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Cefotaxime versus Chloramphenicol for Ampicillin-Resistant *Haemophilus influenzae* Meningitis
A Retrospective Study of 62 Cases

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Cefotaxime (Jacobs et al. 1985; Odio et al. 1986) and other third generation cephalosporins (Aronoff et al. 1984; Barson et al. 1985; Chartrand et al. 1984; Congeni 1984; Del Rio et al. 1983; Kaplan et al. 1984; Rodriguez et al. 1986) were proposed as alternatives to ampicillin and chloramphenicol as initial therapy for suspected bacterial meningitis in infants and children, and even for culture-proven meningitis, irrespective of the ampicillin susceptibility of the micro-organism. The superiority of these cephalosporins over conventional therapy resides particularly in their very potent activity against β-lactamase-producing and ampicillin-resistant *Haemophilus influenzae* (Lapointe & Beyeler 1985; Neu 1982, 1985). Unfortunately, the overall clinical experience with these cephalosporins in meningitis due to ampicillin-resistant *H. influenzae* is small.

The combination of ampicillin and cefotaxime is used routinely at this centre as initial therapy (≥ 48h) for childhood meningitis, pending bacterial isolation and sensitivity testing. Cefotaxime is subsequently limited to patients suffering from meningitis due to ampicillin-resistant *H. influenzae*. The present study includes 36 such cases identified over a 4-year period and treated with cefotaxime. The clinical outcome in these patients was compared with that in 26 other ampicillin-resistant meningitis patients treated in the past with chloramphenicol.

1. Methods

Infants and children with β-lactamase-producing and ampicillin-resistant *H. influenzae* meningitis seen before November 1982 (n = 26) were treated with ampicillin 200 to 400 mg/kg/day + chloramphenicol 100 mg/kg/day in the first 48 hours, and chloramphenicol 100 mg/kg/day alone thereafter; those seen after November 1982 received ampicillin 200 mg/kg/day + cefotaxime 200 mg/kg/day in the first 48 hours, and cefotaxime 200 mg/kg/day alone thereafter. Therapy was usually intravenous, and continued for 10 days.

Microbiological examinations of CSF and blood, and isolation, identification and serotyping of *Haemophilus* isolates were determined as previously described (Kilian 1980; Lapointe et al. 1984). The ampicillin susceptibility of the *H. influenzae* strains was determined by the iodometric β-lactamase test (Catlin 1975) and the agar diffusion method with a 10μg ampicillin disc (Barry & Thornsberry 1980).

In some patients in the cefotaxime group, a second CSF sample was obtained after starting treatment. The bioassay of cefotaxime in the second CSF sample was determined using a β-lactamase-producing and ampicillin-resistant *H. influenzae* type b, biotype 1, as indicator organism (inhouse control 2998). The bioassay could detect cefotaxime levels lower than 0.12 mg/L, resulting in a zone

Table I. Outcome after therapy in 62 infants and children with ampicillin-resistant *H. influenzae* meningitis

	Treatment groups	
	chloramphenicol (n = 26)	cefotaxime (n = 36)
Number (%) of patients with:		
prolonged fever (≥ 7 days)	10 (38.5)	10 (27.8)
secondary fever	7 (26.9)	3 (8.3)
hospital days ≥ 15	10 (38.6)	3 (8.3)
neurological complications	13 (50.0)	8 (22.2)*
other complications	15 (57.7)	10 (27.8)*
sequelae	11 (42.3)	4 (11.1)*
mortality	0 (0.0)	0 (0.00)
Mean time to loss of fever (days)	6.2 ± 4.8	5.5 ± 3.4
Mean number (range) of hospital days	15.6 ± 7.0 (10-42)	11.7 ± 3.5* (9-26)
Total number of complications and/or sequelae:		
neurological	30	14
others[a]	14	9

* = $p < 0.05$ between treatment groups.
[a] Excluding isolated secondary or prolonged fevers.

of inhibition of 13.2 ± 1.4mm (mean ± 1 standard deviation after 45 tests).

The bactericidal titre was determined on the second CSF samples in triplicate using a microtitre technique.

2. *Results*

The demographic, clinical and laboratory data on admission to hospital were comparable in the 2 treatment groups except that significantly ($p < 0.001$) more patients were in poor condition in the otaxime group (89 *vs* 42%), and the CSF leuyte count was significantly lower ($p < 0.05 > 0.02$) in the chloramphenicol group (1.9 *vs* 3.4 × mg/L). The mean age was 14.2 months in the ramphenicol group and 17.9 months in the taxime group.

he clinical outcome after starting antibiotic apy in the 2 treatment groups is summarised ble I. There were significantly fewer neurological and non-neurological complications in the cefotaxime group, and the mean time spent in hospital was significantly shorter.

