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Comparative Trial of Carbenicillin and Ampicillin Therapy for Purulent Meningitis

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A randomized therapeutic trial of carbenicillin (CB) or ampicillin (AMP) in purulent meningitis was performed in 86 pediatric and adult patients (41 *Haemophilus influenzae*, 22 *Streptococcus pneumoniae*, 13 *Neisseria meningitidis*, and 10 of unknown etiology). All isolates, incuding *H. influenzae*, were susceptible to CB and AMP. Median cerebrospinal fluid (CSF) antibiotic concentrations were 0.85 and 1.60 μg/ml for CB and AMP, respectively, during administration of daily doses of 400 mg/kg and 0.65 and 0.45 μg/ml, respectively, on daily doses of 200 mg/kg. Higher CSF concentrations, up to a median concentration of 4.5 μg/ml, were observed in patients with CSF protein concentrations ≥75 mg/100 ml. Clinical responses were equivalent on either antibiotic regimen. Among AMP patients (45), 8 had significant residua and 3 died; among CB patients (41), 5 had residua and none died. However, 38% of *H. influenzae* patients treated with CB had positive CSF cultures on day 1 follow-up lumbar punctures, compared with only 5.8% of AMP patients with *H. influenzae*. The significance of a delay of CSF sterilization among CB-treated patients is unknown, since there was no correlation between persistence of hemophilus organisms and the frequency of adverse outcome. AMP and CB are equivalent for the treatment of bacterial meningitis due to susceptible organisms.

Ampicillin (AMP) has received wide acceptance as a single-antibiotic regimen in the treatment of purulent meningitis (20). Early studies demonstrated that AMP had good in vitro activity against strains of *Haemophilus influenzae* type B and activity equivalent to benzylpenicillin G against strains of *Neisseria meningitidis* and *Streptococcus pneumoniae* (4, 5). Subsequent investigations demonstrated adequate cerebrospinal fluid (CSF) levels after administration of AMP and clinical efficacy comparable to standard antibiotic regimens.

However, since the recent isolation of strains of *H. influenzae* type B resistant to AMP, concern has been expressed over the continued use of AMP for treatment of meningitis in children (6, 14). Resistance to penicillins in hemophilus strains is due in part to the presence of a beta-lactamase with marked activity against benzylpenicillin G and AMP; other semisynthetic penicillins and cephalosporins are hydrolyzed less effectively (2, 7). Chloramphenicol, alone or in combination with a penicillin, has been recommended to treat infections suspected to be due to AMP-resistant strains of *H. influenzae* (1). However, the concern of possible antagonism during the use of antibiotic combinations and the potential for severe toxicity after chloramphenicol administration has prompted an evaluation of alternate antimicrobial regimens.

Other investigators have demonstrated that carbenicillin (CB) is less rapidly destroyed by hemophilus beta-lactamases; minimal inhibitory concentrations (MICs) range from 0.8 to 25 μg of CB per ml (2, 10). Because of pharmacological similarities of CB and AMP, as well as the greater in vitro activity of CB against AMP-resistant strains of *H. influenzae*, a pilot study was performed among meningitis patients alternately treated with either AMP or CB.

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METHODS

Patient selection. Patients older than 2 months of age, with acute purulent meningitis, admitted from 15 March 1975 through 14 March 1976 to the Communicable Disease Service, Los Angeles County-University of Southern California Medical Center, were eligible for study. Informed written consent was obtained from all patients or their designated guardian. Patients were excluded from study if (i) the etiology of meningitis was confirmed or sus-

