ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Apr. 1996, p. 895–898 Vol. 40, No. 4
0066-4804/96/$04.00+0

Relationship of MICs to Efficacy of Cefotaxime in Treatment of *Streptococcus pneumoniae* Infections

RICHARD F. JACOBS,[1]* SHELDON L. KAPLAN,[2] GORDON E. SCHUTZE,[3] ADNAN S. DAJANI,[4] ROBERT J. LEGGIADRO,[5] CHOON-SOO RIM,[6] AND SURENDRA K. PURI[6]

Department of Pediatrics[1] and Division of Pediatric Infectious Diseases, Department of Pediatrics and Pathology,[3] University of Arkansas and Arkansas Children's Hospital, Little Rock, Arkansas; Department of Pediatrics, Baylor College of Medicine and the C. T. Parker Memorial Laboratory, Texas Children's Hospital, Houston, Texas[2]; Division of Infectious Diseases, Children's Hospital of Michigan, and the Department of Pediatrics, Wayne State University School of Medicine, Detroit, Michigan[4]; Le Bonheur Children's Medical Center and University of Tennessee, Memphis, Tennessee[5]; and Hoechst-Roussel Pharmaceuticals, Inc., Somerville, New Jersey[6]

Received 24 August 1995/Returned for modification 18 November 1995/Accepted 19 January 1996

In June 1993, the National Committee for Clinical Laboratory Standards (NCCLS) recommended stringent new interpretive guidelines for antibiotics indicated for *Streptococcus pneumoniae* meningitis. To assess the predictive values of the recommended breakpoints, retrospective data were collected from patients who had *S. pneumoniae* infections and were treated with cefotaxime monotherapy. Susceptibilities based on the NCCLS interpretative categories were compared with clinical and bacteriologic outcomes. In 76 evaluable patients, the most common infections were bacteremia-septicemia ($n = 49$), meningitis ($n = 37$), and lower respiratory tract infection ($n = 14$). Under the NCCLS breakpoints proposed in 1993, 55 isolates would have been classed as susceptible to cefotaxime (MIC, ≤0.25 μg/ml), 18 would have been classed as intermediate (MIC, 0.5 to 1.0 μg/ml), and 2 would have been classed as resistant (MIC, ≥2 μg/ml). Of 75 cefotaxime-treated patients for whom cefotaxime MICs were recorded, 73 were clinically cured or improved (37 of 37 with meningitis and 36 of 38 with other infections). One case of bacteremia and one case of bone-and-joint infection were scored as therapeutic failures because initial monotherapy had to be modified because of an adverse drug reaction. Excluding these patients, there were 18 patients infected with *S. pneumoniae* that would have been classed as not fully susceptible (i.e., MICs ≥ 0.5 μg/ml); all of these patients were cured or improved. The results of this analysis demonstrate that successful treatment with cefotaxime did not correlate well with the guidelines for the susceptibility of pneumococcal isolates to either penicillin or cefotaxime established by the 1993 NCCLS breakpoint recommendations. Because of this study and other similar findings, the NCCLS adopted more clinically relevant guidelines in 1994.

Streptococcus pneumoniae is a common cause of bacterial pneumonia, bacterial meningitis, and acute otitis media (1). Children (2, 8) and the institutionalized elderly (8, 12) are particularly susceptible to *S. pneumoniae* infection. In the United States, the incidence of pneumococcal meningitis is 1.1 cases per 100,000 population per year, but for infants younger than 3 to 5 months the incidence is 30 cases per 100,000 population per year and the mortality rate is 10% (8).

For many years, penicillin has been the therapy of choice for pneumococcal infections. However, resistance to this antibiotic has been increasing in many parts of the world (1, 5, 7, 16, 26) Published reports of problematic penicillin-resistant strains have documented their distribution in locales widely scattered across the United States: Kentucky, Tennessee (5, 17), Connecticut (26), Texas (19), Arkansas (30), New Mexico, Oklahoma, Massachusetts, Colorado, and Alaska (3). Increasingly, strains of *S. pneumoniae* that are resistant to three or more classes of antibiotics are being reported (7, 16).