The nature and distribution of neurological complications and/or sequelae are detailed in table II. The first of the 4 patients classified as having detectable sequelae in the cefotaxime group had apparently permanent bilateral hearing loss at the 3-month follow-up; the second had motor retardation normalised at the 3-month follow-up; the third had minor anomaly of the auditory brain stem potentials (unilateral wave V response at 35dB) at the fourth day of meningitis but was normal at the 2-month follow-up; the fourth patient had minor anomaly of the auditory potentials suggestive of lesion to the brain stem itself but was clinically normal. In the chloramphenicol group, the sequelae were transitory in 3 out of 11 patients. Non-neurological complications occurred in 9 patients on cefotaxime: diarrhoea (4), upper respiratory tract infection (2), anaemia (1), skin eruption (1) and thrombocytopenia (1). There were 14 events in patients on chloramphenicol.

The CSF β-lactamase-producing and ampicillin-resistant *H. influenzae* type B were clearly more susceptible *in vitro* to the ampicillin-cefotaxime

Table II. Numbers of patients with neurological complications or sequelae after a mean duration of follow-up of 12.2 months in the chloramphenicol group and 3.4 months in the cefotaxime group

	Chloramphenicol (n = 26)	Cefotaxime (n = 36)
Apnoea	0	
Ataxia	3	1
Bradycardia	1	0
Brain atrophy	2	0
Cortical vein thrombosis	1	3
Hearing loss	2	2
Hydrocephalus	2	
Hygroma	0	1
Increased intracranial pressure	4	0
Mental retardation	3	0
Motor retardation	4	1
Seizure disorders	2	2
Speech disorders	3	0
Subdural effusion	3	2

Table III. Cefotaxime concentrations and bactericidal activities (MBC) in CSF after ampicillin-cefotaxime and cefotaxime in 13 patients with ampicillin-resistant *H. influenzae* meningitis

	Mean ± 1 SD	Range
Cefotaxime concentration (μg/ml)	3.8 ± 5.8	0.19-19.3
CSF-cefotaxime/MBC ratio	116.5 ± 100.1	2.0-257.1
Bactericidal titre	201.2 ± 284.8	8.0-1024.0

combination (MIC_{90} = 0.03) or cefotaxime alone (MIC_{90} = 0.03) than to ampicillin-chloramphenicol (MIC_{90} = 1.0) or chloramphenicol alone (MIC_{90} = 1.0).

15 patients had a second CSF sample taken after starting therapy in the cefotaxime protocol group. Sterilisation of the control CSF was obtained in 10/10 patients after 18 hours of treatment and in 3/5 before 18 hours. The 2 patients with positive control CSF had *H. influenzae* type B before therapy which was seen on CSF smear and subsequently cultivated after direct plating. In 1 patient the control CSF was obtained within 18 hours of ampicillin-cefotaxime and 4.5 hours of cefotaxime administration; the direct smear was then negative but 1 colony grew in primary culture. In the second patient with positive control CSF, the control CSF was taken within 11 hours of ampicillin-cefotaxime and 5 hours of cefotaxime administration; the direct smear was then negative but 6 colonies grew in primary culture. Both patients recovered uneventfully after 3 days of ampicillin-cefotaxime and 7 days of cefotaxime alone.

The CSF cefotaxime measurements, the CSF bactericidal quotient and the CSF bactericidal titre could be determined in the control samples of 13 of the 15 patients submitted to repeated lumbar puncture; the results are summarised in table III.

3. Discussion and Therapeutic Implications

The results obtained here with 36 patients and those obtained in 29 others reported in 8 previous published studies or case reports (Asmar et al. 1985; Bégué et al. 1984; Belohradsky et al. 1980; Borderon et al. 1981; Campos et al. 1986; Fraise et al. 1986; Jacobs et al. 1985; Pesnel et al. 1984) prove that cefotaxime constitutes a safe and effective therapy of ampicillin-resistant *H. influenzae* meningitis in infants and children. The prognosis of ampicillin-resistant *H. influenzae* meningitis was better with the cefotaxime protocol than with the chloramphenicol protocol as suggested in this study with historical controls. Unfortunately, a definitive conclusion cannot be sustained by randomised and prospective controls. However, sufficient *in vitro* and *in vivo* data have been accumulated to propose the cefotaxime protocol as the first-line antibiotic therapy of ampicillin-resistant (β-lactamase positive) *H. influenzae* type B meningitis. Cefotaxime should be administered in association with ampicillin in infants and children or with ampicillin plus gentamicin in neonates, in suspected bacterial meningitis pending isolation and testing of antibiotic susceptibility of organisms.

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