Review Article

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# TREATMENT OF BACTERIAL MENINGITIS

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FEW diseases have been affected more by the advent of antimicrobial therapy than bacterial meningitis. From its recognition in 1805 to the early 20th century, bacterial meningitis was fatal. Although the introduction of antibiotics made it curable,[1-4] morbidity and mortality from the disease remain unacceptably high. In a recent report, 61 percent of infants who survived gram-negative bacillary meningitis had developmental disabilities and neurologic sequelae.[5] Similarly, in a recent review of 493 episodes of bacterial meningitis in adults, the overall case fatality rate was 25 percent.[6] In this article we highlight epidemiologic trends, review principles of antibiotic pharmacokinetics, and provide practical guidelines for deciding controversial questions about the treatment of patients with bacterial meningitis.[7]

## EPIDEMIOLOGIC TRENDS OF THERAPEUTIC IMPORTANCE

In 1990, the Centers for Disease Control (CDC) published a multistate surveillance study of bacterial meningitis based on data collected in 1986.[8] *Haemophilus influenzae* was the pathogen most commonly identified. The majority of cases were due to three bacteria: *H. influenzae* (45 percent), *Streptococcus pneumoniae* (18 percent), and *Neisseria meningitidis* (14 percent). The incidence rates of infection with specific pathogens were most influenced by age. Among neonates (less than 1 month of age), *S. agalactiae* (group B streptococcus) was the predominant agent, whereas *H. influenzae* was most common in children 1 month to 4 years of age, *N. meningitidis* predominated in older children and young adults (5 to 29 years old), and *S. pneumoniae* was most common in older adults. Case fatality rates varied according to both type of bacteria and age group. For example, the overall case fatality rate of infection was higher for *S. pneumoniae* (19 percent) than for either *N. meningitidis* (13 percent) or *H. influenzae* (3 percent), but that for *S. pneumoniae* meningitis was much lower in children less than 5 years old (3 percent) than in adults over the age of 60 (31 percent).

Recently, the frequency of meningitis due to *H. influenzae* in children has declined dramatically because of widespread vaccination against *H. influenzae* type b. Specifically, from 1985 to 1991 there was an 82 percent reduction in the incidence of *H. influenzae* meningitis in children under five years old.[9] This reduction means that *S. pneumoniae* and *N. meningitidis* have become the predominant causes of meningitis in children one month old or older.[10] A second epidemiologic trend is the worldwide increase in infection with antibiotic-resistant strains of *S. pneumoniae*. Although penicillin-resistant strains of *S. pneumoniae* were first identified in the late 1960s[11] and meningitis due to such strains was first diagnosed in 1974,[12] the incidence of infection with *S. pneumoniae* resistant to penicillin and other $\beta$-lactam antibiotics has increased worldwide in the past decade. The resistance of *S. pneumoniae* to these antibiotics is mediated not by the production of $\beta$-lactamase but by alterations in the penicillin-binding proteins involved in the synthesis of bacterial cell walls.[13]

Although the incidence of infection with penicillin-resistant *S. pneumoniae* was first noted to rise in Spain,[14] Hungary,[15] and South Africa,[16] antibiotic-resistant strains of *S. pneumoniae* have become prevalent in Asia[17] and have emerged as a major problem in the United States.[18] For example, in metropolitan Atlanta from January through October 1994, isolates from 25 percent of patients with invasive pneumococcal infection were resistant to penicillin (7 percent were highly resistant — that is, not inhibited by concentrations of antibiotic of less than 2 $\mu$g per milliliter) and those from 9 percent were resistant to cefotaxime (4 percent were highly resistant).[19] Penicillin and cefotaxime are two of the drugs most commonly used to treat bacterial meningitis. These findings underscore the need for continued nationwide surveillance of antibiotic-resistant *S. pneu-*

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*moniae,* and they necessitate the modification of the treatment guidelines for suspected pneumococcal meningitis in children and adults.

