

Penicillin failure in streptococcal tonsillopharyngitis: causes and remedies

MICHAEL E. PICHICHERO, MD, JANET R. CASEY, MD, THALIA MAYES, BA, ANNE B. FRANCIS, MD,
STEVEN M. MARSOCCI, MD, A. MARIE MURPHY, MD AND WILLIAM HOEGER, MD

Synopsis. Penicillin administered for 10 days has been the treatment of choice for group A beta-hemolytic streptococcal tonsillopharyngitis since the 1950s. The bacteriologic failure rate of 10 days of penicillin therapy ranged from approximately 2 to 10% until the early 1970s. Beginning in the late 1970s bacteriologic and clinical failure rates with penicillin therapy began to increase steadily over time and are now reported to be approximately 30%. The primary cause of penicillin treatment failure in streptococcal tonsillopharyngitis may be lack of compliance with the 10-day therapeutic regimen. Other causes of penicillin treatment failure include reexposure to *Streptococcus*-infected family members or peers; copathogenicity, in which bacteria susceptible to a class of drugs are protected by other, colocalized bacterial strains that lack the same susceptibility; antibiotic-associated eradication of normal protective pharyngeal flora; and penicillin tolerance, whereby streptococcal bacteria repeatedly or continuously exposed to sublethal concentrations of antibiotic become increasingly resistant to eradication. Although 10 days of penicillin therapy is effective in the management of tonsillopharyngitis for many patients, multiple factors may, singly or together, cause treatment failure. A number of antibiotics, particularly the cephalosporins, have been demonstrated to be superior to penicillin at eradicating group A beta-hemolytic *Streptococcus*, and several are effective when administered for 4 to 5 days.

Conclusions. Ten days of penicillin therapy may not be the best therapeutic choice for all pediatric patients. Other antibiotics, shortened courses of the cephalosporins in particular, may be preferable in some cases.

PENICILLIN THERAPY FOR STREPTOCOCCAL TONSILLOPHARYNGITIS

The most common bacterial cause of tonsillopharyngitis is group A beta-hemolytic *Streptococcus pyogenes*, responsible for approximately 15% of cases.¹ Other much less frequently observed bacterial causes of tonsillopharyngitis include *Neisseria gonorrhoeae*, *Arcanobacterium haemolyticum*, *Mycoplasma pneumoniae* and *Chlamydia pneumoniae*.² Studies^{3,4} at the Elmwood Pediatric Group, a private pediatric practice in Rochester, NY, reveal a 16.9% mean incidence (range, 15.2 to 20.0%) of *Streptococcus*-positive throat cultures for 1980 through 1999. The incidence of *Streptococcus*-positive cultures peaks in the United States during the winter when at Elmwood up to 30% of children 5 to 12 years of age and up to 10% of adolescents test positive for a bacterial cause (most often, *Streptococcus*) of tonsillopharyngitis. Peak incidences of viral and idiopathic etiologies of tonsillopharyngitis are 40 and 30%, respectively, for 5- to 12-year old children and 60 and 30%, respectively, for adolescents.

Group A streptococcal tonsillopharyngitis, which shares symptoms with other upper respiratory infections of nonstreptococcal origin, is nearly impossible to diagnose based on clinical manifestations alone. Because it is so difficult to diagnose clinically and because viral etiologies of tonsillopharyngitis are so common, no child at the Elmwood practice receives antibiotics for group A *Streptococcus* unless he or she tests positive for the bacterium in either a rapid group A *Streptococcus* antigen test or a throat culture.

The American Academy of Pediatrics recommends throat culture as the standard of diagnosis for streptococcal tonsillopharyngitis.⁵ They also recommend obtaining a throat culture for confirmatory evidence of negative findings of antigen detection tests.⁵ At variance with this recommendation, data from the Elmwood practice suggest that confirmatory evidence from throat cultures is not necessary when rapid antigen detection tests are *Streptococcus*-negative. In a study conducted from January, 1996, through June, 1999 (T Mayes and ME Pichichero, submitted for publication), only 2.4% (200) of 8234 negative rapid antigen detection test results from children for whom throat cultures were also performed had corresponding throat culture

From the University of Rochester, Rochester, NY.

Key words: Tonsillopharyngitis, penicillin, cephalosporin.

Address for reprints: Michael E. Pichichero, M.D., Elmwood Pediatric Group, University of Rochester, 601 Elmwood Avenue, Box 672, Rochester, NY 14642. Fax 716-273-1289; E-mail mepo@uhura.cc.rochester.edu.

results testing positive for *Streptococcus* (Fig. 1). Because performance of rapid antigen detection tests may vary from practice to practice, these findings at Elmwood may not be generalizable to other settings.

