

High Doses of Cefotaxime in Treatment of Adult Meningitis Due to *Streptococcus pneumoniae* with Decreased Susceptibilities to Broad-Spectrum Cephalosporins

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We treated nine patients (10 episodes) with meningitis caused by *Streptococcus pneumoniae* isolates with decreased susceptibilities to broad-spectrum cephalosporins with high doses of cefotaxime (300 mg/kg of body weight per day; maximum dose, 24 g/day). Early adjunctive therapy with dexamethasone was also administered. Cefotaxime MICs were 0.5 (three episodes), 1 (five episodes), and 2 (two episodes) $\mu\text{g/ml}$, and MBCs ranged from 1 to 4 $\mu\text{g/ml}$. Therapy was well tolerated, and all patients experienced prompt clinical improvement. One patient died 8 days after the end of therapy, the central nervous system infection had already been cured, and the remaining patients recovered without relapses.

Broad-spectrum cephalosporins, especially cefotaxime and ceftriaxone, are widely used in the treatment of suspected pneumococcal meningitis and are considered the treatment of choice for meningitis caused by partially penicillin-resistant pneumococcal strains (26, 28). However, failures with both drugs have been reported (1–3, 5, 6, 10, 11, 13, 18, 24, 25, 28). In most of these cases, the MICs of cefotaxime and ceftriaxone for the causative strains ranged from 0.5 to 2 $\mu\text{g/ml}$, and both drugs were administered at standard doses (cefotaxime, 200 mg/kg of body weight per day [maximum dose, 12 g/day]; ceftriaxone, 100 mg/kg/day [maximum dose, 4 g/day]). Here we report our experience with a high dose of cefotaxime in the treatment of adult pneumococcal meningitis caused by *Streptococcus pneumoniae* for which cefotaxime and ceftriaxone MICs ranged from 0.5 to 2 $\mu\text{g/ml}$.

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Our institution (Hospital de Bellvitge) is a 1,000-bed teaching hospital for adults in Barcelona, Spain. Since 1977, all cases of bacterial meningitis have been prospectively recorded in a computer-associated protocol. In 1979, we started the systematic study of the antibiotic susceptibilities of all pneumococcal isolates (16, 17), and from then until December 1994, 134 cases of pneumococcal meningitis have been included.

For the purposes of the present study, we have identified all cases of pneumococcal meningitis caused by strains with decreased susceptibilities to cefotaxime (defined as MICs of ≥ 0.5 $\mu\text{g/ml}$), and we analyzed those episodes treated with a high dose of cefotaxime. A high dose of cefotaxime is defined as 300 mg/kg/day, with the maximum dose being 24 g/day.

The *S. pneumoniae* isolates were identified by standard methods. Antibiotic susceptibility testing was routinely performed by the disk diffusion technique in Mueller-Hinton agar supplemented with 5% sheep blood (12). For all strains, the MICs and MBCs of penicillin, cefotaxime, and ceftriaxone were de-

termined by the microdilution and macrodilution broth methods (19) at the time of isolation of the pneumococci, and the pneumococci were also tested by the agar dilution method and were serotyped in the Spanish Pneumococcus Reference Laboratory, Majadahonda, Madrid, Spain (20). The strains were frozen at -40°C in 20% skim milk, and the MICs and MBCs for all of the isolates were again determined in 1994. *S. pneumoniae* ATCC 6303 and *S. pneumoniae* ATCC 49619 were used as controls. Until 1988, both cefotaxime and desacetylcefotaxime levels were determined by high-performance liquid chromatography (15); thereafter, they were determined by the microbiological assay (7). This method determines jointly the levels of cefotaxime plus desacetylcefotaxime.

The chi-square test was used to compare proportions.

We identified 23 episodes of pneumococcal meningitis (that occurred in 22 patients) caused by *S. pneumoniae* strains for which cefotaxime and ceftriaxone MICs were ≥ 0.5 $\mu\text{g/ml}$ (range, 0.5 to 2 $\mu\text{g/ml}$). Ten of these 23 episodes were treated with a high dose of cefotaxime, and data for those 10 episodes constitute the basis of this report. Data for 6 of the 10 episodes have been included in previous reports (see footnote a of Table 1).

All 10 episodes were acquired in the community. Details of the patients, the MICs and MBCs for the causative strains, antibiotic therapy, and antibiotic levels in cerebrospinal fluid (CSF) are given in Table 1. One of the patients had two episodes of pneumococcal meningitis within a 3-month interval; the patient had splenectomy and a congenital otocranial fistula and was receiving corticosteroid therapy for Crohn's disease; two patients had chronic alcoholism, one patient had liver cirrhosis, and two patients had diabetes mellitus.

