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Antibiotic Therapy and Acute Outcome of Meningitis Due to *Streptococcus pneumoniae* Considered Intermediately Susceptible to Broad-Spectrum Cephalosporins

TINA Q. TAN,[1,2]* GORDON E. SCHUTZE,[3] EDWARD O. MASON, JR.,[1,4] AND SHELDON L. KAPLAN[1]

Departments of Pediatrics[1] and Microbiology and Immunology,[4] Infectious Diseases Section, Baylor College of Medicine, and Infectious Disease Laboratory, Texas Children's Hospital,[2] Houston, Texas, and Department of Pediatrics and Pathology, Division of Pediatric Infectious Diseases, Arkansas Children's Hospital, University of Arkansas for Medical Sciences, Little Rock, Arkansas[3]

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Children with meningitis due to *Streptococcus pneumoniae* isolates that are relatively or fully resistant to penicillin and have decreased susceptibility to broad-spectrum cephalosporins (MIC, ≥2.0 μg/ml) who have failed treatment with broad-spectrum cephalosporins have been reported. The National Committee for Clinical Laboratory Standards has newly revised guidelines indicating that *S. pneumoniae* isolates associated with meningitis for which the MICs are ≥0.5 μg/ml should be considered resistant to broad-spectrum cephalosporins. This recommendation is not clearly based on data related to clinical outcome and may be too conservative. We present data on five children who had *S. pneumoniae* meningitis due to isolates that were relatively or fully resistant to penicillin (MIC range, 0.125 to 4.0 μg/ml) and had cefotaxime or ceftriaxone MICs of 0.50 to 2.0 μg/ml. Their clinical courses and outcomes were comparable to those of five children with *S. pneumoniae* meningitis due to strains that were relatively or fully resistant to penicillin and were inhibited by cefotaxime at concentrations of ≤0.25 μg/ml, as well as to those of 25 patients with *S. pneumoniae* meningitis due to penicillin-susceptible isolates identified during the same period. Children with meningitis due to *S. pneumoniae* with cefotaxime or ceftriaxone MICs of ≤1.0 μg/ml may be adequately treated with these antibiotics. Further clinical data are required before solid recommendations can be made regarding cephalosporin breakpoints for *S. pneumoniae*.

The first case of penicillin-resistant *Streptococcus pneumoniae* meningitis in the United States was reported by Naraqi et al. (17) in 1974. Additional cases of meningitis caused by *S. pneumoniae* relatively resistant (MIC, 0.1 to 1.0 μg/ml) or fully resistant (MIC, >2.0 μg/ml) to penicillin have been reported over the last 15 to 18 years (1, 6, 10, 11, 14, 20, 21, 23, 26, 27). The broad-spectrum cephalosporins ceftriaxone and cefotaxime are the most commonly recommended antibiotics for treatment of meningitis due to penicillin-resistant *S. pneumoniae*, although the optimal antibiotic therapy for meningitis due to penicillin-resistant *S. pneumoniae* has not been established (11, 13, 15, 16, 23, 27). However, over the last 4 years, children with meningitis due to *S. pneumoniae* isolates which have decreased susceptibility to broad-spectrum cephalosporins (MICs, ≥2.0 μg/ml) and who have been unsuccessfully treated with broad-spectrum cephalosporins have been reported (2–5, 9, 12, 21).

The National Committee for Clinical Laboratory Standards has established new guidelines stating that *S. pneumoniae* isolates associated with meningitis for which the MICs are ≥0.5 μg/ml should be considered resistant to broad-spectrum cephalosporins. However, this recommendation is not clearly based on data related to clinical outcome.

We present our experience with five children who had *S. pneumoniae* meningitis due to isolates that were relatively or fully resistant to penicillin (MIC range, 0.125 to 4.0 μg/ml) and had cefotaxime or ceftriaxone MICs ranging from 0.50 to 2.0 μg/ml. All were treated with cefotaxime, and their clinical courses and outcomes were compared with those of five patients with *S. pneumoniae* meningitis due to strains that were relatively or fully resistant to penicillin and were inhibited by cefotaxime at concentrations of ≤0.25 μg/ml and with those of 25 patients with *S. pneumoniae* meningitis due to penicillin-susceptible isolates identified during the same period.