## PRINCIPLES OF ANTIMICROBIAL THERAPY FOR BACTERIAL MENINGITIS

### The Need for Bactericidal Activity in Cerebrospinal Fluid

Bacterial meningitis is an infection in an area of impaired host resistance. Specific antibody and complement are frequently absent from the cerebrospinal fluid in patients with the disease,[20] resulting in inefficient phagocytosis and therefore in rapid bacterial multiplication (to concentrations of 10 million or more colony-forming units per milliliter of cerebrospinal fluid).[21] Optimal antibiotic treatment requires that the drug have a bactericidal effect in the cerebrospinal fluid. Patients with pneumococcal and gram-negative bacillary meningitis who are treated with bacteriostatic antibiotics have poor clinical outcomes.[22] Similarly, in animals with experimental meningitis, a bactericidal effect is necessary for sterilization of the cerebrospinal fluid and survival.[23]

### Factors Influencing Bactericidal Activity in Cerebrospinal Fluid

The three major factors affecting the bactericidal activity of an antibiotic in cerebrospinal fluid are its relative degree of penetration into the fluid, its concentration there, and its intrinsic activity in infected fluid. The penetration of an antibiotic into cerebrospinal fluid is primarily influenced by the characteristics of the antibiotic and the integrity of the blood–brain barrier (Table 1).[24,25] When the barrier is intact, penetration is limited because vesicular transport across cells is minimal and the junctions between the endothelial cells of the cerebral microvasculature are tight.[26] However, during meningitis there is an increase in vesicular transport across cells in meningeal arterioles and complete separation of the tight junctions between endothelial cells in meningeal venules.[27,28] These changes result in increased permeability of the blood–brain barrier, so that for many antibiotics (such as $\beta$-lactams) the degree of cerebrospinal fluid penetration increases to 5 to 10 percent of the serum concentration.[25] For other antibiotics more highly soluble in lipids (such as chloramphenicol, rifampin, and trimethoprim), penetration into cerebrospinal fluid is high (reaching 30 to 40 percent of the serum concentration) even when the meninges are not inflamed.

The concentration of antibiotic in cerebrospinal fluid needed for maximal bactericidal activity is not known. In experimental meningitis, maximal bactericidal activity occurs when the concentration of antibiotic is 10 to 30 times the minimal bactericidal concentration against the organism in vitro.[29,30] One explanation for this difference is that infected cerebrospinal fluid decreases the activity of the antibiotic. For example, in infected cerebrospinal fluid the low pH (ranging from 6.7 to 7.1) reduces the activity of aminoglycosides, and the increased concentration of protein reduces the concentration of active free drug in the case of the highly protein-bound $\beta$-lactams (especially the cephalosporins).[24,30] In addition, in experimental meningitis the growth of *S. pneumoniae* in cerebrospinal fluid is substantially slower at higher temperatures. Since the activity of $\beta$-lactam (i.e., penicillin G) on bacterial cell-wall synthesis depends on bacterial cell division, fever may impair its bactericidal effect in vivo (Table 1).[31]

**TABLE 1.** FACTORS INFLUENCING THE BACTERICIDAL ACTIVITY OF ANTIBIOTICS IN CEREBROSPINAL FLUID.

| |
|---|
| **Factors that increase the penetration and concentration of the antibiotic** |
| Increased permeability of the blood–brain barrier |
| Characteristics of the antibiotic |
| Small molecular size |
| Low degree of binding to protein |
| Low degree of ionization at physiologic pH |
| High solubility in lipids |
| **Factors that reduce the activity of the antibiotic** |
| Low pH of fluid |
| High concentration of protein in fluid |
| High temperature of fluid |

### Potential Hazards of Bactericidal Activity in Cerebrospinal Fluid

Because bactericidal therapy often results in bacteriolysis of the pathogen, treatment can promote the release of biologically active cell-wall products in the cerebrospinal fluid (that is, the lipopolysaccharide of gram-negative bacteria and the teichoic acid and peptidoglycan of streptococci). This release of cell-wall fragments can increase the production of cytokines (interleukin-1, interleukin-6, and tumor necrosis factor $\alpha$) in cerebrospinal fluid, exacerbating inflammation and further damaging the blood–brain barrier.[32-34] However, in recent studies of experimental *Escherichia coli* meningitis, cerebrospinal fluid bacteriolysis occurred initially after antibiotic therapy, but the amount of bacterial endotoxin ultimately released was much less than that released by bacteria not exposed to antibiotics.[35] Therefore, achieving a rapid bactericidal effect in cerebrospinal fluid remains a primary goal of therapy.

