Treatment of β-Hemolytic Streptococcal Pharyngitis with Cefaclor or Penicillin

Efficacy and Interaction with β-Lactamase–Producing Organisms in the Pharynx

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The recommended treatment for group A β-hemolytic streptococcal pharyngitis has continued to be penicillin given in parenteral or oral form. Treatment failures, as determined by the continued presence of the streptococcal organism in the pharynx, however, do occur in 6% to 25% of patients treated with penicillin. Furthermore, β-lactamase produced by other bacteria in the pharynx could potentially inactivate the penicillin, resulting in increased treatment failures or infection relapses. A study was undertaken to compare the efficacy of cefaclor, which is relatively resistant to inactivation by β-lactamase, with penicillin for eradicating the group A β-hemolytic streptococcal organism from the throats of 93 patients with pharyngitis. Additionally, extensive cultures for potential β-lactamase–producing organisms were conducted on 37 patients; 27% of these had one or more pharyngeal organisms that were producing β-lactamase. No statistically significant difference was found between the clinical responses or the bacteriological cure rates of those treated with cefaclor and those treated with penicillin when stratified by the presence or absence of β-lactamase–producing organisms. The prevalence of β-lactamase–producing organisms in the pharynx, however, was increased after treatment with penicillin, whereas no change was noted following treatment with cefaclor. *J Fam Pract 1991; 32:138-144.*

The importance of adequate treatment of pharyngitis caused by group A β-hemolytic streptococcus (GABHS) continues to be stressed in the medical literature as a result of recent articles documenting the continued risk of subsequent rheumatic fever[1–3] and the potential virulence of the organism.[4] Despite the consistent susceptibility of the GABHS organism to penicillin, treatment of this infection is only 75% to 94% successful in eradicating the organism.[5–7] Several recent studies have suggested that β-lactamase in the pharynx, produced by other organisms, may play a role in inactivating the penicillin used to treat the infection, resulting in inadequate treatment.[8–12]

The study reported here was designed to evaluate the efficacy of penicillin, an antibiotic inactivated by β-lactamase, and cefaclor, a semisynthetic cephalosporin that is relatively resistant to β-lactamase activity, in the eradication of GABHS in the pharynx of patients with clinical pharyngitis. The effects of the two treatments on the prevalence of β-lactamase–producing organisms in the pharynx and of these organisms on treatment outcomes were evaluated in a subset of patients.

Methods

Patients 1 month of age or older who presented with a sore throat or poor eating to one of four primary care offices in four states were evaluated for potential admission to the study. Patients were ineligible if they were allergic to penicillin or cephalosporins, if they were pregnant, if they had a history of renal or hepatic impairment, if they had significant underlying disease or concomitant infections that could preclude evaluation of response to treatment, or if they had taken an antibiotic in the pre-

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vious 3 days. Each patient's pharynx was swabbed with two swabs made of a polyester fiber (Dacron): one was used to perform one of several rapid in-office tests for detecting the presence of GABHS; the other was used for a pharyngeal culture (see below). Whenever the in-office test suggested the presence of GABHS, that patient was invited to participate in the study.

The study protocol was explained to all eligible patients, and informed consent was obtained. The physician or study coordinator interviewed the patients regarding current symptoms and signs, past and current medical problems, and allergies. A brief physical examination was performed by the physician, with emphasis on the upper respiratory tract system and skin.

Microbiological Testing

Pharyngeal cultures for GABHS were performed by swabbing the tonsillar areas and posterior pharynx with a polyester fiber swab, which was then placed in transport media or plated directly onto trypticase soy sheep blood agar (TSA-SBA, BBL Microbiology Systems, Cockeysville, Md). Cultures were incubated at 35°C under 3% to 5% carbon dioxide atmosphere and examined at 24 and 48 hours for the presence of morphologic characteristics typical of GABHS colonies, which were confirmed by type-specific antisera (BBL Microbiology Systems). Other significant isolates were identified using standard microbiological techniques.