MATERIALS AND METHODS

All clinical isolates of *S. pneumoniae* recovered from 1 January 1989 to 30 June 1993 in the microbiology laboratories of Texas Children's Hospital, Houston, and Arkansas Children's Hospital, Little Rock, were routinely screened for penicillin susceptibility with a 1-μg oxacillin disk by the Kirby-Bauer disk diffusion method. Strains which showed a zone of inhibition less than 20 mm in diameter were considered possibly resistant to penicillin and underwent additional testing for confirmation (18). Resistance was confirmed by broth macrotube dilution with Mueller-Hinton medium supplemented with 3% laked horse blood. MIC determination was accomplished with a final inoculum of 1×10^5 to 3×10^5 CFU/ml. Intermediate resistance to penicillin was defined as 0.1 μg/ml < MIC ≤ 1.0 μg/ml, and full resistance to penicillin was defined as a MIC of ≥2.0 μg/ml. Strains with penicillin MICs of >0.1 μg/ml were tested for susceptibility to cefotaxime and ceftriaxone by broth macrotube dilution as described above.

Approval for a retrospective chart review was obtained from the respective hospital committees on clinical investigation and from each patient's private physician. The complete medical record of each child was reviewed, and data were collected by

* Corresponding author. Mailing address: Texas Children's Hospital, 6621 Fannin Street, MC 3-2371, Houston, TX 77030. Phone: (713) 770-4330. Fax: (713) 770-4347.

using a standardized form. Information concerning age, gender, race, underlying conditions, cerebrospinal fluid (CSF) parameters, antibiotic therapy, other possible risk factors, and outcome was obtained. The charts of children with pneumococcal meningitis whose isolates were susceptible to penicillin and were identified over the same time period were also reviewed.

A patient was considered afebrile if his or her rectal temperature was <38.1°C for 24 h. An acute response to therapy was considered good if the child became afebrile, signs and symptoms of the infection resolved, any repeat CSF cultures were sterile, and no obvious neurologic deficits were detected at discharge. Hearing testing was performed by testing auditory brainstem evoked responses prior to discharge or at follow-up. Children with neurologic sequelae were seen by a neurologist and were followed up for various lengths of time.

RESULTS

Ten penicillin-resistant and 25 penicillin-susceptible CSF isolates were identified. The resistant isolates were divided into two groups based on their cefotaxime MICs. Five patients were in a group with cefotaxime MICs of ≥0.50 μg/ml, and five patients were in a group with cefotaxime MICs of ≤0.25 μg/ml. These patients were compared with the 25 patients with CSF isolates fully susceptible to penicillin. One patient with *S. pneumoniae* meningitis and sickle cell disease was moribund on arrival at the hospital and died 11 h later. The child was not included in the study. This patient's isolate had a penicillin MIC of 4.0 μg/ml and a cefotaxime MIC of 2.0 μg/ml and was resistant by ceftizoxime disk screening.

Patients with *S. pneumoniae* isolates having cefotaxime MICs of ≥0.50 μg/ml. Isolates from five patients had penicillin MICs ranging from 1.0 to 4.0 μg/ml (Table 1). The mean age of the patients was 16 months, and 60% of these children were females. Three of the patients were Caucasian, one was Afro-American, one was Hispanic, and none had an underlying condition.

The initial CSF parameters for these patients showed a mean leukocyte (WBC) count of 1,579/mm^3. The mean protein and glucose concentrations were 219 and 37 mg/dl, respectively. All of the patients had Gram stains positive for gram-positive cocci and cultures positive for *S. pneumoniae*.

All of the patients were treated with cefotaxime for a total dose of 200 to 225 mg/kg/day divided into doses administered every 6 to 8 h for courses ranging from 10 to 18 days. One patient each also received ampicillin for 2 days and nafcillin for 4 days. Two patients also received a 4-day course of dexamethasone. Three of the patients had positive blood cultures at the time of admission; all had repeat blood cultures which were negative within 48 h of the initial positive culture. Three of the patients had repeat lumbar punctures; two were performed within 72 h of the initial positive CSF culture, and one was performed after 14 days. All repeat CSF cultures were negative. The patients became afebrile within 3 to 6 days, and all responded well to therapy with no adverse sequelae. Auditory brainstem evoked response test results were normal for all of the children.