pected not to be due to *S. pneumoniae, H. influenzae,* or *N. meningitidis,* (ii) there was a clinical indication for use of a second antimicrobial agent, or (iii) a significant history of penicillin allergy was obtained. The diagnosis of meningitis was confirmed by a positive CSF or blood culture in association with a consistent clinical presentation and CSF changes. Ten patients were included who had negative blood or CSF cultures or Gram stains (i.e., "purulent, unknown"). These patients satisfied two or more of the following criteria: (i) a predominate polymorphonuclear leukocyte pleocytosis (≥500 cells/mm^3) (ii) a protein level of ≥100 mg/100 ml, or (iii) a glucose level of ≥50% of a simultaneously obtained serum glucose value. All patients were assigned a severity classification from 1 to 4 at the time of admission as follows: 4, coma, semicoma, or severe hypotension; 3, convulsions without coma or shock; 2, temperature, ≥105°F (41°C), symptoms for 5 days, or the presence of a complicating disease or marked lethargy; or 1, none of the above.

Treatment regimens. All eligible patients were randomized (nonblinded) by hospital number to receive either CB or AMP. The first 20 patients received either AMP or CB (10 in each treatment group) in a daily dose of 200 mg/kg administered intravenously in six divided doses following an initial loading dose of 65 mg/kg. All subsequent patients received either antibiotic in a daily dose of 400 mg/kg intravenously in six divided doses after the same loading dose; this regimen was selected to evaluate the effect of higher dosage on obtainable CSF antibiotic concentrations. Further, at the lower dose, it was noted that patients with *H. influenzae* more frequently had positive cultures from CSF samples on day 1 if they were receiving CB (five of seven patients) as compared with AMP (one of three patients). Each patient's clinical response was recorded, and attempts were made to obtain CSF on days 1 (12 to 24 h after initiation of treatment), 3, 7, 10, 14, and 21 after the initiation of teatment. Therapy was terminated when the following criteria were met: (i) CSF glucose level was ≥50% of a simultaneously obtained blood sugar value, (ii) CSF protein was ≤75 mg/100 ml, (iii) CSF leukocyte cell count was ≤30/mm^3 with ≤20% polymorphonuclear leukocytes, and (iv) the patient was afebrile for 5 days. If the above criteria were not met at 28 days, therapy was arbitrarily terminated, unless other clinical indications were present to continue therapy (i.e., subdural effusion, pyarthrosis, etc.).

Bacteriology. MICs and minimal bactericidal concentrations (MBCs) of chloramphenicol, AMP, and CB were determined against all available isolates. Susceptibility studies against *H. influenzae* strains were done in modified Levinthal broth as previously described (8), whereas Mueller-Hinton broth (BBL) with 1% supplement B (Difco) and Trypticase soy broth (BBL) were utilized in susceptibility studies against *N. meningitidis* and *S. pneumoniae*, respectively. Beta-lactamase assays were done against all *H. influenzae* isolates by the method of Thornsberry et al. (10).

Microbiological assay. All CSF samples were submitted for microbiological assay for CB or AMP. Whenever possible, a simultaneous serum sample was also obtained. Specimens were immediately refrigerated at 4°C and submitted to assay within 96 h of collection; preliminary observations noted <10% loss in antibiotic activity when samples were held for 5 days at this temperature.

A modification of the standard microbiological assay of Simon and Yin was utilized (9). Assays were performed identically for both antibiotics, except that a temperature of 30°C was utilized for AMP assays, and 25°C was used for CB. Nutrient agar (Difco; pH 6.8) was utilized in both assays; test plates were inoculated with 1.6 ml of a *Bacillus subtilus* spore suspension (Difco) prepared by the addition of one vial of spores to 50 ml of 0.1 phosphate buffer (pH 7.4). Standard curves, appropriately diluted in CSF or serum, were obtained simultaneously by the inclusion of three control wells (0.8, 6.24, and 40 μg/ml).

RESULTS

Patient population. During the study period, 99 patients with purulent meningitis were admitted; 86 were eligible for randomized treatment with CB or AMP and 13 were excluded from study. Eight patients were excluded from randomization to AMP treatment; three patients died before initiation of treatment (one each with infection due to *H. influenzae, N. meningitis,* and *Escherichia coli*), three patients had meningitis due to organisms other than those included for study, and two patients received an inappropriate dosage of AMP. Five patients were excluded from treatment with CB; two patients were allergic to penicillin, and three patients had meningitis due to organisms other than those included for study.

