Penicillins in the Treatment of Bacterial Meningitis

ALLEN W. MATHIES, Jr., Ph D, M D, Professor of Paediatrics, University of Southern California School of Medicine and the Communicable Disease Service, Los Angeles County-University of Southern California Medical Center

Although bacterial meningitis is of low incidence in the United States and other temperate countries, it continues to maintain the respect of both physicians and lay people alike because of its high case fatality rate and high morbidity rates.

Three specific organisms are responsible for the majority of the cases of bacterial meningitis in individuals over two months old. These are Neisseria meningitidis, Haemophilus influenzae type B, and Streptococcus pneumoniae. N. meningitidis, the meningococcus, occurs in both epidemic and non-epidemic form whereas the other two agents are endemic. Prior to the advent of specific therapy meningococcal meningitis had a mortality rate of approximately 70 per cent. In addition, the survivors often suffered marked residua. The mortality rate was reduced first by specific anti-sera and subsequently by the addition of sulphonamides; it was not markedly altered by the introduction of penicillin. Similarly, H. influenzae with a mortality rate of approximately 98 per cent had the major drop in case fatality and morbidity rates with the use of specific anti-serum and sulphonamides. Penicillin alone was not evaluated in any large numbers of cases and the recommendation continued to be a combination of serum plus sulphonamides. When other antibiotics such as streptomycin, tetracycline and chloramphenicol were evaluated in haemophilus meningitis, results comparable to the serum-sulphonamide results were achieved. In contrast, the mortality rate of pneumococcal meningitis that approached 100 per cent prior to specific therapy was not reduced by serum and sulphonamide much below 80 per cent and only dropped to between 20 and 40 per cent after the introduction of high-dose penicillin therapy. By the end of the 1950s and early 1960s the overall case fatality rates in large series of patients with bacterial meningitis were approximately 10 to 15 per cent with marked individual series variation dependent upon the type of patient treated. Serum therapy was discontinued and physicians relied on antibiotics and sulphonamides to control these infections. The historical use of multiple drugs to achieve low case fatality rates and the variation in
susceptibility of the three major organisms to antibiotics resulted in a triple therapy that was widely recommended in the early 1960s. This regimen consisted of sulphonamides for the meningococcus, penicillin for the pneumococcus, and chloramphenicol or tetracycline for *H. influenzae* type B. All three drugs were given initially and then, after identification of the organism, usually two agents were continued to the completion of therapy.

**IN VITRO STUDIES**

When ampicillin became available in the early 1960s *in vitro* studies indicated that this antibiotic with the toxicity of penicillin G had marked activity against all three organisms. Table 1 lists the minimum bactericidal concentrations

| Drug              | No. of isolates | Concentration (µg/ml) |
|-------------------|-----------------|-----------------------|
|                   |                 | ≤ 0-8  | 1-6–3-13 | 6-25–12-5  | 25–50 | > 100 |
| Sulpha            | 54              | 29-5  | 14-8     | 12-9       | 9-4   | 39-4  |
| Penicillin G      | 77              | 94-8  | 2-6      | 1-3        | 1-3   |       |
| Ampicillin        | 131             | 97-5  | 1-5      | 1-0        |       |       |
| Chloramphenicol   | 109             | 45-6  | 38-4     | 14-5       |       | 1-5   |
| Tetracycline      | 51              | 68-5  | 27-5     | 2-0        | 2-0   |       |

of various antibiotics against *N. meningitidis*. As can be noted in the table the susceptibility of the meningococcus to sulphonamides has changed markedly from the historical experience of extreme susceptibility. In 1954 Love and Finland reported meningococcal strains that were resistant to sulphonamide *in vitro*. Clinical failures secondary to resistant organisms were not reported, however, probably because of the use of double or multiple therapy. In 1963 the first indication that sulphonamide-resistant meningococci were clinically important was reported from the San Diego Naval Training Base in California. Since that time the sulphonamide-resistant meningococcus has spread throughout the United States. No difference in susceptibility to penicillin G, ampicillin, or other antibiotics has been noted. Similarly, the pneumococcus remains sensitive to penicillin G as well as to ampicillin (Table 2). Of most interest was the comparison of ampicillin in relationship to the drugs usually recommended for the treatment of *H. influenzae* type B meningitis. Only 70 per cent of the isolates tested were sensitive to chloramphenicol at a level of 0-8 µg/ml or less. In contrast, 89 per cent of the strains were sensitive to ampicillin in a similar concentration (Table 3). All the first 126 isolates of *H. influenzae* tested were killed by ampicillin in concentrations of 1-6 µg/ml
TABLE 2. Minimum bactericidal concentrations of various antibiotics against S. pneumoniae (percentage)