Penicillin administered for 10 days has been the treatment of choice for group A beta-hemolytic streptococcal tonsillopharyngitis since the 1950s when 9 to 11 days of parenteral or oral penicillin therapy was demonstrated to be effective at eradicating group A beta-hemolytic *Streptococcus* in approximately 90% of patients.⁶⁻⁸ These early studies as well as studies^{9, 10} conducted as late as the 1980s also show that at least 10 days of penicillin therapy is necessary for eradication of group A beta-hemolytic *Streptococcus* in most patients: 9- to 11-day courses of penicillin therapy were consistently more effective than 5- to 7-day courses. On the basis of data from these studies, the 10-day course of penicillin therapy continues as the standard for treatment of tonsillopharyngitis in the United States.

FAILURE RATES WITH PENICILLIN THERAPY

A review¹¹ of the published literature indicates that the bacteriologic failure rate of 10 days of penicillin therapy ranged from approximately 2 to 10% until the early 1970s, a result consistent with the findings of the earliest controlled penicillin studies.⁶⁻⁸ Beginning in the late 1970s, however, bacteriologic and clinical failure rates with penicillin therapy began to increase steadily over time and are now reported to be approximately 30%.^{2, 12, 13}

Data from 2140 episodes of group A beta-hemolytic *Streptococcus* tonsillopharyngitis treated from 1975 to 1996 at the Elmwood Pediatric Group show that the incidence of recurrence of tonsillopharyngitis after treatment with penicillin or amoxicillin sharply increased from 1975 to 1979, when 30- and 60-day recurrence rates were 9.0 and 10.7%, respectively, to 1980 to 1984, when the corresponding recurrence rates were 25.9 and 38.7%, respectively (Table 1).¹⁴ The

overall 30-day treatment failure rate for 1721 tonsillopharyngitis episodes treated with penicillin or amoxicillin was 21%.

CAUSES OF PENICILLIN FAILURE

The primary cause of penicillin treatment failure in group A beta-hemolytic *Streptococcus* tonsillopharyngitis may be lack of compliance with the therapeutic regimen. Compliance rates with oral penicillin regimens for tonsillopharyngitis have been reported to be as low as 8% by the ninth day of treatment.¹⁵ Poor compliance often arises from patients' administration of antibiotic only until they begin to feel that they are improving; for tonsillopharyngitis significant clinical improvement in the absence of bacterial eradication may occur as early as 2 days after onset of therapy. The temptation to abbreviate therapy may be especially strong in pediatric patients taking penicillin suspensions, which are unpalatable and sometimes require forceful administration by a parent. Parents noting significant improvement in their child beginning 2 or 3 days after initiation of therapy may be inclined to forgo antibiotic therapy rather than forcefully administer it. The desire to conserve antibiotic therapy for subsequent respiratory infections may also motivate parents to truncate a 10-day penicillin regimen.

The use of partial courses of antibiotics saved from previous infections may be harmful because it could indirectly foster the development of bacterial resistance. The potency of antibiotics declines over time with storage, and administration of low potency antibiotics promotes the selection of resistant organisms. In a study of 941 children,¹⁶ administration of lower than clinically recommended daily doses of beta-lactam antibiotics compared with higher doses was associated with an increased risk of pharyngeal carriage of penicillin-resistant *Streptococcus pneumoniae*. These data highlight the importance of educating the parent (and, where applicable, the patient) about the value of compliance with the antibiotic regimen. Parents and patients should understand that symptomatic improvement does not signal bacteriologic cure and that the full course of antibiotic therapy needs to be completed.

A second cause of penicillin treatment failure, reexposure to *Streptococcus*-infected family members or peers, may cause recurrence or persistence of streptococcal tonsillopharyngitis. The risk of reinfection may be particularly high in closed environments such as day-care settings and schools. Reinfection may occur not only via exposure to infected individuals but also through exposure to contaminated objects. Brook and Guber¹⁷ found that even after children ($n = 104$) had completed a 10-day course of penicillin therapy for group A beta-hemolytic *Streptococcus* tonsillopharyngitis, 19% of removable orthodontic devices and 11% of toothbrushes harbored the organism. The authors con-

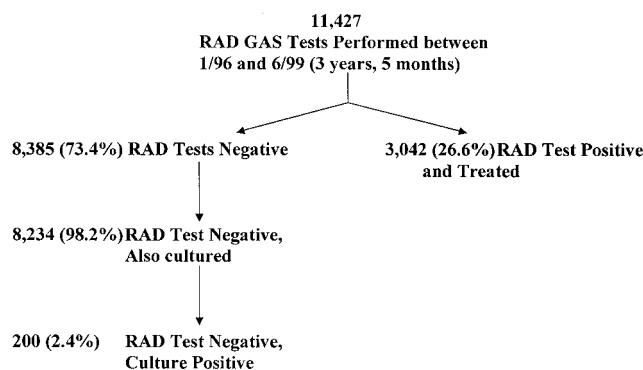


FIG. 1. Patient status results using rapid antigen detection (RAD) test for group A streptococci (GAS) with culture confirmation of negative tests for the study period between January, 1996, and June, 1999. Adapted with permission from Mayes and Pichichero (submitted for publication).

