Efficacy of Cephalexin Two vs. Three Times Daily vs. Cefadroxil Once Daily for Streptococcal Tonsillopharyngitis

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Summary: The purpose of this study was to compare the bacteriologic and clinical efficacy of oral cephalexin twice vs. three times daily vs. cefadroxil once daily as therapy for group A beta-hemolytic streptococcal (GABHS) tonsillopharyngitis. A prospective open-label, observational cohort study was conducted over 18 months (January 2000–June 2001). Children enrolled had an acute onset of symptoms and signs of a tonsillopharyngeal illness and a laboratory-documented GABHS infection. Follow-up examination and laboratory testing occurred 21 ± 4 days following enrollment. Two hundred seventy-one patients were enrolled (intent to treat group): 63 received cephalexin twice daily, 124 received cephalexin three times daily, and 84 received cefadroxil once daily. Fifty-three children did not return for the follow-up visit, leaving 218 patients in the per-protocol group: 54 cephalexin twice-daily treated, 94 cephalexin 3-times daily treated, and 70 cefadroxil once-daily treated. In the per-protocol group, bacteriologic cure for those treated with cephalexin twice daily was 87%, for cephalexin 3 times daily, it was 81% and for cefadroxil once daily it was 81% (p=0.61). The clinical cure rate for cephalexin twice-daily treatment was 91%; for three-times daily, it was 86%; and for cefadroxil once daily, it was 84% (p=0.56). Because treatment allocation was not randomized, logistic regression analysis was used to adjust for treatment group differences. Younger age of patient was significantly associated with bacteriologic (p=0.04) and clinical (p=0.01) failure independent of treatment group but in the adjusted logistic model no differences were found among the 3 treatment regimens. Cephalexin dosed twice daily or three times daily and cefadroxil dosed once daily appear equivalent in bacteriologic and clinical cure of GABHS tonsillopharyngitis.
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Introduction

The American Academy of Pediatrics (AAP) Red Book Committee states that a 10-day course of a narrow-

spectrum (first-generation) cephalosporin is an acceptable alternative to penicillin for treatment of group A beta hemolytic streptococcal (GABHS) tonsillopharyngitis.[1] The cephalosporins are particularly recommended for persons allergic to penicillin, noting however that "as many as 15% of penicillin-allergic persons also are allergic to cephalosporins," which is perhaps incorrect.[2-6] The American Heart Association (AHA) Committee on Rheumatic Fever recognizes cephalosporins as "acceptable alternatives" to penicillin, "particularly for penicillin-allergic individuals."[7] The AHA states that 20% of penicillin-allergic persons are also cephalosporin-allergic, which is also perhaps incorrect.[2-6] The AHA also notes that "narrow-spectrum cephalosporins such as cefadroxil or cephalexin are probably preferable to the broader-spectrum cephalosporins" for treatment of GABHS tonsillopharyngitis.

There are exceedingly few studies in which different cephalosporins have been compared in the treatment of GABHS tonsillopharyngitis[8-13] and none that have compared the AAP and AHA preferred agents—cephalexin and cefadroxil. Furthermore, cephalexin when first licensed was indicated for GABHS tonsillopharyngitis using 4 times daily dosing; this schedule is a major compliance barrier. Although the package insert for cephalexin now states that cephalexin may be administered on an every 12-hour schedule for 10 days for treatment of GABHS, we could find only 1 study where 4 versus 2 times daily dosing schedules were compared.[8] Therefore, in this study we compare the bacteriologic and clinical efficacy of cephalexin given twice daily, or 3 times daily and cefadroxil once daily as 10-day treatment for GABHS tonsillopharyngitis.

Methods

Study Setting

The Elmwood Pediatric Group (EPG) is a private pediatric practice located in suburban Rochester, New York (greater metropolitan population of 1 million). The practice population is representative of the economic, racial, and ethnic diversity of suburban Rochester. During the current study, the group consisted of 10 board-certified pediatricians and 2 pediatric nurse practitioners. There is a laboratory at the office practice with Clinical Laboratory Improvement Act (CLIA) level III certification.