| Drug        | No. of isolates | Concentration (µg/ml) |
|-------------|-----------------|-----------------------|
|             |                 | < 0-8 | 1-6-3-13 | 6-25-12-5 | 25-50 | > 100 |
| Penicillin G| 78              | 96-1  | 3-9      | —         | —     | —     |
| Ampicillin  | 120             | 99-0  | 1-0      | —         | —     | —     |
| Chloramphenicol | 116      | 30-8  | 43-9     | 24-0      | 1-3   | —     |

TABLE 3. Minimum bactericidal concentrations of various antibiotics against H. influenzae type B (percentage)

| Drug        | No. of isolates | Concentration (µg/ml) |
|-------------|-----------------|-----------------------|
|             |                 | < 0-8 | 1-6-3-13 | 6-25-12-5 | 25-50 | > 100 |
| Chloramphenicol | 288            | 70-5  | 22-5     | 7-0       | —     | —     |
| Tetracycline | 14              | 71-1  | 21-3     | 7-6       | —     | —     |
| Penicillin G | 244             | 82-9  | 15-5     | 1-6       | —     | —     |
| Ampicillin  | 323             | 88-9  | 5-4      | 5-3       | 0-9   | 1-5   |

or less. Subsequently, we have encountered organisms more resistant to ampicillin and now have five isolates with minimum bactericidal concentrations of 100 µg/ml. Each of these isolates is from blood or cerebrospinal fluid and hence must be considered pathogenic. Three of the five patients with these ‘resistant’ isolates responded rapidly to ampicillin. The other two patients had prolonged courses and in one of them the therapy was switched to chloramphenicol after 21 days of ampicillin. Overall, the in vitro results encouraged the use of ampicillin as a single antibiotic for the treatment of bacterial meningitis.

CLINICAL STUDIES
The Communicable Disease Service of the Los Angeles County-USC Medical Center serves as a referral hospital for patients of all ages and all socio-economic groups from the seven million population in Los Angeles County. About 70 to 80 per cent of all patients with bacterial meningitis in Los Angeles County are referred to this service. Over the course of several years controlled trials compared ampicillin with regimens of single drug or multiple drug therapy which were recommended as standard methods of treatment of bacterial meningitis. These results are reported elsewhere (Mathies et al., 1966; Wehrle et al., 1967).

As indicated before, mortality rates vary in reported series because of basic
differences in the patient population. One of the major factors affecting outcome is the age of the patient. Bacterial meningitis is essentially a paediatric disease and 72 per cent of all the patients treated are ten years of age or less (Fig. 1). One-third of all the patients treated were less than a year old, although the age distribution varies markedly with the aetiology of the bacterial meningitis. As shown in Fig. 2 almost all the patients with *H. influenzae* type B are under the age of six. Meningococcal meningitis is also predominantly a disease of the young, but there is a far greater incidence of meningococcal disease in teenagers and young adults. In contrast, the pneumococcus occurs predominantly in the very young, less than one year old, and falls off to a very low rate in the middle years, occurring in those patients who have had head injury, haemoglobinopathy, or previous foci in the ear and sinuses. The pneumococcus, however, becomes the predominant cause of meningitis in patients over forty. The category ‘purulent unknown, no isolate’, refers to a group of patients who have all the clinical and laboratory features of bacterial meningitis with the exception that no bacteria are isolated. This group follows the age distribution of the meningococcal group and probably largely represents patients with meningococcal disease who have received previous antibiotic therapy and, hence, no organism is isolated. This rather sharp differentia-
Fig. 2. Age distribution of bacterial meningitis patients by specific aetiology.