TABLE 1. Recurrences of streptococcal tonsillopharyngitis after penicillin or amoxicillin therapy: Elmwood Pediatric Group, 1975 to 1996Adapted With permission from Pichichero et al., 1998.¹⁴

Years	No. of Episodes Treated with Penicillin or Amoxicillin	% of Patients with Recurrence within 30 Days	% Patients with Recurrence within 60 Days
1975–1979	437	9	10.7
1980–1984	429	25.9	38.7
1985–1989	363	24.3	39.0
1990–1994	359	22.4	31.7
1995–1996	133	25.9	37.5

cluded that such objects might account for penicillin failure in some tonsillopharyngitis cases.

Copathogenicity, in which bacteria susceptible to a class of drugs are protected by other, colocalized bacterial strains that lack the same susceptibility, is a third explanation for treatment failures in streptococcal tonsillopharyngitis. Copathogenicity in streptococcal tonsillopharyngitis may occur when beta-lactamase-producing organisms such as *Staphylococcus aureus*, *Haemophilus influenzae*, *Haemophilus parainfluenzae* and *Moraxella catarrhalis*, all of which may colonize the inflamed pharynxes of a patient suffering from streptococcal tonsillopharyngitis, inactivate the non-beta-lactamase-stable penicillin before it is able to work against *Streptococcus*.^{18, 19} Without these copathogens, group A beta-hemolytic *Streptococcus* is uniformly sensitive to penicillin *in vitro*.

Antibiotic-associated eradication of normal non-pathogenic pharyngeal flora may also lead to penicillin treatment failure in streptococcal tonsillopharyngitis. Alpha-streptococci in particular may protect the pharynxes from colonization by group A beta-hemolytic *Streptococcus*.²⁰ A number of studies^{21–23} show that after a course of antibiotic therapy, patients whose oropharynxes are recolonized with alpha-streptococci (administered via an oral spray) have a lower incidence of recurrence of tonsillopharyngitis than patients whose oropharynxes are not recolonized. Penicillins such as oral ampicillin have been shown to potently suppress alpha-streptococci²⁴ and thus may impair this protective mechanism.

Penicillin tolerance, whereby streptococcal bacteria repeatedly or continuously exposed to sublethal concentrations of antibiotic become increasingly resistant to eradication, has been also been suggested to cause penicillin treatment failure. However, microbiologic studies^{25–27} of bacterial isolates obtained from *Streptococcus*-infected patients suggest that penicillin tolerance is rarely observed. For example Orrling et al.²⁷ found tolerance rates of less than 0.1% among nearly all group A beta-hemolytic *Streptococcus* isolates obtained from tonsillopharyngitis patients undergoing 10 days of successful (33 patients) or unsuccessful (25 patients) penicillin therapy and from isolates obtained

after either the first or the second treatment failure. Thus, although penicillin tolerance cannot be excluded as a possible contributor to treatment failure, data available to date suggest that tolerance plays a minimal role.

Finally, the increasing prevalence of penicillin treatment failures could be an artifact of an increasing prevalence in the population at large of individuals who are group A beta-hemolytic *Streptococcus* carriers, who, that is, are colonized by *Streptococcus* but do not manifest clinical signs or symptoms of illness. Cultures from these individuals would reflect bacteriologic failure in the absence of clinical infection, a result that in clinical trials would artificially inflate treatment failure rates. Data from the Elmwood Pediatric Group suggest that currently few pediatric patients are streptococcal carriers. In a study²⁸ conducted from October, 1996, through June, 1997, the incidence of carriers of group A beta-hemolytic *Streptococcus* was 2.5% for healthy children ($n = 227$); 4.4% among children with an upper respiratory tract infection of presumed viral etiology ($n = 296$); and 6.9% among children with an upper respiratory tract infection with confirmed viral infection ($n = 87$).

ALTERNATIVE TREATMENT OPTIONS

Although penicillin therapy for 10 days is effective in the management of tonsillopharyngitis for most patients, multiple factors may, singly or together, cause treatment failure. This consideration highlights the need for antibiotic treatment options in addition to penicillin for streptococcal tonsillopharyngitis. A number of antibiotics, particularly the cephalosporins, have been demonstrated to be superior to penicillin at eradicating group A beta-hemolytic *Streptococcus*.