Study Design

This was a prospective, open-label, observational study conducted over 18 months, January 2000 to June 2001. Children with acute onset of symptoms, signs, and a laboratory-documented GABHS tonsillopharyngitis using a rapid antigen detection test or a throat culture were eligible for the study. Those children with a history of penicillin, amoxicillin, or cephalosporin allergy and those children with a history of GABHS carriage were excluded from the study. The choice of antibiotic therapy and dosing frequency was made according to the preference and discretion of the child's physician, and the doses were determined according to the patient's weight. All patients were scheduled for a repeat visit 21 ± 4 days following enrollment. At that time a history, physical examination, and repeat laboratory test (throat culture or rapid antigen detection test) was performed. Patients were deemed compliant by parental report at the follow-up visit if they assured the physician that all medication had been taken as prescribed.

Analysis Groups

The intent-to-treat population included all patients who were enrolled in the study meeting the inclusion and exclusion criteria. The per-protocol population included all patients in the intent-to-treat group who were compliant with treatment and returned for and completed the follow-up visit.

Outcome Definitions

Bacteriologic outcomes were defined as eradication (cure) if the rapid antigen detection assay or throat culture obtained at the follow-up visit was negative for GABHS or as failure if the test result was positive for GABHS, both irrespective of symptoms and signs. Clinical outcomes were classified as success (cure) if the rapid antigen detection test or throat culture result obtained at the follow-up was negative for GABHS and the patient had no symptoms or signs of throat infection, or as failure if the test result was positive for GABHS and symptoms and signs of throat infection were present at the follow-up visit, or as a presumed carrier if the throat culture result was positive and the patient was asymptomatic.

Statistics

To assess possible differences between treatment groups, chi-square test for categorical data and the student t test for continuous variables was used. A p value less than 0.05 was considered significant. Because the treatment allocation was not randomized, logistic regression analysis was done on the per-protocol dataset;

in this analysis presumed GABHS carriers at the end of treatment were deleted. Age of the patient, antibiotic dose/kg of child weight, number of GABHS infections in the past year, days ill before the study visit, enlarged tonsillar size, and tonsillar exudates were the variables included with the treatment variable to predict bacteriologic and clinical cure.

Results

Two hundred seventy-one patients were included in the intent-to-treat study group; 63 received cephalexin twice daily, 124 received cephalexin three times daily, and 84 received cefadroxil once daily. A description of the patient's age, gender, weight, symptoms, signs, and relevant medical history are shown in Table 1. The treatment groups were similar for all parameters except antibiotic dose on a mg/kg calculation and there were statistical differences in the recording of selected signs of tonsillopharyngitis inflammation (Table 1). The similarities and differences seen in the intent-to-treat group were mirrored in the per-protocol group. No child refused to take the antibiotic suspension, and no parents acknowledged medication non-compliance; 53 did not return for the follow-up visit, leaving 218 patients in the per-protocol group; 54 cephalexin twice-daily group, 94 in the cephalexin three-times-daily group, and 70 in the cefadroxil once-daily group.

In the per-protocol analysis the bacteriologic cure rate for children treated with cephalexin twice daily was 87%, for cephalexin three times daily-treated children it was 81% and for ce-

Table 1

DEMOGRAPHIC DATA OF THE INTENT TO TREAT GROUP

Patient Characteristics	Cephalexin BID	Cephalexin TID	Cefadroxil QD
No. of patients	63	124	84
Mean age, yr (range)	6.6 (1–17)	7.5 (2–19)	6.7 (2–14)
Gender (% males)	64	59	57
Antibiotic dose (mg/kg/day); mean ± S.D.*	39 ± 12	31 ± 10	31 ± 9
GABHS infections within past year			
0 episodes (%)	26	17	21
≥1 episode (%)	74	83	79
Days ill before visit			
< 2 days (%)	65	73	74
Sore throat (%)	91	92	89
Fever (%)	59	67	62
Headache (%)	65	66	60
Pharyngeal erythema (%)	100	95	98
Enlarged tonsillar size (%)†	70	56	48
Tonsillopharyngeal exudates (%)‡	54	57	71
Cervical lymphadenopathy (%)	61	63	60

*Significant differences among treatment groups, $p < 0.001$.