The age and, therefore, the bacterial etiology of each treatment group varied considerably (Table 1). Seventy-three percent of CB-treated patients were in the first decade of life, compared with 55% of AMP-treated patients. Male-female ratios were equal among groups, and there were no significant differences as to racial or ethnic groups; 21% of patients in the total study population were black, which is consistent with the base population served by the hospital.

Despite the differences in age and etiology, each treatment group was equivalent in terms of defined admission severity status. Twenty-seven percent and 22% of the patients were in the most severely affected category for CB and AMP treatment groups, respectively. The median number of days ill before admission was the same in both groups (2.0 days). Antibiotic therapy (oral or parenteral penicillins) had been administered before therapy for at least 12 h in 30% of CB and 35% of AMP patients. Forty percent of blood cultures were positive among

TABLE 1. *Comparison of treatment groups by age and etiology*

Etiology	Age of patient					
	11 months	1–10 years	10–19 years	20–39 years	40–59 years	60 years
CB						
H. influenzae	12	12				
S. pneumoniae	3			2	3	
N. meningitidis			3	2		
Unknown	1	1			1	
AMP						
H. influenzae	10	6				1
S. pneumoniae	4	2	2	3	1	2
N. meningitidis	2	1	1	2	2	
Unknown			2	3		2

CB-treated patients, and 52% were positive among AMP-treated patients. Patients with pneumococcal and meningococcal disease had positive blood cultures more often (71 and 53%, respectively) than patients with meningitis due to *H. influenzae* (45%).

There were no significant differences among treatment groups in regard to the presence of associated purulent conditions; otitis media was present at the time of admission in 27% of patients, and 6% of patients had associated suppurative mastoiditis or sinusitis. No significant differences in the median values for admission hemoglobin (corrected for age), leukocyte count, or serum sodium were noted. Fifty-five percent of the children had anemia on admission (as defined by a hemoglobin value of 9.9 g/100 ml, whereas only 16% of adults had anemia as defined by a hemoglobin value of 10.9 g/100 ml).

Response to treatment. There were no apparent differences in clinical response due to the different dosage regimens and, therefore, the groups were analyzed together. The median duration of antibiotic therapy for each treatment group was 13.5 days. Similarly, the duration of hospitalization was the same for CB (17.1 days) and AMP (16.5 days) patients, and there were no differences according to etiology. One patient, with meningitis due to a CB-susceptible *H. influenzae* organism, required 36 days of treatment with CB because of a relapse confirmed by a positive CSF culture 72 h after discontinuing therapy at 16 days; subsequent evaluation failed to reveal a persistent focus of infection. Prolonged AMP treatment was necessary in two infants because of poor clinical responses; one patient with *H. influenzae* required 32 days of therapy because of an associated pyarthrosis (positive joint cultures, day 6 of therapy), and another child required 37 days of treatment because of subdural effusion, although routine CSF cultures were negative on day 1 taps on both children.

The duration of fever after initiation of antibiotic therapy was the same in both treatment groups (3.5 and 4.0 days for CB and AMP, respectively). Prolonged fever due to a probable drug reaction occurred in a child treated with CB for *H. influenzae* meningitis. There were no significant differences among treatment groups in the number of days required to meet the defined CSF criteria. CSF sugar level was generally normal on day 3 (range 0 to 14 days), whereas a return to normal protein concentrations usually required 3 to 7 days.

