

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

MICHAEL E. PICHICHERO, MD

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

From the Elmwood Pediatric Group and University of Rochester Medical Center, Rochester, NY.

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

Reprints not available.

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.<sup>1</sup> 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.<sup>2-12</sup> 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,<sup>13</sup> *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.<sup>14</sup> 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.<sup>15, 16</sup> 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.<sup>10, 17-21</sup> 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

\* Reproduced with permission from Outcomes Management Educational Workshops, Boynton Beach, FL.

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 1992<sup>22</sup> 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 analysis<sup>23</sup> 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.<sup>24, 25</sup> 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.<sup>26</sup> 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.<sup>27</sup> 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.<sup>28-32</sup> This was most clearly demonstrated in a study from the Netherlands conducted from 1986 to 1990.<sup>33</sup> 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.<sup>12, 32, 34-38</sup> 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*.<sup>39</sup> Persistent and recurrent AOM is more frequently caused by antibiotic-resistant *S. pneumoniae* and beta-lactamase-producing *H. influenzae*.<sup>6, 8, 10, 12, 34-38, 40, 41</sup> 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.<sup>42</sup> in this supplement. It confirms the presence of middle ear fluid, and subsequent culture identifies the bacterial pathogen.<sup>43</sup> 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.<sup>8</sup> 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.<sup>43</sup>

**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

\* Reproduced with permission from Outcomes Management Educational Workshops, Boynton Beach, FL.

**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

\* Reproduced with permission from Outcomes Management Educational Workshops, Boynton Beach, FL.

**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

\* Reproduced with permission from Outcomes Management Education Workshop, Boynton Beach, FL.

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).<sup>7, 44, 45</sup> 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.<sup>7, 44, 45</sup> 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).<sup>9, 44-46</sup> 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.<sup>8, 10, 12, 32, 34, 35, 37, 38, 40, 41</sup> 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.<sup>32</sup> 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

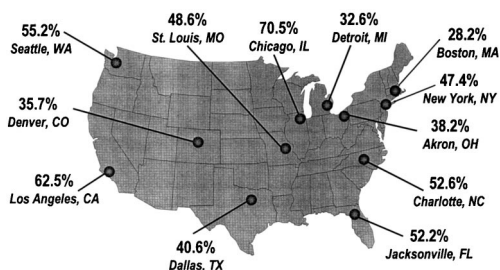


FIG. 1. Prevalence of penicillin-intermediate and -resistant *S. pneumoniae*.<sup>44</sup>

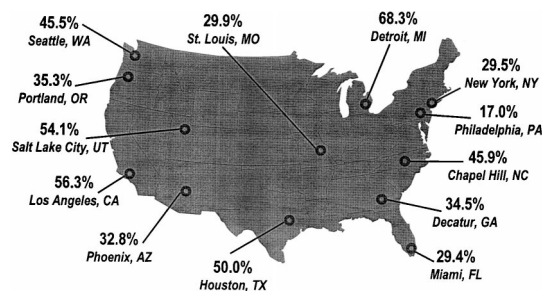


FIG. 2. Prevalence of beta-lactamase-producing *H. influenzae*.<sup>45</sup>

through the winter respiratory season) and in children younger than 2 years of age (Table 3).<sup>10</sup> *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*.<sup>8</sup> One study with cefprozil<sup>32</sup> 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 also could be included.<sup>8, 10, 36, 44, 45</sup> 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.<sup>13</sup> 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*.<sup>9</sup> 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 recommendations<sup>8</sup> or other recently published guidelines.<sup>10</sup>

Starting treatment with high dose amoxicillin for uncomplicated AOM has been included in clinical guidelines<sup>8,10</sup> and endorsed by many recognized authorities in AOM.<sup>9,47-49</sup> 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.<sup>50</sup> and Wannamaker et al.<sup>51</sup> 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.<sup>52,53</sup> 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,<sup>54</sup> and the eradication rate almost always exceeded 90 to 95%.<sup>55,56</sup> 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.<sup>57,58</sup> 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 (cefepodoxime 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.<sup>59,60</sup> 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).<sup>57,58,60-66</sup>

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.<sup>67</sup> 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.<sup>68</sup> and Schaad et al.<sup>69</sup> 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.<sup>70</sup> 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.<sup>71, 72</sup> A recent study<sup>73</sup> 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.<sup>74</sup>

