CURRENT CONCEPTS

Community-Acquired Bacterial Meningitis in Adults

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Bacterial meningitis is a medical, neurologic, and sometimes neurosurgical emergency that requires a multidisciplinary approach. Bacterial meningitis has an annual incidence of 4 to 6 cases per 100,000 adults (defined as patients older than 16 years of age), and Streptococcus pneumoniae and Neisseria meningitidis are responsible for 80 percent of all cases.\(^1,2\) A diagnosis of bacterial meningitis is often considered, but the disease can be difficult to recognize.\(^1-8\) Recommendations for antimicrobial therapy are changing as a result of the emergence of antimicrobial resistance. In this review we summarize the current concepts of the initial approach to the treatment of adults with bacterial meningitis, highlighting adjunctive dexamethasone therapy and focusing on the management of neurologic complications.

**initial approach**

In adults presenting with community-acquired acute bacterial meningitis, the sensitivity of the classic triad of fever, neck stiffness, and altered mental status is low (44 percent), but almost all such patients present with at least two of four symptoms — headache, fever, neck stiffness, and altered mental status (as defined by a score below 14 on the Glasgow Coma Scale).\(^1\) Lumbar puncture is mandatory in any patient in whom bacterial meningitis is suspected, although the procedure can be hazardous (Fig. 1 in the Supplementary Appendix, available with the full text of this article at www.nejm.org). Reports have emphasized the risk of brain herniation as a complication of diagnostic lumbar puncture in patients with meningitis.\(^9-13\) Patients with expanding masses (e.g., subdural empyema, brain abscess, or necrotic temporal lobe in herpes simplex encephalitis) may present with symptoms that appear to be identical with those of bacterial meningitis, and in these patients as well, lumbar puncture may be complicated by brain herniation.\(^5,9\) The withdrawal of cerebrospinal fluid reduces counterpressure from below, thereby adding to the effect of compression from above, increasing the brain shift that may already be present (Fig. 1).\(^9\) Neuroimaging — either cranial computed tomography (CT) or magnetic resonance imaging (MRI) — to detect brain shift is recommended as a precaution in selected patients before lumbar puncture.\(^9,10\) A prospective study involving 301 adults with suspected meningitis confirmed that clinical features can be used to identify patients who are unlikely to have abnormal findings on cranial CT (41 percent of the patients in this study).\(^10\) Of 235 patients who underwent cranial CT, in only 5 patients (2 percent) was bacterial meningitis confirmed, reflecting the heterogeneity of the study group with clinically suspected bacterial meningitis. Cranial imaging should precede lumbar puncture in patients who have new-onset seizures, an immunocompromised state, signs that are suspicious for space-occupying lesions, or moderate-to-severe impairment of consciousness.\(^9,10,13\) When these
criteria are met, indications for cranial imaging before lumbar puncture are present in about 45 percent of patients with bacterial meningitis confirmed by cerebrospinal fluid culture. Lumbar puncture may also be harmful in patients with coagulopathy, because of the chance of needle-induced subarachnoid hemorrhage or of the development of spinal subdural and epidural hematomas. When a diagnosis of bacterial meningitis is probable but neuroimaging is not available, lumbar puncture should be given preference in patients with moderate-to-severe impairment of consciousness or in an immunocompromised state. However, when warning signs of a space-occupying lesion (e.g., new-onset seizure, papilledema, or evolving signs of brain tissue shift) are present, lumbar puncture should not be performed until after neuroimaging has been performed.

Delay in the initiation of antimicrobial therapy can result in poor outcome in this disease. In a retrospective study, patients were stratified as having a low, intermediate, or high risk of adverse
outcome, according to baseline prognostic fac-

tors. The median delay between the time of ar-

rival at the emergency department and the admin-

istration of antibiotics was four hours. Among

patients whose condition worsened while they

were in the emergency department to a category

with a higher risk of having an adverse outcome,

an association was found between the time of

the start of antimicrobial therapy and outcome.

Another retrospective study found an association

between delays in administering antibiotics longer

than six hours after arrival in the emergency

department and death. Delay was most frequent-

ly due to the performance of cranial imaging be-

fore diagnostic lumbar puncture and the transfer

of patients to another hospital. If imaging is per-

formed before lumbar puncture, therapy should

be initiated before the patient is sent for neuro-

imaging (Fig. 1 in the Supplementary Appendix).