†Significant differences among treatment groups, $p=0.02$.

‡Significant differences among treatment groups, $p < 0.001$.

fadroxil once daily it was 81% (p=0.61) (Table 2). Similarly, the clinical cure rate for cephalexin twice daily treatment group (91%) was similar to the clinical cure rate in the cephalexin three times daily (86%) and cefadroxil once daily (84%) treatment groups, p=0.57 (Table 2). Analysis of the intent–to-treat population gave similar results if patients who completed therapy but failed to return for follow-up were presumed to experience bacteriologic eradication and clinical cure.

In the adjusted logistic regression analysis, treatment regimens were confirmed as not significantly different for bacteriologic (p=0.56) or clinical (p=0.51) cure. However, age of the patient was found to be a significant predictor of the bacteriologic (p=0.01) and clinical (p=0.01) cure, with younger patients less frequently experiencing cure. The lack of differences among antibiotic treatments and the presence of differences according to patient age on bacteriologic and clinical outcome were similar when the variable of antibiotic dose on a mg/kg basis, number of GABHS infections in the past year, days ill before the study visit, enlarged tonsillar size and tonsillopharyngeal exudate were added to the model.

Discussion

In our private pediatric group practice setting we found in this study that cephalexin twice daily, cephalexin three times daily, and cefadroxil once daily produce a similar bacteriologic and clinical cure of GABHS tonsillopharyngitis. This result is consistent with cure rates observed in earlier studies[14-26] where cephalexin was administered three or four times daily and where cefadroxil was administered once or twice daily (Table 3).

The serum half-life of cephalexin is 1.1 hours and for cefadroxil is 1.5 hours,[28] which does not suggest that these antibiotics would achieve an optimal effect on GABHS eradication when doses twice or once daily are used, respectively, based on current pharmacokinetic/pharmacodynamic (PK/PD models).[29] Perhaps the PK/PD model does not apply to GABHS tonsillopharyngitis infections? The half-life of penicillin V in serum is 0.6 hours[28] and it can be dosed twice daily[30-32] but not once daily[33] and still achieve a similar bacteriologic cure rate as 3 or 4 times daily dosing.[34-40] We identified one study in which cephalexin was administered twice vs. 4 times daily.[8] In that double-blind, randomized, controlled trial conducted at the Oklahoma Children's Hospital involving a total of 65 children, there was no difference in bacteriologic or clinical cure for the two dosing regimens. Five other studies compared 2 cephalosporins in the treatment of GABHS tonsillopharyngitis;[9-13] 4 studies involved children and 1 study was in adolescents and

Table 2

BACTERIOLOGIC AND CLINICAL OUTCOMES IN THE TREATMENT OF GABHS; PER PROTOCOL GROUP

	Bacteriologic Outcome		Clinical Outcome	
Antibiotic	Number and Percent Cure	Number and Percent Failure	Number and Percent Cure	Number and Percent Failure
Cephalexin BID	n=47	n=7	n=49	n=5
n=54	87*	13	91†	9
Cephalexin TID	n=76	n=18	n=81	n=13
n=94	81*	19	86†	14
Cefadroxil QID	n=57	n=13	n=59	n=11
n=70	81*	19	84†	16

*p=0.61; †p=0.57.