At one of the four study sites, extensive cultures for anaerobes were performed. Swab samples for anaerobe culture were placed into an anaerobic transport media (BBL PortaCul, BBL Microbiology Systems) immediately following collection. These samples were then transported to the laboratory and within 6 hours of collection were plated to prereduced vitamin K–enriched sheep blood agar and incubated at 35°C (in a BBL Microbiology Systems Gas Pak Anaerobe jar) for up to 7 days. Anaerobe cultures were incubated for a minimum of 48 hours before an initial observation was made. At this time all colonies present were isolated to obtain pure culture, and aerotolerance testing was performed. All strict anaerobes were then identified using traditional methods as well as the IDS RapID ANA System (Vitek Systems, Hazelwood, Mo). Susceptibility testing of isolates was performed by the broth disk elution test (Kurzynski method).[13]

β-Lactamase enzyme production was identified using the BBL Cefinase Disk Test (BBL Microbiology Systems).

Treatment

The patient was given a prescription that used a code number to identify the medication to be used. This number corresponded to either cefaclor, 20 mg/kg/d in three divided doses to a maximum of 250 mg three times a day, or penicillin VK, 20 mg/kg/d in three divided doses to a maximum of 250 mg three times a day, each for 10 days. The identity of the antibiotic was unknown to the physician and to the patient, and was randomized by a coding sheet that was available only to the pharmacists dispensing the study medication.

Patients were evaluated again in the office within 48 hours of completing the 10-day course of antibiotic and a third time 28 to 30 days after therapy. At each visit a brief history was taken, including a review of symptoms and questioning about side effects. A physical examination was completed, and repeat aerobic and anaerobic pharyngeal samples for culture were obtained.

At the visit within 48 hours of completing the study medication, the physician defined the clinical response to treatment as cured, improved, relapsed, or failed. The bacteriological response was defined as *pathogen eliminated* if the original GABHS isolated at the pretherapy visit was no longer present in the culture obtained within 48 hours of the discontinuation of therapy, *failed* if the streptococcus was present in that culture; or *unable to evaluate* if the patient violated entry criteria, required another antibiotic, or took the study medication for fewer than 5 days. Relapse indicated the organism was again present at the follow-up visit 28 to 30 days after therapy.

Data Analysis

Frequency distributions of the patient characteristics (history, symptoms, and signs) and the presence of β-lactamase–producing organisms on pharyngeal culture were determined. These characteristics were then stratified by the two types of antibiotic given to assess any statistically significant differences in the baseline characteristics between the two groups using chi-square analyses, odds ratios, and 95% confidence intervals.

The type of antibiotic given was compared with the two outcome measures: the clinical response and the bacteriological response. Chi-square analysis, odds ratios, and 95% confidence intervals were determined.

For those patients with extensive aerobic and anaerobic cultures tested for β-lactamase production, the prevalence of organisms producing this enzyme were calculated and stratified by treatment category. The associations between treatment given and outcome were then stratified by the presence or absence of β-lactamase–

Table 1. Adverse Effects Reported by Patients Taking Cefaclor or Penicillin

Drug	Adverse Effect (No.)	Total
Cefaclor (n = 47)	Diarrhea (3), cough increased (2) rash (1), allergic reaction (1),* injury (1), constipation (1), gingivitis (1), edema (1), agitation (1), respiratory disorder (1), rhinitis (1), hematuria (1)	15
Penicillin (n = 46)	Diarrhea (2), cough increased (2) rash (2), back pain (1), chest pain (1), nausea (1), lymphocytosis (1),* dizziness (1), nervousness (1), sinusitis (1), ear pain (1), otitis media (1)	15

**Required withdrawal from the drug.*

producing organisms in the pharyngeal cultures and the analyses repeated.

Results

A total of 116 patients were enrolled in the study in the four clinic sites (42, 29, 43, and 2 patients, respectively). Of these, 23 were not evaluable: 6 cefaclor-treated and 2 penicillin-treated patients were eliminated because no GABHS was recovered on culture; 1 penicillin-treated patient had insufficient therapy; 3 cefaclor-treated patients had no follow-up culture; 1 cefaclor-treated and 2 penicillin-treated patients had sequential therapy with another antibiotic; and 3 cefaclor-treated and 5 penicillin-treated patients were unevaluable according to the investigator. Therefore, 93 patients were evaluated further.

