



Meningitis

Current Evidence and Best Practice

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The diagnosis and expedient treatment of meningitis is a challenge, and distinguishing the aseptic and bacterial forms of the disease is paramount—and sometimes highly enigmatic.

Herein, the authors review the etiologies of both aseptic and bacterial meningitis.

In addition, diagnostic methods and clinical decision rules are considered, and treatment and potential complications are addressed.

Meningitis is a potentially deadly disease requiring early diagnosis and treatment. The risk of malpractice lawsuits is high, particularly in cases of misdiagnosis or delay in treatment.¹ Litigation and awards for these cases are costly, amounting to millions of dollars each year; often such cases involve children younger than 2 years.¹ There are multiple causes of meningitis, and incidence varies based on the population. Bacterial meningitis has an annual incidence of 4 to 6 cases per 100,000 adults in developed nations,² and this number is likely higher in developing countries. According to the CDC, the mortality associated with bacterial meningitis is approximately 10% to 14% worldwide, and of those patients who recover, approximately 11% to 19% have permanent sequelae.³ This review article summarizes current perspectives in the diagnosis and treatment of meningitis.

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ASEPTIC MENINGITIS

The term *aseptic meningitis* is used to describe “all types of meningitis with negative bacterial cultures from cerebrospinal fluid.”⁴ The etiology of aseptic meningitis is vast. Viruses are most commonly responsible; in addition, fungal, parasitic, postinfectious, medication-related, vasculitis/autoimmune, and neoplastic-related causes are possible. Bacteria (*Mycobacterium tuberculosis*, *Mycoplasma*, and *Borrelia*) can also lead to aseptic meningitis (Table 1).⁵ Lyme disease has been noted to cause aseptic meningitis; Lyme meningitis may be differentiated from other types of aseptic meningitis in patients in Lyme-endemic locations who present with the following: prolonged headache, cranial neuritis, and predominance of cerebrospinal fluid (CSF) mononuclear cells. Aseptic meningitis is more commonly reported in adults than in children.

While the incidence of drug-induced aseptic meningitis (DIAM) is unknown, it has been shown that the four groups of medications most commonly associated with the illness are NSAIDs, antibiotics, intravenous immunoglobulins, and OKT3 monoclonal antibody.

Images: Left: Living Art Enterprises, LLC/Photo Researchers, Inc.; Right: Simon Fraser/RVI, Newcastle Upon Tyne/Photo Researchers, Inc.



ies.⁶ Unfortunately, the symptoms and signs of DIAM are the same as those of infectious meningitis, making diagnosis of this specific phenomenon difficult. It is clear, however, that the incidence of DIAM is higher in women with systemic lupus erythematosus, although the underlying pathogenesis is not yet well understood. In a systematic review of reported aseptic meningitis cases, the time between intake of the associated medication and the start of meningitis symptoms ranged from 45 minutes to 4 months.⁶

Enteroviruses are the most common cause of viral meningitis.⁴ Nucleic acid amplification testing (NAT) has been found to be more sensitive than viral culture in enterovirus detection, and NAT is most likely to be positive within the first 3 days of symptom onset. In addition, the protein concentration and leukocyte count in enterovirus-positive CSF samples are often normal.⁴

ASEPTIC VS BACTERIAL MENINGITIS

Pediatric Decision Rules

The medical literature includes multiple decision rules to help distinguish bacterial from aseptic meningitis; most have been studied in the pediatric population. Currently, no decision rule offers 100% sensitivity and specificity for identifying bacterial versus aseptic meningitis. When comparing these decision rules for use in pediatric patients, the authors of a recent review found that the combination of the following criteria had 98% sensitivity and 61% specificity for bacterial meningitis: positive CSF Gram stain, seizure associated with the presentation, blood neutrophil count $\geq 10,000$ cells/ μL , CSF neutrophil count $\geq 1,000$ cells/ μL , and CSF protein concentration ≥ 80 mg/dL.⁷ This is a negative prediction rule known as the *Bacterial Meningitis Score*.⁸ The absence of all these criteria places patients in a very low risk group for bacterial meningitis.⁹

Several other potential markers of bacterial meningitis have been investigated recently, including CSF lactate and serum procalcitonin levels. In one study, CSF lactate levels greater than 4.2 mmol/L were found to have a positive correlation to bacterial meningitis with 96% sensitivity and 100% specificity.¹⁰

However, while an elevated CSF lactate level has been found to be specific for meningitis, the elevation is also caused by cerebral ischemia and anaerobic metabolism resulting from inflammation and therefore does not add to the diagnosis of bacterial meningitis.¹¹ Because of the poor specificity of elevated lactate levels, lactate measurement is not currently recommended in the typical meningitis workup.

