Practice Guidelines for the Management of Bacterial Meningitis

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OBJECTIVES

The objective of these practice guidelines is to provide clinicians with recommendations for the diagnosis and treatment of bacterial meningitis. Patients with bacterial meningitis are usually treated by primary care and emergency medicine physicians at the time of initial presentation, often in consultation with infectious diseases specialists, neurologists, and neurosurgeons. In contrast to many other infectious diseases, the antimicrobial therapy for bacterial meningitis is not always based on randomized, prospective, double-blind clinical trials, but rather on data initially obtained from experimental animal models of infections. A model commonly utilized is the experimental rabbit model, in which animals are anesthetized and placed in a stereotactic frame. In this procedure, the cisterna magna can be punctured for frequent sampling of CSF and injection of microorganisms. Frequent sampling of CSF permits measurement of leukocytes and chemical parameters and quantitation of the relative penetration of antimicrobial agents into CSF and the effects of meningitis on this entry parameter, the relative bactericidal efficacy (defined as the rate of bacterial eradication) within purulent CSF, and CSF pharmacodynamics. Results obtained from these and other animal models have led to clinical trials of specific agents in patients with bacterial meningitis.

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In this guideline, we will review our recommendations for the diagnosis and management of bacterial meningitis. Recommendation categories are shown in table 1. The guideline represents data published through May 2004.

INITIAL MANAGEMENT APPROACH

The initial treatment approach to the patient with suspected acute bacterial meningitis depends on early recognition of the meningitis syndrome, rapid diagnostic evaluation, and emergent antimicrobial and adjunctive therapy [1]. Our management algorithm for infants and children is shown in figure 1, and that for adults is shown in figure 2. Once there is suspicion of acute bacterial meningitis, blood samples must be obtained for culture and a lumbar puncture performed immediately to determine whether the CSF formula is consistent with the clinical diagnosis. In some patients, the clinician may not emergently perform the diagnostic lumbar puncture (e.g., secondary to the inability to obtain CSF), even when the diagnosis of bacterial meningitis is considered to be likely, or the clinician may be concerned that the clinical presentation is consistent with a CNS mass lesion or another cause of increased intracranial pressure and will thus order a CT scan of the head prior to lumbar puncture. In those patients in whom lumbar puncture is delayed or a CT scan is performed, however, there may be a significant interval between establishing the diagnosis of bacterial meningitis and initiating appropriate therapy. In these patients, blood samples must be obtained for culture and appropriate antimicrobial and adjunctive therapy given prior to lumbar puncture or before the patient is sent for CT. Delay in the initiation of therapy introduces the potential for increased morbidity and mortality, if

Table 1. Infectious Diseases Society of America–United States Public Health Service Grading System for ranking recommendations in clinical guidelines.

Category, grade	Definition
Strength of recommendation	
A	Good evidence to support a recommendation for use; should always be offered
B	Moderate evidence to support a recommendation for use; should generally be offered
C	Poor evidence to support a recommendation; optional
D	Moderate evidence to support a recommendation against use; should generally not be offered
E	Good evidence to support a recommendation against use; should never be offered
Quality of evidence	
I	Evidence from ⩾1 properly randomized, controlled trial
II	Evidence from ⩾1 well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies (preferably from >1 center); from multiple time-series; or from dramatic results from uncontrolled experiments
III	Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees

the patient does indeed have acute bacterial meningitis. The choice of empirical antimicrobial therapy in this situation should be governed by the patient's age and by various conditions that may have predisposed the patient to meningitis. Although the yield of CSF cultures and CSF Gram stain may be diminished by antimicrobial therapy given prior to lumbar puncture, pretreatment blood cultures and CSF findings (i.e., elevated WBC count, diminished glucose concentration, and elevated protein concentration) will likely provide evidence for or against the diagnosis of bacterial meningitis (see What Specific CSF Diagnostic Tests Should Be Used to Determine the Bacterial Etiology of Meningitis?, below). Once CSF analysis is performed, for patients with a positive CSF Gram stain result, targeted antimicrobial therapy can be initiated in adults with bacterial meningitis. In children >1 month of age with bacterial meningitis, however, empirical antimicrobial therapy with vancomycin combined with either cefotaxime or ceftriaxone can be provided pending culture results; this recommendation is based on the concern that interpretation of the CSF Gram stain depends on the expertise of the person reading the slide; some experts would also use this strategy in adults with bacterial meningitis. However, a positive CSF Gram stain result may modify this approach by the addition of another agent (e.g., ampicillin for the presence of gram-positive bacilli) to these 2 standard drugs. If the Gram stain result is negative, empirical antimicrobial therapy is given, with choices of agents based on the patient age and certain predisposing conditions.

The following sections will review in greater detail the evidence for our recommendations in these algorithms. The evidence for these recommendations is framed in the context of specific questions that should be addressed in the patient with suspected or proven bacterial meningitis.

Which Patients with Suspected Bacterial Meningitis Should Undergo CT of the Head prior to Lumbar Puncture?

Complications associated with lumbar puncture are variable, ranging from mild alterations in comfort to life-threatening brain herniation, which may occur in the patient with elevated intracranial pressure [2, 3]. After lumbar puncture, there is normally a mild, transient lowering of lumbar CSF pressure as a result of removal of CSF and continued leakage of CSF from the opening made in the arachnoid membrane that is rapidly communicated throughout the subarachnoid space. In patients with intracranial, space-occupying lesions, there is a relative pressure gradient with downward displacement of the cerebrum and brainstem that can be increased by lumbar puncture, thereby precipitating brain herniation. The incidence of this complication is unknown. In an older study that examined the outcome of lumbar puncture in 129 patients with elevated intracranial pressure, 1.2% of patients with papilledema and 12% of patients without papilledema had unfavorable outcomes within 48 h after the procedure [4]. When these data were combined with a review of 418 patients with papilledema, the authors concluded that the actual risk of serious complications from lumbar puncture in the presence of papilledema was "much less than 1.2%." Two other studies suggested that an incidence of brain herniation was >1%. In addition, another study of 302 infants and children with bacterial meningitis found that brain herniation developed in 6% of patients [5], occurring within 8 h after lumbar puncture in all patients.

In a recent study involving 301 adults with bacterial meningitis [6], the clinical features at baseline that were associated with abnormal findings of a CT scan of the head were an age of ⩾60 years, a history of CNS disease (e.g., mass lesion, stroke, and focal infection), an immunocompromised state (e.g., that due to HIV infection or AIDS, immunosuppressive therapy, or

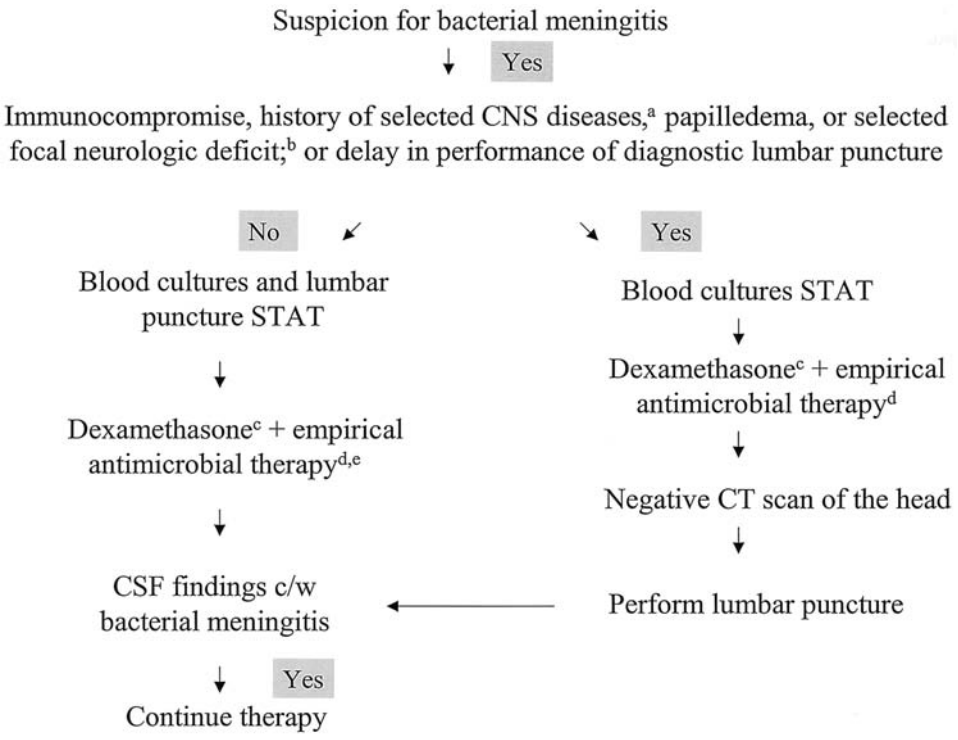

Figure 1. Management algorithm for infants and children with suspected bacterial meningitis. "Stat" indicates that the intervention should be done emergently. C/W, consistent with. [a]Includes those associated with CSF shunts, hydrocephalus, or trauma, those occurring after neurosurgery, or various space-occupying lesions. [b]Palsy of cranial nerve VI or VII is not an indication to delay lumbar puncture. [c]See text for recommendations for use of adjunctive dexamethasone in infants and children with bacterial meningitis. [d]See table 4. [e]Dexamethasone and antimicrobial therapy should be administered immediately after CSF is obtained.