A metaanalysis of 19 clinical trials published between 1970 and 1990 compared cephalosporin with penicillin treatment success in group A beta-hemolytic streptococcal tonsillopharyngitis.²⁹ Studies included in the metaanalysis met the following criteria: (1) random assignment of patients to treatment groups; (2) presence of positive group A beta-hemolytic *Streptococcus* in patients' throat cultures at treatment onset; (3) administration of a 10-day course of therapy, for which

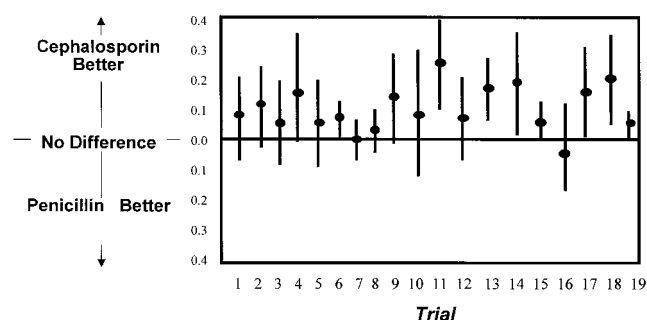


FIG. 2. Ratios of bacteriologic cure rates of group A beta-hemolytic *Streptococcus* for penicillins and cephalosporins across 19 clinical studies. Data expressed as mean ratios with confidence intervals. Adapted with permission from Pichichero and Margolis, 1991.²⁹

compliance was monitored; and (4) use of throat culture at the end of therapy to determine bacteriologic outcome. The results of the metaanalysis demonstrate that across the 19 studies the incidence of bacteriologic

failure of the penicillins (16%) was twice that of the cephalosporins (8%; $P < 0.0001$). The between study consistency in the higher cure rates associated with the cephalosporins (Fig. 2) lends credence to the conclusion that the cephalosporins are superior to the penicillins in eradicating group A beta-hemolytic *Streptococcus* in tonsillopharyngitis. Subsequent studies^{13, 30–48} have repeatedly confirmed the results of this metaanalysis (Table 2).

More recently the Elmwood Pediatric Group examined the incidence of antibiotic treatment failure in streptococcal tonsillopharyngitis at the practice. In episodes treated during the years 1975 through 1996, failure rates were 22% for penicillin, 17% for amoxicillin, 14% for macrolides and 9% for cephalosporins (Table 3).¹⁴ The failures did not appear to be largely attributable to streptococcal carriage rates.²⁸ Nevertheless the proportion of streptococcal tonsillopharyngitis patients with *Streptococcus*-positive cultures after

TABLE 2. Newer studies comparing 10 days of cephalosporin treatment with 10 days of penicillin treatment for streptococcal tonsillopharyngitis

Reference	Study Population	Treatment	N	Bacteriologic Cure (%)	Clinical Cure (%)
Brown et al., 1991 ³⁰	Adult	Cefpodoxime proxetil	93	97	97
		Penicillin V		91	97
Holm et al., 1991 ³¹	Children	Cefadroxil	176	98*	98*
		Penicillin V		86.1	91.1
Reed et al., 1991 ³²	Adult and children	Cefaclor	116	85	87
		Penicillin V		76	87
Milatovic, 1991 ³³	Children	Cefadroxil	239	93.2*	NA
		Penicillin		81	
Holm et al., 1991 ³¹	Adult	Cefadroxil	489	94.3*	97.2*
		Penicillin V		87.7	93.4
McCarty, 1992 ³⁴	Adult	Loracarbef	218	89.9	96.6
		Penicillin V		91.5	93.9
Disney et al., 1992 ³⁵	Children	Cephalexin	525	93	97*
		Penicillin V		89	92
McCarty et al., 1992 ³⁶	Children	Cefprozil	409	91	95*
		Penicillin V		87	88
Ramet et al., 1992 ³⁷	Children	Cefetamet pivoxil	66	94	100
		Penicillin V		91	100
Disney et al., 1992 ³⁸	Children	Loracarbef	233	86.5	97.1
		Penicillin V		81.8	94.3
Block, 1992 ³⁹	Children	Cefixime	110	94*	94*
		Penicillin V		77	75
Muller et al., 1992 ⁴⁰	Children	Loracarbef	344	95*	97
		Penicillin V		87	96
Dajani et al., 1993 ⁴¹	Children	Cefpodoxime proxetil	578	93.1*	92.4
		Penicillin V		81.2	86.9
Gooch et al., 1993 ⁴²	Children	Cefuroxime axetil	533	94.2*	91.9*
		Penicillin V		84.1	81.0
Milatovic et al., 1993 ⁴³	Children	Cefprozil	409	91.3	95.3*
		Penicillin V		87.4	88.1
McCarty, 1994 ⁴⁴	Children	Cefprozil (QD)	151	89*	89*
		Penicillin V		67	74
McCarty, 1994 ⁴⁴	Children	Cefprozil (BID)	359	NA	94
		Penicillin V			88
Pichichero et al., 1994 ⁴⁵	Children	Cefpodoxime proxetil	484	95*	96
		Penicillin V		78	91
Holm et al., 1995 ¹³	Children	Cefuroxime axetil	236	87*	86*
		Penicillin V		56	67
Pichichero et al., 1995 ⁴⁶	Children	Cefibuten	617	91*	97*
		Penicillin V		80	89
Roos et al., 1997 ⁴⁷	Adolescents and adults	Loracarbef	331	90*	91*
		Penicillin V		66	85
Nemeth et al., 1999 ⁴⁸	Children	Cefdinir (QID)	792	94.3*	97.4*
		Penicillin V		70.0	86.3