Of those patients with culture-proven meningitis, the CSF Gram stain or culture was positive in 65 of 77 (84%) at the time of admission. However, on day 1 (12 to 24 h), the CSF Gram stain or culture or both was positive more frequently in CB-treated patients, compared with those treated with AMP (Table 2). Nine of twenty-four CB-treated patients (38%) with infections due to *H. influenzae* had positive CSF cultures on day 1; none of these patients had positive CSF cultures or Gram stains by day 2 or 3. Persistence of organisms on culture did not correlate with an adverse clinical outcome or a more frequent persistent focus of infection among CB-treated patients. However, persistently positive Gram stains or cultures occurred in two AMP-treated patients with *H. influenzae* infections; one had a bilateral otitis media, and the other had a subdural effusion and subsequently died of his infection. Although the latter patient had a positive CSF culture on day 1, a culture obtained on day 3 was negative. Persistently positive CSF cultures or Gram stains or both on day 1 in patients with infections due to *S. pneumoniae* or *N. meningitidis* had no correlation with subsequent clinical course, despite the treatment regimen.

Adverse effects occurred among 27% of CB-treated patients. Eosinophilia (10%) on differential count (four patients), fever (three patients), and rash (three patients) were the most frequent; diarrhea occurred in a single patient. The occurrence of a rash on day 5 of therapy in a CB-treated patient signaled an apparent hy-

persensitivity to penicillin and necessitated its discontinuance; therapy was completed with chloramphenicol. Also, one child with a third episode of meningitis (the episodes were due to *H. influenzae*, *S. pneumoniae*, and *S. pneumoniae*, respectively) was not retreated with CB; chloramphenicol was substituted because of the appearance of marked eosinophilia and fever near the termination of therapy with CB during her second episode of meningitis. Adverse effects among AMP-treated patients were less frequent (17.5%) and included eosinophilia (three patients), fever (two patients), rash (two patients), and diarrhea (one patient). No adverse effects necessitated the discontinuance of AMP therapy.

Morbidity and mortality. Three deaths occurred among 86 patients (3.5%) entered into randomization (Table 3); all deaths occurred among AMP-treated patients. Two deaths, due to *H. influenzae*, occurred in children with severe disease due to susceptible organisms. Deaths in these children occurred on days 6 and 9 of disease and followed early clinical courses characterized by the rapid onset of severe neurological complications. A third death occurred in a young adult with meningitis due to *S. pneumoniae* on day 10 of treatment after complications at surgery to drain a middle ear abscess.

Residua were observed with equal frequency among treatment groups: 12% and 17% of CB- and AMP-treated patients, respectively, had significant residua at the time of discharge. Residua involved systems other than the central nervous system in three patients (i.e., one patient with distal extremity gangrene and two patients with mild decrease in joint range of motion after a pyarthrosis). The remainder of residua reflected mild to severe involvement of the central nervous system, including developmental retardation (six patients), mild monoparesis (one patient), and spastic quadraplegia (two patients). Severe residua occurred more frequently in patients with pneumococcal disease.

Relapses occurred in two patients, one in each treatment group. An infant with pneumococcal meningitis had a recurrence of CSF pleocytosis and fever 48 h after completion of a 10-day course of AMP; although the child was retreated with AMP, no organism was isolated during the second episode. Another infant with *H. influenzae* meningitis relapsed 72 h after completing 10 days of CB therapy, and this organism was again isolated from CSF; this child required retreatment with 14 days of CB.

Microbiology. All organisms isolated were susceptible to the antibiotics utilized (Table 4), and differences in susceptibility to CB or AMP among infecting organisms were not significant. Chloramphenicol was less active, on a weight basis, against all organisms, compared with CB or AMP. All *H. influenzae* isolates were confirmed to be type B and none produced beta-lactamase.

Pharmacology. CSF antibiotic concentrations ranged from 0 to 71 μg/ml. Higher CSF antibiotic concentrations were observed in CSF with high protein concentrations (Table 5). Similarly, higher antibiotic concentrations and CSF/serum ratios were attained in CSF obtained during the first 5 days of therapy (Table 6) in contrast to the later days of therapy.

DISCUSSION

Clinical responses after treatment with either CB or AMP were essentially equivalent.