transplantation), a history of seizure ⩽1 week before presentation, and certain specific abnormal neurologic findings (e.g., an abnormal level of consciousness, an inability to answer 2 consecutive questions correctly or to follow 2 consecutive commands, gaze palsy, abnormal visual fields, facial palsy, arm drift, leg drift, abnormal language). None of these features was present at baseline in 96 of the 235 patients who underwent CT; the CT scan findings were normal in 93 of these patients, yielding a negative predictive value of 97%. Of the 3 remaining patients, only 1 had mild mass effect on CT, and all 3 underwent lumbar puncture with no evidence of brain herniation. These findings need to be validated in different populations of patients suspected of having meningitis. On the basis of these findings, specific guidelines are recommended for adult patients who should undergo CT before lumbar puncture (table 2) (B-II). In addition, some authorities would delay lumbar puncture for 30 min in patients with short, convulsive seizures or would not perform the lumbar puncture at all in those with prolonged seizure, because the seizure may be associated with transient increases in intracranial pressure. This is not the practice for children, however, because seizures occur in up to 30% of children with bacterial meningitis before admission.

What Specific CSF Diagnostic Tests Should Be Used to Determine the Bacterial Etiology of Meningitis?

The diagnosis of bacterial meningitis rests on CSF examination performed after lumbar puncture [1, 7]. Opening pressure is generally in the range of 200–500 mm H_2O, although values may be lower in neonates, infants, and children with acute bacterial meningitis. The CSF appearance may be cloudy, depending on the presence of significant concentrations of WBCs, RBCs, bacteria, and/or protein. In untreated bacterial meningitis, the WBC count is elevated, usually in the range of 1000–5000 cells/mm^3, although this range can be quite broad (<100 to >10,000 cells/mm^3). Bacterial meningitis usually leads to a neutrophil predominance in CSF, typically between 80% and 95%; ~10% of patients with acute bacterial meningitis present with a lymphocyte predominance (defined as >50% lymphocytes or monocytes) in CSF. The CSF glucose concentration is <40 mg/dL in approximately 50%–60% of patients; a ratio of CSF to serum glucose of ⩽0.4 was 80% sensitive and 98% specific for the diagnosis of bacterial meningitis in children >2 months of age. Because the ratio of CSF to serum glucose is higher in term neonates, a ratio of ⩽0.6 is considered to be abnormal in this patient group. The CSF protein concentration

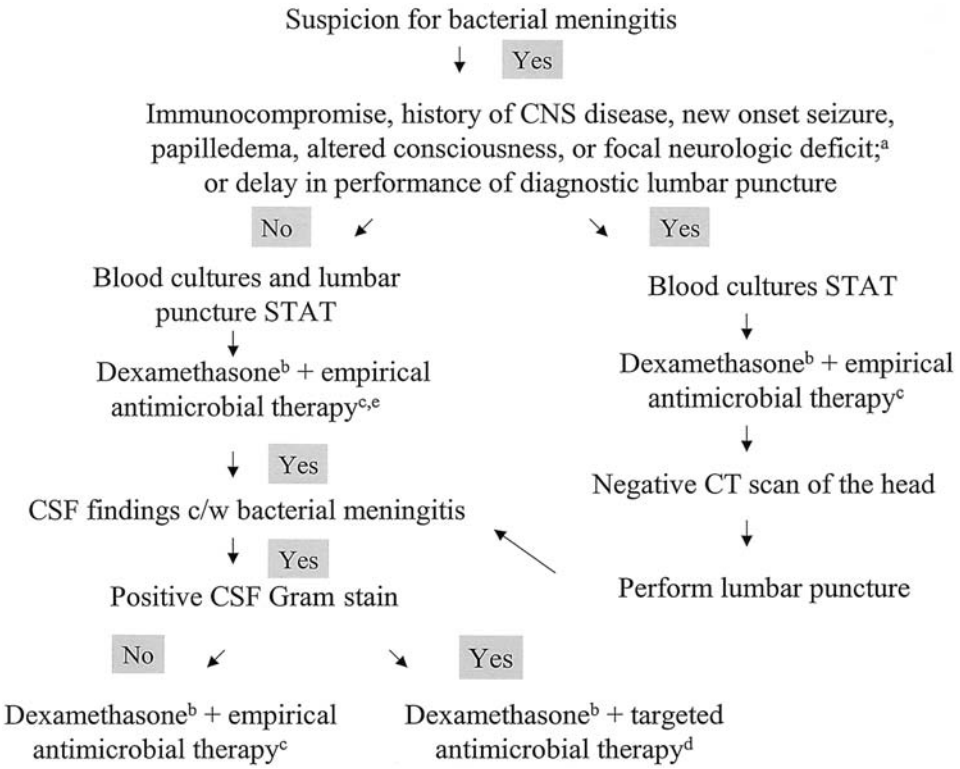

Figure 2. Management algorithm for adults with suspected bacterial meningitis. "Stat" indicates that the intervention should be done emergently. [a]See table 2. [b]See text for specific recommendations for use of adjunctive dexamethasone in adults with bacterial meningitis. [c]See table 4. [d]See table 3. [e]Dexamethasone and antimicrobial therapy should be administered immediately after CSF is obtained.

is elevated in virtually all patients with bacterial meningitis. The results of CSF cultures are positive in 70%–85% of patients who have not received prior antimicrobial therapy, but cultures may take up to 48 h for organism identification. Therefore, several rapid diagnostic tests should be considered to determine the bacterial etiology of meningitis.

Gram stain. Gram stain examination of CSF permits a rapid, accurate identification of the causative bacterium in 60%–90% of patients with community-acquired bacterial meningitis, and it has a specificity of ⩾97% [1]. The likelihood of visualizing the bacterium on Gram stain, however, correlates with the CSF concentration of bacteria—concentrations of $\leqslant 10^3$ colony-forming units (CFU)/mL are associated with a positive Gram stain result 25% of the time; 10^3 to 10^5 CFU/mL yields a positive Gram stain result in 60% of patients, and CSF concentrations of $>10^5$ CFU/mL lead to positive microscopy results in 97% of cases [8]. The probability of visualizing bacteria on a Gram stain can be increased up to 100-fold by using cytospin techniques [9]. The likelihood of having a positive Gram stain result also depends on the specific bacterial pathogen causing meningitis [3, 10]: 90% of cases caused by *Streptococcus pneumoniae,* 86% of cases caused by *Haemophilus influenzae,* 75% of cases caused by *Neisseria meningitidis,* 50% of cases caused by gram-negative bacilli, and approximately one-third of cases of meningitis caused by *Listeria monocytogenes* have positive Gram stain results [11]. Although false-positive CSF Gram stain results may result from observer misinterpretation, reagent contamination, or use of an occluded needle for lumbar puncture (in which an excised skin fragment is contaminated with bacteria), the test is rapid, inexpensive, and highly specific for the diagnosis of bacterial meningitis [3, 12]. However, the yield of CSF Gram stain may be ~20% lower for patients who have received prior antimicrobial therapy. We recommend that all patients being evaluated for suspected meningitis undergo a Gram stain examination of CSF (A-III).

Latex agglutination. Several rapid diagnostic tests have been developed to aid in the etiologic diagnosis of bacterial meningitis. These tests utilize serum containing bacterial antibodies or commercially available antisera directed against the capsular polysaccharides of meningeal pathogens. Available tests include counterimmunoelectrophoresis, coagglutination, and latex agglutination. Latex agglutination is simple to perform, does not require special equipment, and is rapid (results are available in ⩽15 min). Depending on the meningeal pathogen, latex agglutination has shown good sensitivity in detecting the antigens of common meningeal pathogens [10]: 78%–100% for *H. influenzae* type b, 67%–100% for *S. pneumoniae,* 69%–100% for *Streptococcus agalactiae,* and 50%–93% for *N.*

Table 2. Recommended criteria for adult patients with suspected bacterial meningitis who should undergo CT prior to lumbar puncture (B-II).

Criterion	Comment
Immunocompromised state	HIV infection or AIDS, receiving immunosuppressive therapy, or after transplantation
History of CNS disease	Mass lesion, stroke, or focal infection
New onset seizure	Within 1 week of presentation; some authorities would not perform a lumbar puncture on patients with prolonged seizures or would delay lumbar puncture for 30 min in patients with short, convulsive seizures
Papilledema	Presence of venous pulsations suggests absence of increased intracranial pressure
Abnormal level of consciousness	…
Focal neurologic deficit	Including dilated nonreactive pupil, abnormalities of ocular motility, abnormal visual fields, gaze palsy, arm or leg drift

meningitidis. However, a negative bacterial antigen test result does not rule out infection caused by a specific meningeal pathogen.