Patients with *S. pneumoniae* isolates having cefotaxime MICs of ≤0.25 μg/ml. The isolates from five patients had penicillin MICs ranging from 0.125 to 1.0 μg/ml (Table 2). Their mean age was 41.4 months, and 40% of the patients were female. Three of the patients were Afro-American, one was Caucasian, and one was Asian. One child each had non-T,

TABLE 1. Characteristics of children with meningitis due to *S. pneumoniae* with cefotaxime MICs of ≥0.50 μg/ml

Patient no.	Age (mo)	Antibiotic regimen (duration [days])	MIC (μg/ml) of:		Initial CSF findings			Repeat CSF findings			Outcome	Febrile days
			Penicillin	CTX[a]	WBC/mm^3 (% SEGS[b])	Protein; glucose concn (mg/dl)	Gram stain/ culture results	Days into illness	WBC/mm^3 (% SEGS)	Protein; glucose concn (mg/dl)	Gram stain/ culture results	
1	20	CTX (10)	1.0	1.0	1,200 (77)	370; 18	+/+					6	Good; no complications
2	6	AMP[c] (2), CTX (10)	1.0	1.0	4,750 (94)	99; 76	+/+					3	Good; no complications
3	21	CTX (18), DEX[d] (4)	4.0	0.5	154 (85)	397; <10	+/+	3	3,840 (73)	183; 28	−/−	5	Good; no complications
								17	42 (4)	45; 41	−/−	
4	7	CTX (21)	2.0	1.0	1,152 (94)	138; 69	+/+	2	790 (64)	164; 63	−/−	6	Good; no complications
5	26	NAF[e] (4), CTX (10), DEX (4)	4.0	2.0[f]	639 (75)	91; 12	+/+	14	2 (1)	37; 46	−/−	3	Good; no complications

[a] CTX, cefotaxime.
[b] SEGS, segmented neutrophils.
[c] AMP, ampicillin.
[d] DEX, dexamethasone.
[e] NAF, nafcillin.
[f] Ceftriaxone MIC.

TABLE 2. Characteristics of children with meningitis due to *S. pneumoniae* with cefotaxime MICs of ≤0.25 μg/ml

Patient no.	Age (mo)	Antibiotic regimen (duration [days])	MIC (μg/ml) of:		Initial CSF findings			Repeat CSF findings				Outcome
			PCN[a]	CTX[b]	WBC/mm^3 (% SEGS[c])	Protein; glucose concn (mg/dl)	Gram stain/ culture results	Days into illness	WBC/mm^3 (% SEGS)	Protein; glucose concn (mg/dl)	Gram stain/ culture results	Febrile days	
1	61	NAF[d] (1), CTX (10)	0.250	0.125	182 (92)	68; 25	+/+					0.5	Good; no complications
2	5	CTX (2), PCN (7)	0.125	0.125	880 (66)	76; 26	+/+					0	Good; no complications
3	58	CTX (10)	0.125	0.125	4,350 (86)	290; 62	−/+					1.5	Mild bilateral hearing loss
4	11	CTX (10)	1.0	0.250	282 (85)	78; 54	+/+	14	3	24; 43	−/−	3	Good; no complications
5	72	VANC[e] (2), CTX (16), PCN (14)	0.125	0.250	13 (90)	105; 34	+/+					6	Good; no complications

[a] PCN, penicillin.
[b] CTX, cefotaxime.
[c] SEGS, segmented neutrophils.
[d] NAF, nafcillin.
[e] VANC, vancomycin.

non-B acute lymphocytic leukemia and congenital hydrocephalus.

The initial CSF parameters of these patients showed a mean WBC count of 1,141/mm^3. The mean protein and glucose concentrations were 123 and 40 mg/dl, respectively. Four of the five patients yielded CSF specimens that contained gram-positive cocci.