In patients who have not undergone prior imag-

ing and in whom disease progression is apparent,

therapy should be started directly after lumbar

puncture, as well as in all patients with cloudy

cerebrospinal fluid (suggesting the diagnosis of

bacterial meningitis). The opening pressure of the cerebrospinal fluid is elevated in most patients with bacterial meningitis. In a prospective cohort study, 40 percent of the patients had very high opening pressures (>400 mm, as measured with the use of a water manometer), which were associated with lower levels of consciousness but not with adverse outcome. Cerebrospinal fluid findings are important in the differential diagnosis of patients with suspected meningitis. In this disease, pleocytosis (100 to 10,000 white cells per cubic millimeter), elevated protein levels (>50 mg per deciliter [0.5 g per liter]), and decreased cerebrospinal fluid glucose levels (<40 percent of simultaneously measured serum glucose) are usually present. There is usually a predominance of neutrophils (range, 80 to 95 percent) in the cerebrospinal fluid, but a predominance of lymphocytes can occur. Normal or marginally elevated cerebrospinal fluid white-cell counts occur in 5 to 10 percent of patients and are associated with an adverse outcome.

Gram’s staining of cerebrospinal fluid permits the rapid identification of the causative organism (sensitivity, 60 to 90 percent; specificity, ≥97 percent). Bacterial antigen tests have a limited sensitivity, but they may be helpful in patients with findings consistent with bacterial meningi-
tis and negative Gram’s staining and cultures of cerebrospinal fluid. New molecular techniques for detecting bacteria in the cerebrospinal fluid by polymerase chain reaction (PCR) have emerged as powerful tools in the diagnosis of patients with negative cultures of cerebrospinal fluid; such tools have high sensitivity and specificity, although further refinements are needed before PCR can be routinely recommended.

### Table 1. Recommendations for Empirical Antimicrobial Therapy in Adults with Community-Acquired Bacterial Meningitis.

<table>
<thead>
<tr>
<th>Predisposing Factor</th>
<th>Common Bacterial Pathogen</th>
<th>Antimicrobial Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16–50 yr</td>
<td>Neisseria meningitidis, Streptococcus pneumoniae</td>
<td>Vancomycin plus a third-generation cephalosporin†‡</td>
</tr>
<tr>
<td>&gt;50 yr</td>
<td>S. pneumoniae, N. meningitidis, Listeria monocytogenes, aerobic gram-negative bacilli</td>
<td>Vancomycin plus a third-generation cephalosporin plus ampicillin‡§</td>
</tr>
<tr>
<td>Presence of a risk factor¶</td>
<td>S. pneumoniae, L. monocytogenes, Haemophilus influenzae</td>
<td>Vancomycin plus a third-generation cephalosporin plus ampicillin‡§</td>
</tr>
</tbody>
</table>

* For additional information, including alternative antimicrobial therapies, see Table 1 in the Supplementary Appendix, available with the full text of this article at www.nejm.org.
† Only in regions with very low rates of penicillin resistance (<1 percent), monotherapy with penicillin may be considered, although many experts recommend combination therapy for all patients until the results of in vitro susceptibility testing are available.
‡ Cefotaxime and ceftriaxone are the third-generation cephalosporins recommended.
§ Only in regions with very low rates of penicillin resistance and cephalosporin resistance, combination therapy with amoxicillin (ampicillin) and a third-generation cephalosporin may be considered.
¶ Risk factors include alcoholism and altered immune status.
The choice of initial antimicrobial therapy is based on the most common bacteria causing the disease according to the patient’s age and the clinical setting and on patterns of antimicrobial susceptibility (Table 1). After the results of culture and susceptibility testing are available, antimicrobial therapy can be modified for optimal treatment (Table 1 in the Supplementary Appendix). With the worldwide increase in the prevalence of penicillin-resistant pneumococci, combination therapy with vancomycin plus a third-generation cephalosporin (either ceftriaxone or cefotaxime) has become the standard approach to empirical antimicrobial therapy. Although clinical data on the efficacy of rifampin in patients with pneumococcal meningitis are lacking, some authorities would use this agent in combination with a third-generation cephalosporin, with or without vancomycin, in patients with pneumococcal meningitis caused by bacterial strains that, on the basis of local epidemiology, are likely to be highly resistant to penicillin or cephalosporin. Such patients should also receive adjunctive dexamethasone therapy.

Respiratory isolation for 24 hours is indicated for patients with suspected meningococcal infection. Isolation is not required for those with signs of pneumococcal infection (otitis or pneumonia) or with bacteria other than N. meningitidis identified by Gram's staining. Persons who have close contact with the patient must receive chemoprophylaxis to eradicate meningococcal carriage (Table 1 in the Supplementary Appendix).