Clinicians are often compelled to make antibiotic choices before susceptibility data are available (25). In the face of the increasing prevalence of penicillin-resistant strains of *S. pneumoniae*, cefotaxime has been widely used as an empiric treatment for serious infections such as meningitis. It is effective against most meningitis-causing organisms (*S. pneumoniae*, *Haemophilus influenzae* type b, and *Neisseria meningitidis*) (31) and penetrates effectively into cerebrospinal fluid (32).

The current guidelines for penicillin susceptibility established by the National Committee for Clinical Laboratory Standards (NCCLS) for *S. pneumoniae* are as follows: strains inhibited by a penicillin concentration of ≤0.06 μg/ml are deemed susceptible, strains inhibited by a penicillin concentration of 0.1 to 1 μg/ml are defined as intermediate, and strains requiring ≥2 μg/ml for inhibition are considered resistant (10). The guidelines for cefotaxime originally recommended by the NCCLS in 1985 were MICs of ≤8 μg/ml for strain susceptibility and MICs of ≥64 μg/ml for strain resistance (31). However, in 1993, reports of clinical failure in cases of meningitis due to strains of *S. pneumoniae* highly resistant to both penicillin and cephalosporins (7, 11, 17, 27) prompted the NCCLS to propose revised susceptibility breakpoints for cephalosporins. For cefotaxime, the breakpoints proposed in 1993 were as follows: susceptible, MIC ≤ 0.25 μg/ml; intermediate, MIC = 0.5 to 1 μg/ml; and resistant, MIC ≥ 2 μg/ml (10, 17).

In 1991 and 1992, a survey of 508 penicillin-susceptible *S. pneumoniae* isolates found none that were resistant to cefotaxime (6). Furthermore, published data on patients with *S. pneumoniae* infections who were treated with cefotaxime monotherapy do not lend support to the revision in NCCLS

* Corresponding author. Mailing address: Department of Pediatrics, 800 Marshall St. Little Rock, AR 72202. Phone: (501) 320-1416. Fax: (501) 320-3551.

guidelines and breakpoints proposed in 1993 (29). Our clinical experience suggested that cefotaxime can cure patients with pathogens for which the cefotaxime MICs are 0.5 to 1 μg/ml. Therefore, the present study was performed (i) to assess the efficacy of cefotaxime against infections by penicillin-resistant pneumococci and (ii) to assess the appropriateness of both the therapeutic interpretive guidelines and breakpoints proposed in 1993 and these revised breakpoints for cefotaxime published in 1994 by the NCCLS for penicillin-resistant pneumococci, which are as follows: susceptible, MIC ≤ 0.5 μg/ml; intermediate, MIC = 1 μg/ml; and resistant, MIC ≥ 2 μg/ml (21).

MATERIALS AND METHODS

The present study is a retrospective analysis (1989 to 1994) of patient charts from Texas Children's Hospital, Le Bonheur Children's Medical Cener, Children's Hospital of Michigan, and Arkansas Children's Hospital, hospitals where a high incidence of penicillin-resistant *S. pneumoniae* infections had been documented (17, 19, 30). Data from the medical records of 115 patients were obtained. Medical charts were identified for all patients with systemic infections that yielded *S. pneumoniae* as the single pathogen. Charts were then screened. Patients were deemed evaluable if (i) the infection had been treated with cefotaxime alone for at least 2 days regardless of previous or subsequent antibiotic treatment and (ii) data were available on pneumococcal susceptibility to penicillin and cefotaxime, preferably obtained by either the MIC or the Kirby-Bauer method or both (15, 18). All institutions utilized the E test for susceptibility testing. The medical charts of patients who had only simple urinary tract infections were excluded.

The following information was obtained from the medical records: age, sex, race, height, weight, initials, medical records number, microbiologic susceptibility data, clinical diagnosis, signs, symtoms, tests confirming diagnosis, clinical outcome, bacteriologic outcome, and cefotaxime regimen, including dose, frequency, treatment duration, and any concomitant antibiotics.