Serum procalcitonin levels in meningitis have been studied in pediatric patients more often than in adult patients. In one study, a procalcitonin level greater than 5 $\mu\text{g/L}$ had a 94% sensitivity for bacterial meningitis in children, with a specificity of 100%.¹²

TABLE 1. Causes of Aseptic Meningitis

Noninfectious

- Postinfectious/postvaccinal
- Drugs: NSAIDs, TMP-SMX, amoxicillin, IVIG^a, isoniazid, allopurinol, carbamazepine
- Systemic diseases: collagen vascular diseases (eg, SLE, RA), sarcoidosis, Behçet disease, leukemia^b
- Inflammation from nearby brain or epidural abscess
- UTI
- Migraine

Infectious

- Viruses: enteroviruses, herpesviruses, respiratory viruses (eg, adenovirus, rhinovirus), arboviruses, mumps, HIV
- Bacteria: Partially treated meningitis, *Mycoplasma*, *Mycobacterium tuberculosis*, *Borrelia*, *Treponema*, *Brucella*, *Leptospira*
- Fungi
- Parasites: *Toxoplasma*, neurocysticercosis
- Rickettsiae: RMSF, typhus, ehrlichiosis

^a And other immune-modulating drugs.

^b And certain other cancers.

NSAIDs = nonsteroidal anti-inflammatory drugs; TMP-SMX = trimethoprim-sulfamethoxazole; IVIG = intravenous immunoglobulin; SLE = systemic lupus erythematosus; RA = rheumatoid arthritis; UTI = urinary tract infection; HIV = human immunodeficiency virus, RMSF = Rocky Mountain spotted fever. Adapted from Kumar.⁵

TABLE 2. Bacterial Meningitis Decision Rules^a

Bacterial Meningitis Score

- Seizure
- Positive CSF Gram stain
- CSF protein level ≥ 80 mg/dL
- Blood neutrophil count $\geq 10,000$ cells/ μ L
- CSF neutrophil count $\geq 1,000$ cells/ μ L

Meningitest

- Seizure
- Positive CSF Gram stain
- CSF protein level ≥ 50 mg/dL
- Purpura
- Toxic appearance (irritability, lethargy, low capillary refill)
- Serum procalcitonin level ≥ 0.5 ng/mL

^a Hospitalization and antibiotic therapy are warranted in children presenting with any of these criteria. If a child has none of the criteria in the prediction rule, the child's risk for bacterial meningitis is considered very low.

CSF = cerebrospinal fluid.

Adapted from Dubos et al⁷; Nigrovic et al⁸; Dubos et al.¹³

Adult studies have had similar results, but these studies have been small.¹¹ A clinical decision rule for pediatric patients based on the Bacterial Meningitis Score has been evaluated; this rule differs from the Bacterial Meningitis Score in that it incorporates procalcitonin level as a criterion and excludes serum and CSF neutrophil counts. This rule recommends antibiotic therapy and hospitalization for children with meningitis presenting with at least one of the following: seizure, "toxic" appearance, purpura, positive CSF Gram stain, serum procalcitonin level ≥ 0.5 ng/mL, and CSF protein level ≥ 50 mg/dL (Table 2).^{7,8,13} Known as the *Meningitest*, this rule has been shown in studies as well as external validation trials to have a sensitivity of 100% and a specificity of 37% to 62%.⁷ Currently, measurement of procalcitonin is not readily available in most hospitals, but the *Meningitest* may be useful in the future to prevent unnecessary hospitalization and antibiotic therapy in children with aseptic meningitis.⁷

Polymerase Chain Reaction

Given that enterovirus is the most common etiology of viral meningitis, enteroviral polymerase chain reaction (PCR), a form of NAT, has been studied to assist in the diagnosis. As previously noted, research has shown that enteroviral PCR may be more sensitive than viral culture for enterovirus detection.¹¹ PCR results are also reported much faster than culture results, which would decrease length and cost of hospital stay. For this reason, PCR could be a valuable time-saving diagnostic test in suspected viral meningitis.¹¹

DIAGNOSING BACTERIAL MENINGITIS

The pathogens causing bacterial meningitis have shifted since the introduction of the *Haemophilus influenzae* type B vaccination and, more recently, the *Streptococcus pneumoniae* vaccination. However, *S pneumoniae* and *Neisseria meningitidis* remain the most common pathogens of bacterial meningitis in adults in developed countries.