**ADJUNCTIVE DEXAMETHASONE THERAPY**

A recent randomized, placebo-controlled trial involving 301 adults with suspected meningitis in combination with cloudy cerebrospinal fluid, bacteria in the cerebrospinal fluid on Gram's staining, or a cerebrospinal fluid leukocyte count of more than 1000 per cubic millimeter showed that adjunctive treatment with dexamethasone before or with the first dose of antimicrobial therapy reduced the risk of unfavorable outcome from 25 percent to 15 percent (number needed to treat, 10 patients). Mortality was reduced from 15 percent to 7 percent. The benefit was greatest in patients with intermediate disease severity, as defined by a score on the Glasgow Coma Scale on admission of 8 to 11 (scores can range from 3 to 15, with 15 indicating a normal level of consciousness), and in those with pneumococcal meningitis, in whom unfavorable outcomes declined from 52 percent to 26 percent (number needed to treat, four). In patients with pneumococcal meningitis, mortality was reduced from 34 percent to 14 percent. This benefit was a result of reduced mortality from systemic causes. In addition, the benefits of dexamethasone were not offset by any apparent side effects of treatment with dexamethasone.

What are the practical implications of the results of this study? First, in all patients whose condition fulfills the inclusion criteria of the study, dexamethasone (at a dose of 10 mg) should be initiated before or with the first dose of antibiotics and continued for four days (at a dose of 10 mg every six hours). Second, in patients with suspected meningitis, the results of the study support the administration of adjunctive dexamethasone with or before the first dose of empirical antibiotics, although the study did not specifically address this issue. This course may result in the unnecessary treatment of patients who do not have bacterial meningitis, but the potential benefits outweigh any potential risks associated with dexamethasone therapy. Therapy should be discontinued if the patient is found not to have bacterial meningitis. Third, dexamethasone should be continued for four days in patients with bacterial meningitis, regardless of microbial cause or clinical severity. The absence of a significant clinical benefit in some subgroups of patients does not rule out a beneficial effect of dexamethasone in these subgroups, because the study was not powered to analyze all subgroups of interest. Some experts, however, would discontinue dexamethasone if the meningitis is found to be caused by a bacterium other than S. pneumoniae.

In a recent quantitative review of this topic that included the results of five clinical trials, treatment with corticosteroids was associated with a significant reduction in mortality and neurologic sequelae. In the subgroup of patients with meningococcal meningitis, mortality (relative risk, 0.9; 95 percent confidence interval, 0.3 to 2.1) and neurologic sequelae (relative risk, 0.5; 95 percent confidence interval, 0.1 to 1.7) were both reduced, although the results were not statistically significant.

For some adults with suspected meningitis, however, adjunctive dexamethasone can be harmful (Fig. 1 in the Supplementary Appendix). Pa-
tients with septic shock and adrenal insufficiency benefit from corticosteroid therapy in physiologic doses and for longer than four days; however, when there is no evidence of relative adrenal insufficiency, therapy with corticosteroids may be detrimental.27,28 There are no controlled studies of the effects of corticosteroid therapy in a substantial number of patients with both meningitis and septic shock, and therefore corticosteroid therapy cannot be unequivocally recommended for such patients, although the use of low doses, as used by Annane et al,27 (hydrocortisone, 50 mg every 6 hours, and fludrocortisone, 50 μg daily), seems reasonable at present. Starting corticosteroids before or with the first dose of parenteral antimicrobial therapy appears to be more effective than starting corticosteroids after the first dose of antimicrobial therapy.29 In experimentally induced pneumococcal meningitis in animals, bacterial concentrations in the cerebrospinal fluid at the start of therapy appeared to be a more important factor influencing the antimicrobial-induced inflammatory response than the time dexamethasone therapy was initiated.30 There is a point after the first (parenteral) administration of an antimicrobial agent beyond which dexamethasone loses its effectiveness, but this point has not been clearly defined.