Table 3

PAST PUBLICATIONS ON CEPHALEXIN AND CEFADROXIL 10 DAYS TREATMENT OF GABHS TONSILLOPHARYNGITIS

Reference No.	Authors, yr	Agent	Daily Dose	Schedule	Cephalexin or Cefadroxil Percent Cure*
14	Stillerman et al. 1970	Cephalexin	500 mg	TID	90
15	Disney et al. 1971	Cephalexin	30–40 mg/kg	TID	81
16	Stillerman et al 1972	Cephalexin	1,500 mg	TID	89
17	Gau et al. 1972	Cephalexin	20–40 mg	TID	96
18	Rabinovich et al. 1973	Cephalexin	2,000 mg	QID	100
19	Matsen et al. 1974	Cephalexin	2,000 mg	QID	97
20	Disney et al. 1992	Cephalexin	27 mg/kg	QID	93
21	Ginsberg et al. 1980	Cefadroxil	30 mg/kg	TID	93
22	Ginsberg et al. 1982	Cefadroxil	30 mg/kg	BID	86
23	Henness, 1982	Cefadroxil	30 mg/kg	BID	86
24	Pichichero et al. 1987	Cefadroxil	30 mg/kg	QD	90
25	Stromberg et al. 1988	Cefadroxil	1,000–2,000 mg	BID	97
26	Holm et al. 1991	Cefadroxil	5.5–25 mg/kg	BID	98
27	Milatovic et al. 1991	Cefadroxil	25 mg/kg	BID	93

*Percent cure defined as bacteriologic eradication at end of treatment.

QD = once daily, BID = twice daily, TID = three times daily, QID = four times daily.

adults. In all but 1, the drugs produced similar bacteriologic and clinical outcomes.

A concern of pediatricians is the potential for allergic cross-reactivity in children who are considered penicillin allergic.[41-43] On the basis of chemical structure and degradation of the penicillins and cephalosporins, differing conclusions about the likelihood of cross-sensitivity may be reached.[44-49] Patients with histories of penicillin allergy have demonstrated a potential for increased hypersensitivity to first-generation cephalosporins.[3,42,49] Citing early studies and subsequent reviews, the AAP[1] and AHA[7] erroneously caution that 15% to 20% of penicillin-allergic patients are also cephalosporin-allergic. In those studies, which the AAP and AHA possibly relied on, the penicillin allergy was not confirmed with skin tests, the cephalosporin skin test reagent was contaminated with penicillin, and many of the cephalosporin reactions may not have been immunologically mediated. More recent studies suggest cross-sensitivity to first generation cephalosporins in patients with a history of penicillin allergy occurs less frequently than widely thought (4.4% across 7 small studies with n's of 3 to 62; 7.1% across 3 studies with n's of 69 to 255).[2] Second- and third-generation cephalosporins have been linked to a lower incidence of allergic reactions.[5,6,50] A recent study investigated 187 children and adolescents whose adverse reactions to amoxicillin (or amoxicillin/clavulanate) or oral cephalosporin,[4] or both, were sufficient to preclude further use.[4,51] Fifty-four penicillin or amoxicillin reactors with positive skin test results or oral challenges received 83 courses of cephalosporins uneventfully in prospective follow-up.

Because this was not a randomized, controlled trial there are several limitations that should

be acknowledged. The selection of the antibiotic was at the discretion of the physician seeing the patient. This occurred in a consistent manner by each investigator according to his/her preference for a particular antibiotic and regimen; therefore selection bias did not likely occur because more or less ill patients were not more or less likely to see any particular physician. Secondly, in keeping with the general treatment approach advocated at EPG[52,53] and by others,[29] cephalosporin treatment in this study was used more often as a treatment for patients with recurrent GABHS tonsillopharyngitis (74%–83% had ≥ 1 GABHS episode within the previous year) or a history of penicillin treatment failure. Third, there was some variation in the recorded signs of tonsillopharyngitis inflammation. Fourth, we cannot exclude the possibility that compliance differences could have occurred among the groups. Cephalexin and cefadroxil suspensions taste good,[54] but more frequent daily dosing is a compliance barrier.[55] We did not test for antibiotic presence in the urine nor did we recollect and weigh/measure/count remaining medication. However, we have no reason to suspect differential false reporting of compliance by parents among the treatment groups.

