

Evaluating the need, timing and best choice of antibiotic therapy for acute otitis media and tonsillopharyngitis infections in children

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Deciding whether an antibiotic is necessary, when to begin therapy and selecting an optimal drug is an everyday challenge in clinical practice. *In vitro* susceptibility testing which determines the minimum concentration necessary for a particular antibiotic to inhibit or kill most strains of a bacterial species and pharmacodynamic modeling are useful but have limitations. The need for antibiotic therapy for acute otitis media (AOM) has been recently questioned. However, explanations for uniformly positive results with many antibiotic and placebo comparative trials include overdiagnosis of AOM at study entry, inclusion of patients with mild or uncomplicated AOM and broad criteria for the definition of clinical success. Recurrent and persistent AOM does not have as favorable a natural history as uncomplicated AOM; children below 2 years of age benefit most from antibiotic therapy. Selecting the best choice among the many antibiotics that can be used to treat AOM has become more complex over the last decade due to escalating antibiotic resistance among the pathogens that cause this infection. Broader spectrum antibiotics such as cefdinir, the newly introduced third generation cephalosporin, have their most prominent use in the treatment of persistent and recurrent AOM.

In the early 1950s and 1960s penicillin clearly was the best available agent for the treatment of group A streptococcal (GAS) infections. In the 1970s the situation began to change as cephalosporin antibiotics became available. Superior eradication rates with cephalosporins such as cefdinir have now been well-documented. The leading hypothesis to explain the widening gap in efficacy between penicillin and cephalosporins relates to two major concepts: the presence

of copathogens and differential alteration of the normal microbial ecology in the throat as a consequence of the selected therapy. There are positive and negative consequences to early initiation of antibiotic therapy for GAS tonsillopharyngitis. Penicillin has persisting good efficacy in patients older than the age of 12 years and in those who have been ill for >2 days. Shortening therapy for GAS tonsillopharyngitis offers a therapeutic advantage. Cefpodoxime proxetil and cefdinir have a 5-day indication for the treatment of GAS tonsillopharyngitis.

Antibiotics with lower side effect profile, infrequent dosing, good palatability in suspension formulation and efficacy with short duration of treatment may lead to better outcomes because noncompliance often results in failed therapy, persistence of infection and morbidity.

INTRODUCTION

Most children with ear or throat infections seen in the private offices of pediatricians and family physicians as well as hospital outpatient clinics and emergency departments are going to get better because most children are healthy with the capacity to produce a vigorous immune response. The challenge is to sort out which patients need antibiotic therapy and which do not. On the surface this might appear to be a simple task, but in reality there are difficulties in distinguishing between viral and bacterial diseases; and among those with bacterial infections, it is difficult to discern early in the course which patients are going to resolve their infections without the aid of antibiotic therapy and which are going to progress. Added to this clinical uncertainty are the demands of the patient or parent who seeks medical care with an agenda that may include a desire for antibiotics. Perhaps there is a day-care center involved with a policy requiring antibiotic therapy for the return of an ill child with fever or purulent rhinitis. Maybe the parent has already received an antibiotic for a similar illness and seeks the same therapy for their child.

An evaluation of the need, timing and best choice of antibiotic therapy occurs in clinical practice many

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Key words: Acute otitis media, group A streptococci, tonsillopharyngitis, penicillin, cephalosporin antibiotic.

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times every day when children with infections are seen. For guidance we look to published research studies on relevant topics. In evaluating whether decision making in practice should be influenced by results in research studies, a careful assessment of the patient population, the methods of diagnosis and adequacy of follow-up to document outcomes are essential.