* $P < 0.05$ between treatments.

NA, not available; QD, daily; BID, twice a day; QID, four times a day.

TABLE 3. Antibiotic treatment failures in streptococcal pharyngitis: Elmwood Pediatric Group, 1975 to 1996Adapted with permission from Pichichero et al., 1998.¹⁴

Medication	No. of Episodes Treated	% of Patients with Recurrence within 30 Days	Statistical Difference vs. Penicillin
Penicillin	1581	21.8	NA
Amoxicillin	140	16.8	$P = 0.24$
Macrolides	143	14.0	$P = 0.04$
Cephalosporins	254	8.6	$P < 0.001$

NA, not available.

10 days of treatment with oral penicillin V, oral cephalosporins, or oral macrolides did differ somewhat (11, 4 and 7%, respectively).

The superior efficacy of beta-lactamase-stable cephalosporins in the treatment of streptococcal tonsillopharyngitis is consistent with the hypothesis^{18, 19} that co-pathogenic beta-lactamase-producing organisms such as *Staphylococcus aureus* and *Haemophilus influenzae* contribute to treatment failure with penicillins. Beta-lactamase-stable cephalosporins, but not penicillin, are potentially active against these copathogens.

Many nonpenicillin antibiotics are effective against streptococcal tonsillopharyngitis when administered for less than 10 days, a feature that may enhance compliance relative to that observed with 10-day penicillin therapy. For example a 4- to 5-day course of cefuroxime axetil has consistently been shown to be as effective as a 10-day course of penicillin in eradicating *Streptococcus* children with tonsillopharyngitis (Table 4).^{49–52} Cefpodoxime proxetil and cefdinir have been approved by the US Food and Drug Administration as effective therapy in a 5-day course for streptococcal tonsillopharyngitis. Marked differences in treatment failure rates through 3 to 4 weeks after treatment between cefuroxime axetil (8% failures or recurrences) and penicillin V patients (34% failures or recurrences) in another study¹³ stimulated the study investigators to question whether penicillin is the appropriate treatment for recurrent tonsillopharyngitis.

A 5-day course of azithromycin has also been shown to be effective against group A beta-hemolytic *Strepto-*

coccus.⁵³ However, streptococcal resistance to macrolides is becoming increasingly prevalent,⁵⁴ and the necessary dose of 12 mg/kg/day for all 5 days doubles the usual cost of an azithromycin prescription.

CONCLUSIONS

These data demonstrate the promise of alternatives to penicillin for the treatment of streptococcal pharyngitis. Although a 10-day penicillin therapy regimen remains the treatment of choice for the majority of patients, the increasing incidence of penicillin failures and the availability of other effective treatment options that can be administered in shortened regimens are cause for reevaluation of the status of penicillin.

If penicillin is used to treat streptococcal tonsillopharyngitis, research suggests that the timing of initiation of therapy relative to the onset of illness can impact treatment success. In an Elmwood Pediatric Group study,⁵⁵ penicillin treatment success rates were significantly higher for the 162 patients treated at least 2 days after onset of illness (82% success) than for the 193 patients treated less than 2 days after onset of illness (64% success). In another study⁵⁶ the incidence of recurrence of streptococcal tonsillopharyngitis was higher for the 170 patients treated immediately after the onset of symptoms (32% recurrence) than for the 173 patients treated 48 to 56 h after onset of symptoms (11% recurrence). The reason that delaying treatment for at least 48 h after onset of symptoms improves treatment outcomes with penicillin has not been determined. Pharyngeal inflammation tends to be much