## ISSUES OF EMPIRICAL MANAGEMENT

### Timing of the Initial Dose of Antibiotic

Given the potential for neurologic morbidity and mortality, it is important to institute antibiotic therapy promptly, and the accusation of failure to treat bacterial meningitis promptly is a common reason

for malpractice litigation.[36] The intuitive assumption is that a delay in therapy of even a few hours affects the prognosis adversely, but the clinical data are inconclusive. Some conclusions have been inferred indirectly from observational studies comparing morbidity and mortality in patients with bacterial meningitis according to the duration of symptoms before the patient presents to the hospital. More than 20 such studies have been published; in almost half (including all 5 prospective observational cohort studies), there was no correlation between the duration of symptoms and the clinical outcome.[37] Conversely, in a randomized trial comparing cefuroxime with ceftriaxone in the treatment of children with bacterial meningitis, moderate-to-profound hearing loss was more frequent (17 percent) in the cefuroxime-treated group, in which sterilization of cerebrospinal fluid was delayed, than in the ceftriaxone-treated group (4 percent).[38] There are two difficulties with the interpretation of these studies. First, the remembered duration of symptoms may not accurately reflect the actual duration of meningitis. Second, the clinical outcome is affected by many variables (such as age, underlying coexisting illness, the virulence of the pathogen, and the severity of illness), and appropriate multivariable analyses to assess the independent effects of delayed therapy and sterilization of cerebrospinal fluid are lacking. Pending the appearance of data to the contrary, prompt therapy should be the standard of care.

One of the most important factors contributing to delayed diagnosis and therapy is the decision to perform cranial computed tomographic imaging before lumbar puncture.[39] This practice stems from reports in the 1950s and 1960s of neurologic deterioration after lumbar puncture in patients with increased intracranial pressure or intracranial mass lesions. Proponents of the view that imaging should be done first argue that intracranial mass lesions may not be clinically evident, empirical antibiotic therapy can be instituted before imaging, and the delay in lumbar puncture does not affect diagnostic accuracy or outcome. Opponents argue that routine imaging before lumbar puncture wastes time and resources and is done instead of taking an accurate history and performing a physical examination. We believe that when acute meningitis is suspected, only patients with coma, papilledema, or focal neurologic findings require cranial imaging before lumbar puncture. If imaging is indicated, we suggest obtaining blood cultures, instituting empirical antibiotic therapy, and performing lumbar puncture immediately after the imaging if there is no intracranial mass lesion. Instituting antibiotic therapy one to two hours before lumbar puncture will not decrease the diagnostic sensitivity if the culture of cerebrospinal fluid is done in conjunction with testing of cerebrospinal fluid for bacterial antigens and with blood cultures.[40]

#### Empirical Selection of Antibiotic

When lumbar puncture is delayed or a Gram's stain of cerebrospinal fluid is nondiagnostic, empirical therapy is essential and should be directed to the most likely pathogens on the basis of the patient's age and underlying health status (Table 2). In most patients, we recommend therapy with a broad-spectrum cephalosporin (cefotaxime or ceftriaxone), supplemented with ampicillin in young infants (less than 3 months old) and older adults (more than 50 years old), in both of whom *S. agalactiae* and *Listeria monocytogenes* are more prevalent. These recommendations require modification under special circumstances. For example, in immunocompromised patients (such as those with lymphoreticular tumors and those receiving cytotoxic chemotherapy or high-dose glucocorticoid therapy), treatment should include ampicillin (for possible listeria) and a broad-spectrum cephalosporin (such as ceftazidime) that has more inclusive activity against gram-negative organisms. In patients with recent head trauma or neurosurgery and those with cerebrospinal fluid shunts, broad-spectrum antibiotics effective against both gram-positive and gram-negative organisms should be given, such as a combination of vancomycin and ceftazidime. In patients with identifiable bacteria on Gram's staining of cerebrospinal fluid, antibiotic therapy should be directed toward the presumptive pathogen. In all patients, therapy should be modified when the results of cerebrospinal fluid culture and antibiotic-susceptibility testing become available.