IN VITRO TESTING, PHARMACOKINETICS AND PHARMACODYNAMICS

Various methods are used to assess the *in vitro* activity of an antibiotic. Most commonly a minimum inhibitory concentration (MIC) or a minimum bactericidal concentration (MBC) is measured to assess antibiotic activity. The MBC is the more stringent test and is calculated by assessing the antibiotic concentration necessary to kill 99.9% of the defined inocula of bacteria after 24 h of incubation. Usually the MBC is the same or at most twice as high as the MIC value for a particular antibiotic and strain of bacteria. The usefulness and limitations of these tests should be appreciated.¹ The MIC and MBC are values characterizing an antibiotic under strict test tube conditions. The environment at the site of infections of patients rarely corresponds to these *in vitro* susceptibility testing conditions. Changes in oxygen tension, pH and protein binding of an antibiotic all impact the actual performance of an antibiotic *in vivo*. Also antibiotics in patients do not work alone but in conjunction with the host defenses to include activity of inflammatory cells, antibody, complement and other innate host defense mechanisms. MIC and MBC *in vitro* testing does not take into consideration the pharmacokinetic properties of an antibiotic (absorption, distribution, metabolism and excretion).

In recent years more attention has been paid to assessing pharmacokinetic and pharmacodynamic properties of antibiotics.²⁻¹² Pharmacodynamics involves the study and mathematical modeling of predicted antibiotic concentrations to which a pathogen is exposed at a specific site of infection. For beta-lactams such as cefdinir, as described in this supplement by Guay,¹³ *in vivo* bacterial killing occurs as a function of the duration of time the antibiotic concentration exceeds the MIC against a specific bacteria; i.e. cefdinir, like other cephalosporins and other beta-lactams, demonstrates time-dependent bacterial killing in distinction from concentration-dependent killing, typical of fluoroquinolones and aminoglycosides. Although a lot of weight has recently been given to pharmacodynamic principles in identifying preferred antibiotics for various types of infections in both children and adults, there are problems. Human data available for most antibiotics are insufficient to characterize the entire concentration *vs.* time profile at specific sites of infection (middle ear, sinus or tonsillopharynx). Differences

in study design, patient populations and drug assays complicate the interpretation of available results. Much of the data is derived from studies that utilize nonrandom design, small sample sizes and small quantities of sampling material (middle ear fluid, sinus fluid or tonsil). Using small amounts of the samples produces the opportunity for errors in quantitation and/or contamination from peripheral blood cells and serum, which may impact quantitation.¹⁴ Pharmacodynamics relies on mathematical modeling utilizing anticipated mean half-life of drugs and mean absorption, distribution, metabolism and excretion rates. The variability of these pharmacokinetic parameters in the human population may be substantial.^{15, 16} Thus the outcome of infections in patients may not be accurately predicted by *in vitro* pharmacokinetic or pharmacodynamic models of infections. Large, carefully conducted and analyzed clinical efficacy trials are the standard for best choices in antibiotic selection.

ACUTE OTITIS MEDIA

Acute otitis media (AOM) usually is a complication of a viral upper respiratory infection (URI). In most children resolution is rapid, and the numbers of AOM episodes during childhood is low. Some children, however, contract repeated infections, sustaining long intervals of diminished hearing with subsequent delay in language acquisition and perhaps advancement in other developmental milestones. The symptoms and signs associated with AOM have poor sensitivity and specificity.^{10, 17-21} Overdiagnosis of AOM is a common problem (Table 1). Many physicians have considerable difficulty in distinguishing AOM (antibiotics recommended) from otitis media with effusion (OME, antibiotics not generally recommended). They are unaware of the events in the middle ear space that may occur during the natural course of a viral URI. That is, it is not uncommon for Eustachian tube congestion to coincide with nasal congestion accompanying a URI. With blockage of the Eustachian tube, gas from the middle ear space may escape across the tympanic membrane (TM), producing a retracted TM. Retraction of the TM may be easily confused with bulging of the TM without the benefit of pneumatic otoscopy or the aid of tympanometry. When retraction of a TM occurs, this may produce mild otalgia (similar to the discomfort often experienced during airplane pressurization and de-

TABLE 1. Reasons for misdiagnosis of AOM*

Overreliance on history (symptoms)
Failure to remove cerumen
Screaming (crying) makes most tympanic membranes red (red is a very poor sign)
Poor light from otoscope (bulb and battery)
Failure to evaluate tympanic membrane mobility (pneumatic otoscopy)
Inappropriately sized speculum

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pressurization during flight). The otalgia may be accompanied by ear tugging and even sleeplessness. This combination of symptoms in the context of a viral URI prejudices the parent and physician strongly toward the diagnosis of AOM with a prescription for antibiotics to follow. Sometimes during the course of a viral URI and during the time of Eustachian tube blockage, a middle ear effusion may evolve. Thus the presence of fluid behind the TM does not equate to the diagnosis of AOM but may actually represent OME. In reaching a decision on the need for antibiotic therapy, AOM must be distinguished from OME and/or a retracted TM with or without a middle ear effusion, as occurs during a viral URI. Clinicians have difficulty in making such distinctions.

