

COMPARATIVE THERAPEUTIC RESULTS OF PENICILLIN PLUS CHLORAMPHENICOL VERSUS AMPICILLIN PLUS SULBACTAM IN CHILDHOOD MENINGOCOCCEMIA*

*Güler Kanra MD**, Gülten Seçmeer MD**, Hasan Özen MD***
Mehmet Ceyhan MD****, Zafer Ecevit MD****

SUMMARY: Kanra G, Seçmeer G, Özen H, Ceyhan M, Ecevit Z. (Pediatric Infectious Diseases Unit, Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara, Turkey). Comparative therapeutic results of penicillin plus chloramphenicol versus ampicillin plus sulbactam in childhood meningococemia. *Turk J Pediatr* 35: 87-91, 1993.

Fifty-seven cases of meningococemia were evaluated retrospectively. The age of the patients ranged between 2 and 17 years. Of the 57 patients investigated for the efficacy of antibiotic treatment, 31 (54.4%) were treated with benzylpenicillin plus chloramphenicol and 26 (45.6%) with ampicillin plus sulbactam. Patients with criteria for a poor prognosis (presence of disseminated intravascular coagulation, low arterial blood pressure, and altered consciousness) were divided equally into two treatment groups. There were no statistically significant differences between the two treatment groups except for the higher incidence of convulsion in the group given penicillin plus chloramphenicol. The mortality rate was 19.3 percent for patients treated with benzylpenicillin plus chloramphenicol and 7.6 percent for patients treated with ampicillin plus sulbactam ($p = 0.19$; overall mortality rate 14%).
Key words: meningococemia, penicillin plus chloramphenicol, ampicillin plus sulbactam.

Acute fulminant meningococemia is the most severe clinical form of meningococcal infection. It is characterized by an abrupt onset of purpura, shock, disseminated intravascular coagulation (DIC) and rapid progression to death¹. The mortality rate remains at 19 percent with variations depending on the prevalence and clinical features of the disease, the host response and socioeconomic level of the population².

Current regimens employed in the treatment of meningococemia include either benzylpenicillin-G alone or in combination with chloramphenicol, or ampicillin alone³. There are also reports of reduced penicillin sensitivity to meningococci^{4,5}. Recently, sulbactam / ampicillin has been reported to be effective in treating childhood meningitis and other childhood infections^{6,7}. Since a high mortality rate has been observed in patients with meningococemia who were administered

* From the Pediatric Infectious Diseases Unit, Department of Pediatrics, Hacettepe University Faculty of Medicine, Ankara.

** Professor of Pediatrics, Hacettepe University Faculty of Medicine.

*** Pediatrician, Hacettepe University Faculty of Medicine.

**** Associate Professor of Pediatrics, Hacettepe University Faculty of Medicine.

the penicillin plus chloramphenicol regimen and also because of the success achieved by the use of an ampicillin plus sulbactam regimen in treating other childhood infections⁷, we decided to include ampicillin plus sulbactam as a regimen for treating meningococemia.

In this study, 57 cases of acute meningococemia treated at the Hacettepe University Children's Hospital were evaluated retrospectively and the results of treatment were analyzed. There is also a review of the current literature.

Material and Methods

From January 1984 to September 1990, a total of 57 patients diagnosed clinically as having meningococemia and confirmed by laboratory findings were evaluated retrospectively. A diagnosis of meningococemia was established if clinical manifestations of the disease and at least one of the following criteria were present:

1. Cultivation of the microorganism from the blood, cerebrospinal fluid or petechial lesions.
2. Demonstration of Gram-negative diplococci on the Gram-stained smear of CSF or petechial smear^{2, 8}.

Hypotension was defined as arterial systolic pressure values under 85 mmHg for patients over four years of age and a value of 75 mmHg for patients under four years of age⁹.

Fisher's exact Chi-square, the Chi-square and Mann-Whitney U tests were used for statistical analyses. P values < 0.05 were considered significant.

Results

The age of the patients ranged from 2 to 17 years and the male / female ratio was 1.11.

The four prevailing complaints at presentation were fever (98.2%), vomiting (87.7%), purpuric lesions (70.1%) and headache (59.6%). Purpuric lesions were detected in 100 percent of cases, fever in 84.2 percent, signs of meningeal irritation in 80.7 percent, and alterations in consciousness (somnolence, stupor and coma) in 33.3 percent. Table I lists the features exhibited in the patients of both treatment groups. We were unable to discern any differences between the two treatment groups in respect to clinical features, except for the frequency of convulsion.

Laboratory findings on admission revealed leukocyte counts which varied from 2600 to 81000 / mm³ and averaged between 14125 ± 9824 / mm³ in the patients who died, and between 20193 ± 14324 / mm³ in the patients who survived.