#### Empirical Glucocorticoid Therapy

On the basis of evidence that inflammatory cytokines (such as interleukin-1, interleukin-6, and tumor necrosis factor $\alpha$) have a role in the pathophysiology of bacterial meningitis (cerebrospinal fluid inflammation and brain edema), adjunctive glucocorticoid therapy was tested and found to ameliorate meningitis in laboratory animals.[41,42] In four prospective, placebo-controlled, randomized trials in children more than two months old, adjunctive dexamethasone therapy substantially reduced audiologic and neurologic sequelae.[43] Nonetheless, two major controversies remain. First, the majority of children enrolled in these trials were infected with *H. influenzae,* and in a more recent trial adjunctive glucocorticoid therapy reduced bilateral hearing loss only in children with *H. influenzae* meningitis.[44] The benefits of glucocorticoid therapy may not extend to children infected with other pathogens, especially *S. pneumoniae.* In a recent trial involving 56 children with *S. pneumoniae* meningitis, there were substantially fewer audiologic and neurologic sequelae in the glucocorticoid-treated children one year later, but the difference was not statistically significant.[45] Second, the benefit of adjunctive glucocorticoid therapy in adults is even less clear; in only

**TABLE 2.** ANTIBIOTICS RECOMMENDED FOR EMPIRICAL THERAPY IN PATIENTS WITH SUSPECTED BACTERIAL MENINGITIS WHO HAVE A NONDIAGNOSTIC GRAM'S STAIN OF CEREBROSPINAL FLUID.

| GROUP OF PATIENTS | LIKELY PATHOGEN | CHOICE OF ANTIBIOTIC |
|---|---|---|
| Immunocompetent | | |
| Age, <3 mo* | *S. agalactiae, E. coli,* or *L. monocytogenes* | Ampicillin† plus broad-spectrum cephalosporin‡ |
| Age, 3 mo to <18 yr | *N. meningitidis, S. pneumoniae,* or *H. influenzae* | Broad-spectrum cephalosporin‡ |
| Age, 18 to 50 yr | *S. pneumoniae* or *N. meningitidis* | Broad-spectrum cephalosporin§ |
| Age, >50 yr | *S. pneumoniae, L. monocytogenes,* or gram-negative bacilli | Ampicillin¶ plus broad-spectrum cephalosporin§ |
| With impaired cellular immunity | *L. monocytogenes* or gram-negative bacilli | Ampicillin plus ceftazidime |
| With head trauma, neurosurgery, or cerebrospinal fluid shunt | Staphylococci, gram-negative bacilli, or *S. pneumoniae* | Vancomycin plus ceftazidime |

*Specific recommendations depend on the age as well as the condition of the infant. In preterm, low-birth-weight infants less than one month old, vancomycin (15 mg per kilogram of body weight intravenously every six hours) plus ceftazidime (50 to 100 mg per kilogram intravenously every eight hours) is recommended because of the higher risk of nosocomial infection with staphylococci or gram-negative bacilli.

†The preferred dose is 100 mg per kilogram intravenously every eight hours.

‡The preferred dose of cefotaxime is 50 mg per kilogram intravenously every 6 hours; that of ceftriaxone is 50 to 100 mg per kilogram intravenously every 12 hours.

§The preferred dose of cefotaxime is 2 g intravenously every 6 hours; that of ceftriaxone is 2 g intravenously every 12 hours.

¶ The preferred dose is 2 g intravenously every four hours; if penicillin G is given, the preferred dose is 4 million units intravenously every four hours.

one prospective, randomized trial (which was not placebo-controlled or double-blinded) was such therapy beneficial, and then only in the subgroup of patients infected with *S. pneumoniae*.[46]

Although uncertainties remain, we recommend adjunctive dexamethasone therapy in children more than two months of age who have bacterial meningitis, particularly those thought to be infected with *H. influenzae* — that is, children not vaccinated against *H. influenzae* and those with gram-negative coccobacilli on a Gram's stain of cerebrospinal fluid. Dexamethasone therapy should be started intravenously at the same time as, or slightly before, the first dose of antibiotic, at a dose of 0.15 mg per kilogram of body weight every six hours for four days.[47,48] Two days of adjunctive dexamethasone therapy proved beneficial in one trial,[49] and treatment for two days and treatment for four days had similar results in another trial,[50] but neither trial had sufficient statistical power to permit recommending the shorter regimen. In adults with bacterial meningitis, the benefits of adjunctive glucocorticoid therapy are less convincing, and their use should be more limited. We believe that the adults most likely to benefit are those with a high concentration of bacteria in cerebrospinal fluid (that is, those with a positive Gram's stain of cerebrospinal fluid) and evidence of increased intracranial pressure; in such patients we recommend the same regimen (0.15 mg of dexamethasone per kilogram given intravenously every six hours for four days).