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.<sup>75</sup> 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.<sup>76</sup> 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.<sup>77</sup> Subsequent work has shown that antibiotic

therapy will produce 1 day of faster resolution of fever and other symptoms than with analgesics and antipyretics.<sup>71, 78-80</sup> In the absence of any therapy the symptoms of GAS tonsillopharyngitis generally abate by about the fifth day of illness.<sup>81-83</sup> 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,<sup>50, 51</sup> and some researchers question the benefit of any antibiotics.<sup>84-86</sup>

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.<sup>55, 56</sup> 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.<sup>87</sup> 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.<sup>57-60, 88</sup>

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 study<sup>73</sup> 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.<sup>88</sup>

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.<sup>73, 89</sup> 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.<sup>90</sup> Cefuroxime axetil has been studied for a 5-day indication.<sup>91</sup> 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,<sup>92</sup> thereby providing suboptimal (and sub-MIC) concentrations that promote emergence of resistant organisms.<sup>93</sup> 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.<sup>94</sup>

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 Gooch<sup>95</sup> 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.<sup>96, 97</sup> 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 prescribe 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.

## REFERENCES

- Pichichero ME. Resistant respiratory pathogens and extended-spectrum antibiotics. *Am Fam Physician* 1995;52:1739-46.
- Craig WA, Andes D. Pharmacokinetics and pharmacodynamics of antibiotics in otitis media. *Pediatr Infect Dis J* 1996;15:255-9.
- Craig WA. Pharmacokinetic/pharmacodynamic parameters: rationale for antibacterial dosing of mice and men. *Clin Infect Dis* 1998;26:1-10; quiz 11-2.
- Dagan R. Bacteriologic response to oral cephalosporins: are established susceptibility breakpoints appropriate in the case of acute otitis media? *J Infect Dis* 1997;176:1253-9.
- Blumer JL. Pharmacokinetics and pharmacodynamics of new and old antimicrobial agents for acute otitis media. *Pediatr Infect Dis J* 1998;17:1070-5.
- Poole MD. Implications of drug-resistant *Streptococcus pneumoniae* for otitis media. *Pediatr Infect Dis J* 1998;17:953-6.
- Jacobs MR, Bajaksouzian S, Zilles A, Lin G, Pankuch GA, Appelbaum PC. Susceptibilities of *Streptococcus pneumoniae* and *Haemophilus influenzae* to 10 oral antimicrobial agents based on pharmacodynamic parameters: 1997 US Surveillance Study. *Antimicrob Agents Chemother* 1999;43:1901-8.
- Dowell SF, Butler JC, Giebink GS, et al. Acute otitis media: management and surveillance in an era of pneumococcal resistance: a report from the Drug-resistant *Streptococcus pneumoniae* Therapeutic Working Group [published erratum appears in *Pediatr Infect Dis J* 1999 Apr;18:341]. *Pediatr Infect Dis J* 1999;18:1-9.
- Klein JO. Review of consensus reports on management of acute otitis media. *Pediatr Infect Dis J* 1999;18:1152-5.
- Pichichero ME, Reiner SA, Brook I, et al. Controversies in the medical management of persistent and recurrent acute otitis media. *Ann Otol Rhinol Laryngol* 2000;109(Suppl 183):2-12.
- Partnership SaAH. Antimicrobial treatment guidelines for acute bacterial rhinosinusitis. *Otolaryngol Head Neck Surg* 2000;123(Suppl):S1-32.
- Block SL. Causative pathogens, antibiotic resistance and therapeutic considerations in acute otitis media. *Pediatr Infect Dis J* 1997;16:449-56.
- Guay DPD. Pharmacodynamics and pharmacokinetics of cefdinir, an oral extended spectrum cephalosporin. *Pediatr Infect Dis J* 2000;19(Suppl):S141-6.
- Scagliaone F, DG, Arcidiacono MM, et al. Interpretation of middle ear fluid concentrations of antibiotics: comparison between ceftributen, cefixime and azithromycin. *Br J Clin Pharmacol* 1999;47:267-71.
- Sjovell J, Alvan G, Westerlund D. Dose-dependent absorption of amoxicillin and bacampicillin. *Clin Pharmacol Ther* 1985;38:241-50.
- Welling PG, Huang H, Koch PA, Craig WA, Madson PO. Bioavailability of ampicillin and amoxicillin in fasted and nonfasted subjects. *J Pharm Sci* 1977;66:549-52.
- Berman S. Otitis media in children. *N Engl J Med* 1995;332:1560-5.
- Klein JO. Otitis media. *Clin Infect Dis* 1994;19:823-33.