Table I: Clinical and Laboratory Features and Outcome of Patients in Both Treatment Groups

	Ampicillin/Sulbactam n = 26	Penicillin/Chloramphenicol n = 31
Clinical Features and Symptoms (%)		
Age (yrs)	6.48 ± 3.5 #	6.4 ± 4.0
Fever	26 (100)	30 (96.7)
Vomiting	25 (96)	25 (80.6)
Headache	15 (57.6)	19 (61.2)
Lethargy	16 (61.5)	18 (58.0)
Change in level of consciousness	9 (34.6)	10 (32.2)
Hypotension	8 (30.7)	7 (22.5)
Convulsion*	2 (7.6)	5 (16.1)
Other (abdominal pain, diarrhea, arthralgia, etc)	12 (46.1)	13 (41.9)
Laboratory Findings (%)		
WBC Count (/mm ³) (range)	19577 ± 15820 (2600 - 81000)	20045 ± 12078 (5800 - 49000)
CSF leukocyte count > 10 / mm ³	19 (73.0)	25 (80.6)
Laboratory findings of DIC	5 (19.2)	4 (12.4)
Follow-up and Outcome		
Mean time period between onset of complaints and treatment (days)	1.5 ± 0.82	1.2 ± 0.66
Disappearance of symptoms and signs (days)	2.29 ± 1.51	2.52 ± 0.82
Duration of hospitalization (days)	9.12 ± 3.81	10.75 ± 4.82
Case fatality (%)**	2 (7.6)	6 (19.3)

* : p < 0.05

** : p = 0.19

: Plus - minus values are means ± SD

(p > 0.05). There was also no difference in the average leukocyte counts between the two treatment groups: 20045 ± 12078 in penicillin + chloramphenicol group; and 19577 ± 15820 in ampicillin + sulbactam group (p > 0.05). DIC was confirmed by laboratory findings in nine (15.7%) patients.

A CSF specimen which reveals a mere leukocyte count of 10 / mm³ or greater points to a diagnosis of meningitis¹⁰. Forty-four of the total 57 patients had meningitis (77.2%).

When the patients were studied retrospectively, we found that out of 57 patients, 31 had initially been treated with benzylpenicillin G 300000 IU / kg / day given in six divided doses and combined with chloramphenicol 100 mg / kg / day in four divided doses intravenously, while the second group of 26 patients had received ampicillin 400 mg / kg / day plus sulbactam 100 mg / kg / day in four divided doses intravenously.

A total of eight patients (14%) died. While six patients (4, 4, 8, 9, 12, and 14 years of age; 19.3%) treated with penicillin and chloramphenicol died, only two patients (6 and 8 years of age; 7.6%) died in the ampicillin plus sulbactam group ($p = 0.19$, Fisher's exact test). DIC, low blood pressure, and an altered level of consciousness on admission were indications of a poor prognosis, while convulsions, the time petechiae appeared, the age of the patient and a leukocyte count below $10000 / \text{mm}^3$ had no bearing on prognosis. The two treatment groups did not differ from each other in respect to frequency of poor prognostic factors.

Discussion

Despite recent advances in diagnosis and treatment of meningococcal infections, they are still regarded as dreaded diseases, meningococcemia in particular. The fatality rate is reported to be between 8.6 and 43 percent in different studies^{1,11}. In our survey, the overall mortality rate was found to be 14.0 percent.

Another problem encountered in treating patients with meningococcal infections is that resistance develops to antibiotic agents including penicillin^{2,4,5}. The mortality rate was 19.3 percent in the group we treated with penicillin.

Halstensen et al³ reported that there was a significantly lower mortality rate associated with patients treated with penicillin or any other antibiotic in combination with chloramphenicol as compared with patients who were not given chloramphenicol.

They interpreted this finding as due to the effect of chloramphenicol in decreasing the destructive effect of beta-lactam antibiotic agents which prevents abrupt discharge of endotoxin. Rodriguez et al⁴ compared the efficacy of the ampicillin plus chloramphenicol regimen with the ampicillin plus sulbactam regimen in treating pediatric patients with meningitis without considering the type of microorganism involved. They found mortality rates and neurologic sequelae to be lower when using the ampicillin plus sulbactam treatment regimen, which was at least as effective as the other combination.

Since high mortality accompanies meningococcemia, prompt and proper treatment should be initiated as rapidly as possible when this infection is suspected so that complications can be avoided. Even though there were no statistically significant differences between our two treatment groups in respect to therapy,

the lower mortality associated with the ampicillin plus sulbactam treatment group may be reason enough for choosing this regimen in treating childhood meningococcaemia.

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