## PATHOGEN-SPECIFIC THERAPY

### *S. pneumoniae*

In treating meningitis caused by penicillin-susceptible strains of *S. pneumoniae,* penicillin G and ampicillin are equally effective and are the drugs of choice. However, for patients with suspected *S. pneumoniae* meningitis (for which the susceptibilities are unknown) and patients known to have antibiotic-resistant *S. pneumoniae,* the choices are problematic. First, the cerebrospinal fluid concentrations of penicillin achieved with standard high-dose therapy (4 million units every four hours in adults) may not exceed the minimal inhibitory concentration (MIC) or the minimal bactericidal concentration for strains with even intermediate levels of resistance (MIC of penicillin, 0.1 to 1.0 $\mu$g per milliliter).[51,52] Second, broad-spectrum cephalosporins (cefotaxime or ceftriaxone) can be effective against penicillin-resistant strains, but clinical failures have increasingly been reported.[53-56] Almost all the failures have occurred in children who have strains of *S. pneumoniae* for which the MIC of cefotaxime or ceftriaxone is 2 $\mu$g per milliliter or higher, although some reports suggest that treatment may fail when the MICs of the two drugs are $\geq$1.0 $\mu$g per milliliter.[51,55] The current guidelines issued by the National Committee for Clinical Laboratory Standards state that cerebrospinal fluid isolates of *S. pneumoniae* for which the MIC of cefotaxime or ceftriaxone is more than 0.5 $\mu$g per milliliter should be considered to have intermediate resistance

**TABLE 3.** RECOMMENDATIONS FOR ANTIBIOTIC THERAPY IN PATIENTS WITH BACTERIAL MENINGITIS WHO HAVE A POSITIVE GRAM'S STAIN OR CULTURE OF CEREBROSPINAL FLUID.

| TYPE OF BACTERIA | CHOICE OF ANTIBIOTIC |
|---|---|
| **On Gram's staining** | |
| Cocci | |
| Gram-positive | Vancomycin plus broad-spectrum cephalosporin* |
| Gram-negative | Penicillin G† |
| Bacilli | |
| Gram-positive | Ampicillin (or penicillin G) plus aminoglycoside‡ |
| Gram-negative | Broad-spectrum cephalosporin§ plus aminoglycoside |
| **On culture** | |
| *S. pneumoniae* | Vancomycin plus broad-spectrum cephalosporin* |
| *H. influenzae* | Ceftriaxone |
| *N. meningitidis* | Penicillin G |
| *L. monocytogenes* | Ampicillin plus gentamicin |
| *S. agalactiae* | Penicillin G¶ |
| Enterobacteriaceae | Broad-spectrum cephalosporin plus aminoglycoside‖ |
| *Pseudomonas aeruginosa*, acinetobacter | Ceftazidime plus aminoglycoside** |

*The preferred dose of vancomycin is 15 mg per kilogram intravenously every 6 hours up to 2 g per day; in neonates, the cephalosporin of choice is cefotaxime (50 mg per kilogram intravenously every 6 hours); in others, it is ceftriaxone (50 to 100 mg per kilogram intravenously every 12 hours in children; 2 g intravenously every 12 hours in adults). If adjunctive dexamethasone is given in children, the preferred antibiotic regimen remains cefotaxime (or ceftriaxone) plus vancomycin. If adjunctive dexamethasone is given in adults, the preferred regimen is ceftriaxone plus rifampin (600 mg per day). On susceptibility testing, if the isolate of *S. pneumoniae* is susceptible to penicillin or ceftriaxone, either drug can be used alone. If there is any resistance to penicillin (MIC, $\geq$0.1 $\mu$g per milliliter) but susceptibility to ceftriaxone (MIC, $\leq$0.5 $\mu$g per milliliter), ceftriaxone therapy alone can be continued. If there is resistance to both penicillin (MIC, $\geq$0.1 $\mu$g per milliliter) and ceftriaxone (MIC, $>$0.5 $\mu$g per milliliter), combination therapy (ceftriaxone plus either vancomycin or rifampin) should be continued.

