Committee on Infectious Diseases

Treatment of Bacterial Meningitis

The purpose of this report is to review the evidence for efficacy of the new cephalosporin compounds and to provide a basis for determining the most appropriate initial empiric regimen for treating bacterial meningitis in infants and children. For a more complete discussion concerning diagnosis and management of meningitis, the reader is referred to a recently published report by a task force appointed by the American Academy of Pediatrics. This report, however, goes beyond that of the task force by indicating the new cephalosporins as first-line drugs for therapy and by recommending shorter duration of treatment for some patients with meningitis. This report will also address the issue of alternative treatment regimens that might facilitate more rapid discharge from the hospital, less costly management, and home care of some patients with meningitis.

BACKGROUND

New Cephalosporins

Initial empiric antimicrobial therapy for bacterial meningitis entails selection of antibiotics that are effective against the likely etiologic agents and use of proper drug dosages and administration schedules that result in adequate bactericidal activity in CSF. In newborn infants, the initial empiric regimen conventionally used has been ampicillin and an aminoglycoside. In older infants and children, ampicillin and chloramphenicol have been used for more than a decade. The newer cephalosporins (ie, cefuroxime, moxalactam, cefotaxime, ceftiraxone, and ceftazidime) have been evaluated in controlled, prospective studies. Despite their superior in vitro activity against the common meningeal pathogens and greater bactericidal activity in CSF, those cephalosporins do not sterilize CSF cultures more rapidly or improve case-fatality rates when compared with results of conventional antibiotic regimens in neonates or in infants and children. With the exception of one report, follow-up studies of the effect of the new β-lactam antibiotics on long-term morbidity have not been published. That one report showed that morbidity 2 years after moxalactam therapy of Haemophilus meningitis was similar to that after ampicillin or chloramphenicol treatment.

A potential advantage of the new cephalosporins for treatment of meningitis is avoidance of monitoring serum concentrations which is necessary when an aminoglycoside or chloramphenicol is used in neonates or in certain situations when chloramphenicol is used in infants and children. Because aminoglycoside concentrations are unpredictable in serum of neonates, especially in those weighing less than 1,500 g at birth, dosages of these agents should be tailored to achieve concentrations in the range considered therapeutic and nontoxic. Likewise, the aminoglycosides and chloramphenicol should be avoided in patients who have underlying abnormalities in renal or hepatic function, respectively. β-Lactam antibiotics are preferred in those situations unless the concentrations of chloramphenicol or aminoglycosides in serum can be promptly determined. The unpredictable metabolism of chloramphenicol in newborn infants and of the pharmacologic interactions of this agent when administered concomitantly with phenobarbital, phenytoin, or rifampin require that serum concentrations be measured and the dosage adjusted accordingly to avoid toxic or subtherapeutic concentrations. In those situations it might be advisable to use the cephalosporins for therapy to avoid the unnecessary expense of monitoring serum concentrations.

The recommendations in this statement do not indicate an exclusive course of treatment or procedure to be followed. Variations, taking into account individual circumstances, may be appropriate.
Duration of Therapy

For a few patients with meningitis, alternative treatment regimens might be considered to shorten the duration of hospitalization and to provide completion of treatment at home. Several recently published studies\(^4\),\(^15\),\(^16\) have demonstrated that a seven-day course of antibiotic therapy is effective and safe for management of some infants and children with uncomplicated bacterial meningitis. For patients with meningococcal meningitis, general experience for many years has shown that therapy for more than seven days is unnecessary. Abbreviated courses of treatment are inappropriate for infants with meningitis caused by group B streptococci or by Gram-negative enteric bacilli because case-fatality rates are considerably larger in those patients than in older infants and children and because there is no experience with shorter treatment schedules.

A shorter period of hospitalization for patients with meningitis reduces the risk of acquiring nosocomial infections, helps to lessen the total cost of management, and returns the patient to his or her normal environment. The physician in charge is the best person to decide in each individual situation when it is safe for the patient with meningitis to go home. It is unnecessary to perform a lumbar puncture for examination and culture of CSF at completion of therapy in a child who has had an uncomplicated course. This procedure prolongs hospitalization and provides no useful information in identifying the patient in whom a relapse of meningitis will develop.\(^17\)

Home Therapy

With the availability of antibiotics that could potentially be administered at home, some physicians have discharged children from the hospital before completion of conventional treatment regimens for meningitis. In those situations, the remaining few days of therapy are completed at home with either orally administered chloramphenicol or intramuscularly administered ceftriaxone.