- Pelton SI. Otoscopy for the diagnosis of otitis media. *Pediatr Infect Dis J* 1998;17:540-3; discussion 580.
- Faden H, Duffy L, Boeve M. Otitis media: back to basics. *Pediatr Infect Dis J* 1998;17:1105-12; quiz 1112-13.
- Pichichero ME. Acute otitis media: Part I. Improving diagnostic accuracy [see comments]. *Am Fam Physician* 2000;61:2051-6.
- Rosenfeld RM, Vertrees JE, Carr J, et al. Clinical efficacy of antimicrobial drugs for acute otitis media: metaanalysis of 5400 children from thirty-three randomized trials [see comments]. *J Pediatr* 1994;124:355-67.
- Del Mar C, Glasziou P, Hayem M. Are antibiotics indicated as initial treatment for children with acute otitis media? A meta-analysis [see comments]. *BMJ* 1997;314:1526-9.
- Fromm J, Culpepper L, Grob P, et al. Diagnosis and antibiotic treatment of acute otitis media: report from International Primary Care Network. *BMJ* 1990;300:582-6.
- Van Buchem F, Peters MF, Van't Hof MA. Acute otitis media: a new treatment strategy. *Br Med J* 1985;290:1033-7.
- Adler M, McDonald PJ, Trostmann U, Keyserling C, Tack K. Cefdinir versus amoxicillin/clavulanic acid in the treatment of suppurative acute otitis media in children. *Eur J Clin Microbiol Infect Dis* 1997;16:214-9.
- Block SL, Hedrick JA, Kratzer JA, Nemeth MA, Tack KJ. Five-day cefdinir course vs. ten-day cefprozil course for treatment of acute otitis media. *Pediatr Infect Dis J* 2000;19(Suppl):S147-52.
- Ingvansson L, Lundgren K. Penicillin treatment of acute otitis media in children: a study of the duration inhibitor effects of amoxicillin plus clavulanate. *Acta Otolaryngol* 1982;94:283-7.
- Kaleida PH, Casselbrant ML, Rockette HE, et al. Amoxicillin or myringotomy or both for acute otitis media: results of a randomized clinical trial. *Pediatrics* 1991;87:466-74.
- Hoberman A, Paradise JL, Block S, Burch DJ, Jacobs MR, Balanescu MI. Efficacy of amoxicillin/clavulanate for acute otitis media: relation to *Streptococcus pneumoniae* susceptibility. *Pediatr Infect Dis J* 1996;15:955-62.
- Hoberman A, Paradise JL, Burch DJ, et al. Equivalent efficacy and reduced occurrence of diarrhea from a new formulation of amoxicillin/clavulanate potassium (Augmentin) for treatment of acute otitis media in children. *Pediatr Infect Dis J* 1997;16:463-70.
- Pichichero ME, McLinn S, Aronovitz G, et al. Cefprozil treatment of persistent and recurrent acute otitis media. *Pediatr Infect Dis J* 1997;16:471-8.
- Appelman CL, Claessen JQ, Touw-Otten FW, Hordijk GJ, de Melker RA. Co-amoxiclav in recurrent acute otitis media: placebo controlled study. *BMJ* 1991;303:1450-2.
- Pichichero ME, Pichichero CL. Persistent acute otitis media: II. Antimicrobial treatment [see comments]. *Pediatr Infect Dis J* 1995;14:183-8.
- Dagan R, Abramson O, Leibovitz E, et al. Impaired bacteriologic response to oral cephalosporins in acute otitis media caused by pneumococci with intermediate resistance to penicillin [see comments]. *Pediatr Infect Dis J* 1996;15:980-5.
- Pichichero ME. Acute otitis media: part II. Treatment in an era of increasing antibiotic resistance. *Am Fam Physician* 2000;61:2410-6.
- Block SL. Management of acute otitis media in the 1990s: the decade of resistant pneumococcus [in process citation]. *Paediatr Drugs* 1999;1:31-50.
- Pichichero ME. Recurrent and persistent otitis media. *Pediatr Infect Dis* 2000;19:911-6.
- Klein JO. The "in vivo sensitivity test" for acute otitis media revisited. *Pediatr Infect Dis J* 1998;17:774-5.
- Gehanno P, N'Guyen L, Derriennic M, Pichon F, Goehrs JM, Berche P. Pathogens isolated during treatment failures in otitis. *Pediatr Infect Dis J* 1998;17:885-90.
- Leibovitz E, Raiz S, Piglansky L, et al. Resistance pattern of middle ear fluid isolates in acute otitis media recently treated with antibiotics. *Pediatr Infect Dis J* 1998;17:463-9.
- Block SL, McCarty M, Hedrick J, et al. Comparative safety and efficacy of cefdinir vs. amoxicillin/clavulanate in the treatment of acute suppurative otitis media in children. *Pediatr Infect Dis J* 2000;19(Suppl):S159-65.
- Block SL. Tympanocentesis: why, when, how. *Contemp Pediatr* 1999;16:103-27.
- Doern GV, Pfaller MA, Kugler K, Freeman J, Jones RN. Prevalence of antimicrobial resistance among respiratory tract isolates of *Streptococcus pneumoniae* in North America: 1997 results from the SENTRY antimicrobial surveillance program [see comments]. *Clin Infect Dis* 1998;27:764-70.
- Thornesberry C, Ogilvie PT, Holley HP, Sahm DF. Survey of susceptibilities of *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* isolates to 26 antimicrobial agents: a prospective US study. *Antimicrob Agents*