Even if patients have *bona fide* AOM, there is a high spontaneous resolution rate for this infection in some patients. A metaanalysis of studies conducted from 1966 to 1992²² concluded that the overall rate of resolution of AOM without antibiotic therapy was 81%. The benefit of antibiotics in AOM was 13.7% over placebo. In another analysis²³ antibiotics were shown to offer resolution of ear pain approximately 2 days sooner than when no antibiotics were given. These benefits have been considered relatively small by some authorities, leading to a proposal of nontreatment for AOM or a 2-day delay in treatment to see whether symptoms will resolve on their own.^{24, 25} However, these studies should be considered in context; all antibiotics and even placebo perform similarly under certain clinical circumstances. Explanations for positive results with placebo and in many antibiotic comparative trials include: overdiagnosis of AOM at study entry; inclusion of patients mostly >2 years of age; patients with mild or uncomplicated AOM; exclusion of patients with persistent, recurrent or difficult to treat AOM; and broad criteria of the definition of clinical cure or improvement (Table 2). The study by Adler et al.²⁶ republished in this supplement comparing cefdinir once daily, cefdinir twice daily and amoxicillin/clavulanate addressed some of these design issues. Clinical success efficacy rates were 90.8, 88.7 and 89.9%, for the three treatment arms, respectively, at the test of cure visit. The study by Block et al.²⁷ is a second trial evaluating cefdinir, showing its high clin-

ical success rate as a 5-day regimen twice daily (80% cure rate) compared with 10 days of twice daily cefprozil (82.5% cure rate).

The benefits of antibiotic treatment are greatest in children younger than 2 years of age.^{28–32} This was most clearly demonstrated in a study from the Netherlands conducted from 1986 to 1990.³³ For children <2 years of age treated with placebo, 42% had absence of pain or fever after 3 days compared with 73% of amoxicillin/clavulanate-treated children. For children 2 to 12 years of age, 93% had absence of pain or fever after 3 days of nontreatment compared with 87% of the amoxicillin/clavulanate-treated cases.

Recurrent and persistent AOM does not have as favorable a natural history as uncomplicated AOM.^{12, 32, 34–38} Even with effective antibiotic therapy clinical success rates of only 50 to 70% are typical. The organism causing AOM is also an important factor because the spontaneous cure rate from AOM caused by *S. pneumoniae* is ~20%, compared with 50% for *H. influenzae* and 70 to 80% for *M. catarrhalis*.³⁹ Persistent and recurrent AOM is more frequently caused by antibiotic-resistant *S. pneumoniae* and beta-lactamase-producing *H. influenzae*.^{6, 8, 10, 12, 34–38, 40, 41} Identification of patients most likely to have antibiotic-resistant bacteria is important because these patients especially benefit from careful, appropriate antibiotic selection (Table 3).

The standard for the diagnosis of AOM in clinical trials is tympanocentesis as described in a study by Block et al.⁴² in this supplement. It confirms the presence of middle ear fluid, and subsequent culture identifies the bacterial pathogen.⁴³ In clinical practice selected cases of refractory or recurrent AOM should undergo tympanocentesis to guide treatment and avoid unnecessary medical or surgical interventions (Table 4). A recent report from the CDC recommends tympanocentesis as appropriate in cases where second line antibiotic therapy has failed.⁸ Although few physicians are using this procedure in office practice, it is no more difficult than many other commonly performed office surgeries; it has a satisfactory safety record if the patient is properly restrained and adequate visualization of the TM is achieved. Mild sedation may be helpful in some cases.⁴³

TABLE 2. Antibiotic selection in AOM not important*

Clinical efficacy will be equivalent for most drugs and close to placebo when:

1. Overdiagnosis occurs
2. Patients are ≥3 yr old
3. Mild or uncomplicated disease
4. Broad criteria for definition of cure
5. Pathogen is eradicated by host defenses
6. Pathogen is viral