Chloramphenicol when administered orally after the second day of IV therapy has been shown to be safe and effective for management of meningitis.\(^18\) All such patients should have serum concentrations measured because of considerable patient-to-patient variation in absorption and disposition of the drug. In most patients who are treated with orally administered chloramphenicol for meningitis, the CSF concentrations of antibiotics are at least comparable and frequently greater than those after IV therapy.\(^19\)

Once daily IV therapy with ceftriaxone has been shown to be safe and effective in limited numbers of patients.\(^20\),\(^21\) and it might, therefore, represent an alternative mode of home therapy for some children with meningitis. Ceftriaxone can also be administered IM. The serum concentration-time curves after IM and IV administration are essentially bioequivalent.\(^22\) A problem with using ceftriaxone IM is that the solution for injection should contain no more than 250 mg/mL. This volume is impractical. For example, a 15-kg child receiving an 80-mg/kg daily dose requires 4.8 mL of fluid. This is too large a volume for injection at a single site in an infant, so the dose must be divided in two equal doses.

RECOMMENDATIONS

Initial Empiric Therapeutic Regimens: Neonatal Meningitis

Ampicillin combined with either an aminoglycoside or a cephalosporin (ie, cefotaxime or cefazidime) is satisfactory for initial empiric therapy of neonatal meningitis. In the hospitalized low birth weight premature infant in whom nosocomial *Pseudomonas* infection is a possibility, cefazidime is preferred over cefotaxime.

Meningitis in Infants and Children (Table)

Ampicillin and chloramphenicol have been and continue to be effective and relatively safe for initial empirical treatment of nonneonatal meningitis. Alternatively, the new cephalosporins are equally acceptable for initial therapy. Of those available for therapy, sufficient experience from properly conducted clinical trials exists only for ceftazidime\(^5\),\(^4\) cefotaxime\(^8\),\(^9\) moxalactam\(^2\),\(^5\) and ceftriaxone.\(^6\),\(^7\) Because moxalactam is relatively inactive against group B streptococci and *Streptococcus pneumoniae*, this drug should not be used singly for initial empirical therapy of meningitis. Selection of one of the other cephalosporins must be based on personal experience, availability of the drug in the hospital formulary, dosing schedules, and cost. Because the total experience with all of these new agents is considerably smaller than with the conventional regimens for treating meningitis, continued evaluation of those new β-lactam antibiotics is warranted. In the first 6 to 8 weeks of life it is advisable to add ampicillin to the cephalosporin regimen because of the possibility of *Listeria* or enterococcus as causative agents.

If facilities for monitoring serum concentra-
TABLE. Antimicrobial Agents for Treatment of Meningitis*

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Duration of Treatment in Neonates</th>
<th>Infants and Children</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0–7 d</td>
<td>8–28 d</td>
</tr>
<tr>
<td>Amikacin†</td>
<td>15–20 div q 12</td>
<td>20–30 div q 8</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>100–150 div q 12</td>
<td>150–200 div q 8 or 6</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>100 div q 12</td>
<td>150 div q 8 or 6</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>80–100 div q 12 or once daily†</td>
<td>200 div q 6</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>60 div q 12</td>
<td>90 div q 8</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>240 div q 8</td>
<td>250–400,000 div q 4–6</td>
</tr>
<tr>
<td>Chloramphenicol†</td>
<td>25 once daily</td>
<td>50 div q 12</td>
</tr>
<tr>
<td>Gentamicin†</td>
<td>5 div q 12</td>
<td>7.5 div q 12</td>
</tr>
<tr>
<td>Kanamycin†</td>
<td>15–20 div q 12</td>
<td>20–30 div q 8</td>
</tr>
<tr>
<td>Methicillin</td>
<td>100–150 div q 12 or 8</td>
<td>150–200 div q 8 or 6</td>
</tr>
<tr>
<td>Nafcillin</td>
<td>100–150 div q 12</td>
<td>150–200 div q 8 or 6</td>
</tr>
<tr>
<td>Penicillin G</td>
<td>100,000–150,000 div q 12</td>
<td>150,000–200,000 div q 8 or 6</td>
</tr>
<tr>
<td>Ticarcillin</td>
<td>150–225 div q 12 or 8</td>
<td>225–300 div q 8 or 6</td>
</tr>
<tr>
<td>Tobramycin†</td>
<td>4 div q 12</td>
<td>6 div q 8</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>20 div q 12</td>
<td>30 div q 8</td>
</tr>
</tbody>
</table>

* Doses are given in mg/kg (U/kg for penicillin G) divided (div) every (q) 12, 8, 6, or 4 hours.
† If optimal dosage should be based on determination of serum concentrations, especially in low birth weight infants.
‡ If a one-dose daily regimen is used, the committee recommends that on the first day an 80-mg/kg dose be given at diagnosis, at 12 hours and 24 hours, and then every 24 hours thereafter.