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**INTENSIVE CARE MANAGEMENT**

Monitoring in a neurologic–neurosurgical intensive care unit is recommended in order to recognize changes in the patient’s consciousness and the development of new neurologic signs, monitor for subtle seizures, and treat severe agitation effectively.31 Practical recommendations and admission criteria are given in Table 2 (and Fig. 1 in the Supplementary Appendix). Bacterial meningitis is often associated with septic shock, which is an important predictor of outcome.1,32 Patients with meningitis and septic shock may require insertion of a Swan–Ganz catheter, to measure cardiac output, the cardiac index, systemic vascular resistance, and pulmonary wedge pressures in order to assess intravascular volume and cardiac function.33 Adrenocorticoid insufficiency in patients with septic shock must be treated with low doses of corticosteroids.27 Care should be taken to estimate and replace imperceptible fluid loss through the skin and lungs in patients who are febrile.31

Patients with bacterial meningitis are at risk of acute hyponatremia, although most cases are mild.1,8,32 Hyponatremia may be a result of cerebral salt wasting, the syndrome of inappropriate antidiuretic hormone secretion, or exacerbation by aggressive fluid resuscitation.31,33,34 This lack of clarity about the mechanism has resulted in the clinical dilemma with regard to whether intravenous fluids should be restricted in bacterial meningitis.34 In children with bacterial meningitis, fluid restriction does not improve either brain edema or outcome.33,35 Therefore, adult patients with meningitis should be treated with the goal of a normovolemic state. A core body temperature of more than 40°C probably would need to be treated with techniques of cooling by conduction or antipyretic agents to avoid excessive fluid loss. In experimentally induced meningitis in animals, moderate hypothermia ameliorates inflammatory changes, although no clinical studies have been performed.36,37

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**DECLINE IN CONSCIOUSNESS**

For patients with a decline in consciousness, or those whose condition fails to improve after the initiation of appropriate antimicrobial therapy, brain imaging is indicated. The indication for repeated imaging is often arbitrarily based on the clinical status of the patient, the time between the decline in consciousness and the initiation of adequate therapy, and the results of previous imaging studies.

A common cause of a decline in consciousness in bacterial meningitis is clinical evidence of meningoencephalitis (Table 3). The release of proinflammatory mediators in the subarachnoid space leads to an inflammatory response in the central nervous system that contributes to an increased permeability of the blood–brain barrier, cerebral edema, and increased intracranial pressure.38 On neuroimaging, early signs of brain edema are the disappearance of sylvian fissures and a narrowing of ventricular size. In patients with an advanced stage of brain edema and raised intracranial pressure, basal cisterns and sulci may become obliterated. Several supportive therapies have been described, although no therapy has been proved to have clinical efficacy.8,39–43

A recent study in Sweden reported findings on the use of measurements of continuous intracranial pressure and cerebral perfusion pressure...
in the treatment of patients with severe bacterial meningitis. In this observational study, intracranial pressure was successfully lowered in most patients by a broad range of measures and with the use of an unconventional volume-targeted (“Lund concept”) intracranial pressure management protocol. The mean intracranial pressure was significantly higher and cerebral perfusion pressure was markedly decreased in patients who did not survive (in spite of treatment). Management of intracranial pressure is not routine in bacterial meningitis, and randomized comparative studies of various treatment regimens should be performed. Nevertheless, in patients with impending cerebral herniation, monitoring of intracranial pressure may be considered, but the outcome is expected to be poor. The use of osmotic diuretics to control intracranial pressure may be an option, although there are no definitive data on the efficacy of this approach. Scores on the Glasgow Coma Scale can range from 3 to 15, with 15 indicating a normal level of consciousness.

Seizures and acute hydrocephalus are other frequent causes of deteriorating consciousness. Patients with seizures or a clinical suspicion of prior seizure should receive anticonvulsant therapy, but the low incidence of this complication does not justify prophylaxis. A rare cause of the deterioration of consciousness in meningitis is nonconvulsive status epilepticus. If seizures have occurred and the patient does not awaken or consciousness waxes and wanes, an electroencephalogram is indicated. In patients with acute hydrocephalus, a lumbar puncture can allow the measurement of cerebrospinal fluid pressure.
temporary lumbar drain may effectively reduce intracranial pressure; performing a ventriculostomy may also be considered. In patients with mild enlargement of the ventricular system with no clinical deterioration, a spontaneous resolution may occur, and invasive procedures are therefore withheld. Cerebral infarcts may involve large vascular territories and may cause brain swelling and a mass effect, which may result in a decline in consciousness.  

Focal neurologic abnormalities

In meningitis, focal cerebral abnormalities (hemiparesis, monoparesis, or aphasia) are most commonly caused by stroke, seizures, or a combination of the two (Table 3). Activation of inflammation and coagulation are closely related and interdependent. The possibility of cerebral venous thrombophlebitis should be considered in patients with deterioration of consciousness, seizures, fluctuating focal neurologic abnormalities, and stroke with nonarterial distribution; MRI with venous-phase studies confirms the diagnosis. Treatment of cerebral thrombophlebitis in bacterial meningitis is directed toward the infection.