- Chemother 1999;43:2612-23.
46. Doern GV, Brueggemann AB, Pierce G, Holley HP Jr, Rauch A. Antibiotic resistance among clinical isolates of *Haemophilus influenzae* in the United States in 1994 and 1995 and detection of beta-lactamase-positive strains resistant to amoxicillin-clavulanate: results of a national multicenter surveillance study. *Antimicrob Agents Chemother* 1997;41:292-7.
  47. McCracken GH Jr. Considerations in selecting an antibiotic for treatment of acute otitis media. *Pediatr Infect Dis J* 1994;13:1054-7.
  48. Klein JO. Clinical implications of antibiotic resistance for management of acute otitis media. *Pediatr Infect Dis J* 1998;17:1084-9; discussion 1099-100.
  49. Block SL. Strategies for dealing with amoxicillin failure in acute otitis media. *Arch Fam Med* 1999;8:68-78.
  50. Denny FW, Wannamaker LW, Brink WR, et al. Prevention of rheumatic fever: treatment of the preceding streptococcal infection. *JAMA* 1950;143:151-3.
  51. Wannamaker LW, Rammelkamp CR, Denny FW, et al. Prophylaxis of acute rheumatic fever: by treatment of preceding pharyngitis with various amounts of depot penicillin. *Am J Med* 1951;10:673-95.
  52. Schwartz RH, Wientzen RL Jr, Pedreira F, Feroli EJ, Mella GW, Guandolo VL. Penicillin V for group A streptococcal pharyngotonsillitis: a randomized trial of seven vs. ten days' therapy. *JAMA* 1981;246:1790-5.
  53. Gerber MA, Randolph MF, Chanatry J, Wright LL, De Meo K, Kaplan EL. Five vs. ten days of penicillin V therapy for streptococcal pharyngitis. *Am J Dis Child* 1987;141:224-7.
  54. Horn DL, Zabriskie JB, Austrian R, et al. Why have group A streptococci remained susceptible to penicillin? Report on a symposium. *Clin Infect Dis* 1998;26:1341-5.
  55. Markowitz M, Gerber MA, Kaplan EL. Treatment of streptococcal pharyngotonsillitis: reports of penicillin's demise are premature. *J Pediatr* 1993;123:679-85.
  56. Shulman ST, Gerber MA, Tanz RR, Markowitz M. Streptococcal pharyngitis: the case for penicillin therapy [see comments]. *Pediatr Infect Dis J* 1994;13:1-7.
  57. Pichichero ME, Margolis PA. A comparison of cephalosporins and penicillins in the treatment of group A beta-hemolytic streptococcal pharyngitis: a meta-analysis supporting the concept of microbial copathogenicity [see comments]. *Pediatr Infect Dis J* 1991;10:275-81.
  58. Pichichero ME. The rising incidence of penicillin treatment failures in group A streptococcal tonsillopharyngitis: an emerging role for the cephalosporins? *Pediatr Infect Dis J* 1991;10(Suppl):S50-5.
  59. Pichichero ME, Green JL, Francis AB, et al. Recurrent group A streptococcal tonsillopharyngitis. *Pediatr Infect Dis J* 1998;17:809-15.
  60. Pichichero ME, Casey JR, Mayes T, et al. Penicillin failure in streptococcal tonsillopharyngitis: causes and remedies. *Pediatr Infect Dis J* 2000;19:917-23.
  61. Brook I. Penicillin failure and copathogenicity in streptococcal pharyngotonsillitis. *J Fam Pract* 1994;38:175-9.
  62. Brook I, Gober AE. Role of bacterial interference and beta-lactamase-producing bacteria in the failure of penicillin to eradicate group A streptococcal pharyngotonsillitis. *Arch Otolaryngol Head Neck Surg* 1995;121:1405-9.
  63. Brook I. Microbial factors leading to recurrent upper respiratory tract infections. *Pediatr Infect Dis J* 1998;17(Suppl):S62-7.
  64. Roos K, Grahn E, Holm SE, Johansson H, Lind L. Interfering alpha-streptococci as a protection against recurrent streptococcal tonsillitis in children. *Int J Pediatr Otorhinolaryngol* 1993;25:141-8.
  65. Falck G, Grahn-Hakansson E, Holm SE, Roos K, Lagergren L. Tolerance and efficacy of interfering alpha-streptococci in recurrence of streptococcal pharyngotonsillitis: a placebo-controlled study. *Acta Otolaryngol* 1999;119:944-8.