Patient Characteristics

Of the 93 patients, 76% were between the ages of 3 and 15 years (mean age 11.7 years), 50% were female, 75% white, 24% black, and 1% Hispanic. Fifty-seven percent complained of fever, 59% of headache, 20% of lymphadenopathy, 20% of irritability, 21% of cough, and 30% of rhinitis. Patients in the cefaclor-treated group (n = 47) did not differ significantly from those in the penicillin-treated group (n = 46) for any of the variables listed.

Fifteen adverse effects were reported by 13 cefaclor-treated patients; 13 penicillin-treated patients also reported 15 adverse effects (Table 1). No significant difference in adverse effects was observed between the two treatment groups.

Table 2. Clinical Outcome Over the Duration of the Study, Stratified by Treatment Group

Treatment Group	Clinical Outcome			
	Cure No. (%)	Improvement No. (%)	Relapse No. (%)	Failure No. (%)
Cefaclor (n = 47)	38 (81)	3 (6)	4 (9)	2 (4)
Penicillin (n = 46)	40 (87)	0 (0)	6 (13)	0 (0)

Percent cured or improved (cefaclor—87%, penicillin—87%): odds ratio 1.02, χ^2 = 0.07, P = .79.

Table 3. Bacteriologic Outcome at 48 Hours After Therapy and at 28 to 30 Days After Therapy, Stratified by Treatment Group

Treatment Group	Pathogen Eliminated 48 h After Therapy No. (%)	Recurrence 28–30 d After Therapy No. (%)	Final Outcome*	
			Cure No. (%)	Failure/ Recurrence No. (%)
Cefaclor (n = 47)	43 (91)	3 (6)	40 (85)	7 (15)
Penicillin (n = 46)	40 (87)	5 (11)	35 (76)	11 (24)

**Odds ratio = 1.8, 95% confidence interval 0.46–7.06, χ^2 = 0.70, P = .40.*

Cefaclor vs Penicillin

The clinical outcomes of the patients, stratified by treatment groups, are given in Table 2; 87% of both the cefaclor-treated patients and the penicillin-treated patients were clinically cured or improved. Similarly, eradication of the GABHS organism compared with failure to eliminate this organism did not differ significantly between these groups (Table 3).

The association between the clinical diagnosis of cure and the bacteriological elimination of the organism is statistically significant (Table 4). Only one half of the clinical relapses or failures in each treated group, however, was associated with the continued presence of GABHS by culture at 48 hours after completing the original treatment.

Table 4. Clinical vs Bacteriologic Outcomes at 28 to 30 Days After Therapy, Stratified by Treatment Group*

Clinical Outcome	Bacteriologic Response		*P* Value
	Pathogen Eliminated	Pathogen Not Eliminated	
Cefaclor			
Cured or improved	38	1	
Relapsed or failed	3	3	.005†
Penicillin			
Cured or improved	37	3	
Relapsed or failed	3	3	.02‡

**Values for clinical response were missing on 2 patients.*
†Odds ratio = 38.0, Fisher's exact test.
‡Odds ratio = 12.33, Fisher's exact test.

Table 5. Clinical Response Stratified by Treatment and Whether β-Lactamase–Producing Organisms Were Present at the First Visit*

Response	Cefaclor	Penicillin	*P* Value†
β-Lactamase–producing organisms present			
Cured or improved	3	3	
Relapsed or failed	1	1	.79
No β-lactamase–producing organisms present			
Cured or improved	11	10	
Relapsed or failed	2	2	.67

**Five patients were eliminated from the analysis: 2 penicillin-treated and 1 cefaclor-treated patients received antibiotics for another indication after the second visit, and 2 patients had missing data.*
†Fisher's exact test.