The clinical outcome for each patient was graded according to signs, symptoms, and test results at the end of cefotaxime therapy, regardless of whether therapy was subsequently continued with another agent. The clinical response was considered a cure if all preexisting signs and symptoms of infection resolved satisfactorily after cefotaxime treatment. The clinical response was considered improved if signs and symptoms were ameliorated in comparison with those observed at baseline. If signs and symptoms remained the same or worsened or if antibiotics had to be changed for any reason after more than 3 days of treatment, the clinical response was considered a failure. If additional antibiotics were added to the therapy regimen within the first 2 days of treatment, the case was considered nonevaluable. Though retrospective analysis of the patients' clinical charts suggested that two nonevaluable patients may have been infected with a cefotaxime-resistant strain, their exclusion did not affect the overall results because both had satisfactory responses to cefotaxime and vancomycin therapy.

The bacteriologic response was considered satisfactory when the causative pathogen was eradicated as demonstrated by posttreatment culture, when it was presumed eradicated because clinical resolution of infection precluded follow-up cultures, or when it was eradicated and a different pathogen appeared but the patient had no clinical evidence of a new infection.

RESULTS

Seventy-six of the 115 cases submitted for this study were evaluable. The remaining cases were excluded because other antibiotics were used concomitantly with cefotaxime. The excluded cases were reviewed for evidence of infection with a bacterial strain resistant to cefotaxime. In one excluded meningitis case, vancomycin plus cefotaxime therapy for 7 days resolved the infection, but the patient's treatment was completed with an additional 6 days on penicillin G monotherapy. For the organism isolated from this patient, the reported cefotaxime sensitivity was ≤8 μg/ml (an actual endpoint MIC was not determined) and the penicillin MIC was 0.06 μg/ml. In another case of meningitis, initial cefotaxime plus vancomycin therapy for 2 days resolved the infection, but chloramphenicol was then substituted for cefotaxime for a further 10 days. The cefotaxime MIC for the bacterial strain isolated from this patient was 4 μg/ml.

Eighty-eight percent of the evaluable cases were children under 2 years of age; the oldest patient was 66 years of age. The male-to-female ratio was 2:1. Among evaluable patients, the most common types of infections were bacteremia-septicemia (n = 49) and meningitis (n = 37) and then lower respiratory tract infection, bone-and-joint infection, intra-abdominal infection, and one case of otitis media. Bacteremia-septicemia often occurred in conjunction with other types of infection. Twelve cases of meningitis and all cases of lower respiratory tract infection were accompanied by bacteremia-septicemia. One patient had a three-site infection: meningitis, lower respiratory tract infection, and septicemia.

TABLE 1. Number of pretreatment pneumococcal isolates (one determination per evaluable patient) by level of susceptibility to penicillin and cefotaxime

Drug (no. of isolates tested) and MIC (μg/ml)[a]	No. of isolates (%)[b]
Penicillin (76)	
<0.1	52 (68)
0.1–1	22 (29)
≥2	2 (3)
Cefotaxime (1993 proposed guidelines) (75)	
≤0.25	55 (73)
0.5–1	18 (24)
≥2	2 (3)
Cefotaxime (current guidelines) (75)	
≤0.5	71 (95)
1	2 (3)
≥2	2 (3)

[a] Data for cefotaxime susceptibility exclude one patient for whom no MIC was obtained.

[b] MICs were determined by the E test except for cefotaxime tested against one isolate. However, the disk zone diameter as determined by the Kirby-Bauer method was 37.5 mm, suggesting a high level of susceptibility to the antibiotic.