  66. Roos K, Holm SE, Grahn-Hakansson E, Lagergren L. Recolonization with selected alpha-streptococci for prophylaxis of recurrent streptococcal pharyngotonsillitis: a randomized placebo-controlled multicentre study. *Scand J Infect Dis* 1996;28:459-62.
  67. Pichichero ME. The treatment of group A beta-hemolytic streptococcal tonsillopharyngitis and prevention of rheumatic fever. In: Narula JVR, Reddy KS, Tandon R, eds. *Rheumatic fever*. Washington, DC: American Registry of Pathology, 1999:371-99.
  68. Pacifico L, Scopetti F, Ranucci A, et al. Comparative efficacy and safety of 5-day azithromycin and 10-day penicillin V treatment of group A beta-hemolytic streptococcal pharyngitis in children. *Antimicrob Agents Chemother* 1996;40:1005-8.
  69. Schaad UB, Heynen G. Evaluation of the efficacy, safety and toleration of azithromycin vs. penicillin V in the treatment of acute streptococcal pharyngitis in children: results of a multicenter, open comparative study. The Swiss Tonsillopharyngitis Study Group. *Pediatr Infect Dis J* 1996;15:791-5.
  70. Catanzaro FJ, Stetson CA, Morris AJ, et al. The role of the streptococcus in the pathogenesis of rheumatic fever. *Am J Med* 1954;17:749-55.
  71. Pichichero ME, Disney FA, Talpey WB, et al. Adverse and beneficial effects of immediate treatment of group A beta-hemolytic streptococcal pharyngitis with penicillin. *Pediatr Infect Dis J* 1987;6:635-43.
  72. el-Daheer NT, Hijazi SS, Rawashdeh NM, al-Khalil IA, Abu-Ektaish FM, Abdel-Latif DI. Immediate vs. delayed treatment of group A beta-hemolytic streptococcal pharyngitis with penicillin V. *Pediatr Infect Dis J* 1991;10:126-30.
  73. Pichichero ME, Hoeger W, Marsocci SM, Murphy AM, Francis AB, Dragalin V. Variables influencing penicillin treatment outcome in streptococcal tonsillopharyngitis. *Arch Pediatr Adolesc Med* 1999;153:565-70.
  74. Stjernquist-Desatnik A. SP, Walder M. Penetration of penicillin V to tonsillar surface fluid in healthy individuals and in patients with acute tonsillitis. *J Laryngol Otol* 1993;107:309-12.
  75. Mar CD. Managing sore throat: a literature review. *Med J Aust* 1992;156:644-9.
  76. Snellman LW, Stang HJ, Stang JM, Johnson DR, Kaplan EL. Duration of positive throat cultures for group A streptococci after initiation of antibiotic therapy. *Pediatrics* 1993;91:1166-70.
  77. Denny FW. Effect of treatment on streptococcal pharyngitis: is the issue really settled? *Pediatr Infect Dis* 1985;4:352-4.
  78. Nelson JD. The effect of penicillin therapy on the symptoms and signs of streptococcal pharyngitis. *Pediatr Infect Dis* 1984;3:10-13.
  79. Randolph MF, Gerber MA, DeMeo KK, Wright L. Effect of antibiotic therapy on the clinical course of streptococcal pharyngitis. *J Pediatr* 1985;106:870-5.
  80. Krober MS, Bass JW, Michels GN. Streptococcal pharyngitis: placebo-controlled double-blind evaluation of clinical response to penicillin therapy. *JAMA* 1985;253:1271-4.
  81. Brink W, Rammelkamp C, Denny FW, et al. Effect of penicillin and aureomycin on natural course of streptococcal tonsillitis and pharyngitis. *Am J Med* 1951;10:300-8.
  82. Chamovitz R, Rammelkamp CH, Wannamaker LW, et al. The effect of tonsillectomy on the incidence of streptococcal respiratory disease and its complications. *Pediatrics* 1960;26:355-67.
  83. Denny FW, Wannamaker LW, Hahn ED, et al. Comparative effects of penicillin aureomycin, and terramycin on streptococcal tonsillitis and pharyngitis. *Pediatrics* 1953;11:7-14.
  84. Middleton DB, D'Amico F, Merenstein JH. Standardized symptomatic treatment versus penicillin as initial therapy for streptococcal pharyngitis. *J Pediatr* 1988;113:1089-94.
  85. Dagnelie CF, van der Graaf Y, De Melker RA. 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;46:589-93.
  86. Little P, Williamson I, Warner G, Gould C, Gantley M, Kinmonth AL. Open randomised trial of prescribing strategies in managing sore throat. *BMJ* 1997;314:722-7.
  87. Gerber MA, Tanz RR, Kabat W, et al. Potential mechanisms