Role of β-Lactamase–producing Organisms

At the initial visit, 44 isolates of organisms that can produce β-lactamase were isolated from 35 evaluable patients (performed at one of the four sites). Of these organisms, 18% (8/44) produced β-lactamase and occurred in 8 of the 35 patients evaluated (23%). β-Lactamase–producing organisms included *Staphylococcus aureus* (5), *Bacteroides melaninogenicus* (1), other *Bacteroides* species (1), and *Hemophilus influenzae* (1). The distributions of these organisms did not vary significantly among those assigned to the cefaclor-treated group and those assigned to the penicillin-treated group.

All 35 patients were *clinically* improved or cured at the first follow-up visit. The presence or absence of β-lactamase–producing organisms and their association with clinical cure or improvement, as well as relapse or failure by the time of the final visit, stratified by treatment group, are given in Table 5. No clinically or statistically significant differences were noted.

Table 6. Bacteriological Response Throughout the Entire Course of Study, Stratified by Treatment Used and Whether β-Lactamase–Producing Organisms Were Present at the First Visit*

Response	Cefaclor	Penicillin	*P* Value†
β-lactamase–producing organisms present			
GABHS organism eradicated	4	2	.21
GABHS organism not eradicated or recurred	0	2	
β-lactamase–producing organisms absent			
GABHS organism eradicated	12	10	.19
GABHS organism not eradicated or recurred	1	4	

**Of 38 evaluable patients, 2 penicillin-treated and 1 cefaclor-treated patients were eliminated from the study because they received antibiotics for another indication after the second visit.*
†Fisher's exact test.
GABHS—Group A β-hemolytic streptococcus.

Table 7. Prevalence of Patients with β-Lactamase–Producing Organisms in the Pharynx Before Treatment and 28 to 30 Days Following Treatment with Cefaclor or Penicillin

Treatment Group	Before Treatment No. (%)	After Treatment No. (%)	*P* Value*	Relative Risk
Cefaclor (n = 16)	4 (25)	5 (31)	.50	1.23
Penicillin (n = 18)	4 (22)	11 (61)	.02	2.75

**Fisher's exact test.*

The association between the presence of any β-lactamase–producing organisms and the *bacteriological* elimination of GABHS over the course of the study is illustrated in Table 6. No statistically significant difference in the eradication of the GABHS was noted between the two treatment groups. Because there were so few patients in each group, however, the power to detect the differences noted is small.

At the onset of the study, β-lactamase–producing organisms were present in similar numbers of patients in each treatment group. At 28 to 30 days following treatment, the percentage of patients with β-lactamase–producing organisms present in the group treated with cefaclor was unchanged but was increased in the group treated with penicillin (Table 7, Figure 1). The types of

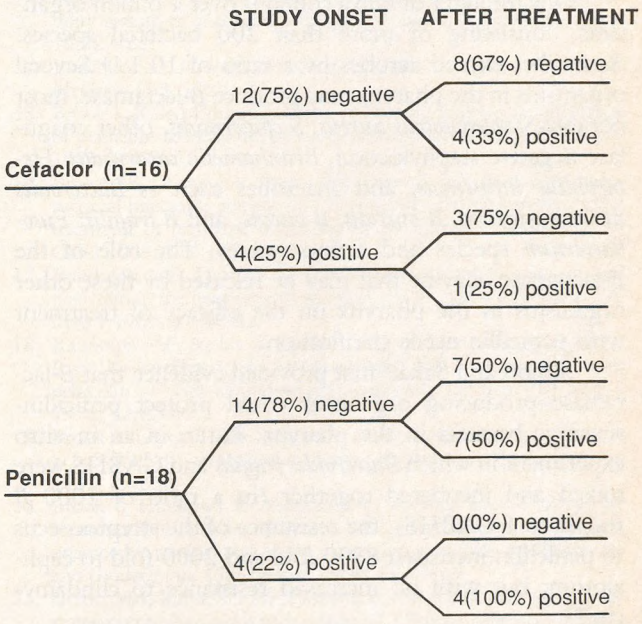

Figure 1. Change in the prevalence of patients with β-lactamase–producing organisms in the pharynx 28 to 30 days following treatment with cefaclor or penicillin.