All patients had been assessed for the presence of pathogens before they were treated with cefotaxime. Ninety-seven percent of patients (n = 74) were infected with *S. pneumoniae* alone. The remaining two patients each had one additional pathogen isolated, *Streptococcus viridans* in a peritonitis patient and *Staphylococcus epidermidis* in a meningitis patient. Fifty *S. pneumoniae* isolates were obtained from blood, thirty-seven were obtained from cerebrospinal fluid, three were obtained from peritoneal fluid, and three were obtained from bone and/or joint aspirate. The susceptibility to penicillin and cefotaxime of pneumococcal isolates from each patient was determined (Table 1). For 81% of isolates (30 of 37) from meningitis patients and 66% of isolates (25 of 38) from other infections, cefotaxime MICs were ≤0.25 μg/ml.

Sixty-eight percent of isolates (n = 52) were susceptible to penicillin, 29% were intermediate, and 3% were resistant (Table 1). According to the standards proposed by the NCCLS in 1993, 73% of isolates (n = 55) would have been considered susceptible to cefotaxime (MIC, ≤0.25 μg/ml), 24% would have been considered intermediate (MIC, 0.5 to 1 μg/ml), and 3% would have been considered resistant (MIC, ≥2 μg/ml). In contrast, under the new NCCLS guidelines approved in June 1994, 95% of isolates (71 of 75) are considered susceptible to cefotaxime (MIC, ≤0.5 μg/ml), 3% are considered intermediate (MIC, 1 μg/ml), and 3% are considered resistant (MIC, ≥2 μg/ml).

The cefotaxime dosage, determined by body weight, was 100 to 150 mg/kg/day for 11 patients, 151 to 200 mg/kg/day for 32 patients, 201 to 250 mg/kg/day for 31 patients, and 251 to 300 mg/kg/day for 2 patients. The duration of cefotaxime treatment was 4 days or less for 15 patients, 5 days for 5 patients, 6 to 7

TABLE 2. Clinical response rates of patients according to cefotaxime MIC for pneumococcal isolates

Infection	No. of clinical responders[a]/total patients (%) by cefotaxime MIC (μg/ml)			
	≤0.5	1	≥2	Total
Meningitis	36/36 (100)	0	1/1 (100)	37/37 (100)
Other infections	33/35 (94)	2/2 (100)	1/1 (100)	36/38 (95)
Total infections	69/71 (97)	2/2 (100)	2/2 (100)	73/75 (97)

[a] Responders are patients classified as cured and improved; the data exclude one patient for whom no MIC was obtained.

days for 8 patients, 8 to 10 days for 8 patients, 11 to 14 days for 34 patients, and more than 15 days for 6 patients.

The clinical response rates to cefotaxime are shown in Table 2 according to cefotaxime MIC. The overall improved and cure rate for evaluable meningitis patients was 100%. Cefotaxime also yielded a high rate of clinical resolution for pneumococcal infections other than meningitis. Two nonmeningitis cases were recorded as failures because the antibiotic regimen had modified following an adverse drug reaction. The cefotaxime MIC for the pathogen isolated from one of these patients was <0.125 μg/ml; for the isolate from the other, the cefotaxime MIC was 0.5 μg/ml and the penicillin MIC was 4 μg/ml. Excluding these two dropouts, the clinical response rate (cured and improved) was 100%. Bacteriologic response was satisfactory (eradicated or presumed eradicated) in all patients. Microbiologic proof of eradication of the pneumococcus was obtained in 43% of meningitis cases and 58% of other infections (Table 3). The remaining infections were presumed cured by virtue of clinical resolution of the symptoms and release from the hospital.

DISCUSSION

Since *S. pneumoniae* strains with increased resistance to penicillin have become more comon (16), the expanded-spectrum cephalosporins (e.g., cefotaxime and ceftriaxone) have been favored for the treatment of serious infections (2). However, some strains that are highly resistant to penicillin are also resistant to cephalosporins (22), and a number of clinical failures with cephalosporins have been reported (11, 20, 27). to compound the problem, exposure to antibiotics during the few months prior to a current infection appears to increase the risk that the current pathogen will be resistant to penicillin (28, 33).