†The preferred dose is 300,000 units per kilogram per day intravenously up to 24 million units per day.

‡The preferred dose of ampicillin is 100 mg per kilogram intravenously every eight hours in children and 2 g every four hours in adults. Gentamicin should be given intravenously in a loading dose of 1.5 mg per kilogram, followed by 1 to 2 mg per kilogram every eight hours.

§Cefotaxime or ceftriaxone should be given; in patients with recent head trauma or neurosurgery and those with cerebrospinal fluid shunts, ceftazidime is recommended (50 to 100 mg per kilogram intravenously every eight hours, for a total dose of up to 2 g every eight hours).

¶In neonates, intravenous gentamicin can be added to penicillin for the first 72 hours until susceptibility testing is completed and a clinical response is observed. Thereafter, many pediatricians use penicillin alone, for a total of 10 to 14 days of therapy.

‖Cefotaxime or ceftriaxone should be given; gentamicin should be instituted intravenously at first, but if the clinical or microbiologic response is poor, intrathecal (or intraventricular) gentamicin can be added in a supplemental daily dose (5 to 10 mg in adults, 1 to 2 mg in infants).

**Ceftazidime should be given at a dose of 50 to 100 mg per kilogram intravenously every eight hours for a total dose of up to 2 g every eight hours.

to cephalosporins,[57] although some regard this recommendation as too conservative.[58]

As a result, alternative antimicrobial drugs have been used in patients with *S. pneumoniae* meningitis that is thought or proved to be resistant to penicillin and cephalosporins. Chloramphenicol, despite long-standing use worldwide, has proved disappointing in several regions, especially South Africa. There, 20 of 25 children with penicillin-resistant *S. pneumoniae* meningitis treated with chloramphenicol had poor outcomes (death, serious neurologic deficit, or a poor clinical response) despite presumptive susceptibility to chloramphenicol on the basis of MIC testing or Kirby–Bauer disk testing. Presumably, this occurred because the minimal bactericidal concentration of chloramphenicol for 14 of the isolates was 4 $\mu$g per milliliter or higher, so that the concentration of chloramphenicol in the cerebrospinal fluid was probably too low for adequate bactericidal activity.[59] Similarly, in Dallas 12 of 16 penicillin-resistant isolates of *S. pneumoniae* from blood or cerebrospinal fluid were associated with minimal bactericidal concentrations of 8 $\mu$g per milliliter or more.[60]

As the MIC of penicillin for *S. pneumoniae* increases, resistance increases to other antibiotics, including cephalosporins, chloramphenicol, trimethoprim–sulfamethoxazole, and erythromycin, but not vancomycin. Therefore, vancomycin may be the most effective treatment for *S. pneumoniae* meningitis in the era of $\beta$-lactam resistance. However, concern about the penetration of vancomycin into cerebrospinal fluid in adults[61] has prompted studies of combination regimens. In experimental *S. pneumoniae* meningitis, the combination of vancomycin and ceftriaxone was synergistic even against strains for which the MIC of ceftriaxone was high (4 $\mu$g per milliliter).[62] However, in animals given dexamethasone concomitantly, the penetration of vancomycin into the cerebrospinal fluid was reduced and sterilization of cerebrospinal fluid was delayed. Only the combination of ceftriaxone and rifampin effectively sterilized the cerebrospinal fluid with respect to the highly resistant strains of *S. pneumoniae* when dexamethasone was given.[63]