- for failure to eradicate group A streptococci from the pharynx. *Pediatrics* 1999;104(4 Part 1):911-17.
88. Pichichero ME. Streptococcal pharyngitis: updating penicillin's role. *J Respir Dis Pediatrician* (in press).
89. Lan AJ, Colford JM, Colford JM Jr. The impact of dosing frequency on the efficacy of 10-day penicillin or amoxicillin therapy for streptococcal tonsillopharyngitis: a meta-analysis. *Pediatrics* 2000;105:E19.
90. Pichichero ME, Gooch WM III. Comparison of cefdinir and penicillin V in the treatment of pediatric tonsillopharyngitis. *Pediatr Infect Dis J* 2000;19:S171-3.
91. Pichichero ME. Short course antibiotic therapy for respiratory infections: a review of the evidence. *Pediatr Infect Dis* 2000;19:929-37.
92. Pichichero ME. Understanding antibiotic overuse for respiratory tract infections in children. *Pediatrics* 1999;104:1384-8.
93. Guillemot D, Carbon C, Balkau B, et al. Low dosage and long treatment duration of beta-lactam: risk factors for carriage of penicillin-resistant *Streptococcus pneumoniae*. *JAMA* 1998;279:365-70.
94. Nelson JD. Clinical importance of compliance and patient tolerance. *Infect Dis Clin Pract* 1994;3:158-60.
95. Powers J, Gooch WM III, Oddo LP. Comparison of the palatability of the oral suspension of cefdinir vs. amoxicillin/clavulanate potassium, cefprozil and azithromycin in pediatric patients. *Pediatr Infect Dis J* 2000;19(Suppl):S174-80.
96. Steele RW, Estrada B, Begue RE, Mirza A, Travillion DA, Thomas MP. A double-blind taste comparison of pediatric antibiotic suspensions. *Clin Pediatr (Phila)* 1997;36:193-9.
97. Angelilli ML, Toscani M, Matsui DM, Rieder MJ. Palatability of oral antibiotics among children in an urban primary care center. *Arch Pediatr Adolesc Med* 2000;154:267-70.