Cephalosporins are superior to penicillin in bacteriologic and clinical cure of GABHS tonsillopharyngitis.[52,56] They are particularly useful for children younger than 12 years of age,[32] for those who are ill less than 2 days before treatment[32,57,58] for those with recurrent infections,[30,57,58] for carriers,[54] and for those who are penicillin allergic.[1,7] In this study, we have shown that the first-generation oral cephalosporins, cefadroxil, given once daily and cephalexin, given twice or thrice daily, are equally efficient in both bacteriologic and clinical cure of GABHS tonsillopharyngitis in children.

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REFERENCES

1. Pickering LK, Peter G, Baker CJ, Gerber MA, MacDonald NE, Orenstein WA, Patriarca P, Committee on Infectious Diseases. *2000 Red Book: Report of the Committee on Infectious Diseases*, 25th ed. Elk Grove Village, IL: American Academy of Pediatrics, 2002.
2. Kelkar PS, Li JT-C. Cephalosporin allergy. *N Engl J Med.* 2001;345:804-809.
3. Anne S, Reisman RE. Risk of administering cephalosporin antibiotics to patients with histories of penicillin allergy. *Ann Allergy Asthma Immunol.* 1995;74:167-170.
4. Pichichero ME, Pichichero DM. Diagnosis of penicillin, amoxicillin, and cephalosporin allergy: reliability of examination assessed by skin testing and oral challenge. *J Pediatr.* 1998; 132:137-143.
5. Norrby SR. Side effects of cephalosporins. *Drugs.* 1987; 34(Suppl 2):105-120.
6. Lin RY. A perspective on penicillin allergy. *Arch Intern Med.* 1992;152:930-937.
7. Dajani A, Taubert K, Ferrieri P, Peter G, Shulman S, Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease of the Council on Cardiovascular Disease in the Young, the American Heart Association. *Pediatrics.* 1995;96:758-764.
8. Tarpay MM, Chartrand M, Cox A. The extended microbiology of group A streptococcal pharyngitis observations during a double-blind controlled study of cephalexin twice versus four-times daily. *Infection.* 1984; 12:181-184.
9. Barbhaiya RH, Shukla UA, Gleason CR, et al. Phase I study of multiple-dose cefprozil and comparison with cefaclor. *Antimicrob Agents Chemother.* 1990;34:1198-1203.
10. McCarty JM, Renteria A, Doyle CA, Durham SJ, Hamilton H, Wilber RB, for the Cefprozil Multicenter Study Group. Cefprozil vs. cefaclor in the treatment of pharyngitis and tonsillitis. *Infect Med.* 1992; 9(Suppl C):33-43.
11. Randolph M. Clinical comparison of once-daily cefadroxil and thrice-daily cefaclor in the treatment of streptococcal pharyngitis. *Chemotherapy.* 1988;34:512-518.
12. Christenson JC, Swenson E, Gooch WM III, Herrod JN. Comparative efficacy and safety of cefprozil (BMY-28100) and cefaclor in the treatment of acute group A beta-hemolytic streptococcal pharyngitis. *Antimicrob Agents Chemother.* 1991;35:1127-1130.
13. 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;13:846-850.
14. Stillerman M, Isenberg HD. Streptococcal pharyngitis therapy: comparison of cyclacillin, cephalexin, and potassium penicillin V. *Antimicrob Agents Chemother.* 1970;10:270-276.
15. Disney FA, Breese BB, Green JL, Talpey WB, Tobin JR. Cephalexin and penicillin therapy of childhood beta-hemolytic streptococcal infections. *Postgrad Med J.* 1971;47(Suppl):47-51.
16. Stillerman M, Isenberg HD, Moody M. Streptococcal pharyngitis therapy. Comparison of cephalexin, phenoxymethyl penicillin, and ampicillin. *Am J Dis Child.* 1972;123:457-461.
17. Gau DW, Horn RF, Solomon RM, Johnson P, Leigh DA. Streptococcal tonsillitis in general practice. A comparison of cephalexin and penicillin therapy. *Practitioner.* 1972;208:276-281.
18. Rabinovitch M, MacKenzie R, Brazeau M, Marks MI. Treatment of streptococcal pharyngitis. I. Clinical evaluation. *Can Med Assoc J.* 1973;108:1271-1274.