Although these regimens have not yet been studied in humans and recommendations for management are evolving, the increasing prevalence of antibiotic-resistant *S. pneumoniae* warrants the combination of ceftriaxone plus vancomycin in patients with a Gram's stain of cerebrospinal fluid that is suggestive of *S. pneumoniae*. This regimen should be continued if the *S. pneumoniae* isolate is resistant to penicillin (MIC, $\geq$0.1 $\mu$g per milliliter) and to ceftriaxone and cefotaxime (MIC, $>$0.5 $\mu$g per milliliter). In adults treated with adjunctive dexamethasone, ceftriaxone plus rifampin is the preferred combination regimen pending studies of susceptibility. In children treated with dexamethasone, the penetration of vancomycin into cerebrospinal fluid is not reduced, so ceftriaxone plus vancomycin can still be given (Table 3).[64] Unless the isolate of *S. pneumoniae* is known to be susceptible to penicillin, we recommend a second lumbar puncture in 24 to 48 hours to document bacteriologic cure, because adjunctive dexamethasone therapy may prevent adequate clinical assessment of the response to therapy.[63]

#### *H. influenzae*

Recommendations for the treatment of *H. influenzae* meningitis are affected by the widespread prevalence of β-lactamase–producing strains. These strains accounted for 32 percent of the 1304 isolates tested in the survey published most recently by the CDC.[8] Although chloramphenicol is often effective, because resistance to it is rare in the United States (appearing in 0.1 percent of 1025 isolates tested),[8] broad-spectrum cephalosporins came into wide use when they were found to be as effective as ampicillin plus chloramphenicol in the treatment of *H. influenzae* meningitis. We currently recommend cefotaxime or ceftriaxone for patients with *H. influenzae* meningitis, because of the evidence of superior sterilization of cerebrospinal fluid and the lower incidence of hearing loss as compared with that following treatment with other cephalosporins (such as cefuroxime).[37]

#### *N. meningitidis*

Penicillin and ampicillin are effective therapy for *N. meningitidis* meningitis, although rare isolates of β-lactamase–producing strains have high-level resistance (MIC, ≥250 μg per milliliter).[65] Clinical isolates with altered penicillin-binding proteins and intermediate resistance to penicillin (MIC, 0.1 to 1.0 μg per milliliter) have been identified in Europe, South Africa, and recently, North Carolina.[66-68] The clinical importance of such resistance is unclear, because most patients with meningitis due to these intermediately resistant strains can be treated effectively with penicillin.[69,70] At present, penicillin is the drug of choice for *N. meningitidis* meningitis. For patients who do not have adequate responses, the bacterial isolates should be formally tested and the therapy changed to ceftriaxone (or cefotaxime) if the isolate is resistant to penicillin (MIC, ≥0.1 μg per milliliter).

### Less Common Pathogens

Ampicillin and penicillin are the treatments of choice for *Listeria monocytogenes* meningitis. However, neither drug is bactericidal against listeria in vitro, and mortality rates as high as 30 percent have been reported.[71] These observations and the enhanced bactericidal activity in experimental listeria meningitis when penicillin (or ampicillin) is combined with gentamicin have prompted many to recommend that combination.[72,73] We recommend ampicillin (or penicillin) plus gentamicin for patients of all ages who have listeria meningitis. Trimethoprim–sulfamethoxazole is bactericidal against listeria in vitro and has been a successful alternative in specific patients.[74] Despite being effective in vitro, chloramphenicol and vancomycin have proved ineffective in patients with systemic listeria infection.[21,75] Meropenem is active in vitro and in laboratory animals with listeria meningitis, but there are inadequate data to recommend its use in humans.[76]

For neonates with meningitis due to *S. agalactiae* (group B streptococcus), the combination of ampicillin and gentamicin is the therapy of choice because of the in vitro synergy of these drugs and reports of penicillin-tolerant strains.[77] In adults with group B streptococcal meningitis, the benefit of the combination therapy over penicillin (or ampicillin) is unproved, and mortality is influenced primarily by the presence of underlying illness.[78]

Before 1980, the outcome of therapy of bacterial meningitis due to gram-negative bacilli was often poor. Chloramphenicol was ineffective because its effect against the gram-negative bacilli in cerebrospinal fluid was only bacteriostatic.[21] Although aminoglycosides were bactericidal in vitro, systemic therapy with gentamicin and amikacin was not highly effective because of inadequate penetration into cerebrospinal fluid. Unfortunately, in neonates with gram-negative meningitis, the intrathecal administration of aminoglycosides was ineffective,[79] and the mortality rate of patients given intraventricular aminoglycoside therapy was higher than that of patients given intravenous aminoglycoside therapy.[80] Subsequent smaller case series suggested that individualized dosing of aminoglycosides through an intraventricular reservoir may lead to better outcomes.[81]