Accounts for ~60–80% of cases

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TABLE 3. Antibiotic selection in AOM is important*

Clinical efficacy may differ when resistant pathogens are causative. Risk factors are:

1. Antibiotic use in the preceding month
2. Persistent or recurrent AOM
3. Infection during winter/spring months
4. Infection while receiving antibiotic prophylaxis
5. Age <2 yr
6. Day-care attendance

Accounts for ~20–40% of cases

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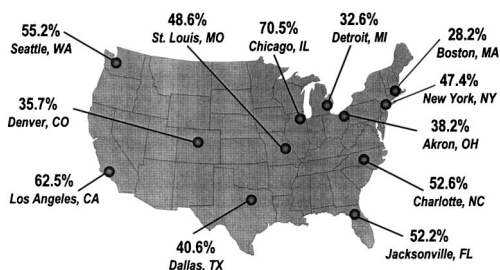
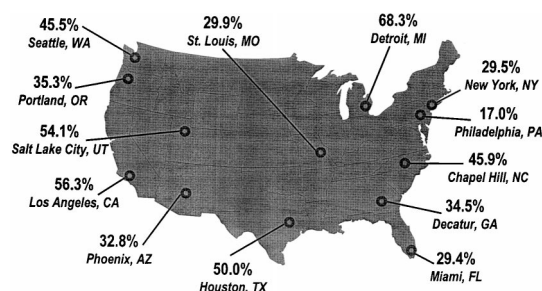
TABLE 4. Tympanocentesis indications in primary care*

Child crying or clearly in pain; bulging tympanic membrane
Toxic appearing and/or high fever
Following two sequential/successive apparent antibiotic failures for the same AOM episode

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Selecting the best choice among the many antibiotics that can be used to treat AOM is a challenge. This situation has become more complex over the last decade due to escalating antibiotic resistance among the pathogens that cause AOM. Resistance of *S. pneumoniae* to penicillin (and standard dose amoxicillin) ranges from 30 to 60% in the United States (Fig. 1).^{7, 44, 45} Because resistance genes are frequently linked, it is quite likely that a single course of amoxicillin therapy will not only cause the selection of an amoxicillin-resistant organism but concurrently the organism will have the necessary genetic information to develop resistance to the trimethoprim-sulfamethoxazole and to the macrolide class of antibiotics.^{7, 44, 45} Thus concurrent simultaneous resistance to amoxicillin, sulfa antibiotics (e.g. trimethoprim-sulfamethoxazole) and to macrolides (e.g. erythromycin-sulfisoxazole, clarithromycin and azithromycin) may be seen often. Beta-lactamase production by Gram-negative organisms inactivates amoxicillin, and a rising percentage of the two major Gram-negative organisms causing AOM, *H. influenzae* and *M. catarrhalis*, produce beta-lactamase 40 to 55% and 90 to 100% of the time, respectively (Fig. 2).^{9, 44-46} Resistance among *H. influenzae* to trimethoprim-sulfamethoxazole is increasing. Efficacy of azithromycin against *H. influenzae* has been noted to be no greater than placebo.

The presence of antibiotic resistant bacteria in AOM occurs more frequently in patients who have been recently treated.^{8, 10, 12, 32, 34, 35, 37, 38, 40, 41} In a 1997 study a 46% rate of penicillin-resistant *S. pneumoniae* was found in patients recently treated for AOM; 33% of these strains were highly resistant.³² Resistant AOM pathogens also occur more frequently in children who attend day care, in the late winter to early spring (due to the accumulative effect of antibiotic prescribing

**FIG. 1.** Prevalence of penicillin-intermediate and -resistant *S. pneumoniae*.⁴⁴**FIG. 2.** Prevalence of beta-lactamase-producing *H. influenzae*.⁴⁵

through the winter respiratory season) and in children younger than 2 years of age (Table 3).¹⁰ *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* are rare causes of AOM; therefore selection of antibiotic therapy should not target these organisms as primary pathogens.