Table 8. β-Lactamase–Producing Organisms Present for Cefaclor and Penicillin Treatment Groups at Each Visit

Organism Present	Original Visit		48 Hours After Treatment		28 to 30 Days After Treatment	
	Penicillin	Cefaclor	Penicillin	Cefaclor	Penicillin	Cefaclor
Staphylococcus aureus	3	2	6	0	6	4
Bacteroides melaninogenicus	0	1	4	3	3	2
Bacteroides species (other)	1	0	2	2	0	0
Hemophilus influenzae	0	1	1	2	2	0
Branhamella catarrhalis	0	0	1	1	3	2
Fusobacterium varium	0	0	0	1	0	0
Peptococcus species	0	0	1	0	0	0
Gamma streptococcus	0	0	1	0	0	0
Actinomyces	0	0	0	0	0	1
Total	4	4	16	9	12	7

β-lactamase–producing organisms isolated at each visit are indicated in Table 8.

Discussion

Effective eradication of the GABHS organism is associated with a decreased risk of subsequent rheumatic fever; hence, the substantial risk (6% to 25%)[5–7] of ineffective therapy incurred when penicillin is used is of concern. Penicillin is inactivated by the β-lactamase enzyme. If the antimicrobial action of penicillin takes place in an environment in which other organisms are producing this enzyme, inactivation could occur, resulting in decreased or absent antimicrobial activity.

One milliliter of saliva contains over 1 billion organisms, consisting of more than 200 bacterial species. Anaerobes exceed aerobes by a ratio of 10:1.[14] Several organisms in the pharynx may produce β-lactamase, most notably *Staphylococcus aureus, S epidermidis,* other coagulase negative staphylococci, *Branhamella catarrhalis, Hemophilus influenzae,* and anaerobes such as *Bacteroides melaninogenicus, B buccalis, B buccae,* and *B fragilis; Fusobacterium* species and actinomycetes. The role of the β-lactamase enzyme that may be released by these other organisms in the pharynx on the efficacy of treatment with penicillin needs clarification.

Simon and Sakai[8] first provided evidence that β-lactamase–producing organisms could protect penicillin-sensitive bacteria in the pharynx. Later, in an in vitro experiment in which *Bacteroides fragilis* and GABHS were mixed and incubated together (in a ratio of 1000 *B fragilis* to 1 GABHS), the resistance of the streptococcus to penicillin increased 8500-fold and 2000-fold to cephalothin, but with no increased resistance to clindamycin.[11]

The role of β-lactamase–producing organisms in the efficacy of treatment for GABHS pharyngitis is not clear. Some studies have indicated that patients who failed to respond to penicillin treatment were more likely to harbor penicillinase-producing *Staphylococcus aureus* or β-lactamase–producing organisms in the pharynx than were those who responded to treatment,[9,15] but others have not found such an association.[10] In this study no significant difference was found in the response to treatment when patients with β-lactamase–producing organisms were compared with those without β-lactamase–producing organisms in the pharynx. The numbers of patients who failed to respond to therapy, however, were small, and hence the power to detect what could be a clinically significant difference in efficacy was low (Table 6).

Nonetheless, several previous studies do suggest that greater eradication of the GABHS organisms can be obtained with medications that are not inactivated by β-lactamase than with penicillin. These studies evaluated treatment with lincomycin,[16,17] clindamycin,[18–20] cefadroxil[21,22] and cefuroxime.[23] Brook and Hirokawa[20] have demonstrated that clindamycin (β-lactamase resistant) was much more effective than penicillin in eradicating GABHS from the pharynx of patients with recurrent tonsillitis (96% of whom had β-lactamase–producing organisms present). Others have found good rates of GABHS eradication in the pharynx using cefaclor (96% eradication and 8.4% recurrence)[24] or cefadroxil (92% and 89% cure rates for cefadroxil and penicillin, respectively)[25] compared with penicillin. This study indicated that the efficacy of eradicating GABHS from the pharynx in patients with or without β-lactamase–producing organisms present was equivalent using cefaclor or penicillin therapy. While no statistically significant difference was seen in treatment efficacy with cefaclor compared with penicillin in patients with β-lactamase–producing organisms present, a trend was observed, and a larger confirmatory study is needed.