Nevertheless, the routine use of latex agglutination for the etiologic diagnosis of bacterial meningitis has recently been questioned. In one study of 901 CSF bacterial antigen tests performed over a 37-month period [13], no modification of therapy occurred in 22 of 26 patients with positive test results. False-positive results, although uncommon, may occasionally result in unnecessary treatment and prolonged hospitalization. One study of 344 CSF specimens submitted for bacterial antigen assays found that 10 specimens represented true infection (by culture criteria), for a sensitivity of 70% and specificity of 99.4% [14]; a positive CSF antigen test result did not affect clinical therapy or hospital course, and there were 3 false-negative and 2 false-positive test results. Furthermore, in patients with culture-negative meningitis, CSF latex agglutination had a sensitivity of only 7% in one study [15], although the denominator included all patients with abnormal CSF findings (i.e., CSF glucose concentration of <34 mg/dL, ratio of CSF to blood glucose of <0.23, CSF protein concentration of >220 mg/dL, leukocyte count of >2000 leukocytes/mm^3, or total neutrophil count of >1180 neutrophils/mm^3). Given that bacterial antigen testing does not appear to modify the decision to administer antimicrobial therapy and that false-positive results have been reported, the Practice Guideline Committee does not recommend routine use of this modality for the rapid determination of the bacterial etiology of meningitis (D-II), although some would recommend it for patients with a negative CSF Gram stain result (C-II). Latex agglutination may be most useful for the patient who has been pretreated with antimicrobial therapy and whose Gram stain and CSF culture results are negative (B-III).

Limulus lysate assay. Lysate prepared from the amebocyte of the horseshoe crab, *Limulus polyphemus,* has been suggested as a useful test for patients with suspected gram-negative meningitis, because a positive test result suggests the presence of endotoxin in the sample [10]; a correctly performed assay can detect ~10^3 gram-negative bacteria/mL of CSF and as little as 0.1 ng/mL of endotoxin. One study demonstrated a sensitivity of 93% and a specificity of 99.4%, compared with cultures for gram-negative bacteria [10], although another study demonstrated a sensitivity of only 71% in neonates with gram-negative meningitis [16], suggesting that the test was not sensitive enough to serve as a screening procedure for the diagnosis of gram-negative meningitis in neonates. Furthermore, this test does not distinguish between specific gram-negative organisms, a negative test result does not rule out the diagnosis of gram-negative meningitis, test results rarely influence patient treatment, and the test is not routinely available in clinical laboratories. Therefore, we do not recommend routine use of the *Limulus* lysate assay for patients with meningitis (D-II).

PCR. PCR has been utilized to amplify DNA from patients with meningitis caused by the common meningeal pathogens *(N. meningitidis, S. pneumoniae , H. influenzae* type b, *S. agalactiae,* and *L. monocytogenes)* [1, 10]. In one study of CSF samples obtained from 54 patients with meningococcal disease or from patients who underwent CSF analysis and who did not have meningococcal meningitis [17], the sensitivity and specificity of PCR were both 91%. In another study using a semi-nested PCR strategy for simultaneous detection of *N. meningitidis, H. influenzae,* and streptococci in 304 clinical CSF samples (including 125 samples obtained from patients with bacterial meningitis), the diagnostic sensitivity was 94% and the specificity was 96% [18], although some false-positive results were obtained. The clinical utility of PCR for the diagnosis of bacterial meningitis was also assessed with use of a broad range of bacterial primers. The test characteristics for broad-based PCR demonstrated a sensitivity of 100%, a specificity of 98.2%, a positive predictive value of 98.2%, and a negative predictive value of 100% [19]. Therefore, broad-based PCR may be useful for excluding the diagnosis of bacterial meningitis, with the potential for influencing decisions to initiate or discontinue antimicrobial therapy. Although PCR techniques appear to be promising for the etiologic diagnosis of bacterial meningitis, further refinements of the available techniques may

lead to their use in patients with bacterial meningitis for whom the CSF Gram stain result is negative (B-II).

What Laboratory Testing May Be Helpful in Distinguishing Bacterial from Viral Meningitis?

In patients with CSF findings consistent with a diagnosis of bacterial meningitis, but in whom the CSF Gram stain and culture results are negative, there is no test that is definitive for or against the diagnosis of bacterial meningitis. A combination of test results, however, may permit an accurate prediction of the likelihood of bacterial versus viral meningitis. In one analysis of 422 patients with acute bacterial or viral meningitis, a CSF glucose concentration of <34 mg/dL, a ratio of CSF to blood glucose of <0.23, a CSF protein concentration of >220 mg/dL, a CSF leukocyte count of >2000 leukocytes/mm^3, or a CSF neutrophil count of >1180 neutrophils/mm^3 were individual predictors of bacterial, rather than viral, meningitis, with ⩾99% certainty [20]. This model was validated in one retrospective review of adult patients with bacterial or viral meningitis [21], although proof of the clinical utility of this model will require a prospective application. This model, however, should not be used to make clinical decisions regarding the initiation of antimicrobial therapy in individual patients with meningitis. Therefore, other diagnostic tests have been examined.

Determination of lactate concentration. Elevated CSF lactate concentrations may be useful in differentiating bacterial from nonbacterial meningitis in patients who have not received prior antimicrobial therapy. In one study of 78 patients with acute meningitis in which CSF lactate concentrations of >4.2 mmol/L were considered to be a positive discriminative factor for bacterial meningitis [22], the sensitivity of the test was 96%, the specificity was 100%, the positive predictive value was 100%, and the negative predictive value was 97%. However, despite the high sensitivity and positive predictive value of CSF lactate concentrations in the diagnosis of bacterial meningitis, the results are generally nonspecific and provide little additional diagnostic information. Furthermore, other factors (e.g., cerebral hypoxia/ischemia, anaerobic glycolysis, vascular compromise, and metabolism of CSF leukocytes) also may elevate CSF lactate concentrations. Therefore, measurement of CSF lactate concentrations is not recommended for patients with suspected community-acquired bacterial meningitis (D-III). However, measurement of CSF lactate concentrations was found to be superior to use of the ratio of CSF to blood glucose for the diagnosis of bacterial meningitis in postoperative neurosurgical patients, in which a CSF concentration of 4.0 mmol/L was used as a cutoff value for the diagnosis [23]. The sensitivity was 88%, the specificity was 98%, the positive predictive value was 96%, and the negative predictive value was 94%. CSF lactate concentrations may be valuable in this subgroup of patients, in whom the usual CSF findings—elevated WBC counts (total and differential), positive Gram stain results, diminished glucose concentrations, and elevated protein concentrations—are neither sensitive nor specific to reliably distinguish bacterial from a nonbacterial meningeal syndrome. Therefore, in the postoperative neurosurgical patient, initiation of empirical antimicrobial therapy should be considered if CSF lactate concentrations are ⩾4.0 mmol/L, pending results of additional studies (B-II).

Determination of C-reactive protein (CRP) concentration. Several acute-phase reactants have been examined for their usefulness in the diagnosis of acute bacterial meningitis. However, none is diagnostic for bacterial meningitis, and they should not be used to determine whether an individual patient should receive antimicrobial therapy. CRP, which is made in the liver and secreted within 6 h after an acute inflammatory reaction, has been measured in patients with meningitis [24]. A published meta-analysis has examined the utility of measurement of serum and CSF concentrations of CRP to distinguish bacterial from viral meningitis [25]. In this compilation of studies, measurement of serum concentrations of CRP had a sensitivity that ranged from 69% to 99% and a specificity that ranged from 28% to 99%; in spite of these wide ranges, the OR for serum CRP concentration in the diagnosis of bacterial meningitis was 150 (95% CI, 44–509). In another study published after the meta-analysis that included 385 consecutive patients with CSF culture–proven bacterial meningitis and 182 children with proven or presumed bacterial meningitis [26], serum CRP concentrations were capable of distinguishing Gram stain–negative bacterial meningitis, with a sensitivity of 96%, a specificity of 93%, and a negative predictive value of 99%. CSF concentrations of CRP have also been evaluated for distinguishing bacterial from viral meningitis [25]; the sensitivity ranged from 18% to 100%, and the specificity ranged from 75% to 100%, with an OR of 241 (95% CI, 59–980). Measurement of serum CRP concentration may be helpful in patients with CSF findings consistent with meningitis, but for whom the Gram stain result is negative and the physician is considering withholding antimicrobial therapy, on the basis of the data showing that a normal CRP has a high negative predictive value in the diagnosis of bacterial meningitis (B-II).