TABLE 3. *Residua and deaths by etiology and treatment group*

Etiology	CB		AMP	
	Residua	Death	Residua	Death
H. influenzae[a]	3	0	2	2
S. pneumoniae[b]	1	0	5	1
N. meningitidis[c]	1	0	0	0
Unknown	0	0	1	0

[a] Residua included residual joint disease (two) and developmental retardation (three).
[b] Residua included severe neurological impairment (three) and developmental retardation (three).
[c] Residua included gangrene with amputation (one).
[d] Residua included mild monoparesis.

TABLE 2. *Incidence of positive CSF stain and culture on day 1 of treatment by treatment group and etiology*

Etiology	% Positive on day 1 with:			
	CB		AMP	
	Gram stain	Culture	Gram stain	Culture
H. influenzae	38 (9/24)	38	11.7 (2/17)	5.8
S. pneumoniae	0 (0/7)	0	21.0 (3/14)	7.1
N. meningitidis	40 (2/5)	0	28.0 (2/7)	0

There were no significant differences between treatment groups in mortality or morbidity. Median CSF concentrations of both antibiotics attained during therapy were similar and exceeded the respective MIC of all isolated organisms. No *H. influenzae* isolates were resistant to AMP and none produced beta-lactamase.

During CB treatment of meningitis due to *H. influenzae*, 38% of the patients had positive CSF cultures on day 1. Despite this, persistently positive Gram stains did not correlate with a subsequent adverse clinical outcome. Wilson and Haltalin noted that 23% of patients with *H. influenzae* meningitis treated with AMP had positive CSF cultures obtained at a mean time of 26 h after the initiation of treatment (18). These investigators noted that persistently positive CSF cultures were more frequent when Levinthal medium was used and suggested that these persistent organisms may represent L-forms due to their unusual "fried-egg" appearance. All our CSF cultures were cultured on chocolate agar, and an atypical colony morphology was not observed.

The performance of a lumbar puncture before completion of 24 h of therapy may explain persistently positive cultures in this study. All day 1 CSF cultures were obtained betweeen 12 and 24 h after initiation of therapy, and CB and AMP patients were comparable in respect to the times of CSF collection. All patients, regardless of treatment or etiology, had negative CSF cultures and Gram stain if obtained at greater than 24 h after the initiation of therapy.

Evaluation of therapy with repeat CSF cultures is required, particularly if the possibility of strains of AMP-resistant *H. influenzae* is considered. However, the first CSF collection should await completion of at least 24 h of therapy; persistently positive cultures, in the face of clinical improvement and improvement of other CSF indexes, may not be an indication to change antibiotic therapy. However, a reevaluation with a subsequent CSF culture at a 24-h interval is advised because continued positive cultures of susceptible organisms beyond 24 h of treatment may signal the presence of a persistent focus of infection or an antibiotic-resistant organism.

Median CSF concentrations of CB and AMP on day 1 exceeded the median MIC of all organisms by 8- to 16-fold. However, measured CSF concentrations did not always exceed the determined MIC of an infecting organism in individ-

TABLE 4. *Antibiotic susceptibilities to bacterial isolates*

Organism	No.	Antibiotic	MIC		MBC	
			Median	Range	Median	Range
H. influenzae	42	CB	0.20	0.1–0.40	0.20	0.1–0.40
		AMP	0.20	0.1–0.40	0.20	0.1–0.80
		CM[a]	0.80	0.4–0.80	1.60	0.8–3.13
S. pneumoniae	14	CB	0.05	0.05–0.20	0.10	0.1–0.20
		AMP	0.05	0.05–0.20	0.10	0.1–0.20
		CM	3.13	0.8–6.25	6.25	1.6–6.25
N. meningitidis	8	CB	0.025	0.025–0.05	0.025	0.025–0.05
		AMP	0.035	0.025–0.050	0.050	0.05
		CM	1.60		3.13	

[a] CM, Chloramphenicol.