A factor further complicating the outcome of penicillin therapy for GABHS pharyngitis is that data in this study and others indicate the use of penicillin is associ-

ated with an increase in the prevalence of β-lactamase–producing organisms in the pharynx. A study by Brook and Gober[26] reported a prevalence of β-lactamase–producing organisms in the pharynx of 14% of 21 patients prior to treatment for otitis media or pharyngitis and in 48% of patients following penicillin therapy. Follow-up at 85 to 90 days after therapy indicated a residual increase in the prevalence of β-lactamase–producing organisms.[27] Furthermore, the likelihood of isolating ampicillin-resistant *H influenzae* increased in children who had received antibiotics earlier.[28] The prevalence of β-lactamase–producing organisms in patients who have taken repeated courses of antibiotics is also increased; the prevalence in the pharynges of patients with recurrent or chronic tonsillitis or pharyngitis is high, ranging from 74% to 96%.[20,29,30] In this study, no significant change was found in the prevalence of β-lactamase–producing organisms in the pharynx of patients treated with cefaclor, but a 2.75-fold increased prevalence was observed in patients treated with penicillin.

The primary limitation of this study was the low number of patients with complete β-lactamase evaluation available, therefore limiting the power of the study to detect a difference in the efficacy of the two drugs in patients with β-lactamase production documented. The suggestion that patients with β-lactamase–producing organisms present were less likely to have GABHS eliminated from the pharynx requires confirmation with a larger study.

Summary

Cefaclor and penicillin do not differ dramatically in their efficacy in treating group A β-hemolytic streptococcal pharyngitis. This study confirms, however, that patients treated with penicillin are more likely to harbor β-lactamase–producing organisms after treatment, with the effect lasting at least 1 month after therapy. No evidence of an increased prevalence of β-lactamase–producing organisms was found after treatment with cefaclor. Further study is needed to clarify the role of β-lactamase–producing organisms in the efficacy of treatment of streptococcal pharyngitis.