Broader spectrum antibiotics have their most prominent usefulness in the treatment of persistent and recurrent AOM. The CDC drug-resistant *S. pneumoniae* therapeutic working group identified high dose amoxicillin (80 mg/kg/day), amoxicillin/clavulanate (40 mg/kg/day amoxicillin plus 40 mg/kg/day amoxicillin/clavulanate for a total dose of 80 mg/kg/day amoxicillin), cefuroxime axetil (30 mg/kg/day) and ceftriaxone (50 mg/kg/day up to three injections) as recommended therapies for penicillin-resistant *S. pneumoniae*.⁸ One study with cefprozil³² supported its inclusion as an appropriate choice with the other agents selected by the CDC group. *In vitro* activity and pharmacokinetic/pharmacodynamic modeling suggested that cefprozil proxetil also could be included.^{8, 10, 36, 44, 45} At the time of the CDC recommendation, data were not available for the new broad spectrum cephalosporin, cefdinir. Its *in vitro* activity and pharmacokinetic/pharmacodynamic profile is described in this supplement by Guay.¹³ The activity of cefdinir appears to resemble those of cefuroxime, cefprozil and high dose amoxicillin or amoxicillin/clavulanate for treatment of penicillin-intermediate and -resistant *S. pneumoniae* as well as beta-lactamase-producing *H. influenzae* and *M. catarrhalis*.

In identifying a best choice antibiotic, the selection perhaps should be based on the local prevalence of penicillin-resistant *S. pneumoniae*.⁹ In areas of lower rates of penicillin resistant strains (<20%), beta-lactamase-producing pathogens may be selected more often after amoxicillin failure. Thus the main target of therapy would be enhanced coverage of beta-lactamase-producing Gram-negative organisms. In communities with a higher rate of penicillin-resistant *S. pneumoniae* (>20%), the primary strategy would be directed toward these strains, following the CDC recommendations⁸ or other recently published guidelines.¹⁰

Starting treatment with high dose amoxicillin for uncomplicated AOM has been included in clinical guidelines^{8,10} and endorsed by many recognized authorities in AOM.^{9,47-49} A decision point to switch therapy after 48 h of treatment (on the third day) gives the first selected antibiotic sufficient time to work but avoids a lengthy delay in recognizing the possibility of failed therapy, likely due to resistant organisms. Traditional second line antibiotics become first line choices if the patient has already been on an antibiotic in the preceding month.

GAS TONSILLOPHARYNGITIS

The benefits of antibiotic therapy in treatment of GAS tonsillopharyngitis were firmly established by the seminal studies of Denny et al.⁵⁰ and Wannamaker et al.⁵¹ in the late 1940s when injectable penicillin was shown to dramatically reduce the incidence of acute rheumatic fever among military recruits. A subsequent transition to oral penicillin therapy as the treatment of choice occurred in the mid-1950s as the oral formulation of penicillin became more widely available. Many clinicians are unaware that oral penicillin was never shown to prevent acute rheumatic fever. Instead the guiding principle was eradication of GAS from the tonsillopharynx. Thus throat culture demonstration of equivalent eradication by oral penicillin compared with injectable penicillin led the American Heart Association to endorse 10 days of oral penicillin therapy as the treatment of choice. Subsequent studies showed that shortening the duration of oral penicillin therapy to 5 or 7 days led to a significant reduction in bacteriologic eradication of GAS from the tonsillopharynx.^{52,53} Thus the 10-day regimen with oral penicillin was firmly ensconced as the necessary duration with this agent.

In the 1950s and 1960s penicillin clearly was the best available agent for the treatment of GAS infections. The organism was, as it is now, exquisitely sensitive to penicillin,⁵⁴ and the eradication rate almost always exceeded 90 to 95%.^{55,56} Erythromycin found a niche in treatment of the penicillin-allergic patient. It was almost as effective as penicillin and avoided the safety issues of induction of a penicillin allergy reaction. In the 1970s the situation began to change.^{57,58} Cephalosporin antibiotics became available, initially the first generation agents (e.g. cephalexin and cefadroxil) and later the second generation (cefactor, cefuroxime axetil, cefprozil, loracarbef) and the third generation (cefpodoxime proxetil, cefixime, ceftibuten, ceftriaxone and most recently cefdinir). Studies were designed to compare the cephalosporins with penicillins; usually the sample size was selected to show equivalence between the two agents. However, beginning in the 1970s and escalating to the current times, wider differences in bacteriologic eradication have been noted between penicillin and the cephalo-

sporin antibiotics.^{59,60} The leading hypothesis to explain this widening gap in efficacy relates to two major concepts: the copathogen hypothesis; and the alteration of normal microbial ecology hypothesis (Table 5).^{57,58,60-66}