All patients were initially treated with a broad-spectrum parenterally administered cephalosporin (one received ceftriaxone [50 mg/kg/dose every 12 h], and four received cefotaxime [200 to 225 mg/kg/day divided into doses administered every 6 to 8 h]). In addition, one patient each also received vancomycin, nafcillin, and penicillin. One patient was discharged home on an additional 7-day course of amoxicillin-clavulanic acid. Four of the patients had positive blood cultures at the time of admission; all had repeat cultures within 36 h of the initial positive culture, and all were negative. Two patients became afebrile within 24 h, and one each became afebrile at 36 h, 72 h, and 7 days. All patients responded well to therapy, with only one patient developing mild bilateral sensorineural hearing loss as an adverse sequela.

Patients with penicillin-susceptible CSF *S. pneumoniae* isolates. Twenty-five patients with penicillin-susceptible *S. pneumoniae* ranged in age from 4 days to 156 months (mean, 22.5 months), and 30% were females. Thirty-six percent were Afro-American, 48% were Caucasian, and 20% were Hispanic. Four patients had underlying conditions; one each had asplenia, chronic juvenile myelogenous leukemia, mental retardation, and unilateral hearing loss secondary to trauma.

The initial CSF parameters of these patients showed WBC counts ranging from 3 to 105,000/mm^3 (mean, 5,248/mm^3), with 0 to 100% neutrophils. The ranges of protein and glucose concentrations were 10 to 1,690 mg/dl and <1 to 109 mg/dl, respectively. Seventy-two percent of the patients yielded CSF containing gram-positive cocci.

Twenty-four (96%) of the 25 patients were initially treated parenterally with a broad-spectrum cephalosporin (3 received ceftriaxone, and 21 received cefotaxime). One patient was initially treated with ampicillin and gentamicin. Eleven (44%) of the patients were switched to penicillin G to complete therapy once the antimicrobial susceptibilities were known. Fourteen (56%) of 25 patients had positive blood cultures; 6 patients had repeat blood cultures within 24 to 72 h of the initial positive culture, and all were negative. Thirteen (52%) of the patients had repeat lumbar punctures, six patients within 5 days of beginning therapy and the remainder at the end of therapy; all repeat CSF cultures were negative. One patient was not febrile at admission, 19 (76%) of the patients became afebrile within 5 days, 4 (16%) of the patients became afebrile by 15 days, and 1 patient was afebrile at 25 days. The mean duration of fever for these 25 patients with penicillin-susceptible pneumococci was 4.3 days. Nine of the patients developed adverse sequelae (two developed unilateral hearing loss, three developed severe bilateral hearing loss, one developed facial palsy, two developed hydrocephalus with multiple infarcts, one developed a left cerebellar infarction with hydrocephalus requiring a ventriculoperitoneal shunt and brainstem dysfunction, one developed vein of Galen and transverse sinus thrombosis, and two developed hemiparesis).

DISCUSSION

The continued increase in the number of children with systemic infections due to *S. pneumoniae* resistant to penicillin emphasizes the need to identify alternative antibiotics for the treatment of these infections. Broad-spectrum parenterally

TABLE 3. Characteristics of children who had meningitis due to *S. pneumoniae* and were unsuccessfully treated with cefotaxime or ceftriaxone[a]