19. Matsen JM, Torstenson O, Siegel SE, Bacaner H. Use of available dosage forms of cephalexin in clinical comparison with phenoxymethyl penicillin and benzathine penicillin in the treatment of streptococcal pharyngitis in children. *Antimicrob Agents Chemother.* 1974;6:501-506.
20. Disney FA, Dillon H, Blumer JL, et al. Cephalexin and penicillin in the treatment of group A beta-hemolytic streptococcal throat infections. *Am J Dis Child.* 1992;146:1324-1327.
21. Ginsburg CM, McCracken GH Jr, Crow SD, Steinberg JB, Cope E. A controlled comparative study of penicillin V and cefadroxil therapy of group A streptococcal tonsillopharyngitis. *J Int Med Res.* 1980;8(Suppl):82-86.
22. Ginsburg CM, McCracken GH Jr, Steinberg JB, et al. Treatment of Group A streptococcal pharyngitis in children. Results of a prospective, randomized study of four antimicrobial agents. *Clin Pediatr (Phila).* 1982; 21:83-88.
23. Henness DM. A clinical experience with cefadroxil in upper respiratory tract infection. *J Antimicrob Chemother.* 1982;10(Suppl B):125-135.
24. Pichichero ME, Disney FA, Aronovitz GH, Talpey WB, Green JL, Francis AB. Randomized, single-blind evaluation of cefadroxil and phenoxymethyl penicillin in the treatment of streptococcal pharyngitis. *Antimicrob Agents Chemother.* 1987;31:903-906.
25. Stromberg A, Schwan A, Cars O. Five versus ten days treatment of group A streptococcal pharyngotonsillitis: a randomized controlled clinical trial with phenoxymethylpenicillin and cefadroxil. *Scand J Infect Dis.* 1988;20:37-46.
26. 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(10 Suppl):S68-71.
27. Milatovic D. Evaluation of cefadroxil, penicillin and erythromycin in the treatment of streptococcal tonsillopharyngitis. *Pediatr Infect Dis J.* 1991; 10(10 Suppl):S61-63.
28. O'Grady F, Lambert HP, Finch RG, Greenwood D. *Antibiotic and Chemotherapy: Anti-infective Agents and Their Use in Therapy*, 7th ed. New York: Churchill Livingstone, 1997:217-219; 256-267.
29. Craig WA, Andes D. Pharmacokinetics and pharmacodynamics of antibiotics in otitis media. *Pediatr Infect Dis J.* 1996;15(3):255-259.
30. Holm S, Henning C, Grahn E, Lomberg H, Staley H. 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;27:221-228.
31. Roos K, Larsson P. Loracarbef versus phenoxymethylpenicillin in the treatment of recurrent streptococcal pharyngotonsillitis. *Scand J Infect Dis.* 1997;29:141-145.
32. Pichichero ME, Hoeger W, Marsocci SM, et al. Variables influencing penicillin treatment outcome in streptococcal tonsillopharyngitis. *Arch Pediatr Adolesc Med.* 1999;153:565-570.
33. Gerber MA, Randolph MF, DeMeo K, Feder HM Jr, Kaplan EL. Failure of once-daily penicillin V therapy for streptococcal pharyngitis. *Am J Dis Child.* 1989;143:153-155.
34. Disney FA, Hanfling MJ Hausinger SA. Loracarbef (LY163892) vs. penicillin VK in the treatment of streptococcal pharyngitis and tonsillitis. *Pediatr Infect Dis J.* 1992;11(8 Suppl): S20-26.
35. 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;11:919-925.
36. Dajani AS, Kessler SL, Mendelson R, Uden DL, Todd WM. Cefpodoxime proxetil vs. penicillin V in pediatric streptococcal pharyngitis/tonsillitis. *Pediatr Infect Dis J.* 1993;12:275-279.
37. Gooch WM 3rd, 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;37:159-163.
38. 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;13:846-850.
39. Pichichero ME, McLinn SE, Gooch WM 3rd, Rodriquez W, Goldfarb J, Reidenberg BE. Ceftibuten vs. penicillin V in group A beta-hemolytic streptococcal pharyngitis. Member of the Ceftibuten Pharyngitis International Study Group. *Pediatr Infect Dis J.* 1995;14(7 Suppl):S102-107.
40. Nemeth MA, McCarty J, Gooch WM 3rd, Henry D, Keyserling CH, Tack KJ. Comparison of cefdinir and penicillin for the treatment of streptococcal pharyngitis. *Clin Ther.* 1999; 21:1525-1532.
41. Assem E, Vickers M. Tests for penicillin allergy in man. II. The immunological cross-reaction between penicillins and cephalosporins. *Immunology.* 1964; 27:255-269.
42. Anderson JA. Cross-sensitivity to cephalosporins in patients allergic to penicillin. *Pediatr Infect Dis.* 1986; 5:557-561.
43. Saxon A, Beall GN, Rohr AS, Adelman DC. Immediate hypersensitivity reactions to beta-lactam antibiotics. *Ann Intern Med.* 1987;107:204-215.
44. Abraham E. The chemistry of new antibiotics. *Am J Med.* 1965;39:692-696.
45. Flynn E. Biological and chemical studies of the cephalosporins. *Antimicrob Agents Chemother.* 1966;6:715-726.
46. Newton GG, Hamilton-Miller JM. Cephaloridine: chemical and biochemical aspects. *Postgrad Med J.* 1967; 43(Suppl):10-37.
47. Grieco M. Cross-allergenicity of the penicillins and the cephalosporins. *Arch Intern Med.* 1967;119:141-145.
48. Scholand JF, Tennebaum JI, Cerilli GJ. Anaphylaxis to cephalothin in a patient allergic to penicillin. *JAMA.* 1968;206:130-132.
49. Petz LD. Immunologic cross-reactivity between penicillins and cephalosporins: a review. *J Infect Dis.* 1978; 137(Suppl):S74-S79.
50. Mendelson LM, Ressler G, Rosen JP, Selcow JE. Routine elective penicillin