The copathogen hypothesis predicts enhanced efficacy for cephalosporins because they are stable in the environment of beta-lactamase production from cocolonizing normal bacterial flora in the tonsillopharynx. Coeradication of beta-lactamase-producing organisms may also effect an enhanced eradication rate of GAS. Cocolonizing, beta-lactamase-producing, normal bacterial flora of the throat most frequently cited as copathogens are species of *Staphylococcus aureus*, *H. influenzae*, *M. catarrhalis* and anaerobes. Conceptually one would predict that the presence of these organisms, with elaboration of beta-lactamase (or release of beta-lactamase on death of the organism), could provide a microenvironment in the tonsillopharynx such that as penicillin enters the area of infection it would be degraded before it could exert its bactericidal effect on GAS. Thus antibiotics with high potency against GAS and that are beta-lactamase-stable, such as amoxicillin/clavulanate or the second and third generation cephalosporins, including cefdinir, would prove superior to penicillin in eradication of GAS.

A second hypothesis to explain superior bacteriologic outcomes for cephalosporins compared with penicillins involves the action of these two antibiotic classes against throat alpha-streptococci. These organisms are normal flora and apparently serve as part of the innate immunity of the human host against GAS colonization and infection. Alpha-streptococci occupy a microbial niche on tonsillopharyngeal epithelial cells and elaborate bacteriocins (natural antibiotic substances) that prevent colonization by GAS. Alteration of this natural microbial ecology by eradication of alpha-streptococci is much more easily accomplished by penicillin and amoxicillin than by the cephalosporins. This is because the bactericidal activity of penicillin and amoxicillin is greater than the cephalosporin class against these organisms. Therefore the use of penicillin, amoxicillin or amoxicillin/clavulanate diminishes the advantage offered by an innate immune defense mechanism.

Tetracycline and sulfa antibiotics, e.g. trimethoprim-sulfamethoxazole, are not effective therapy for GAS.⁶⁷ The macrolides are mainly used for patients with proved penicillin allergy (IgE-mediated). Erythromy-

TABLE 5. Explanations for superior results with cephalosporin treatment of group A streptococcal tonsillopharyngitis

Active in presence of beta-lactamase copathogens in the throat
Cause less disturbance of microbial ecology/innate immunity
More effective if symptoms present <2 days
More effective in younger children

cin, clarithromycin and azithromycin all have an indication and Food and Drug Administration approval for use in treatment of GAS infections. Erythromycin and clarithromycin should be used for 10 days as therapy. Azithromycin can be used for 5 days. However, many clinicians are unaware that the proper dosing of azithromycin for GAS tonsillopharyngitis is 12 mg/kg/day for all 5 days of therapy. This is a double dosing regimen compared with the AOM indication. If a patient has AOM and concurrent GAS tonsillopharyngitis (as occurs in 5 to 15% of children with AOM), then inadequate therapy would be provided by the otitis media regimen. Outside of the United States many countries have licensed azithromycin for a 3-day indication in the treatment of GAS tonsillopharyngitis. This is troubling because reports by Pacifico et al.⁶⁸ and Schaad et al.⁶⁹ clearly show inferior bacteriologic eradication by a 3-day regimen with azithromycin compared with 10 days of penicillin.