Patient (reference)	Age (mo)	Antibiotic regimen (duration [days])	MIC (μg/ml) of:		Initial CSF findings			Repeat CSF findings				Febrile days	Outcome
			PCN	CTX	WBC/mm³ (% SEGS)	Protein; glucose concn (mg/dl)	GS/culture results	Days into illness	WBC/mm³ (% SEGS)	Protein; glucose concn (mg/dl)	GS/culture results		
1 (4)	30	CTR (4), VANC (16), RIF (14), PCN (12), DEX (8)	0.5	2.0	627 (79)	246; 2	+/+	5	311,000	890; 8	+/+	9	Good; recovered
								7	186,000		−/+		
								14	159		−/−		
2 (22)	13	CTX (10), VANC (16), CHLOR (7), DEX (4)	0.5	≤8.0	400 (46)	172; 2	+/+	6			NS/+	NS	Bilateral cerebral infarcts
								8			−/−		
3 (22)	13	CXM (3), CTR (3), VANC (5), CHLOR (13)	2.0	≤8.0[b]	3	14; 114	−/+	3	940	131; 68	+/+	4	Good
								6	790 (75)	66; 29	NS/−		
4 (22)	4	CTX (5), VANC (3), CHLOR (12)	0.5	≤8.0	2,475 (68)	87; 81	NS/+	5	566 (37)	106; <30	+/+	12	Moderate unilateral neurosensory hearing loss
								7			−/−		
5 (9)	9	CTR (6), VANC (10)	2.0	4.0	1	224; 57	−/+	6	580 (93)	86; 65	NS/+	NS	Good
								7			−/−		
6 (3)	19	PEN (3), CTX (3), CHLOR (4), IMI/CIL (14)	1.0	2.0			NS/+	3			+/+	NS	Good
								7			+/+		
								14			−/−		
7 (2)	72	AMP (3), CTX (17), CHLOR (14), ERYT (20)	2.0	2.0			NS/+	3			NS/+	16	Good
								7			NS/+		
								16			NS/−		
8 (12)	28	CTR (6), DEX (2), CHLOR (1), VANC (14), RIF (2)	4.0	2.0	236 (64)	140; 30	+/+	6	773 (78)	41; 75	−/+	6	Good
								7	1,221 (65)	46; 54	−/+		
								9	80 (8)	32; 68	−/−		

[a] Abbreviations: CTR, ceftriaxone; VANC, vancomycin; RIF, rifampin; PCN, penicillin; DEX, dexamethasone; CTX, cefotaxime; CHLOR, chloramphenicol; CXM, cefuroxime; IMI/CIL, imipenem-cilastatin; AMP, ampicillin; ERYT, erythromycin; GS, gram stain; NS, not stated; SEGS, segmented neutrophils.

[b] Ceftriaxone MIC.

administered cephalosporins have been suggested as an alternative treatment regimen for systemic *S. pneumoniae* infections; however, there is considerable debate as to what the correct in vitro interpretative susceptibility criteria should be concerning the MIC breakpoint of cefotaxime or ceftriaxone in the treatment of penicillin-resistant *S. pneumoniae* meningitis. The National Committee for Clinical Laboratory Standards recommends tentative breakpoints of cefotaxime and ceftriaxone for *S. pneumoniae* such that isolates for which the MICs are ≤0.25 μg/ml are considered susceptible, those for which the MICs are between 0.5 and 1.0 μg/ml are considered intermediately resistant, and those for which the MICs are ≥2.0 μg/ml are considered resistant. The new National Committee for Clinical Laboratory Standards guidelines also dictate that *S. pneumoniae* isolates recovered from patients with meningitis for which the MICs indicate intermediate resistance to cefotaxime or ceftriaxone be considered resistant to these and other beta-lactam antibiotics (19). These breakpoints, however, have not been correlated with the clinical course and outcome of patients with bacterial meningitis due to isolates with cefotaxime or ceftriaxone MICs in the range considered to indicate intermediate resistance, and the breakpoint for susceptibility may be too conservative. The basis for these recommendations is not clear, since the children with cefotaxime or ceftriaxone treatment failures generally had isolates for which the MICs were ≥2.0 μg/ml (Table 3). Three cases of treatment failures (one unpublished) have had isolates with cefotaxime MICs of 0.5 and 1.0 μg/ml. Limited clinical data are presented, but two of these cases failed to improve clinically after six days of conventional ceftriaxone therapy; the method of MIC determination in one case is unclear (5, 7, 8). MICs of ≤8.0 μg/ml were reported for three cases, and thus the actual MICs cannot be determined.