In a patient with rapid deterioration, subdural empyema should be considered. Clues to the diagnosis are the presence of sinusitis and mastoiditis (and recent surgery for either of these disorders). Seizures and epilepsia partialis continua are relatively common in patients with subdural empyema. In most patients with subdural empyema, contrast-enhanced CT shows hypodense collections. However, MRI may be needed to image the localization of the subdural empyema.
at the convexity.\textsuperscript{31} In the majority of patients with subdural empyema, surgical drainage by craniotomy is indicated.\textsuperscript{50}

Abnormalities of the cranial nerves are caused by the meningeal inflammatory process or by an increase in cerebrospinal fluid pressure.\textsuperscript{8} The most frequent cranial-nerve abnormality is the involvement of the eighth cranial nerve, which is reflected in a hearing loss in 14 percent of patients.\textsuperscript{1} A cochlear implant may eventually be needed by some severely affected patients.\textsuperscript{51}

**Repeated Lumbar Puncture**

The analysis of the cerebrospinal fluid should be repeated only in patients whose condition has not responded clinically after 48 hours of appropriate antimicrobial therapy. Repeated lumbar puncture is especially essential in the treatment of patients with pneumococcal meningitis caused by penicillin-resistant or cephalosporin-resistant strains and who receive adjunctive dexamethasone therapy and vancomycin.\textsuperscript{21,26} Dexamethasone reduces inflammation of the cerebrospinal fluid and therefore may decrease the permeability of selected antimicrobial agents across the blood–brain barrier and, as a consequence, impede the penetration of vancomycin into the subarachnoid space.\textsuperscript{26,52} Treatment failures have been reported in adults who received vancomycin and adjunctive dexamethasone.\textsuperscript{53} If lumbar puncture is repeated, Gram’s staining and culture of the cerebrospinal fluid should be negative after 24 hours of appropriate antimicrobial therapy.

**Outcome**

Community-acquired meningitis caused by \textit{S. pneumoniae} has high case fatality rates, reported as from 19 to 37 percent.\textsuperscript{1,4-9,31,46} In up to 30 percent of survivors, long-term neurologic sequelae develop, including hearing loss and other focal neurologic deficits.\textsuperscript{1,4-8,32,46} The mortality and morbidity for meningococcal meningitis are lower than those for pneumococcal meningitis, with case fatality rates of 3 to 13 percent and morbidity rates of 3 to 7 percent.\textsuperscript{1,4-6} The strongest risk factors for an unfavorable outcome are those indicative of systemic compromise, impaired consciousness, low white-cell count in the cerebrospinal fluid, and infection with \textit{S. pneumoniae}.\textsuperscript{1} All cohort studies were performed before dexamethasone was routinely administered; now that routine dexamethasone therapy has been implemented, complications and sequelae are expected to decline.\textsuperscript{1,24,26} Cognitive impairment occurs fre-
quently after bacterial meningitis. In one prospective study, cognitive impairment was detected in 27 percent of adults who had a good recovery from pneumococcal meningitis. Cognitive impairment consisted mainly of cognitive slowness, which was related to lower scores on questionnaires measuring the quality of life.

Although such advances are promising, it is unlikely that additional adjunctive therapies will be studied in controlled trials in patients with bacterial meningitis. Progress is more likely to come from investigations into preventive measures, especially the use of available vaccines and the development of new vaccines. Meningitis caused by *Haemophilus influenzae* type B has been nearly eliminated in the Western world since routine vaccination with the *H. influenzae* type B conjugate vaccine was initiated. The introduction of conjugate vaccines against *S. pneumoniae* may substantially reduce the burden of childhood pneumococcal meningitis and may even produce herd immunity among adults. The approval in 2005 of a conjugate meningococcal vaccine against serogroups A, C, Y, and W135 is also an important advance that may decrease the incidence of this devastating infection.

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**FUTURE DIRECTIONS**

Recent advances in experimentally induced bacterial meningitis in animals include the role of oxygen–glucose deprivation of hippocampal neurons as a complication of meningitis, the role of cytokines, and the protective roles of nuclear factor-κB1 and brain-derived neurotrophic factor. Although such advances are promising, it is unlikely that additional adjunctive therapies will be studied in controlled trials in patients with bacterial meningitis.

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