TABLE 4. Studies comparing 4 to 5 days of cefuroxime axetil treatment with 10 days of penicillin V treatment for tonsillopharyngitis

Study	Design	Age (yr)	N	Country and Setting	Drug	Cefuroxime Axetil/Penicillin	
						Bacteriologic cure (%)	Clinical cure (%)
Gehanno, 1991 ⁴⁹	Randomized, comparative, multicenter	5–70 (mean <30)	170	100 general practices in France	Cef 250 mg BID; penicillin 1 million units TID	96/96 (NS)	99/96 (NS)
Aujard et al., 1995 ⁵⁰	Randomized, comparative, multicenter	2–15	308	4400 community pediatric or general practices in France	Cef 20 mg/kg/day BID; penicillin 45 mg/kg/day TID	87.6/87.4 (NS)	94.8/96.1 (NS)
Adam et al., 2000 ⁵¹	Randomized, open label, comparative, multicenter	1–18	2364	137 pediatric centers in Germany	Cef 250 mg BID or 20 mg/kg/day BID; penicillin 50 000 IU/kg/day TID	90/84.1 ($P = 0.001$)	97.2/93.3 ($P = 0.001$)

Cef, cefuroxime axetil; BID, twice a day; TID, three times a day; NS, not significant.

more marked a few days after initiation of symptoms than immediately after symptom onset. Possibly the greater degree of pharyngeal inflammation 48 h after onset of symptoms increases drug penetration (and consequently drug efficacy) relative to that occurring immediately after symptom onset.

Streptococcal tonsillopharyngitis is a serious illness necessitating effective intervention. The substantial economic and humanistic costs of antibiotic treatment failure in pediatric streptococcal tonsillopharyngitis include increased risk of progression to chronic illness and development of complications such as rheumatic fever; lost time of the parent from work and the child from school; diminished patient and/or parent trust when ineffective treatment is prescribed; and increased medical expenditures related to additional medication use, additional office visits and laboratory tests and additional consulting time with the patient. Ten days of penicillin therapy may not be the best therapeutic choice for all pediatric patients. Other antibiotics, shortened courses of the cephalosporins in particular, may be preferable in some cases.