TABLE 3. Bacteriologic response rates of patients according to cefotaxime MIC for pneumococcal isolates[a]

Infection and bacteriologic response	No. of patients (%) according to cefotaxime MIC (μg/ml)			
	≤0.5	1	≥2	Total
Meningitis				
Eradicated	16 (44)	0	0	16 (43)
Presumed eradicated	20 (56)	0	1 (100)	21 (57)
Total bacteriologic response	36 (100)	0	1 (100)	37 (100)
Other infections				
Eradicated	20 (57)	2 (100)	0	22 (58)
Presumed eradicated	15 (43)	0	1 (100)	16 (42)
Total bacteriologic response	35 (100)	2 (100)	1 (100)	38 (100)
Total infections				
Eradicated	36 (51)	2 (100)	0	38 (51)
Presumed eradicated	35 (49)	0	2 (100)	37 (49)
Total bacteriologic response	71 (100)	2 (100)	2 (100)	75 (100)

[a] Excludes one patient for whom no MIC was obtained.

In response to the changing resistance patterns, the NCCLS considerably lowered the susceptibility breakpoints for expanded-spectrum cephalosporins to levels comparable to those used for penicillin. In the present study, however, the penicillin and cefotaxime MICs for the pneumococcal isolates were different; more isolates were reported to be susceptible to cefotaxime than to penicillin (Table 1). Furthermore, the overall clinical response rate (cure and improvement rates) for infections caused by organisms for which the cefotaxime MIC was <1 μg/ml was 97%.

Other reports have shown that pneumococcal isolates resistant to penicillin were susceptible to a variety of cephalosporins (23), and cefotaxime has produced good clinical results in adults with meningitis caused by strains resistant to penicillin (13). These findings and those of the present study show treatment success with cefotaxime regardless of pneumococcal resistance to penicillin.

In this study, all evaluable infections responded clinically to cefotaxime treatment regardless of cefotaxime MICs (Table 2), except two that required modification of therapy because the patients developed adverse reactions. Tan and colleagues also demonstrated that pediatric patients with meningitis benefited clinically from cephalosporin treatment even if the MICS for the isolates were 0.5 to 1 μg/ml, regardless of penicillin susceptibility; in their study, no meningitis relapse occurred (29). These data and the data from the present study imply that successful clinical outcomes can be obtained with cefotaxime treatment for infections with isolates for which the MICs are up to 1 μg/ml. This suggests that the susceptibility breakpoints proposed in 1993 were unnecessarily stringent. The number of patients in the present study who were treated for infections caused by resistant strains of *S. pneumoniae* (cefotaxime MIC, ≥2 μg/ml), is too low to support recommendations for the use of expanded-spectrum cephalosporins in such cases.

It has been demonstrated that cefotaxime has effective penetration into the cerebrospinal fluid (4, 32). The concentration of cefotaxime in cerebrospinal fluid after administration of a dosage of 200 mg/kg/day, similar to the doses used in this study, ranges from 1.5 to 6.0 μg/ml during the acute phase of meningitis (24). These cefotaxime levels should be more than adequate to eradicate most *S. pneumoniae* strains.

In the present analysis, all treated cases of meningitis were cured or improved, though cefotaxime MICs for the pathogens ranged up to 8 μg/ml. This may be due to the postantibiotic effect of cefotaxime on gram-positive pathogens or to synergy with desacetylcefotaxime, the major active metabolite of the drug. Such effects have been demonstrated in vitro (9, 14). For patients with pneumococcal meningitis due to isolates for which the MICs are ≥2 μg/ml, combination therapy with vancomycin plus an expanded-spectrum cephalosporin (cefotaxime or ceftriaxone) should be standard. In cases in which the MIC is 1 μg/ml (intermediate), the NCCLS recommends that maximum doses of cefotaxime be used (21).

Because of this study and other supportive data, the NCCLS Subcommittee on Antimicrobial Susceptibility Testing approved the revised breakpoint guidelines in 1994.

ACKNOWLEDGMENT

We thank Jennie Andersen for her work reviewing medical records.