The source of infection was pericranial fistula in four episodes, acute otitis media in four episodes, pneumonia in one episode, and unknown in one episode (an elderly woman with liver cirrhosis). Mental status on admission was alert for two patients, obtunded for six patients, and comatose for two patients; two patients presented with seizures, and one patient presented with hemiparesis. All but one patient had fever (axillary temperature, $\geq 38^{\circ}\text{C}$). A diagnosis of pneumococcal meningitis was established by a positive CSF culture in eight episodes and by positive blood cultures and characteristic CSF

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TABLE 1. Characteristics of 10 episodes of adult meningitis caused by *S. pneumoniae* strains for which cefotaxime MICs were ≥ 0.5 $\mu\text{g/ml}$ and which were treated with high doses of cefotaxime

Episode ^a	Yr of infection	Age (yr)/sex ^b	Serotype	MIC/MBC ($\mu\text{g/ml}$)		Cefotaxime therapy		CSF cefotaxime levels ($\mu\text{g/ml}$) (time of therapy) ^c
				Penicillin	Cefotaxime	Total daily dose (g)	Duration (days)	
1 ^d	1984	25/F	23	4/4	1/2	9	14	0.7 (day6) ^e
2 ^d	1985	25/F	23	4/4	1/2	9	14	1.5 (day9) ^e
3	1985	50/M	23	1/2	0.5/1	24	14	2.7 (60 h) ^e
4	1987	47/M	9	2/2	0.5/1	24	14	ND ^f
5	1989	66/F	9	4/4	2/2	21	10	ND
6	1991	37/M	6	2/2	0.5/1	20	10	2.4 (24 h) ^g
7	1992	62/F	23	4/4	2/4	24	10	3.6 (36 h) ^g
8	1992	78/F	14	2/4	1/1	18	10	ND
9	1993	71/M	14	2/4	1/2	20	10	8 (24 h) ^g
10	1994	56/F	6	2/2	1/1	20	14	ND

^a Episodes 1 to 4 were mentioned in reference 28, where they were referred to as patients 13a, 13b, 9, and 10, respectively. Episode 5 is also cited in reference 27 and was referred as patient 3. Episode 6 was mentioned on page 1166 and in Table 3 of reference 4.

^b F, female; M, male.

^c CSF samples were obtained 4 to 6 h after the administration of the last dose of cefotaxime.

^d Episodes 1 and 2 occurred in the same patient within an interval of 3 months. Her weight was 30 kg.

^e These values denote the cefotaxime levels determined by high-performance liquid chromatography. The desacetylcefotaxime levels were 3.8 $\mu\text{g/ml}$ in episode 1, 3.6 $\mu\text{g/ml}$ in episode 2, and 15.3 $\mu\text{g/ml}$ in episode 3.

^f ND, not done.

^g These levels were determined by microbiological assay.

cytochemical findings in two episodes. Blood cultures were positive for eight of the nine episodes on which they were performed. No patient presented with shock.

High-dose cefotaxime therapy was administered from the beginning in five episodes (episodes 1, 2, 3, 4, and 8) (Table 1), while in the other five episodes (episodes 5, 6, 7, 9, and 10) it was administered after therapeutic failure with other antibiotics occurred. Episodes 5 and 10 failed therapy with vancomycin and were cured with high-dose cefotaxime. Episodes 6 and 7 were initially treated with ceftriaxone, 4 g in a single daily dose (the maximum daily dose recommended by the manufacturer), which represented 65 and 55 mg/kg, respectively (ceftriaxone MICs, 1 and 2 $\mu\text{g/ml}$, respectively). After a clear initial improvement and at 48 h of therapy, both patients presented with a recrudescence of the clinical manifestations, with the reappearance of fever, a lowering of the level of consciousness, and an increase in meningeal signs; at 72 h of ceftriaxone therapy, Gram staining of CSF showed gram-positive diplococci in the CSF of both patients, and they were considered therapeutic failures. At this point, therapy was switched to high-dose cefotaxime and it was followed in both patients by rapid improvement and a final cure. Cultures of CSF from both patients before cefotaxime therapy were negative (however, no neutralizing agents for beta-lactam antibiotics were used in CSF cultures). Patient 9 was a 71-year-old man with bacteremic pneumococcal pneumonia, who showed clinical manifestations of central nervous system infection on his third day of therapy with intravenous penicillin G (2 MU/4 h), in spite of the favorable course of the pneumonia and the negative blood cultures. A lumbar puncture disclosed the presence of meningitis, and therapy with high-dose cefotaxime was initiated, with rapid improvement and a final cure. However, the patient died suddenly 8 days after the end of therapy. Postmortem studies showed both an atheromatous plaque in the common coronary artery that caused an important degree of obstruction and vasculitic lesions of the meningeal vessels at the brain stem. CSF and brain cultures were sterile.