REFERENCES

1. Tanz RR, Shulman ST. Diagnosis and treatment of group A streptococcal pharyngitis. *Semin Pediatr Infect Dis* 1995;6: 69–78.
2. Pichichero ME. Group A streptococcal tonsillopharyngitis: cost-effective diagnosis and treatment. *Ann Emerg Med* 1995; 25:390–403.
3. Pichichero ME, Disney FA, Green JL, et al. Comparative reliability of clinical, culture, and antigen detection methods for the diagnosis of group A beta-hemolytic streptococcal tonsillopharyngitis. *Pediatr Ann* 1992;21:798–805.
4. Pichichero ME. Data on file, 1999.
5. American Academy of Pediatrics. Group A streptococcal infections. In: Peter G, ed. 1997 Red Book. Report of the Committee on Infectious Diseases. 24th ed. Elk Grove Village, IL: American Academy of Pediatrics; 1997:483–94.
6. Wannamaker LW, Denny FW, Perry WD, et al. The effect of penicillin prophylaxis on streptococcal disease rates and the carrier state. *N Engl J Med* 1953;249:1–7.
7. Breese BB. Treatment of beta hemolytic streptococcal infections in the home: relative value of available methods. *JAMA* 1953;44:1–13.
8. Bernstein SH, Feldman HA, Harper OF Jr, et al. Observations in air force recruits of streptococcal diseases and their control with orally administered penicillin. *J Lab Clin Med* 1954;44:1–13.
9. Schwartz RH, Wientzen Jr RL, Pedreira F, et al. Penicillin V for group V streptococcal pharyngitis: a randomized trial of seven vs. ten days' therapy. *JAMA* 1981;246:1790–5.
10. Gerber MA, Randolph MF, Chanatry J, et al. Five vs. ten days of penicillin V therapy for streptococcal pharyngitis. *Am J Dis Child* 1987;141:224–227.
11. Pichichero ME. Controversies in the treatment of streptococcal pharyngitis. *Am Fam Physician* 1990;42:1567–76.
12. Stillerman M. Comparison of oral cephalosporins with penicillin therapy for group A streptococcal pharyngitis. *Pediatr Infect Dis* 1986;5:649–54.
13. Holm S, Henning C, Grahn E, et al. Is penicillin the appropriate treatment for recurrent tonsillopharyngitis? Results from a comparative randomized blind study of cefuroxime axetil and phenoxymethylpenicillin in children. The Swedish Study Group. *Scand J Infect Dis* 1995;27:221–8.
14. Pichichero ME, Green JL, Francis AB, et al. Recurrent group A streptococcal tonsillopharyngitis. *Pediatr Infect Dis J* 1998; 17:809–15.
15. Bergman A, Werner R. Failure of children to receive penicillin by mouth. *N Engl J Med* 1963;268:1334–8.
16. 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.
17. Brook I, Gober AE. Persistence of group A beta-hemolytic streptococci in toothbrushes and removable orthodontic appliances following treatment of pharyngotonsillitis. *Arch Otolaryngol Head Neck Surg* 1998;124:993–5.
18. Brook I. Penicillin failure and copathogenicity in streptococcal pharyngotonsillitis. *J Fam Pract* 1994;38:175–9.
19. 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.
20. Brook I. Microbial factors leading to recurrent upper respiratory tract infections. *Pediatr Infect Dis J* 1998;17(Suppl): S62–7.
21. Roos K, Grahn E, Holm SE, et al. Interfering alpha-streptococci as a protection against recurrent streptococcal tonsillitis in children. *Int J Pediatr Otorhinolaryngol* 1993; 25:141–8.
22. Falck G, Grahn-Hakansson E, Holm SE, et al. Tolerance and efficacy of interfering alpha-streptococci in recurrence of streptococcal pharyngotonsillitis: a placebo-controlled study. *Acta Otolaryngol* 1999;119:944–8.
23. Roos K, Holm SE, Grahn-Hakansson E, et al. Recolonization with selected alpha-streptococci for prophylaxis of recurrent streptococcal pharyngotonsillitis: a randomized placebo-controlled multicenter study. *Scand J Infect Dis* 1996;28: 459–62.
24. Yoshioka H, Fujita K, Maruyama S, et al. Changes in aerobic pharyngeal flora related to antibiotic use and the emergence of Gram-negative bacilli. *Clin Pediatr* 1982;21:460–2.
25. Stjernquist-Desatne A, Orrling A, Schalen C, et al. Penicillin tolerance in group A streptococci and treatment failure in streptococcal tonsillitis. *Acta Otolaryngol Suppl* 1992;492:68–71.
26. van Asselt GJ, Mouton RP, van Boven CP. Penicillin tolerance and treatment failure in group A streptococcal pharyngotonsillitis. *Eur J Clin Microbiol Infect Dis* 1996;15:107–15.
27. Orrling A, Stjernquist-Desatne A, Schalen C, et al. Treatment failure in streptococcal pharyngotonsillitis: an attempt to identify penicillin tolerant *Streptococcus pyogenes*. *Scand J Infect Dis* 1996;28:143–7.
28. Pichichero ME, Marsocci SM, Murphy ML, et al. Incidence of streptococcal carriers in private pediatric practice. *Arch Pediatr Adolesc Med* 1999;153:624–8.
29. 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. *Pediatr Infect Dis J* 1991;10:275–81.
30. Brown RJ, Batts DH, Hughes GS, et al. Comparison of oral cefpodoxime proxetil and penicillin V potassium in the treatment of group A streptococcal pharyngitis/tonsillitis. The Cefpodoxime Pharyngitis Study Group. *Clin Ther* 1991;13: 579–88.
31. Holm SE, Roos K, Stromberg A. A randomized study of treatment of streptococcal pharyngotonsillitis with cefadroxil or phenoxymethylpenicillin (penicillin V). *Pediatr Infect Dis J* 1991;10(Suppl):S68–71.
32. Reed BD, Huck W, Zazove P. Treatment of beta-hemolytic streptococcal pharyngitis with cefaclor or penicillin: efficacy and interaction with beta-lactamase-producing organisms in the pharynx. *J Fam Pract* 1991;32:138–44.
33. Milatovic D. Evaluation of cefadroxil, penicillin, and erythromycin in the treatment of streptococcal tonsillopharyngitis. *Pediatr Infect Dis J* 1991;10(Suppl):S61–3.
34. McCarty J. Loracarbef versus penicillin VK in the treatment of streptococcal pharyngitis and tonsillitis in an adult population. *Am J Med* 1992;92:74S–79S.