REFERENCES

1. **Allen, K. D.** 1991. Penicillin-resistant pneumococci. J. Hosp. Infect. **17:**3–13.
2. **Appelbaum, P. C.** 1987. World-wide development of antibiotic resistance in pneumococci. Eur. J. Clin. Microbiol. **6:**367–377.
3. **Appelbaum, P. C.** 1992. Antimicrobial resistance in *Streptococcus pneumoniae*: an overview. Clin. Infect. Dis. **15:**77–83.
4. **Asmar, B. I., M. C. Thirumoorthi, J. A. Buckley, D. M. Kobos, and A. S. Dajani.** 1985. Cefotaxime diffusion into cerebrospinal fluid of children with meningitis. Antimicrob. Agents Chemother. **28:**138–140.
5. **Block, S., P. Wright, R. Finger, R. Leggiadro, M. Appleton, S. Kahn, and R. Hutchenson.** 1994. Drug-resistant *Streptococcus pneumoniae*—Kentucky and Tennessee, 1993. JAMA **271:**421–422.
6. **Breiman, R. F., J. C. Butler, F. C. Tenover, J. A. Elliott, and R. R. Facklam.** 1994. Emergence of drug-resistant pneumococcal infections in the United States. JAMA **271:**1831–1835.
7. **Caputo, G. M., P. C. Appelbaum, and H. H. Liu.** 1993. Infections due to penicillin-resistant pneumococci: clinical, epidemiologic, and microbiologic features. Arch. Intern. Med. **153:**1301–1310.
8. **Chesney, P. J.** 1992. The escalating problem of antimicrobial resistance in *Streptococcus pneumoniae*. Am. J. Dis. Child. **146:**912–916.
9. **Craig, W. A.** 1995. Interrelationship between pharmacokinetics and pharmacodynamics in determining dosage regimens for broad-spectrum cephalosporins. Diagn. Microbiol. Infect. Dis. **22:**89–96.
10. **Friedland, I. R., and G. H. McCracken, Jr.** 1994. Management of infections caused by antibiotic-resistant *Streptococcus pneumoniae*. N. Engl. J. Med. **331:**377–382.
11. **Friedland, I. R., S. Shelton, M. Paris, S. Rinderknecht, S. Ehrett, K. Krisher, and G. H. McCracken, Jr.** 1993. Dilemmas in diagnosis and management of cephalosporin-resistant *Streptococcus pneumoniae* meningitis. Pediatr. Infect. Dis. J. **12:**196–200.
12. **Haglund, L. A., G. R. Istre, D. A. Pickett, D. F. Welch, D. P. Fine, and the Pneumococcus Study Group.** 1993. Invasive pneumococcal disease in central Oklahoma: emergence of high-level penicillin resistance and multiple antibiotic resistance. J. Infect. Dis. **168:**1532–1536.
13. **Jacobs, M. R.** 1992. Treatment and diagnosis of infections caused by drug-resistant *Streptococcus pneumoniae*. Clin. Infect. Dis. **15:**119–127.
14. **Jones, R. N., A. L. Barry, and R. R. Packer.** 1984. The activity of cefotaxime and desacetylcefotaxime alone and in combination against anaerobes and staphylococci. Diagn. Microbiol. Infect. Dis. **2:**37S–46S.
15. **Jorgenson, J. H., M. J. Ferraro, M. L. McElmeel, J. Spargo, J. M Swenson, and F. C. Tenover.** 1994. Detection of penicillin and extended-spectrum cephalosporin resistance among *Streptococcus pneumoniae* clinical isolates by use of the E test. J. Clin. Microbiol. **32:**159–163.
16. **Klugman, K. P.** 1990. Pneumococcal resistance to antibiotics. Clin. Microbiol. Rev. **3:**171–196.
17. **Leggiadro, R. J., F. F. Barrett, P. J. Chesney, Y. Davis, and F. C. Tenover.** 1994. Invasive pneumococci with high level penicillin and cephalosporin resistance at a mid-south children's hospital. Pediatr. Infect. Dis. J. **13:** 320–322.