TABLE 5. *Relationship of CSF antibiotic concentrations (micrograms of antibiotic per milliliter) to dose and CSF protein concentration (milligrams per 100 ml)*

Drug regimen (mg/kg per 24 h)	Drug concn								
	CSF protein concn ≤74 mg/100 ml			CSF protein concn ≥75 mg/100 ml			CSF protein concn ≥200 mg/100 ml		
	Median	Range	No. of specimens	Median	Range	No. of specimens	Median	Range	No. of specimens
CB (200)	0.65	0–2.2	18	1.30	0.22–41	21	9.10	0.33–41	9
AMP (200)	0.45	0.1–2.3	15	2.20	0.37–30	14	13.80	0.37–30	8
CB (400)	0.85	0–71	41	4.50	0–60	24	8.5	3.2–13.5	2
AMP (400)	1.60	0–11.5	44	4.50	0–50	47	26.0	0–50	12

TABLE 6. *Relationship of CSF antibiotic concentrations and ratios (CSF/serum) versus day of treatment*

Drug regimen[a]	Index	Drug concn/ratio			
		Days 1-5	No. of specimens	Day 6	No. of specimens
CB (200)	Concentration[b]	1.2 (0.02-19)	29	0.42 (0-4.2)	26
	Ratio (%) median[c]	14.5%	20	5.8%	21
AMP (200)	Concentration	0.90 (0.1-14)	14	0.062 (0.1-30)	17
	Ratio (%) median	23.0%	13	4.2%	17
CB (400)	Concentration	1.5 (0-71)	34	1.20 (0-60)	37
	Ratio (%) median	8.3%	17	6.3%	26
AMP (400)	Concentration	3.4 (0-50)	47	1.85 (0-40)	46
	Ratio (%) median	14%		9.5%	36

[a] Daily dose in milligrams per kilogram.
[b] Concentration in micrograms per 100 ml.
[d] CSF/serum antibiotic concentration ratio.

ual cases. The median CSF concentrations of AMP reported in this study are comparable to those previously observed by other investigators (13,18). Further, Thrupp and co-workers noted increased CSF antibiotic concentrations during severe inflammation (13). The higher CSF antibiotic concentrations correlated with the higher levels of CSF protein, earlier days of therapy, and high CSF cell counts. The highest CSF concentrations were observed in patients with severe disease involvement, particularly adults with pneumococcal disease. Median CSF antibiotic concentrations increased with administration of increased doses.

CB has been suggested as a possible alternative to chloramphenicol for meningitis due to AMP-resistant *H. influenzae* (10). The attainable CSF concentration of CB, the in vitro susceptibility of hemophilus strains, and the clinical response documented in this study suggest that CB is adequate for AMP-susceptible *H. influenzae* infections, as well as those due to *N. meningitidis* and *S. pneumoniae*. However, lower cost, as well as the exquisite susceptibility of the meningococcus and pneumococcus to benzylpenicillin, make it the drug of choice for infections due to these organisms.

The susceptibiliy of strains of AMP-resistant *H. influenzae* to beta-lactam antibiotics has been shown to depend on inoculum size (15). When smaller inocula (i.e., 10^5 organisms/ml) of AMP-resistant organisms are utilized in susceptibility studies, apparent in vitro susceptibility to CB may be demonstrated. However, apparent in vitro susceptibility may not adequately predict clinical success. Feldman (3) has demonstrated concentrations of bacteria as high as 3.0×10^8 organisms/ml in the CSF of children with *H. influenzae* meningitis. Despite these high concentrations of bacteria, antibiotic therapy was usually effective; persistently positive cultures were observed only in children with an initial concentration of $\geq 10^7$ organisms/ml. Clinically, it remains undetermined whether CB can effectively treat infections due to AMP-resistant *H. influenzae*. Despite a theoretical advantage of this antibiotic against AMP-resistant *H. influenzae*, meningitis due to an AMP-resistant strain has, as yet, not been treated with CB. Chloramphenicol remains the drug of choice for these infections, and further clinical trials will be required to define the role of CB.

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