35. Disney FA, Dillon H, Blumer JL, et al. Cephalixin and penicillin in the treatment of group A beta-hemolytic streptococcal throat infections. *Am J Dis Child* 1992;146:1324-7.
36. McCarty JM, Renteria A. Treatment of pharyngitis and tonsillitis with cefprozil: review of three multicenter trials. *Clin Infect Dis* 1992;15(Suppl 2):S224-30.
37. Ramet J, Pierard D, Vandenberghe P, et al. Comparative study of cefetamet pivoxil and penicillin V in the treatment of group A beta-hemolytic streptococcal pharyngitis. *Chemotherapy* 1992;28(Suppl 2):S33-7.
38. Disney FA, Hanfling MJ, Hausinger SA. Loracarbef *vs.* penicillin VK in the treatment of streptococcal pharyngitis and tonsillitis. *Pediatr Infect Dis J* 1992;11(Suppl):S20-6.
39. Block SL, Hedrick JA, Tyler RD. Comparative study of the effectiveness of cefixime and penicillin V for the treatment of streptococcal pharyngitis in children and adolescents. *Pediatr Infect Dis J* 1992;11:919-25.
40. Muller O, Spierer Z, Wettich K. Loracarbef *versus* penicillin V in the treatment of streptococcal pharyngitis and tonsillitis. *Infection* 1992;20:301-8.
41. Dajani AS, Kessler SL, Mendelson R, et al. Cefpodoxime proxetil *vs.* penicillin V in pediatric streptococcal pharyngitis/tonsillitis. *Pediatr Infect Dis J* 1993;12:275-9.
42. Gooch WM, McLinn SE, Aronovitz GH, et al. Efficacy of cefuroxime axetil suspension compared with that of penicillin V suspension in children with group A streptococcal pharyngitis. *Antimicrob Agents Chemother* 1993;37:159-63.
43. Milatovic D, Adam D, Hamilton H, et al. Cefprozil *versus* penicillin V in treatment of streptococcal tonsillopharyngitis. *Antimicrob Agents Chemother* 1993;37:1620-3.
44. McCarty JM. Comparative efficacy and safety of cefprozil *versus* penicillin, cefaclor and erythromycin in the treatment of streptococcal pharyngitis and tonsillitis. *Eur J Clin Microbiol Infect Dis* 1994;13:846-50.
45. Pichichero ME, Gooch WM, Rodriguez W, et al. Effective short-course treatment of acute group A beta-hemolytic streptococcal tonsillopharyngitis. Ten days of penicillin V *vs.* 5 days of 10 days of cefpodoxime therapy in children. *Arch Pediatr Adolesc Med* 1994;148:1053-60.
46. Pichichero ME, McLinn SE, Gooch WM, et al. Ceftibuten *vs.* penicillin V in group A beta-hemolytic streptococcal pharyngitis. Members of the Ceftibuten Pharyngitis International Study Group. *Pediatr Infect Dis J* 1994;14(Suppl):S102-7.
47. Roos K, Larsson P. Loracarbef *versus* phenoxymethylpenicillin in the treatment of recurrent streptococcal pharyngotonsillitis. *Scand J Infect Dis* 1997;29:141-5.
48. Nemeth MA, Gooch WM, Hedrick J, et al. Comparison of cefdinir and penicillin for the treatment of pediatric streptococcal pharyngitis. *Clin Ther* 1999;21:1525-32.
49. Gehanno P. Traitement des angines a streptocoque beta hemolytique du groupe A par le cefuroxime axetil pendant 4 jours: etude comparative a la penicilline V pendant 10 jours. *Med Mal Infect* 1991;21:66-70.
50. Aujard Y, Boucot I, Brahimi N, et al. Comparative efficacy and safety of four-day cefuroxime axetil and ten-day penicillin treatment of group A beta-hemolytic streptococcal pharyngitis in children. *Pediatr Infect Dis J* 1995;14:295-300.
51. Adam D, Scholz H, Helmerking M. Comparison of short-course (5-day) cefuroxime axetil with a standard 10-day oral penicillin V regimen in the treatment of tonsillopharyngitis. *J Antimicrob Chemother* 2000;45(Suppl):23-30.
52. Gehanno P, Chichie D. Tonsillopharyngitis: evaluation of short-term treatment with cefuroxime axetil *versus* standard 10-day penicillin V therapy. *Br J Clin Pract* 1995;49:28-32.
53. Tarlow MJ. Macrolides in the management of streptococcal pharyngitis/tonsillitis. *Pediatr Infect Dis J* 1997;16:444-8.
54. Bassetti M, Manno G, Collida A, et al. Erythromycin resistance in *Streptococcus pyogenes* in Italy. *Emerging Infectious Diseases* <http://www.Medscape.com/govmt/CDC/EID/2000;2000/v06.n02/e0602.12.bass/e0602.12.bass-01.html>. Accessed May 16, 2000.
55. Pichichero ME, Hoeger W, Marsocci SM, et al. Variables influencing penicillin treatment outcome in streptococcal tonsillopharyngitis. *Arch Pediatr Adolesc Med* 1999;153:565-70.
56. El-Dahar NT, Nijazi SS, Rawashdeh NM, et al. Immediate *vs.* delayed treatment of group A beta-hemolytic streptococcal pharyngitis with penicillin V. *Pediatr Infect Dis J* 1991;10:126-30.