18. **Macias, E. A., E. O. Mason, Jr., H. Y. Ocera, and M. T. LaRocco.** 1994. Comparison of E test with standard broth microdilution for determining antibiotic susceptibilities of penicillin-resistant strains of *Streptococcus pneumoniae*. J. Clin. Microbiol. **32:**430–432.
19. **Mason, E. O., Jr., S. L. Kaplan, L. B. Lamberth, and J. Tillman.** 1992. Increased rate of isolation of penicillin-resistant *Streptococcus pneumoniae* in a children's hospital and in vitro susceptibilities to antibiotics of potential therapeutic use. Antimicrob. Agents Chemother. **36:**1703–1707.
20. **Musher, D. M.** 1992. Infections caused by *Streptococcus pneumoniae*: clinical spectrum, pathogenesis, immunity, and treatment. Clin. Infect. Dis. **14:**801–807.
21. **National Committee for Clinical Laboratory Standards.** 1994. Performance standards for antimicrobial susceptibility testing. M100-S5. National Committee for Clinical Laboratory Standards, Villanova, Pa.
22. **Neu, H. C.** 1992. The crisis in antibiotic resistance. Science **257:**1064–1073.
23. **Parkinson, A. J., M. Davidson, M. A. Fitzgerald, L. R. Bulkow, and D. J. Parks.** 1994. Serotype distribution and antimicrobial resistance patterns of invasive isolates of *Streptococcus pneumoniae*: Alaska 1986–1990. J. Infect. Dis. **170:**461–464.
24. **Peretti, P., L. Sueri, M. Tosi, R. Ciammarughi, G. P. Cadeo, and B. Milanesi.** 1984. Cefotaxime in the cerebrospinal fluid and serum in patients with purulent meningitis. J. Antimicrob. Chemother. **14**(Suppl. B)**:**117–123.
25. **Simberkoff, M. S.** 1994. Drug-resistant pneumococcal infections in the United States. JAMA **271:**1875–1876.
26. **Simpson, E. H., M. L. Cartter, and J. L. Hadler.** 1994. Prevalence of penicillin-resistant *Streptococcus pneumoniae*—Connecticut, 1992–1993. JAMA **271:**1572.
27. **Sloas, M. M., F. F. Barrett, P. J. Chesney, B. K. English, B. C. Hill, F. C. Tenover, and R. J. Leggiadro.** 1992. Cephalosporin treatment failure in penicillin- and cephalosporin-resistant *Streptococcus pneumoniae* meningitis. Pediatr. Infect. Dis. J. **11:**662–666.
28. **Tan, T. Q., E. O. Mason, Jr., and S. L. Kaplan.** 1993. Penicillin-resistant systemic pneumococcal infections in children: a retrospective case-control study. Pediatrics **92:**761–767.
29. **Tan, T. Q., G. E. Schutze, E. O. Mason, Jr., and S. L. Kaplan.** 1994. Antibiotic therapy and acute outcome of meningitis due to *Streptococcus pneumoniae* considered intermediately susceptible to broad-spectrum cephalosporins. Antimicrob. Agents Chemother. **38:**918–923.
30. **Thompson, J. W., M. J. Lewno, and G. E. Schutze.** 1994. Antibiotic-resistant pneumococcal disease at Arkansas Children's Hospital, 1990 to 1993. Pediatr. Infect. Dis. J. **13:**408–409.
31. **Todd, P. A., and R. N. Brogden.** 1990. Cefotaxime: an update of its pharmacology and therapeutic use. Drugs **40:**608–651.
32. **Trang, J. M., R. F. Jacobs, G. L. Kearns, A. L. Brown, T. G. Wells, F. L. Underwood, and R. B. Kluza.** 1985. Cefotaxime and desacetylcefotaxime pharmacokinetics in infants and children with meningitis. Antimcrob. Agents Chemother. **28:**791–795.
33. **Welby, P. L., D. S. Keller, J. L. Cromien, P. Tebas, and G. A. Storch.** 1994. Resistance to penicillin and non-beta-lactam antibiotics of *Streptococcus pneumoniae* at a children's hospital. Pediatr. Infect. Dis. J. **13:**281–287.