With the advent of the broad-spectrum cephalosporins (moxalactam, cefotaxime, ceftriaxone, and ceftazidime), clinical outcomes improved remarkably (success rates, 85 to 90 percent), because of the high level of activity of these antibiotics against gram-negative pathogens and their high degree of penetration into cerebrospinal fluid.[82] Ceftazidime, in particular, has enhanced activity against *Pseudomonas aeruginosa* and has proved very effective (cure rate, 70 to 75 percent, with or without concomitant systemic aminoglycoside therapy).[83,84] Other promising antimicrobial drugs are aztreonam,[85] trimethoprim–sulfamethoxazole,[86] ciprofloxacin,[87] and meropenem.[88] Clinical experience with imipenem in patients with gram-negative bacillary meningitis is very limited; in one series of 21 children, imipenem was associated with a high rate of seizures (33 percent).[89] Although there are no results of comparative trials, we recommend ceftazidime combined with a parenterally administered aminoglycoside as first-line therapy for patients with gram-negative bacillary meningitis. In patients who do not have a response, we recommend another lumbar puncture with cerebrospinal fluid culture and antibiotic-susceptibility testing. If gram-negative bacilli continue to grow in cultures of cerebrospinal fluid and resistance develops to cephalosporin during therapy, intrathecal (or intraventricular) therapy with aminoglycosides or alternative systemic antibiotics can be given on the basis of the results of susceptibility studies.

**TABLE 4.** GUIDELINES FOR THE DURATION OF ANTIBIOTIC THERAPY.

| PATHOGEN | SUGGESTED DURATION OF THERAPY (DAYS) |
|---|---|
| *H. influenzae* | 7 |
| *N. meningitidis* | 7 |
| *S. pneumoniae* | 10–14 |
| *L. monocytogenes* | 14–21 |
| Group B streptococci | 14–21 |
| Gram-negative bacilli (other than *H. influenzae*) | 21 |

## DURATION OF ANTIBIOTIC THERAPY

The optimal duration of antibiotic treatment in patients with bacterial meningitis is unclear, even for the most common pathogens. Traditionally, a range of 7 to 10 days is recommended for meningococcal meningitis, and longer courses (10 to 21 days) are recommended with other pathogens. In a randomized trial of therapy with ceftriaxone in children with nonmeningococcal meningitis (primarily *H. influenzae* disease), 7 days of therapy was as effective as 10 days of therapy.[90] Clinical trials of patients with meningococcal meningitis showed that seven-day treatment regimens (including penicillin, cefotaxime, ceftriaxone, and chloramphenicol) were very effective, and the vast majority of patients were cured in four to five days.[91,92] Single-dose therapy with an oil-based preparation of chloramphenicol was as effective as a five-day regimen of penicillin in treating meningococcal meningitis in Nigeria.[93] Although single-dose therapy is potentially useful during epidemics in developing nations with limited resources, we do not recommend it as a standard choice. There are no comparative studies of the duration of treatment in patients with meningitis caused by *S. pneumoniae, L. monocytogenes, S. agalactiae,* or enteric gram-negative bacilli. We recommend that the duration of therapy be tailored to the individual patient on the basis of the clinical and microbiologic response, but general pathogen-specific guidelines are outlined in Table 4.

## CONCLUSIONS

The treatment of bacterial meningitis was revolutionized by antimicrobial drugs, but therapeutic problems continue. Management decisions regarding the timing and choice of empirical antibiotic therapy, the need for cranial imaging, and the benefits of adjunctive glucocorticoid therapy remain controversial.[94] The successful implementation of *H. influenzae* vaccination and the worldwide use of antibiotics have led to changes in the epidemiology of meningitis and to the emergence of antibiotic resistance. As microbiologic cure within the cerebrospinal fluid becomes increasingly difficult, the need for vaccines against *N. meningitidis* and *S. pneumoniae* will increase.[95,96] In the next millennium, our success will depend on worldwide scrutiny of the patterns of antibiotic resistance, continued development of new antimicrobial drugs, and more judicious use of the drugs we already have.

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