Subsequent Therapy

Once the causative agent of meningitis has been identified and the susceptibility of the organism defined, the single most appropriate antibiotic or combination of antibiotics should be selected. Penicillin G or ampicillin is preferred for treatment of disease caused by group B streptococci, Neisseria meningitidis, and susceptible strains of Streptococcus pneumoniae. Strains of pneumococci that are relatively resistant to penicillin are best treated with chloramphenicol or vancomycin until results of susceptibility studies are available. There is inadequate experience to determine whether cefotaxime or ceftriaxone would be effective in treating meningitis caused by these organisms. Ampicillin is preferred for Listeria monocytogenes and β-lactamase-negative strains of Haemophilus influenzae, whereas chloramphenicol or one of the new cephalosporins should be used for β-lactamase-positive strains. For neonatal meningitis caused by Gram-negative enteric bacilli, specific therapy should be based on results of susceptibility studies. Cefotaxime, or ceftazidime for Pseudomonas meningitis, should be satisfactory when used singly or in combination with an aminoglycoside.

Duration of Therapy

Duration of treatment for bacterial meningitis is dependent on the clinical response and the organism causing disease. For neonatal meningitis caused by group B streptococci or L monocytogenes, 14 days of treatment are usually satisfactory. By contrast, infants with disease caused by Gram-negative enteric bacilli require a minimum of 3 weeks of therapy and, in some infants with delayed sterilization of CSF cultures, 4 to 6 weeks may be required. For infants and children with uncomplicated Haemophilus meningitis, therapy for seven to ten days is usually satisfactory, whereas for pneumococcal meningitis ten days of treatment is preferred. For meningococcal meningitis, therapy for seven days is effective.

Home Therapy

Until there is additional information the committee does not recommend early discharge from the hospital for home management of infants and children with bacterial meningitis. It is recognized, however, that some physicians use this alternative treatment. For those physicians the decision to discharge early a patient with meningitis must be based on the clinical condition of the patient, the reliability of the parents to assess the child at home and to follow instructions, the ability of the child to swallow and retain medication given orally, and the availability of a visiting nurse service or of a home therapy team to administer antibiotics IV or IM and to assess the clinical status of the patient. Discharge should not occur unless the patient is alert, stable, and cooperative and not before the seventh day of inpatient management. If the decision is to provide oral chloramphenicol therapy, it is mandatory for the physician to document adequate absorption of
the agent before discharge. Therapeutic serum concentrations of chloramphenicol are from 15 to 25 μg/mL. Rifampin therapy should be delayed until chloramphenicol is stopped because serum concentrations of the latter agent could be reduced by concomitant administration of rifampin. At the present time there is insufficient experience with using ceftriaxone IM for treatment of meningitis. It would be preferable to have a nurse or physician administer this drug IV through a heparin lock; this would ensure at least daily observation of the patient by an experienced health care provider.

As previously recommended, arrangements should be made for a hearing evaluation and neurologic examination within several weeks of completing therapy.

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REFERENCES
15. Lin TY, Chrane DF, Nelson JD, et al: Seven days of ceftriaxone therapy is as effective as ten days treatment for bacterial meningitis. JAMA 1985;253:3559–3563
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*Pediatrics* 1988;81:904

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**ERRATA**

In the commentary, "Child Health and the 1987 Nobel Peace Prize" by Lars Å. Hanson, MD, PhD, which appeared in the May 1988 issue (*Pediatrics* 1988;81:229–230), two errors were made in editing:

1. The last sentence of the first paragraph should read: "In each of the last 5 years I have been the person responsible for nominating the President of Costa Rica for the Nobel Peace Prize. Costa Rica's accomplishments in child health constitute a major reason for the nomination, and, for this reason the background will be given briefly here."

2. The last two sentences of the third paragraph should read: "A well-perceived reorganization of the health system was initiated by him, based in large part on research by Dr Leonardo Mata. This reorganization emphasized immunizations, safe drinking water, improved waste disposal, improved health information, education and communication, and a dramatically improved coverage of the population by a system of primary health care (E. Mohs, *Pediatr Infect Dis* 1982;1:212–216)."

*Pediatrics* apologizes to Costa Rica and to Dr Hanson, Dr Arias, Dr Mohs, Dr Mata, and the Nobel Committee for these errors.

In the American Academy of Pediatrics' statement, "Treatment of Bacterial Meningitis" by the Committee on Infectious Diseases (*Pediatrics* 1988;81:904–907), there is an error on p 906 in the last sentence under the heading, "Subsequent Therapy." The words, "Cefotaxime, or," should be deleted and the sentence should read: "Ceftazidime for *Pseudomonas* meningitis should be satisfactory when used singly or in combination with an aminoglycoside."
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*Pediatrics* 1988;81;904

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