Another factor that influences the outcome of therapy is the condition of the patient at the time of admission. We used the following criteria for classification: patients who were comatose or in shock at the time of admission were considered to be in a 4+ category; 3+ were patients who had convulsions but neither coma nor shock; the 2+ category included patients who had one or more of the following at the time of admission: temperature of over 105°F, symptoms for more than five days, marked lethargy or complicating underlying disease such as pneumonia, mastoiditis, etc.; and in the 1+ category were patients with bacterial meningitis with none of the above...
features. Prior antibiotic therapy was not considered an important factor as over 50 per cent of all the patients had had at least some antibiotic before admission.

As can be seen in Table 4 the condition of the patient at the time of admission to the hospital varies with the agent responsible for the meningitis. In *H. influenzae* type B, meningococcal and 'pusulent unknown' meningitis, the majority of the patients were in the 1+ or 2+ category. In contrast, over 50 per cent of the patients with pneumococcal disease fell into the 4+ category,

| Aetiology                | 1+   | 2+   | 3+   | 4+   | No. of patients |
|--------------------------|------|------|------|------|----------------|
| *Haemophilus influenzae* | 46.1 | 27.9 | 13.0 | 13.0 | 523            |
| *Neisseria meningitidis*| 38.9 | 29.9 | 4.3  | 26.7 | 411            |
| *Streptococcus pneumoniae*| 26.0 | 13.0 | 7.5  | 53.5 | 200            |
| Purulent, no isolate     | 57.2 | 21.6 | 8.1  | 12.9 | 185            |
| Total                    | 42.3 | 25.3 | 8.7  | 23.4 | 1319           |

Table 4. Aetiologic differences in admission severity grading (percentage)

| Aetiology                | 1+   | 2+   | 3+   | 4+   |
|--------------------------|------|------|------|------|
| *Haemophilus influenzae* | 93.8 | 5.0  | 1.2  |      |
| *Neisseria meningitidis*| 95.0 | 3.8  | 1.2  |      |
| *Streptococcus pneumoniae*| 82.7 | 13.5 | 3.8  |      |
| Purulent, no isolate     | 92.5 | 5.7  | 1.8  |      |
| Total                    | 92.8 | 5.6  | 1.6  |      |

Table 5. Influence of admission severity grading on outcome (percentage)

| Aetiology                | 1+   | 2+   | 3+   | 4+   |
|--------------------------|------|------|------|------|
| *Haemophilus influenzae* | 89.8 | 5.8  | 4.4  |      |
| *Neisseria meningitidis*| 88.8 | 11.2 | 0.0  |      |
| *Streptococcus pneumoniae*| 53.4 | 33.3 | 13.3 |      |
| Purulent, no isolate     | 73.3 | 20.0 | 6.7  |      |
| Total                    | 82.8 | 12.1 | 5.1  |      |

L= survived with no residua; R= residua; D= Death

many being shocked and in coma. The overall distribution reflects the very large number of patients who have *H. influenzae* or meningococcal disease. The influence of the admission severity grading on the outcome is illustrated in Table 5. Patients who enter in the 1+ category have a good prognosis, over
90 per cent recovering without known sequelae; the residua occurring in 3.8 to 13.5 per cent of these patients include mental retardation, deafness, blindness, or hemiparesis. The mortality rate is relatively low, irrespective of the aetiology of the meningitis. At the other end of the spectrum, in the 4+ category, the mortality rate is high, ranging from 18.2 to 40.2 per cent with the pneumococcus accounting for the highest rates both in deaths and residua. In the two middle categories there are two figures that stand out. One is the 10.5 per cent mortality in meningococcal patients categorised as 2+ on admission. The explanation for this higher figure is not entirely clear; it may represent patients with undiagnosed shock who were put into the wrong category. The 13.3 per cent case mortality in 3+ pneumococcal patients is similarly out of line with that of the other bacteria. Pneumococcal meningitis is often associated with cerebritis, and local infarction of the brain, which may cause convulsions without coma, and may adversely affect the prognosis.