Because of discrepancies in the MIC results obtained by different methods, Friedland et al. (9) and Tauber et al. (24) used a rabbit meningitis model to determine which method of ceftriaxone MIC determination best correlates with the in vivo response to ceftriaxone therapy by using a patient's isolate. The isolate studied had a ceftriaxone MIC of <0.5 μg/ml as determined by a commercial MIC panel but an MIC of 4.0 μg/ml when evaluated by the conventional microtiter broth dilution technique. The investigators demonstrated that when this isolate was used to induce meningitis, there was little change in bacterial concentrations in CSF, even when higher doses of ceftriaxone were used, but when a pneumococcal strain with a ceftriaxone MIC of 0.5 μg/ml was used to induce meningitis, the same dose of ceftriaxone reduced bacterial concentrations in CSF significantly. On the basis of these experimental data, the investigators propose that broad-spectrum cephalosporins alone may not be sufficient therapy for any *S. pneumoniae* CSF strain with a cefotaxime or ceftriaxone MIC of ≥1.0 μg/ml, regardless of the initial clinical response. This model provides important information which the National Committee for Clinical Laboratory Standards may have considered in its decision to revise the MIC breakpoint guidelines for penicillin-resistant *S. pneumoniae* causing meningitis.

Early detection of *S. pneumoniae* strains from CSF with decreased susceptibility to broad-spectrum cephalosporins is critical because of reports of treatment failures with parenterally administered broad-spectrum cephalosporins. To evaluate a disk diffusion test that uses a 30-μg ceftizoxime disk, Tenover et al. (25) screened pneumococcal isolates for cephalosporin resistance. They tested 33 pneumococcal strains, including 9 that were cefotaxime-ceftriaxone resistant (MICs, 4 to 32 μg/ml). They found that all of the pneumococcal isolates with cefotaxime or ceftriaxone MICs of 4 to 32 μg/ml produced zone diameters of under 15 mm. One isolate with a cefotaxime MIC of 2 μg/ml produced a zone size of 9 to 12 mm, while all of the remaining pneumococcal isolates with cefotaxime and ceftriaxone MICs of ≤2 μg/ml produced zone sizes of over 16 mm. Therefore, the researchers concluded that isolates of pneumococci demonstrating zones of inhibition under 15 mm in diameter around a 30-μg ceftizoxime disk, especially those with no zone of inhibition, are likely to be resistant and cefotaxime and ceftriaxone MICs should be determined. Friedland et al. (8) performed Kirby-Bauer disk susceptibility tests with five standard cephalosporin disks (cephalothin, ceftriaxone, ceftizoxime, cefotaxime, and cefuroxime, all at 30 μg/ml) on 23 penicillin-resistant (MIC range, 0.1 to >2.0 μg/ml) pneumococcal strains, including 5 strains for which the ceftriaxone MICs were ≥2.0 μg/ml. They found that the cefuroxime disk clearly distinguished strains for which the ceftriaxone MICs were ≥2.0 μg/ml from those for which the MICs were <2.0 μg/ml and that the ceftizoxime disk provided the clearest means of distinguishing strains for which the MICs were ≥1.0 μg/ml from more susceptible strains. Which screening test should be employed on a routine basis is not certain.

On the basis of our limited number of patients, the clinical outcome of children who had meningitis due to penicillin-resistant *S. pneumoniae* for which the cefotaxime or ceftriaxone MICs are 0.50 to 1.0 μg/ml and who were treated with a parenterally administered broad-spectrum cephalosporin was comparable at the time of discharge to that of patients with penicillin-resistant or -susceptible isolates for which the cefotaxime or ceftriaxone MICs were ≤0.25 μg/ml. There were no meningitis relapses in any of these patients. Our patients provide a clinical basis upon which cefotaxime or ceftriaxone MIC breakpoints for *S. pneumoniae* can be considered. On the basis of this experience, a broad-spectrum cephalosporin should be initiated and continued in the treatment of a patient with penicillin-resistant *S. pneumoniae* meningitis in areas where high-level cephalosporin resistance (MIC, ≥2.0 μg/ml) has not been reported. In a child with meningitis found to have an *S. pneumoniae* isolate with a cefotaxime or ceftriaxone MIC of 0.5 to 1.0 μg/ml, cefotaxime or ceftriaxone can be continued if the patient is improving clinically (more alert and active, fever decreasing, etc.) and repeat CSF parameters suggest successful therapy (especially negative Gram stain and culture). If the patient fails to improve or if the CSF culture remains positive, alternative therapy is required. Vancomycin and chloramphenicol are the most commonly recommended agents in this circumstance.

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