Determination of procalcitonin concentration. Elevated serum concentrations of the polypeptide procalcitonin, which are observed in patients with severe bacterial infection, were shown to be useful in differentiating between bacterial and viral meningitis [24]. In a study of 59 consecutive children hospitalized for meningitis [27], the sensitivity of measurements of the serum procalcitonin concentration (using a cutoff of >5.0 μg/L) for the diagnosis of bacterial meningitis was 94%, and the specificity was 100%. In adults, serum concentrations >0.2 ng/mL had a sensitivity and specificity of up to 100% for the

diagnosis of bacterial meningitis [28], although false-negative results have been reported by others (sensitivity, 69%) [29]. At present, because measurement of serum procalcitonin concentrations is not readily available in clinical laboratories, recommendations on its use cannot be made at this time (C-II).

PCR. In patients who present with acute meningitis, an important diagnostic consideration is whether the patient has enteroviral meningitis. Rapid detection of enteroviruses by PCR has emerged as a valuable technique that may be helpful in establishing the diagnosis of enteroviral meningitis. Enteroviral RT-PCR has been tested in clinical settings by numerous investigators and has been found to be more sensitive than viral culture for the detection of enterovirus, with a sensitivity and specificity of 86%–100% and 92%–100%, respectively [30]. In addition, the time to identification of the enterovirus using RT-PCR is significantly reduced (from hours to a day), compared with cell culture [31], which may lead to shortened patient hospitalization, decreased use of antimicrobial therapy for treatment of presumed bacterial meningitis, and reduced need for ancillary diagnostic tests (B-II).

How Quickly Should Antimicrobial Therapy Be Administered to Patients with Suspected Bacterial Meningitis?

There are no prospective clinical data on the relationship of the timing of antimicrobial administration of antimicrobial agents to clinical outcome in patients with bacterial meningitis [1, 32]. All existing studies examined only the duration of symptoms—not the duration of meningitis—prior to antimicrobial administration. On the basis of clinical findings, it cannot be determined with certainty when the seeding of the CNS by the meningeal pathogen occurred. However, most physicians would intuitively agree that the longer the duration of symptoms in patients with bacterial meningitis, the more likely the possibility of experiencing an adverse outcome, although there are no definitive data to support this belief. This concept is supported by results of studies showing that poor outcome is associated with greater amounts of antigen or a larger number of microorganisms in CSF samples obtained before initiation of antimicrobial therapy [33, 34] and that delayed CSF sterilization after 24 h of antimicrobial therapy is a risk factor for subsequent neurologic sequelae [35, 36]. The assumption that any delay in administration of antimicrobial therapy might be associated with an adverse clinical outcome has been the basis for malpractice claims against physicians who have been accused of failure to promptly diagnose and treat bacterial meningitis [37].

Ethical considerations clearly preclude the design of human studies to assess the outcome for patients in whom antimicrobial therapy is deliberately delayed. To address the question of whether a delay in diagnosis and treatment affects outcome in patients with bacterial meningitis, several large reviews examined the available published literature. In one review of 4707 patients in 22 studies, the duration of symptoms before initiation of antimicrobial therapy was assessed with regard to the subsequent development of sequelae [38]. The studies were heterogeneous with regard to patient demographic data, study numbers, causative microorganisms, and length of follow-up. Furthermore, there was often incomplete reporting of relevant data, and not all studies contained basic study design components. The author of this review suggested that, if the clinical presentation was that of a nonspecific illness (i.e., general nonfocal symptoms), a short delay (<3–5 days) did not appear to alter the risk of sequelae or death. However, in the case of fulminant meningitis, a delay in the initiation of antimicrobial therapy seemed to be unconnected to outcome; and for patients with a history of clinically overt meningitis, an inappropriate delay incrementally increased the risk of permanent injury. In a subsequent literature review of 27 studies (including many of the studies in the previous review) analyzing a total of 5585 patients up to August 1995, only 20% of all studies specifically defined any "symptoms" in their analysis and could not identify whether specific "symptoms" denoted a "premeningitis" phase or heralded the onset of bacterial seeding of the CNS [39]. The author suggested that, because there are no pathognomonic clinical features of bacterial meningitis, opinions based on reviews of an individual patient's clinical course and symptomatic progression were interpretive at best and could not dictate with certainty when seeding of the CNS occurred.

These issues have also been examined in several retrospective studies. In one retrospective review of 305 patients hospitalized in the United Kingdom with a diagnosis of bacterial meningitis [40], 53 patients (17.4%) received an antimicrobial agent prior to admission; there was only 1 death (1.9%) among the 53 patients who received an antimicrobial, compared with 30 deaths (12%) among the 252 who had not. These results led the British Infection Society Working Party to recommend parenteral administration of appropriate antimicrobial therapy without delay to all adult patients in whom the diagnosis of bacterial meningitis is suspected while arranging urgent transfer to the hospital [41]. In another recent retrospective cohort study of 269 adult patients with community-acquired bacterial meningitis in the United States [42], 3 baseline clinical features were associated with adverse outcome: hypotension, altered mental status, and seizures. These 3 factors were used to create a prognostic model that predicted clinical outcome, in which patients were stratified into 3 prognostic stages of low, intermediate, or high risk for adverse outcome based on these clinical features. The results demonstrated that a delay in initiation of antimicrobial therapy after patient arrival in the emergency department was associated with adverse clinical outcome when the patient's condition advanced from a low- or intermediate-risk stage to a high-risk stage of prognostic severity. These data sup-

Table 3. Recommendations for antimicrobial therapy in adult patients with presumptive pathogen identification by positive Gram stain.

Microorganism	Recommended therapy	Alternative therapies
Streptococcus pneumoniae	Vancomycin plus a third-generation cephalosporin[a,b]	Meropenem (C-III), fluoroquinolone[c] (B-II)
Neisseria meningitidis	Third-generation cephalosporin[a]	Penicillin G, ampicillin, chloramphenicol, fluoroquinolone, aztreonam
Listeria monocytogenes	Ampicillin[d] or penicillin G[d]	Trimethoprim-sulfamethoxazole, meropenem (B-III)
Streptococcus agalactiae	Ampicillin[d] or penicillin G[d]	Third-generation cephalosporin[a] (B-III)
Haemophilus influenzae	Third-generation cephalosporin[a] (A-I)	Chloramphenicol, cefepime (A-I), meropenem (A-I), fluoroquinolone
Escherichia coli	Third-generation cephalosporin[a] (A-II)	Cefepime, meropenem, aztreonam, fluoroquinolone, trimethoprim-sulfamethoxazole

NOTE. All recommendations are A-III, unless otherwise indicated. In children, ampicillin is added to the standard therapeutic regimen of cefotaxime or ceftriaxone plus vancomycin when *L. monocytogenes* is considered and to an aminoglycoside if a gram-negative enteric pathogen is of concern.

[a] Ceftriaxone or cefotaxime.
[b] Some experts would add rifampin if dexamethasone is also given (B-III).
[c] Gatifloxacin or moxifloxacin.
[d] Addition of an aminoglycoside should be considered.

port the assumption that treatment of bacterial meningitis before it advances to a high level of clinical severity improves outcome.

What evidence-based recommendations can be made with regard to the timing of antimicrobial administration in patients who present with suspected or proven bacterial meningitis? The key factor would appear to be the need to administer antimicrobial therapy before the patient's clinical condition advances to a high level of clinical severity, at which point the patient is less likely to have a full recovery after treatment with appropriate antimicrobial therapy. However, the outcome of bacterial meningitis is multifactorial and does not always correlate with duration of symptoms, because some patients who receive diagnoses and are treated within a few hours of arrival develop significant sequelae, whereas others who are symptomatic for days have a seemingly normal outcome. Therefore, it is not possible to ascertain when the high level of clinical severity is reached. The logical and intuitive approach is to administer antimicrobial therapy as soon as possible after the diagnosis of bacterial meningitis is suspected or proven. This may include administration prior to hospital admission if the patient initially presents outside the hospital. This concept has been supported by 2 recent retrospective studies [43, 44]. One demonstrated a reduction in mortality with early administration of antimicrobial therapy [43], and the other showed a benefit in terms of neurologic outcome and survival in patients who received antimicrobial therapy before the patient's level of consciousness deteriorated to <10 on the Glasgow Coma Scale [44]. However, on the basis of the available evidence, we think that there are inadequate data to delineate specific guidelines on the interval between the initial physician encounter and the administration of the first dose of antimicrobial therapy (C-III). That being said, bacterial meningitis is a neurologic emergency, and appropriate therapy (see What Specific Antimicrobial Agents Should Be Used in Patients with Suspected or Proven Bacterial Meningitis?, below) should be initiated as soon as possible after the diagnosis is considered to be likely.

What Specific Antimicrobial Agents Should Be Used in Patients with Suspected or Proven Bacterial Meningitis?