Table 6. Results of antibiotic therapy (percentage) ampicillin versus non-ampicillin

|                      | Live | Residua | Die | No. of patients |
|----------------------|------|---------|-----|----------------|
| **Ampicillin therapy** |      |         |     |                |
| *H. influenzae*       | 91.4 | 4.4     | 4.2 | 337            |
| *N. meningitidis*     | 84.5 | 9.7     | 5.8 | 206            |
| *S. pneurnoniae*      | 64.0 | 16.0    | 20.0| 100            |
| Purulent, no isolate  | 93.5 | 4.8     | 1.6 | 62             |
| **Total**             | 85.7 | 7.7     | 6.6 | 705            |
| **Non-ampicillin therapy** |      |         |     |                |
| *H. influenzae*       | 87.3 | 7.8     | 4.9 | 181            |
| *N. meningitidis*     | 82.1 | 7.3     | 10.6| 151            |
| *S. pneurnoniae*      | 59.1 | 15.9    | 25.0| 88             |
| Purulent, no isolate  | 82.0 | 10.3    | 7.7 | 78             |
| **Total**             | 79.9 | 9.5     | 10.6| 498            |

In our controlled studies of meningitis therapy, the ampicillin and control groups were composed of patients of equivalent age and severity grading (Mathies et al., 1966; Wehrle et al., 1967). The results of ampicillin therapy in comparison with therapy other than ampicillin alone are illustrated in Table 6. This represents a compilation of patients treated over a period of five years and many of them have been previously reported (Mathies et al., 1966; Wehrle et al., 1967). The ampicillin was given intravenously at a dose of 150 mg/kg/day in six divided doses. An additional rapid infusion of 50 mg/kg was given at the time of admission. Non-ampicillin therapy consisted either of penicillin G for meningococcal or pneumococcal disease at a dose of
15 million units per day in six divided doses plus a five million unit rapid infusion at the time of admission, or chloramphenicol 100 mg/kg/24 hr in six divided doses intravenously, and for *H. influenzae* type B, penicillin and chloramphenicol in similar doses for the ‘purulent unknown, without isolates’. In patients receiving multiple drug therapy a combination of ampicillin, chloramphenicol, and streptomycin was employed. Included in the previous tables are 115 patients not included in the therapy table as their treatment was too diverse to evaluate adequately. Fifty-five of them had some ampicillin plus another antibiotic, and 61 had no ampicillin but a variety of other antibiotics. The overall outcome was similar in these two groups. The outcome in those patients treated with ampicillin alone was slightly better in all aetiologies than in the non-ampicillin alone treated patients. Both the mortality and the residual rates were lower in the ‘ampicillin alone’ patients. The difference between the overall mortality rates is statistically significant at the 2 per cent level. Because of these good results in a large number of patients we have continued to use ampicillin alone as the antibiotic of choice in the management of patients with bacterial meningitis who are two months of age or over.

It is unlikely that in the future a new antibiotic or modification of a currently existing antibiotic will markedly change the overall outcome in bacterial meningitis. Analysis of the bad results (i.e. death and residua) indicates that often the die is cast prior to the time that the patient receives any antibiotic therapy. Most of the deaths occur within the first 24 to 48 hours, and antibiotic therapy may not have an opportunity to exert any influence on the outcome. I believe that any further reduction in morbidity and mortality will come not from antibiotic or chemotherapeutic advances but rather from the introduction and widespread use of vaccines that will prevent rather than cure the disease.

**Acknowledgements**

The investigations were supported in part by Public Health Service Grants 5–T01–AI00275 and 5–R01–AI08011 from the National Institute of Allergy and Infectious Diseases, by contract DA–49–193–MD–2874 from the US Army Research and Development Command, Commission on Acute Respiratory Diseases, Office of the Surgeon General, Department of the Army, and the Hastings Foundation Fund.

**References**

Love, B. D., Jr. and Finland, M. (1954) *American Journal of Medical Science*, 228, 534.
Mathies, A. W., Jr. Leedom, J. M., Thrupp, L. D., Ivler, D., Portnoy, B., and Wehrle, P. F. (1966) *Antimicrobial Agents and Chemotherapy*, 1965, p. 610.
Wehrle, P. F., Mathies, A. W., Leedom, J. M. and Ivler, D. (1967) *Annals of the New York Academy of Sciences*, 143, 488.