA, Gwaltney JM Jr, Kaplan EL, Schwartz RH. Diagnosis and management of group A streptococcal pharyngitis: a practice guideline. *Clin Infect Dis*. 1997;25:574-583.
116. Little PS, Williamson I. Are antibiotics appropriate for sore throats? costs outweigh the benefits. *BMJ*. 1994;309:1010-1011.
117. Lin RY. A perspective on penicillin allergy. *Arch Intern Med*. 1992;152:930-937.
118. Taubert KA, Rowley AH, Shulman ST. Nationwide survey of Kawasaki disease and acute rheumatic fever. *J Pediatr*. 1991;119:279-282.
119. Levine OS, Schwartz B. Monitoring trends in acute rheumatic fever in the United States [letter]. *Ped Infect Dis J*. 1995;14:823.
120. Stollerman GH. Rheumatic fever. *Lancet*. 1997; 349:935-942.
121. Howie JGR, Foggo BA. Antibiotics, sore throats and rheumatic fever. *J R Coll Gen Pract*. 1985; 35:223-224.
122. Gordis L, Lilienfeld AM, Rodriguez R. A community-wide study of acute rheumatic fever in adults: epidemiologic and preventive factors. *JAMA*. 1969;210:862-865.
123. Annegers JF, Pillman NL, Weidman WH, Kurland LT. Rheumatic fever in Rochester, Minnesota, 1935-1978. *Mayo Clin Proc*. 1982;57:753-757.
124. Wallace MR, Garst PD, Papadimos TJ, Oldfield EC III. The return of acute rheumatic fever in young adults. *JAMA*. 1989;262:2557-2561.
125. Haight TH. Erythromycin therapy of respiratory infections, I: controlled studies on the comparative efficacy of erythromycin and penicillin in scarlet fever. *J Clin Lab Med*. 1954;43:15-30.
126. Gwaltney JM Jr, Phillips CD, Miller RD, Riker DK. Computed tomographic study of the common cold. *N Engl J Med*. 1994;330:25-30.
127. Gwaltney JM Jr. Acute community-acquired sinusitis. *Clin Infect Dis*. 1996;23:1209-1225.
128. Jousimies-Somer HR, Savolainen S, Ylikoski JS. Bacteriological findings of acute maxillary sinusitis in young adults. *J Clin Microbiol*. 1988; 26:1919-1925.
129. Pitkäranta A, Arruda E, Malmberg H, Hayden FG. Detection of rhinovirus in sinus brushings of patients with acute community-acquired sinusitis by reverse transcription-PCR. *J Clin Microbiol*. 1997;35:1791-1793.
130. Williams JW Jr, Simel DL, Roberts L, Samsa GP. Clinical evaluation for sinusitis: making the diagnosis by history and physical examination. *Ann Intern Med*. 1992;117:705-710.
131. Lindbæk M, Hjortdahl P, Johnsen ULH. Randomised, double-blind, placebo controlled trial of penicillin V and amoxycillin in treatment of acute sinus infections in adults. *BMJ*. 1996;313: 325-329.
132. Hansen JG, Schmidt H, Rosborg J, Lund E. Predicting acute maxillary sinusitis in a general practice population. *BMJ*. 1995;311:233-236.
133. Lindbæk M, Hjortdahl P, Johnsen ULH. Use of symptoms, signs, and blood tests to diagnose acute sinus infections in primary care: comparison with computed tomography. *Fam Med*. 1996; 28:183-188.
134. Berg O, Carenfelt C. Analysis of symptoms and clinical signs in the maxillary sinus empyema. *Acta Otolaryngol (Stockh)*. 1988;105:343-349.
135. Van Buchem FL, Knottnerus JA, Schrijnemaekers VJJ, Peeters MF. Primary-care-based randomised placebo-controlled trial of antibiotic treatment in acute maxillary sinusitis. *Lancet*. 1997;349:683-687.
136. Gananca M, Trabulsi LR. The therapeutic effects of cyclacillin in acute sinusitis: in vitro and in vivo correlations in a placebo-controlled study. *Curr Med Res Opin*. 1973;1:362-368.
137. Stalman W, van Essen GA, van der Graaf Y, De Melker RA. The end of antibiotic treatment in adults with acute sinusitis-like complaints in general practice? a placebo-controlled double-blind randomized doxycycline trial. *Br J Gen Pract*. 1977;47:794-799.
138. Rantanen T, Arvilommi H. Double-blind trial of doxicycline in acute maxillary sinusitis: a clinical and bacteriological study. *Acta Otolaryngol*. 1973;76:58-62.
139. Lindbæk M, Daastad E, Dolvik S, Johnsen U, Lærum E, Hjortdahl P. Antibiotic treatment of patients with mucosal thickening in the paranasal sinuses, and validation of cut-off points in sinus CT. *Rhinology*. 1998;36:7-11.
140. Herman JM. Patients' willingness to take risks in the management of pharyngitis. *J Fam Pract*. 1984;19:767-772.
141. Bradley CP. Uncomfortable prescribing decisions: a critical incident study. *BMJ*. 1992;304: 294-296.
142. 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.
143. Virji A, Britten N. A study of the relationship between patients' attitudes and doctors' prescribing. *Fam Pract*. 1991;8:314-319.
144. Webb S, Lloyd M. Prescribing and referral in general practice: a study of patients' expectations and doctors' actions. *Br J Gen Pract*. 1994;44: 165-169.
145. Himmel W, Lippert-Urbanke E, Kochen MM. Are patients more satisfied when they receive a prescription? the effect of patient expectations in general practice. *Scand J Prim Health Care*. 1997; 15:118-122.
146. Macfarlane J, Holmes W, Macfarlane R, Britten N. Influence of patients' expectations on antibiotic management of acute lower respiratory tract illness in general practice: questionnaire study. *BMJ*. 1997;315:1211-1214.
147. Cockburn J, Pit S. Prescribing behaviour in clinical practice: patients' expectations and doctors' perceptions of patients' expectations—a questionnaire study. *BMJ*. 1997;315:520-523.
148. Sanchez-Menegay C, Stalder H. Do physicians take into account patients' expectations? *J Gen Intern Med*. 1994;9:404-406.
149. Hong JS, Philbrick LT, Schorling JB. Treatment of upper respiratory infections: do patients really want antibiotics? *Am J Med*. 1999;107:511-515.
150. Cowan PF. Patient satisfaction with an office visit for the common cold. *J Fam Pract*. 1987;24: 412-413.
151. Sanchez-Menegay C, Hudes ES, Cummings SR. Patient expectations and satisfaction with medical care for upper respiratory infections. *J Gen Intern Med*. 1992;7:432-434.
152. Braun BL, Fowles JB. Characteristics and experiences of parents and adults who want antibiotics for cold symptoms. *Arch Fam Med*. 2000; 9:589-595.
153. Herz MJ. Antibiotics and the adult sore throat—an unnecessary ceremony. *Fam Pract*. 1988;5:196-199.
154. Gonzales R, Wilson A, Crane LA, et al. What's in a name? public knowledge, attitudes, and experiences with antibiotic use for acute bronchitis. *Am J Med*. 2000;108:83-85.
155. Bean RB, Bean WB, eds. *Sir William Osler: Aphorisms From His Bedside Teachings and Writings*. Springfield, Ill: Charles C Thomas; 1961:105.