Once the diagnosis of bacterial meningitis is established by CSF analysis, antimicrobial therapy should be initiated. Targeted antimicrobial therapy is based on presumptive pathogen identification by CSF Gram stain (table 3), although (as stated above) the combination of vancomycin plus either ceftriaxone or cefotaxime is used for infants and children—and recommended by some experts for adults—with suspected bacterial meningitis. Empirical antimicrobial therapy is initiated either when the lumbar puncture is delayed (e.g., in those patients sent for CT of the head [see Which Patients with Suspected Bacterial Meningitis Should Undergo CT of the Head prior to Lumbar Puncture?, above]) or for patients with purulent meningitis and a negative CSF Gram stain result (table 4). The choice of specific antimicrobial agents for targeted or empirical therapy is based on the current knowledge of antimicrobial susceptibility patterns of these pathogens. For initial therapy, the assumption should be that antimicrobial resistance is likely. Evidence-based recommendations for specific agents and dosages are reviewed in tables 5 and 6, respectively.

What Is the Role of Adjunctive Dexamethasone Therapy in Patients with Bacterial Meningitis?

Consideration should be given to administration of adjunctive dexamethasone in certain patients with suspected or proven

bacterial meningitis. The rationale for use is derived from experimental animal models of infection, which have shown that the subarachnoid space inflammatory response during bacterial meningitis is a major factor contributing to morbidity and mortality [1]. Attenuation of this inflammatory response may be effective in decreasing many of the pathophysiologic consequences of bacterial meningitis, such as cerebral edema, increased intracranial pressure, altered cerebral blood flow, cerebral vasculitis, and neuronal injury, as mediated by proinflammatory cytokine expression [45–47].

On the basis of these experimental observations, numerous clinical trials were undertaken to assess the efficacy of adjunctive dexamethasone in patients with bacterial meningitis. Studies have varied such that: (1) not all were placebo controlled, (2) various antimicrobial agents were used (some of which may not have been adequate for the treatment of bacterial meningitis), (3) dexamethasone was administered at different times in relation to the first antimicrobial dose, and (4) patients had varying levels of illness severity. In making evidence-based recommendations, it is prudent to analyze the data according to patient age.

Neonates. There is only 1 published trial that has evaluated the efficacy of adjunctive dexamethasone in neonates with bacterial meningitis [48]. In this randomized—but not placebo-controlled—trial involving 52 full-term neonates, patients were given dexamethasone 10–15 min before the first antimicrobial dose. Mortality was 22% in the treated group and 28% in the control group ($P = .87$). At follow-up examination up until the age of 2 years, 30% of the dexamethasone-treated patients and 39% of the control group had neurologic sequelae. The study size was small and underpowered. At present, there are insufficient data to make a recommendation on the use of adjunctive dexamethasone in neonates with bacterial meningitis (C-I).

Infants and children. There have been 15 published trials on the use of adjunctive dexamethasone in infants and children with bacterial meningitis [49–63]. Three of the trials were retrospective [54, 60, 62]. The remainder were prospective; all were randomized, and all but 1 [59] were placebo controlled. In a meta-analysis of clinical studies published during 1988–1996 [64], adjunctive dexamethasone (0.15 mg/kg every 6 h for 2–4 days) had confirmed benefit for *H. influenzae* type b meningitis and, if commenced with or before antimicrobial therapy, suggested benefit for pneumococcal meningitis in children. Evidence of clinical benefit was greatest for hearing outcomes. In patients with meningitis caused by *H. influenzae* type b, dexamethasone reduced hearing impairment overall (combined OR, 0.31; 95% CI, 0.14–0.69), whereas in patients with pneumococcal meningitis, dexamethasone only suggested protection for severe hearing loss if given early (combined OR, 0.09; 95% CI, 0.0–0.71). Since publication of the meta-analysis, 2 additional studies of adjunctive dexamethasone have been

Table 4. Recommendations for empirical antimicrobial therapy for purulent meningitis based on patient age and specific predisposing condition (A-III).

Predisposing factor	Common bacterial pathogens	Antimicrobial therapy
Age		
<1 month	*Streptococcus agalactiae, Escherichia coli, Listeria monocytogenes, Klebsiella* species	Ampicillin plus cefotaxime or ampicillin plus an aminoglycoside
1–23 months	*Streptococcus pneumoniae, Neisseria meningitidis, S. agalactiae, Haemophilus influenzae, E. coli*	Vancomycin plus a third-generation cephalosporin[a,b]
2–50 years	*N . meningitidis, S. pneumoniae*	Vancomycin plus a third-generation cephalosporin[a,b]
>50 years	*S. pneumoniae, N. meningitidis, L. monocytogenes,* aerobic gram-negative bacilli	Vancomycin plus ampicillin plus a third-generation cephalosporin[a,b]
Head trauma		
Basilar skull fracture	*S. pneumoniae, H. influenzae,* group A β-hemolytic streptococci	Vancomycin plus a third-generation cephalosporin[a]
Penetrating trauma	*Staphylococcus aureus,* coagulase-negative staphylococci (especially *Staphylococcus epidermidis),* aerobic gram-negative bacilli (including *Pseudomonas aeruginosa)*	Vancomycin plus cefepime, vancomycin plus ceftazidime, or vancomycin plus meropenem
Postneurosurgery	Aerobic gram-negative bacilli (including *P. aeruginosa), S . aureus*, coagulase-negative staphylococci (especially *S. epidermidis)*	Vancomycin plus cefepime, vancomycin plus ceftazidime, or vancomycin plus meropenem
CSF shunt	Coagulase-negative staphylococci (especially *S. epidermidis), S. aureus,* aerobic gram-negative bacilli (including *P. aeruginosa), Propionibacterium acnes*	Vancomycin plus cefepime,[c] vancomycin plus ceftazidime,[c] or vancomycin plus meropenem[c]

[a] Ceftriaxone or cefotaxime.
[b] Some experts would add rifampin if dexamethasone is also given.
[c] In infants and children, vancomycin alone is reasonable unless Gram stains reveal the presence of gram-negative bacilli.

Table 5. Recommendations for specific antimicrobial therapy in bacterial meningitis based on isolated pathogen and susceptibility testing.

Microorganism, susceptibility	Standard therapy	Alternative therapies
Streptococcus pneumoniae		
Penicillin MIC		
<0.1 μg/mL	Penicillin G or ampicillin	Third-generation cephalosporin,[a] chloramphenicol
0.1–1.0 μg/mL[b]	Third-generation cephalosporin[a]	Cefepime (B-II), meropenem (B-II)
⩾2.0 μg/mL	Vancomycin plus a third-generation cephalosporin[a,c]	Fluoroquinolone[d] (B-II)
Cefotaxime or ceftriaxone MIC ⩾1.0 μg/mL	Vancomycin plus a third-generation cephalosporin[a,c]	Fluoroquinolone[d] (B-II)
Neisseria meningitidis		
Penicillin MIC		
<0.1 μg/mL	Penicillin G or ampicillin	Third-generation cephalosporin,[a] chloramphenicol
0.1–1.0 μg/mL	Third-generation cephalosporin[a]	Chloramphenicol, fluoroquinolone, meropenem
Listeria monocytogenes	Ampicillin or penicillin G[e]	Trimethoprim-sulfamethoxazole, meropenem (B-III)
Streptococcus agalactiae	Ampicillin or penicillin G[e]	Third-generation cephalosporin[a] (B-III)
Escherichia coli and other Enterobacteriaceae[g]	Third-generation cephalosporin (A-II)	Aztreonam, fluoroquinolone, meropenem, trimethoprim-sulfamethoxazole, ampicillin
Pseudomonas aeruginosa[g]	Cefepime[e] or ceftazidime[e] (A-II)	Aztreonam,[e] ciprofloxacin,[e] meropenem[e]
Haemophilus influenzae		
β-Lactamase negative	Ampicillin	Third-generation cephalosporin,[a] cefepime, chloramphenicol, fluoroquinolone
β-Lactamase positive	Third-generation cephalosporin (A-I)	Cefepime (A-I), chloramphenicol, fluoroquinolone
Staphylococcus aureus		
Methicillin susceptible	Nafcillin or oxacillin	Vancomycin, meropenem (B-III)
Methicillin resistant	Vancomycin[f]	Trimethoprim-sulfamethoxazole, linezolid (B-III)
Staphylococcus epidermidis	Vancomycin[f]	Linezolid (B-III)
Enterococcus species		
Ampicillin susceptible	Ampicillin plus gentamicin	…
Ampicillin resistant	Vancomycin plus gentamicin	…
Ampicillin and vancomycin resistant	Linezolid (B-III)	…

NOTE. All recommendations are A-III, unless otherwise indicated.