Besides cefotaxime therapy, dexamethasone was administered to all patients for a median of 2 days beginning at the same time or a few minutes before the antibiotic therapy. In addition, patients 4, 6, 7, 8, and 9 were initially given a bolus of

mannitol and intravenous phenytoin, and patient 10 received only phenytoin. After the initiation of therapy, the mean time in which a clear improvement of consciousness was observed was 1.7 days, and the mean time for the fever to decrease below 38°C was 1.4 days. Except for one patient with catheter phlebitis, fever did not reappear after defervescence, and no patients had neurological complications during therapy. Three patients had moderate and transient elevations in their liver enzyme levels, another patient had moderate hyperamylasemia, and two patients had catheter-associated phlebitis. In seven patients, repeated lumbar punctures were performed between 24 and 60 h of cefotaxime therapy, and in all of them Gram stains and cultures of CSF were negative. All but one of the patients recovered, and there were no relapses. After a mean follow-up of 6 months, only one patient had seizures as sequelae.

Among the other 13 episodes identified during the study period, one patient with an initial critical condition died on the second day of penicillin therapy, and another patient died on the first day of illness before any therapy was initiated. The other 11 patients survived. They were treated with vancomycin (7 patients), vancomycin-rifampin (2 patients), chloramphenicol (1 patient), and ceftriaxone (1 patient). All 11 patients also received dexamethasone, 8 patients also received mannitol, and 9 patients also received phenytoin. After the initiation of therapy, the mean time to improvement of consciousness was 2.2 days, and the mean time for the fever to decrease below 38°C was 2.6 days. Among the patients treated with vancomycin, the dosage had to be increased in one patient after therapeutic failure, two patients had bilateral hypacusia, another patient had acute pancreatitis, and another patient had a skin rash (27). One patient treated with vancomycin-rifampin had seizures, and one patient treated with chloramphenicol died because of a late unrelated complication. Overall, the outcomes were similar to those among the patients treated with high-dose cefotaxime; however, this was not a comparative study, and firm conclusions cannot be made.

The frequency of *S. pneumoniae* isolates in CSF for which cefotaxime MICs were ≥ 0.5 $\mu\text{g/ml}$ rose significantly through the study period: 6 of 76 strains (7.8%) from 1979 to 1986 versus 17 of 58 strains (29.3%) from 1987 to 1994 ($P = 0.002$).

The MICs of cefotaxime or ceftriaxone have not exceeded 2 $\mu\text{g/ml}$.

Today, determination of cefotaxime or ceftriaxone susceptibility in vitro has become mandatory for every *S. pneumoniae* strain isolated from CSF (16, 17). The definitions of cephalosporin resistance for *S. pneumoniae* strains isolated from CSF have been progressively modified (14, 19, 20); the National Committee for Clinical Laboratory Standards has recently suggested that those isolates for which cefotaxime and ceftriaxone MICs are $\leq 0.5 \mu\text{g/ml}$ be considered susceptible, that those isolates for which MICs are $1 \mu\text{g/ml}$ be considered intermediately resistant, and that isolates for which those MICs are $\geq 2 \mu\text{g/ml}$ be considered resistant (21). However, it is not clear whether these breakpoints are adequate for clinical purposes. To date, some failures in patients infected with pneumococci for which MICs are $0.5 \mu\text{g/ml}$ have been reported (5, 25, 28), and in the present series, one patient (patient 6) failed therapy after receiving a conventional dosage of ceftriaxone, reinforcing our criteria that standard doses of these cephalosporins are unreliable for such patients. On the other hand, our patients infected with isolates for which the cefotaxime MICs were $2 \mu\text{g/ml}$ have responded to a high dose of this antibiotic. These observations suggest that pneumococci for which cefotaxime or ceftriaxone MICs are from 0.5 to $2 \mu\text{g/ml}$ could be better classified as intermediately resistant.

To date, the clinical experience in treating cephalosporin-resistant pneumococcal meningitis is very limited, and its most appropriate therapy is not yet well known. Besides other suggested alternatives (6, 8, 9, 18, 22, 23, 28), the possibility of overcoming the problem of decreased cephalosporin susceptibility by increasing the dosage in order to achieve higher antibiotic levels in CSF deserves attention. The experience with high-dose cefotaxime that we have reported here has been fully satisfactory, and if it is confirmed by further studies, it might allow for the continuing use of cefotaxime, but in a high-dose regimen, as first-line empiric therapy for suspected adult pneumococcal meningitis. In areas where pneumococcal strains with higher levels of resistance to broad-spectrum cephalosporin have been detected, a high dose of cefotaxime may be administered in combination with vancomycin. Furthermore, for cases of adult meningitis caused by pneumococcal strains for which cefotaxime MICs range from 0.5 to $2 \mu\text{g/ml}$, the administration of high doses of cefotaxime appears to be safe and effective.

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