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References

1. Veasy LG, Wiedmeier SE, Orsmond GS, et al. Resurgence of acute rheumatic fever in the intermountain area of the United States. N Engl J Med 1987; 316:421–7.
2. Hosier DM, Craenen JM, Teske DW, Wheller JJ. Resurgence of acute rheumatic fever. Am J Dis Child 1987; 141:730–3.
3. Wallace MR, Garst PD, Papadimos TJ, Oldfield EC III. The return of acute rheumatic fever in young adults. JAMA 1989; 262:2557–61.
4. Stevens DL, Tanner MH, Winship J, et al. Severe group A streptococcal infections associated with a toxic shock-like syndrome and scarlet fever toxin A. N Engl J Med 1989; 321:1–7.
5. Breese BB, Disney FA, Talpey WB. Beta-hemolytic streptococcal illness. Am J Dis Child 1966; 112:21–7.
6. Gastanaduy AS, Kaplan EL, Huwe BB, et al. Failure of penicillin to eradicate group A streptococci during an outbreak of pharyngitis. Lancet 1980; 2:498–502.
7. Gerber MA, Randolph MF, Chanatry J, et al. Five vs ten days of penicillin V therapy for streptococcal pharyngitis. Am J Dis Child 1987; 141:224–7.
8. Simon HJ, Sakai W. Staphylococcal antagonism to penicillin-G therapy of hemolytic streptococcal pharyngeal infection: effect of oxacillin. Pediatrics 1963; 31:463–9.
9. Knudsin RB, Miller JM. Significance of the *Staphylococcus aureus* carrier state in the treatment of disease due to group A streptococci. N Engl J Med 1964; 271:1395–7.
10. Quie PG, Pierce HC, Wannamaker LW. Influence of penicillinase-producing staphylococci on the eradication of group A streptococci from the upper respiratory tract by penicillin treatment. Pediatrics 1966; 37:467–76.
11. Brook I, Yokum P. In vitro protection of group A beta-hemolytic streptococci from penicillin and cephalothin by *Bacteroides fragilis*. Chemotherapy 1983; 29:18–23.
12. Brook I. The role of beta-lactamase–producing bacteria in the persistence of streptococcal tonsillar infection. Rev Infect Dis 1984; 6:601–7.
13. Kurzynski TA, Yrios JW, Helstad AG, Field CR. Aerobically incubated thioglycolate broth disk method for antibiotic susceptibility testing of anaerobes. Antimicrob Agents Chemother 1976; 10:727–32.
14. Rosebury T. Microorganisms indigenous to man. New York: McGraw-Hill, 1962.
15. Brook I. Role of beta-lactamase–producing bacteria in the failure of penicillin to eradicate group A streptococci. Pediatr Infect Dis 1985; 4:491–5.
16. Breese BB, Disney FA, Talpey WB, Green J. Beta-hemolytic streptococcal infection: comparison of penicillin and lincomycin in the treatment of recurrent infections or the carrier state. Am J Dis Child 1969; 117:147–52.
17. Randolph MF, DeHaan RM. A comparison of lincomycin and penicillin in the treatment of group A streptococcal infections. Del Med J 1969; 41:51–62.
18. Randolph MF, Redys JJ, Hibbard EW. Streptococcal pharyngitis Part III—streptococcal recurrence rates following therapy with penicillin or with clindamycin (7-chlorolincomycin). Del Med J 1970; 42:87–92.
19. Brook I, Leyva F. The treatment of the carrier state of group A beta-hemolytic streptococci with clindamycin. Chemotherapy 1981; 27:360–7.
20. Brook I, Hirokawa R. Treatment of patients with a history of recurrent tonsillitis due to group A beta-hemolytic streptococci: a prospective randomized study comparing penicillin, erythromycin and clindamycin. Clin Pediatr 1985; 24:331–6.
21. Gerber MA, Randolph MF, Chanatry J, et al. Once daily therapy for streptococcal pharyngitis with cefadroxil. J Pediatr 1986; 109:531–7.
22. Ginsburg CM, McCracken GH, Crow SD, et al. A controlled comparative study of penicillin V and cefadroxil therapy of group A streptococcal tonsillopharyngitis. J Int Med Res 1980(suppl 1); 8:82–6.

23. Gooch WM, Swenson E, Higbee MD, et al. Cefuroxime axetil and penicillin V compared in the treatment of group A beta-hemolytic streptococcal pharyngitis. Clin Ther 1987; 9:670–7.
24. Kammer RB. Cefaclor in management of streptococcal pharyngitis, otitis media, and skin infections. Ann Otol Rhinol Laryngol 1981 (suppl); 90:79–81.
25. Beisel L. Efficacy and safety of cefadroxil in bacterial pharyngitis. J Int Med Res 1980(suppl 1); 8:87–93.
26. Brook I, Gober AE. Emergence of beta-lactamase-producing aerobic and anaerobic bacteria in the oropharynx of children following penicillin chemotherapy. Clin Pediatr (Phila) 1984; 23:338–9.
27. Brook I. Emergence and persistence of beta-lactamase–producing bacteria in the oropharynx following penicillin treatment. Arch Otolaryngol Head Neck Surg 1988; 114:667–70.
28. Kaplan SL, Mason EO, Kvernland SJ. Effects of prior antibiotics on the susceptibility of *Haemophilus influenzae* type B to ampicillin. Pediatrics 1981; 67:269–71.
29. Brook I, Yocum P, Friedman EM. Aerobic and anaerobic bacteria in tonsils of children with recurrent tonsillitis. Ann Otol Rhinol Laryngol 1981; 90:261–3.
30. Brook I. Beta-lactamase–producing bacteria in head and neck infection. Laryngoscope 1988; 98:428–31.