[a] Ceftriaxone or cefotaxime.
[b] Ceftriaxone/cefotaxime-susceptible isolates.
[c] Consider addition of rifampin if the MIC of ceftriaxone is >2 μg/mL.
[d] Gatifloxacin or moxifloxacin.
[e] Addition of an aminoglycoside should be considered.
[f] Consider addition of rifampin.
[g] Choice of a specific antimicrobial agent must be guided by in vitro susceptibility test results.

published [62, 63]. The first was a retrospective study involving children with pneumococcal meningitis and showed that, in the dexamethasone group, there was a higher incidence of moderate or severe hearing loss (46% vs. 23%; $P = .016$) or any neurologic deficits (55% vs. 33%; $P = .02$) [62]. However, children in the dexamethasone group more frequently required intubation and mechanical ventilation and had a lower initial CSF glucose concentration. Furthermore, there were no data on use of specific antimicrobial agents in each group, and the dexamethasone was given later than in other studies (i.e., within 60 min of the first antimicrobial dose). Thus, it is possible that the clinical benefit was not as optimal as was anticipated. In a recently published randomized, placebo-controlled, double-blind trial of adjunctive dexamethasone in children in Malawi [63], the overall number of deaths (31% vs. 31%; $P = .93$) and presence of sequelae at final outcome (28% vs. 28%; $P = .97$) were not significantly different in the children who received adjunctive dexamethasone. However, the Malawian children enrolled in this trial had severe disease associated with malnutrition and HIV infection, and they presented after a delay, which resulted in very high case-fatality rates and significant long-term morbidity [65]. Adjunctive dexamethasone does not reverse the CNS damage that develops as a result of existent cerebral edema, increased intracranial pressure, or neuronal injury that is present at diagnosis. Furthermore, more than one-third of children received antimicrobial therapy before admission, and >30% were given second-line antimicrobial therapy because of inadequate clinical or microbiologic response.

Table 6. Recommended dosages of antimicrobial therapy in patients with bacterial meningitis (A-III).

	Total daily dose (dosing interval in hours)			
	Neonates, age in days			
Antimicrobial agent	0–7[a]	8–28[a]	Infants and children	Adults
Amikacin[b]	15–20 mg/kg (12)	30 mg/kg (8)	20–30 mg/kg (8)	15 mg/kg (8)
Ampicillin	150 mg/kg (8)	200 mg/kg (6–8)	300 mg/kg (6)	12 g (4)
Aztreonam	…	…	…	6–8 g (6–8)
Cefepime	…	…	150 mg/kg (8)	6 g (8)
Cefotaxime	100–150 mg/kg (8–12)	150–200 mg/kg (6–8)	225–300 mg/kg (6–8)	8–12 g (4–6)
Ceftazidime	100–150 mg/kg (8–12)	150 mg/kg (8)	150 mg/kg (8)	6 g (8)
Ceftriaxone	…	…	80–100 mg/kg (12–24)	4 g (12–24)
Chloramphenicol	25 mg/kg (24)	50 mg/kg (12–24)	75–100 mg/kg (6)	4–6 g (6)[c]
Ciprofloxacin	…	…	…	800–1200 mg (8–12)
Gatifloxacin	…	…	…	400 mg (24)[d]
Gentamicin[b]	5 mg/kg (12)	7.5 mg/kg (8)	7.5 mg/kg (8)	5 mg/kg (8)
Meropenem	…	…	120 mg/kg (8)	6 g (8)
Moxifloxacin	…	…	…	400 mg (24)[d]
Nafcillin	75 mg/kg (8–12)	100–150 mg/kg (6–8)	200 mg/kg (6)	9–12 g (4)
Oxacillin	75 mg/kg (8–12)	150–200 mg/kg (6–8)	200 mg/kg (6)	9–12 g (4)
Penicillin G	0.15 mU/kg (8–12)	0.2 mU/kg (6–8)	0.3 mU/kg (4–6)	24 mU (4)
Rifampin	…	10–20 mg/kg (12)	10–20 mg/kg (12–24)[e]	600 mg (24)
Tobramycin[b]	5 mg/kg (12)	7.5 mg/kg (8)	7.5 mg/kg (8)	5 mg/kg (8)
TMP-SMZ[f]	…	…	10–20 mg/kg (6–12)	10–20 mg/kg (6–12)
Vancomycin[g]	20–30 mg/kg (8–12)	30–45 mg/kg (6–8)	60 mg/kg (6)	30–45 mg/kg (8–12)

NOTE. TMP-SMZ, trimethoprim-sulfamethoxazole.

[a] Smaller doses and longer intervals of administration may be advisable for very low–birth weight neonates (<2000 g).
[b] Need to monitor peak and trough serum concentrations.
[c] Higher dose recommended for patients with pneumococcal meningitis.
[d] No data on optimal dosage needed in patients with bacterial meningitis.
[e] Maximum daily dose of 600 mg.
[f] Dosage based on trimethoprim component.
[g] Maintain serum trough concentrations of 15–20 μg/mL.

Despite some variability in result of published trials, we believe the available evidence supports the use of adjunctive dexamethasone in infants and children with *H. influenzae* type b meningitis (A-I). Dexamethasone should be initiated 10–20 min prior to, or at least concomitant with, the first antimicrobial dose, at 0.15 mg/kg every 6 h for 2–4 days. Adjunctive dexamethasone should not be given to infants and children who have already received antimicrobial therapy, because administration of dexamethasone in this circumstance is unlikely to improve patient outcome (A-I). In infants and children with pneumococcal meningitis, there is controversy concerning the use of adjunctive dexamethasone therapy (C-II). The 2003 statement by the Committee on Infectious Diseases of the American Academy of Pediatrics on the use of steroids for pneumococcal meningitis is as follows: "For infants and children 6 weeks of age and older, adjunctive therapy with dexamethasone may be considered after weighing the potential benefits and possible risks. Experts vary in recommending the use of corticosteroids in pneumococcal meningitis; data are not sufficient to demonstrate clear benefit in children" [66, p. 493]. Furthermore, the incidence of pneumococcal meningitis in children has decreased dramatically since the recommendation for use of the 7-valent pneumococcal conjugate vaccine, and it is unlikely that the efficacy of adjunctive dexamethasone will be determined definitively in further randomized trials conducted in the United States.

Adults. There have been 5 published trials of adjunctive dexamethasone in adults with bacterial meningitis [67–71]; 3 were randomized and placebo controlled [68, 69, 71], 1 was randomized but not placebo controlled [67], and 1 was a systemic sampling open cohort study [70]. In 4 of the 5 studies [67–70], results were inconclusive, such that definitive recommendations for use of adjunctive dexamethasone in adults could not be made. However, a recently published prospective, randomized, placebo-controlled, double-blind multicenter trial did provide important data on the use of adjunctive dexamethasone in adults with bacterial meningitis [71]. A total of 301 adults (age, ⩾17 years) were randomized to receive dexamethasone (10 mg q6h for 4 days) or placebo, the first dose being administered 15–20 min prior to the first antimicrobial

dose. At 8 weeks after enrollment, the percentage of patients with an unfavorable outcome (15% vs. 25%; $P = .03$) and death (7% vs. 15%; $P = .04$) was significantly lower in the dexamethasone group. Among the subgroup of patients with pneumococcal meningitis, benefit was evident in those who received adjunctive dexamethasone, with a lower percentage of unfavorable outcomes (26% vs. 52%; $P = .006$) and deaths (14% vs. 34%; $P = .02$). Benefits were not seen in other subgroups with meningitis caused by other meningeal pathogens, although patient numbers in those groups were small. In all groups, dexamethasone appeared to be the most beneficial in patients with moderate-to-severe disease on the Glasgow Coma Scale.

On the basis of the available evidence on the use of adjunctive dexamethasone in adults, we recommend use of dexamethasone (0.15 mg/kg q6h for 2–4 days with the first dose administered 10–20 min before, or at least concomitant with, the first dose of antimicrobial therapy) in adults with suspected or proven pneumococcal meningitis (A-I). Some experts would only administer adjunctive dexamethasone if the patient had moderate-to-severe disease (Glasgow Coma Scale score, $\leqslant 11$). However, we think that adjunctive dexamethasone should be initiated in all adult patients with suspected or proven pneumococcal meningitis, because assessment of the score may delay initiation of appropriate therapy. Dexamethasone should only be continued if the CSF Gram stain reveals gram-positive diplococci, or if blood or CSF cultures are positive for *S. pneumoniae*. Adjunctive dexamethasone should not be given to adult patients who have already received antimicrobial therapy, because administration of dexamethasone in this circumstance is unlikely to improve patient outcome (A-I). The data are inadequate to recommend adjunctive dexamethasone to adults with meningitis caused by other bacterial pathogens, although some authorities would initiate dexamethasone in all adults, because the etiology of meningitis is not always ascertained at initial evaluation (B-III).