The timing of therapy for treatment of GAS tonsillopharyngitis is a complex issue. A delay of therapy of up to 9 days can be accommodated without compromising the beneficial effects of antibiotics on the prevention of acute rheumatic fever.⁷⁰ An intentional delay of 2 to 3 days has been advocated for patients with recurrent tonsillopharyngitis, because the delay is associated with a reduction in recurrences of GAS infection.^{71, 72} A recent study⁷³ suggests that patients who present with GAS tonsillopharyngitis after 2 days of symptoms respond with a higher rate of bacteriologic eradication after penicillin therapy than patients who present within the first 48 h of illness. A possible explanation offered for this difference is that several days of illness leads to a greater degree of tonsillopharyngeal inflammation and consequently better penetration of penicillin to the site of infection.⁷⁴

A delay in therapy has possible negative consequences to include progression to suppurative complications, persistent contagion and a slower resolution of symptoms. The benefit of antibiotic therapy for GAS tonsillopharyngitis with regard to prevention of suppurative complications has been proved.⁷⁵ It seems logical that earlier therapy would more likely preclude the development of suppurative complications as opposed to delayed therapy. Within 24 to 48 h of initiation of antibiotics, patients are no longer contagious to others with regard to spread of the organism.⁷⁶ This is a very important feature and points to the cost benefits of early antibiotic therapy in terms of getting children back to school and parents back to work earlier and a child on the road to recovery faster. The benefits of antibiotics on resolution of symptoms were clouded by misinterpretation of early clinical studies that were thought to suggest no advantage on symptom resolution.⁷⁷ Subsequent work has shown that antibiotic

therapy will produce 1 day of faster resolution of fever and other symptoms than with analgesics and antipyretics.^{71, 78–80} In the absence of any therapy the symptoms of GAS tonsillopharyngitis generally abate by about the fifth day of illness.^{81–83} It is this natural history of resolution of symptoms but persistence of the organism that opens the door to the possibility of development of acute rheumatic fever and prolonged contagion to others. Nevertheless it should be noted that the spontaneous cure rate of GAS tonsillopharyngitis is approximately 50% by the tenth day after illness onset,^{50, 51} and some researchers question the benefit of any antibiotics.^{84–86}

The best choice of antibiotic for GAS tonsillopharyngitis has come under debate. If the guiding principle of GAS treatment is eradication of the streptococcus, then current recommendations for the treatment of streptococcal pharyngitis with penicillin should be reexamined. Some authorities continue to advocate penicillin as the best choice for all patients suspected or confirmed to have GAS tonsillopharyngitis.^{55, 56} Their recommendation is largely based on the proven efficacy of injectable penicillin for the prevention of acute rheumatic fever, its continued *in vitro* potency against GAS and its low cost of acquisition as therapy. It has been suggested that the superior bacteriologic eradication by cephalosporins involves an excessive inadvertent enrollment of streptococcal carriers.⁸⁷ An alternative view highlights the facts that bacteriologic eradication is the critical determiner of prevention of acute rheumatic fever, that oral penicillin has never been shown to prevent rheumatic fever (only injectable penicillin G in peanut or sesame oil has that attribute), that *in vitro* potency against GAS is only part of the formula for success in an environment where beta-lactamase-producing organisms may coexist, that acquisition cost of antibiotic is a very small portion of the total cost of treatment and care with the far greater cost associated with loss of time from work and school in unsuccessfully treated patients and most importantly that compliance with a 10-day regimen of penicillin is an infrequent occurrence.^{57–60, 88}

The best choice of antibiotic for the treatment of GAS tonsillopharyngitis has become increasingly complex and rivals the complexities associated with best choice selections for AOM. One recent study⁷³ suggests that penicillin continues to have a high bacteriologic eradication rate in individuals older than 12 years (adolescents and adults), in those who have been ill for more than 2 days and in those who have infrequent occurrences of streptococcal infections (lack of recurrent disease). Cephalosporins may find their niche, especially in the treatment of GAS infections in patients younger than 6 years and with some frequency in those between 6 and 12 years of age, for those who have been

ill for <2 days at the time of clinical presentation and for those whose economic circumstance places a heavier price on failed therapy because of the cost associated with loss of time from school and work.⁸⁸

In the compliance arena there is no contest between 5-day and 10-day therapy. Because oral penicillin cannot be successfully used for 10 days, some offer injectable penicillin as a remedy for this compliance shortcoming, but most clinicians avoid the use of injectable penicillin because of its pain on injection and increased risk of allergic reaction. Another deterrent to oral penicillin, widely recognized by practicing clinicians, is its unpleasant taste, which represents a compliance barrier. Also routine dosing three times daily for penicillin is difficult to accomplish; twice daily dosing should be prescribed more often because it has similar efficacy.^{73, 89} Use of amoxicillin in preference to penicillin for the GAS indication is a reflection of the practical adjustment in antibiotic selection that often occurs to enhance compliance.