allergy skin testing in children and adolescents; study of sensitization. *J Allergy Clin Immunol.* 1984;73(1 pt 1):76-81.

51. Pichichero ME, Pichichero DM. Selecting skin testing reagents to predict amoxicillin and cephalosporin allergy. *Pediatr Asthma Allergy Immunol.* 1997;11:79-93.
52. Pichichero ME. Cephalosporins are superior to penicillin for treatment of streptococcal tonsillopharyngitis: is the difference worth it? *Pediatr Infect Dis J.* 1993;12:268-274.
53. Pichichero ME, Green JL, Francis AB, et al. Recurrent group A streptococcal tonsillopharyngitis. *Pediatr Infect Dis J.* 1998;17:809-815.
54. Steele RW, Estrada B, Begue RE, Mirza A, Travillion DA, Thompson MP. A double-blind taste comparison of pediatric antibiotic suspensions. *Clin Pediatr.* 1997;36:193-199.
55. Eisen SA, Miller DK, Woodward RS, Spitznagel E, Przybeck TR. The effect of prescribed daily dose frequency on patient medication compliance. *Arch Intern Med.* 1990;150:1881-1884.
56. 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; 10:275-281.
57. Pichichero ME, Disney FA, Talpey WB, et al. Adverse and beneficial effects of immediate treatment of group A beta-hemolytic streptococcal pharyngitis in an emergency department. *Pediatr Infect Dis J.* 1986; 5:655.
58. 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: 126-130.
59. Gerber MA, Tanz RR, Kabat W, et al. Potential mechanisms for failure to eradicate group A streptococci from the pharynx. *Pediatrics.* 1999;104:911-917.