Pneumococcal meningitis. Despite the clinical trials that have demonstrated the benefits of adjunctive dexamethasone in infants, children, and adults with bacterial meningitis (see What Is the Role of Adjunctive Dexamethasone Therapy in Patients with Bacterial Meningitis?, above), concerns have been raised about whether use of adjunctive dexamethasone may be harmful in patients with pneumococcal meningitis caused by highly penicillin- or cephalosporin-resistant strains [1]; these patients may require antimicrobial therapy with vancomycin, and the diminished inflammatory response induced by dexamethasone might reduce CSF vancomycin penetration and delay CSF sterilization. This finding has been observed in experimental animal models of resistant pneumococcal meningitis [72, 73], although larger vancomycin dosages may circumvent the effect of corticosteroids on CSF vancomycin penetration [74]. CSF vancomycin penetration was not reduced in a small study of children with bacterial meningitis, when compared with concentrations achieved in historical controls [75]. The published trials have not examined outcome in patients with these resistant isolates who have received adjunctive dexamethasone. In the recent study in adults cited above [71], only 72% of 108 CSF pneumococcal isolates were submitted for in vitro susceptibility testing, and all were susceptible to penicillin, an unusual finding in the United States and in many areas of the world. Although it would be optimal to evaluate the efficacy of adjunctive dexamethasone in patients with meningitis caused by highly resistant pneumococci, given the difficulty in enrolling adequate numbers of patients with these resistant strains into a clinical trial, it is unlikely that this question will be definitively answered in the near future [76]. We recommend that adjunctive dexamethasone be administered to all adult patients with pneumococcal meningitis, even if the isolate is subsequently found to be highly resistant to penicillin and cephalosporins (B-III). Careful observation and follow-up are critical to determine whether dexamethasone is associated with adverse clinical outcome. For data on outcome in patients with meningitis caused by resistant pneumococcal isolates, case reports and small case series may help ascertain whether dexamethasone is harmful to these patients. Furthermore, in patients with suspected pneumococcal meningitis who receive adjunctive dexamethasone, addition of rifampin to the empirical combination of vancomycin plus a third-generation cephalosporin may be reasonable pending culture results and in vitro susceptibility testing (B-III).

Once the Bacterial Etiology of Meningitis Is Established, What Specific Antimicrobial Agents Should Be Used for Treatment?

Once a bacterial pathogen is isolated and in vitro susceptibility testing is performed, antimicrobial treatment should be modified for optimal therapy. Our recommendations (with alternative suggestions), based on the isolated microorganism, are listed in table 5. Recommended dosages of antimicrobial agents in neonates, children, and adults are shown in table 6. There are no placebo-controlled trials of specific antimicrobial agents in patients with bacterial meningitis. Since their development, penicillins and sulfonamides have been the standard, but much has changed as a result of widespread antimicrobial resistance against these drugs and the need for development of newer agents. Decisions on the choice of a specific antimicrobial agent are based on knowledge of in vitro susceptibility and relative penetration into CSF in the presence of meningeal inflammation (whether gleaned from experimental animal models or patients). Clinical trials have most often compared newer agents with what has been determined to be "standard" antimicrobial therapy, even though this "standard" therapy has not always been extensively studied in patients. The following sections will review specific classes of antimicrobial agents that have been

recently examined for their role in patients with bacterial meningitis and will include our evidence-based recommendations for use of these agents in patients with bacterial meningitis.

Cephalosporins. The treatment of bacterial meningitis has been revolutionized by the availability of the third-generation cephalosporins [1, 77]. In patients with *H. influenzae* type b meningitis, the emergence of β-lactamase–producing strains and resistance to chloramphenicol has made these agents the drugs of choice for empirical therapy for *H. influenzae* meningitis, pending results of in vitro susceptibility testing. In clinical trials, the third-generation cephalosporins have been found to be superior to chloramphenicol and cefuroxime (a second-generation cephalosporin) and are recommended for the treatment of childhood bacterial meningitis [36, 78, 79] (A-I). In patients with pneumococcal and meningococcal meningitis, the third-generation cephalosporins are recommended in patients with meningitis caused by strains that are not susceptible to penicillin (MIC, $\geq$0.1 μg/mL) [1, 80, 81] (A-III).

The third-generation cephalosporins are also quite effective in meningitis caused by aerobic gram-negative bacilli (e.g., *Escherichia coli* or *Klebsiella* species); cure rates of 78%–94% have been reported, compared with mortality rates of 40%–90% for previous regimens that usually included an aminoglycoside, with or without chloramphenicol [82–84] (A-II). However, given the increasing frequency of antimicrobial resistance among gram-negative bacilli, especially in the hospital setting, in vitro susceptibility testing of isolates is critical to guide antimicrobial therapy. One agent, ceftazidime, has also shown efficacy in several studies of patients with *Pseudomonas* meningitis [85, 86] (A-II). A fourth-generation cephalosporin, cefepime, has been shown to be safe and therapeutically equivalent to cefotaxime in the treatment of bacterial meningitis in infants and children [87, 88]. Cefepime also has greater in vitro activity than the third-generation cephalosporins against *Enterobacter* species and *Pseudomonas aeruginosa* and has been used successfully in some patients with meningitis caused by these bacteria [89], making it a useful agent in the treatment of patients with bacterial meningitis (A-II).

Vancomycin. Vancomycin has been evaluated in the therapy of bacterial meningitis caused by penicillin-resistant pneumococci [90]. In a study of 11 adult patients with pneumococcal meningitis caused by strains with intermediate resistance to penicillin [91], vancomycin therapy was associated with clinical failure in 4 patients; however, the dosage of vancomycin used (15 mg/kg daily) was below standard recommendations. There were no failures in 14 subsequent patients treated with ceftriaxone in this study. The concomitant administration of dexamethasone with the subsequent decrease in inflammation and poor entry of vancomycin into CSF may have contributed to this negative outcome. On the basis of these findings, vancomycin is not recommended in the treatment of bacterial meningitis caused by isolates that are susceptible to other agents (i.e., penicillins and cephalosporins) (E-II). Even in patients with meningitis caused by highly penicillin- and cephalosporin-resistant strains, vancomycin should be combined with a third-generation cephalosporin (A-III) and should not be used as a single agent [1, 81]. When used for the treatment of bacterial meningitis, vancomycin should be administered to maintain serum vancomycin trough concentrations of approximately 15–20 μg/mL (B-III). Intrathecal administration of vancomycin may be considered in patients who are not responding to parenteral administration (B-III).

Rifampin. Rifampin has many properties that make it an excellent agent for the treatment of meningitis, including good CSF penetration and in vitro activity against many meningeal pathogens. However, when used alone, resistance rapidly develops, such that rifampin must be used in combination with other antimicrobial agents. Clinical data on the efficacy of rifampin in patients with bacterial meningitis are lacking, but some authorities would use this agent in combination with a third-generation cephalosporin, with or without vancomycin, in patients with pneumococcal meningitis caused by highly penicillin- or cephalosporin resistant strains [81, 92]. Rifampin should only be added if the organism is shown to be susceptible and there is a delay in the expected clinical or bacteriologic response (A-III). Rifampin should also be combined with vancomycin in patients with CSF shunt infections caused by staphylococci, especially in cases in which the shunt cannot be removed [93] (A-III).

Carbapenems. Two carbapenem agents have been studied in patients with bacterial meningitis. Imipenem has been successfully used in 2 patients with pneumococcal meningitis caused by penicillin- and cephalosporin-resistant strains [94, 95] and in 1 patient with *Acinetobacter* meningitis [96], although the potential for seizure activity (which was 33% in one study of children with bacterial meningitis) [97] argues against its use in most patients with bacterial meningitis (D-II). Meropenem, which has a broad range of in vitro activity and less seizure proclivity than imipenem, has been studied in both children and adults with bacterial meningitis [98–100]. In these studies, meropenem has been shown to have clinical and microbiologic outcomes similar to those of cefotaxime or ceftriaxone and can be recommended as an alternative to these agents for treatment of bacterial meningitis (A-I). Meropenem has also been used successfully in isolated patients with pneumococcal meningitis caused by highly penicillin- and cephalosporin-resistant strains [100, 101]. However, in a recent study of 20 cefotaxime-resistant *S. pneumoniae* isolates [102], 4 were intermediate and 13 were resistant to meropenem, suggesting that meropenem may not be a useful alternative agent for treatment of pneumococcal isolates that are highly resistant to penicillin and cephalosporins (D-II). However, meropenem may

be useful in patients with meningitis caused by gram-negative isolates that are resistant to standard therapy [102–104]. Meningitis caused by gram-negative bacilli that produce extended-spectrum β-lactamases or those that may hyperproduce β-lactamases (i.e., *Enterobacter* species, *Citrobacter* species, or *Serratia marcescens*) may best be treated with a regimen that contains meropenem (A-III).