Currently only two cephalosporins, cefpodoxime proxetil and cefdinir, have a 5-day indication approved by the Food and Drug Administration for the treatment of streptococcal pharyngitis. The clinical and bacteriologic efficacy of cefdinir 10- and 5-day regimens is reviewed in this supplement.⁹⁰ Cefuroxime axetil has been studied for a 5-day indication.⁹¹ The principle advantage of cefdinir would be its availability in a 5-day indication as a more palatable formulation in comparison with cefpodoxime proxetil and cefuroxime axetil. Ceftriaxone by single injection might have an appeal in clinical circumstances where children are toxic, are vomiting or refuse all oral medications; however, a single injection of ceftriaxone is inadequate therapy, and the number of injections required for successful eradication beyond one has not been determined.

COMPLIANCE FEATURES AS AN ATTRIBUTE FOR BEST CHOICE ANTIBIOTICS

Overprescribing antibiotics for an excessive duration typically leads to tapering of use as the patient improves,⁹² thereby providing suboptimal (and sub-MIC) concentrations that promote emergence of resistant organisms.⁹³ Leftover antibiotic is typically saved for future use in a similar indication, and subsequent surreptitious use again contributes to selection of resistant bacteria.

Antibiotics that produce a higher rate of side effects will be taken less often and for a shorter duration by the patient because of such side effects. With the onset of moderate to severe diarrhea, diaper rash, other rash, yeast vaginitis in adolescent girls, vomiting, etc., patients generally will not comply with the completion of an antibiotic regimen. Thus selection of an agent with

the lowest side effect profile is a best choice if efficacy among agents is similar.⁹⁴

Patients and parents find it difficult to administer an antibiotic more often than twice a day, because in our current society with two working parents the interaction between parent and child occurs in the morning before school and work and again in the evening after the activities of the day have been completed. In those time frames antibiotic dosages can be administered as part of a daily routine. A midday dose administered at day care, by a school nurse or after school may or may not be remembered or may lead to leaving of the prescription at day care or school, resulting in omission of the evening dose and next day morning dose. Thus a once or twice a day regimen is a best choice if efficacy and safety are otherwise similar.

Few tasks are more daunting to a parent than to force an antibiotic into their ill child's mouth with the child refusing. Thus a palatable suspension of antibiotic has distinct advantages over unpalatable preparations. In this supplement Powers and Gooch⁹⁵ review a taste evaluation of antibiotics administered to children in association with AOM. Previous studies have evaluated antibiotic suspension palatability in adult and pediatric patients.^{96, 97} The study by Powers and Gooch relies on a "smile face scale" that can be used only in somewhat older children. Children 4 to 8 years old were studied, and their taste acceptability ratings may in fact differ from those of a 6- to 36-month-old, the age of peak incidence of AOM. Although most of these taste studies have been performed with antibiotic suspensions, it should be kept in mind that tablets also can produce an aftertaste because the antibiotic is absorbed, returns through the blood stream to the saliva glands and is excreted there.

Cost also can be a compliance determiner because if the antibiotic prescribed is not on the managed care organization formulary, the patient may be obliged to pay for the full prescription, or in a tier pharmaceutical copay system the patient may be obliged to pay a higher copay with certain antibiotics than with others. If the acquisition cost to the patient is a purchase barrier, either a callback occurs requiring additional expenditure of office personnel and physician time to represcribe an alternative antibiotic, or in some cases because of embarrassment, the patient may not fill the prescription and the child goes untreated. The cost of a slower recovery because of a marginally effective drug or one with a dosing frequency or taste/aftertaste that cannot be accommodated can lead to ineffective therapy. The cost of failed therapy thereby extends the loss of work for parents and school attendance for children and causes return office visits, additional alternative antibiotic prescribing and additional follow-up visits. In the worst case enhanced morbidity may occur. Thus

although acquisition cost is important with compliance, the total cost of care of an illness is highest for failed therapies.

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