Fluoroquinolones. The fluoroquinolones (especially ciprofloxacin) have been used successfully in some patients with meningitis due to gram-negative organisms [105–109]. However, on the basis of limited published literature, these agents should only be utilized for meningitis caused by multidrug-resistant gram-negative bacilli, or when patients have not responded to or cannot receive standard antimicrobial therapy (A-III). The newer fluoroquinolones (e.g., trovafloxacin, gatifloxaxin, and moxifloxacin) have enhanced in vitro activity against *S. pneumoniae* and have been studied in experimental animal models of pneumococcal meningitis. Trovafloxacin was compared with ceftriaxone, with or without vancomycin, in a multicenter, randomized trial in children with bacterial meningitis (27% of cases caused by *S. pneumoniae*) [110]. The overall efficacy in both treatment groups was comparable in terms of CSF sterilization and clinical success at the end of treatment. Although trovafloxacin is no longer utilized because of concerns of liver toxicity, these data suggest the potential usefulness of the new fluoroquinolones in patients with bacterial meningitis [111]. Pending results of ongoing trials, these agents (i.e., gatifloxacin and moxifloxacin) should only be used as alternative agents in patients with bacterial meningitis (B-II). Because these agents have not been studied in newborns and children with bacterial meningitis, they should only be considered in these patients who are not responding to standard therapy.

In Patients Who Develop Bacterial Meningitis after Placement of CSF Shunt, Is It Necessary to Administer Antimicrobial Therapy by the Intraventricular Route?

There are numerous reported methods for the treatment of CSF shunt infections, but no randomized, prospective studies have ever been performed. The principles of antimicrobial therapy for CSF shunt infections are generally the same as those for the treatment of acute bacterial meningitis. However, direct instillation of antimicrobial agents into the ventricles through either an external ventriculostomy or shunt reservoir is occasionally necessary in patients who have shunt infections that are difficult to eradicate or who cannot undergo the surgical components of therapy (A-III). No antimicrobial agent has been approved by the US Food and Drug Administration for intraventricular use, and the specific indications are not well-defined. Antimicrobial dosages have been used empirically (table 7), with dosage adjustments and dosing intervals based on the ability of the agent to achieve adequate CSF concentrations [113–115]. After administration of the first intraventricular dose, additional doses can be determined by calculation of the "inhibitory quotient." Prior to administration of the next intraventricular dose, a sample of CSF is withdrawn to obtain the trough CSF concentration. The inhibitory quotient is then determined by taking the trough CSF concentration divided by the MIC of the agent for the isolated bacterial pathogen; it should exceed 10–20 for consistent CSF sterilization [116]. Although not standardized, this approach is reasonable to ensure that adequate CSF concentrations of specific antimicrobial agents are attained (B-III).

In Patients with CSF Shunts Who Develop Bacterial Meningitis Directly from the Shunt (and Not from Hematogenous Dissemination of Encapsulated Microorganisms), Does the Shunt Need to Be Removed for Optimal Therapy, and When Can a New Shunt Be Implanted?

Removal of all components of the infected shunt and some component of external drainage, in combination with appropriate antimicrobial therapy, appears to be the most effective treatment for CSF shunt infections [115, 116]; the ventriculitis of the shunt infection appears to clear more rapidly with the drainage catheter, and the presence of the catheter allows continued treatment of the hydrocephalus until the infection has cleared (A-II). Success rates are lower when the shunt is treated in situ, because of the ability of many of these microorganisms to adhere to prostheses and survive antimicrobial therapy.

The timing of shunt reimplantation is dependent upon the isolated microorganism, the extent of infection as defined by

Table 7. Recommended dosages of antimicrobial agents administered by the intraventricular route (A-III).

Antimicrobial agent	Daily intraventricular dose, mg
Vancomycin	5–20[a]
Gentamicin	1–8[b]
Tobramycin	5–20
Amikacin	5–50[c]
Polymyxin B	5[d]
Colistin	10
Quinupristin/dalfopristin	2–5
Teicoplanin	5–40[e]

NOTE. There are no specific data that define the exact dose of an antimicrobial agent that should be administered by the intraventricular route.

[a] Most studies have used a 10-mg or 20-mg dose.
[b] Usual daily dose is 1–2 mg for infants and children and 4–8 mg for adults.
[c] The usual daily intraventricular dose is 30 mg.
[d] Dosage in children is 2 mg daily.
[e] Dosage of 5–10 mg every 48–72 h in one study [112].

Table 8. Duration of antimicrobial therapy for bacterial meningitis based on isolated pathogen (A-III).

Microorganism	Duration of therapy, days
Neisseria meningitidis	7
Haemophilus influenzae	7
Streptococcus pneumoniae	10–14
Streptococcus agalactiae	14–21
Aerobic gram-negative bacilli[a]	21
Listeria monocytogenes	⩾21

[a] Duration in the neonate is 2 weeks beyond the first sterile CSF culture or ⩾3 weeks, whichever is longer.

culture of samples obtained after externalization and, occasionally, on CSF findings (B-II) [115, 116]. In patients with infections caused by coagulase-negative staphylococci and normal CSF findings, the presence of negative CSF culture results after externalization generally confirms that removal of the hardware affected a cure, and the patient can be reshunted on the third day after removal. If CSF abnormalities are present and a coagulase-negative staphylococcus is isolated, 7 days of antimicrobial therapy are recommended prior to reshunting as long as additional CSF culture results are negative and the ventricular protein concentration is appropriate (<200 mg/dL); if additional culture results are positive, antimicrobial therapy is continued until CSF culture results remain negative for 10 consecutive days before a new CSF shunt is placed. For shunt infections caused by *S. aureus*, 10 days of negative culture results are recommended prior to reshunting and for gram-negative bacilli, a 10–14-day course of antimicrobial therapy should be used, although longer durations may be needed depending on the clinical response. Some experts also suggest that consideration be given to a 3-day period off antimicrobial therapy to verify clearing of the infection prior to shunt reimplantation; although this approach is optional, it may not be necessary for all patients (C-III).

What Are the Indications for Repeated Lumbar Puncture in Patients with Bacterial Meningitis?

In patients with bacterial meningitis who have responded appropriately to antimicrobial therapy, repeated CSF analysis to document CSF sterilization and improvement of CSF parameters is not routinely indicated. Repeated CSF analysis should be performed, however, for any patient who has not responded clinically after 48 h of appropriate antimicrobial therapy (A-III). This is especially true for the patient with pneumococcal meningitis caused by penicillin- or cephalosporin-resistant strains, especially for those who have also received adjunctive dexamethasone therapy [81, 92]. The neonate with meningitis due to gram-negative bacilli should undergo repeated lumbar punctures to document CSF sterilization, because the duration of antimicrobial therapy is determined, in part, by the result (A-III). In patients with CSF shunt infections, the presence of a drainage catheter after shunt removal allows for monitoring of CSF parameters to ensure that the infection is responding to appropriate antimicrobial therapy and drainage.

What Is the Duration of Antimicrobial Therapy, Based on the Isolated Pathogen?

The duration of antimicrobial therapy in the patient with bacterial meningitis has often been based more on tradition than on evidence-based data [117, 118]. Our recommendations are shown in table 8. However, it must be emphasized that these guidelines are not standardized and that the duration of therapy may need to be individualized on the basis of the patient's clinical response. Pending further data, intravenous antimicrobial therapy is recommended for the duration of treatment to ensure that adequate CSF concentrations of specific antimicrobial agents are attained.

What Specific Criteria Should Be Used for Outpatient Antimicrobial Therapy in the Patient with Bacterial Meningitis?

Patients with bacterial meningitis have often remained hospitalized for the duration of treatment with intravenous antimicrobial therapy. However, outpatient antimicrobial therapy may be appropriate in selected patients, and this may lead to decreased costs of hospitalization, decreased risk of development of nosocomial infections, and improved quality of life [119, 120]. Although concerns have been raised about the potential risk of serious complications in patients with bacterial meningitis, complications (when they occur) usually happen within the first 2–3 days of treatment and are exceedingly rare after 3 or 4 days of appropriate antimicrobial therapy. Criteria

Table 9. Criteria for outpatient antimicrobial therapy in patients with bacterial meningitis (A-III).

Inpatient antimicrobial therapy for ⩾6 days
Absence of fever for at least 24–48 h prior to initiation of outpatient therapy
No significant neurologic dysfunction, focal findings, or seizure activity
Clinical stability or improving condition
Ability to take fluids by mouth
Access to home health nursing for antimicrobial administration
Reliable intravenous line and infusion device (if needed)
Daily availability of a physician
Established plan for physician visits, nurse visits, laboratory monitoring, and emergencies
Patient and/or family compliance with the program
Safe environment with access to a telephone, utilities, food, and refrigerator

NOTE. From [119, 120].

that may be used to determine which patients with bacterial meningitis can receive outpatient antimicrobial therapy are shown in table 9 (B-III). It must be emphasized, however, that patient selection for outpatient antimicrobial therapy for bacterial meningitis must be carefully performed, and close medical follow-up is essential.

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