Signs and Symptoms

The signs and symptoms of meningitis can vary, and the classic triad of fever, neck stiffness, and altered mental status may not always be present. A 2004 prospective study found that this triad was present in only 44% of 696 cases of community-acquired bacterial meningitis in 671 adult patients.¹⁴ However, the most common symptoms in this study were headache (87%), neck stiffness (83%), fever (77%), and altered mental status as demonstrated by a Glasgow Coma Scale score below 14 (69%); 95% of the patients with bacterial meningitis had two of these four clinical features. The classic triad was also present more commonly in patients with pneumococcal meningitis (58%) than in those with meningococcal meningitis (27%).¹⁴ Rash was seen in 26% of patients and was most frequently associated with meningococcal disease. Rash also occurred in patients with cultures positive for *S pneumoniae*, *Staphylococcus aureus*, *H influenzae*, *Listeria monocytogenes*, and group B streptococcus.

Kernig and Brudzinski signs, together with nuchal rigidity, are the classic "meningeal signs," but they do not occur in most cases of bacterial meningitis. A prospective study of 297 adults evaluated these signs and

found that they were 5% sensitive and 95% specific for bacterial meningitis, while nuchal rigidity was 30% sensitive and 68% specific.¹⁵

Another study evaluated the jolt accentuation test, in which the examiner has the patient rotate his or her head in a horizontal fashion at a rate of two to three times per second. If the headache is exacerbated by the exercise, this constitutes a positive result. In the study, this test had 97% sensitivity and 60% specificity for bacterial meningitis.¹⁶

Nosocomial bacterial meningitis is a rare complication of invasive neurologic procedures. It occurs in 0.8% to 1.5% of patients following craniotomy, 4% to 17% of patients with internal ventricular drains, and 8% of patients with external ventricular drains.¹⁷ There is also a 1.4% incidence of meningitis after moderate to severe head trauma. Factors associated with increased risk of meningitis during and after neurosurgery include concomitant skin infection at the site of surgery, duration

of surgery longer than 4 hours, and postoperative CSF leak. Prophylactic antibiotics have been shown to decrease risk. The bacterial pathogens most commonly associated with neurosurgery are coagulase-negative staphylococci and aerobic gram-negative bacilli. Those associated with ventricular drain placement are usually skin flora such as coagulase-negative staphylococci, and therefore treatment of bacterial meningitis in this setting should target these specific pathogens.¹⁷

Lumbar Puncture

Typically, bacterial meningitis is diagnosed by lumbar puncture. In general, the opening pressure of the CSF is elevated in patients with bacterial meningitis.² Classically, CSF analysis shows a white blood cell (WBC) count $>1,000$ cells/ μL , neutrophils comprising $>80\%$ of the differential, an elevated protein level (>50 mg/dL), and a decreased glucose level ($<40\%$ of serum levels).² In CSF with a WBC count <300 cells/ μL , $<20\%$

neutrophils, and normal protein and glucose levels, viral meningitis is more common. However, there are case reports of bacterial meningitis with normal or low WBC counts in the CSF.^{2,18} Multiple retrospective studies have shown that up to 19% of patients with bacterial disease documented by culture had a CSF WBC count lower than 100 cells/ μ L.¹⁸ The 2004 prospective study of 696 cases of bacterial meningitis in adults found that 12% of patients did not have any individual CSF abnormalities.^{14,18}

Gram stain is an important test in the diagnosis of bacterial meningitis. The sensitivity and specificity of Gram staining in the diagnosis are 60% to 90% and greater than 97%, respectively.² The value of the Gram stain decreases by up to 20% if the patient has had previous antibiotic therapy.¹¹ The likelihood of a positive Gram stain is also dependent on the bacteria involved: positive Gram stain results are seen in one-third of *L monocytogenes* cases, 75% of *N meningitidis* cases, 86% of *H influenzae* cases, and 90% of *S pneumoniae* cases.¹¹

The latex agglutination test is a rapid diagnostic tool with 50% to 100% sensitivity for bacteria, depending on the pathogen. This test uses antibodies for certain pathogens to detect antigen in the patient's blood. It is most sensitive for *H influenzae* and least sensitive for *N meningitidis*.¹¹ Because the test does not usually change treatment decisions if positive, it may be more helpful in the patient who has been treated with antibiotics and whose Gram stain and CSF culture results are negative.¹¹ In this situation, a positive latex agglutination test would identify pathogens in the blood even after treatment with antibiotics has resulted in normal CSF findings.

Blood Cultures

Blood cultures should be drawn routinely before antibiotic administration when meningitis is suspected. Multiple studies have found that blood cultures are positive in 50% to 90% of meningitis cases^{14,19}; therefore, blood culture can be helpful in isolating the organism when CSF is drawn hours after antibiotic administration or in cases in which a CSF sample has not been obtained.

CT Before Lumbar Puncture

CT of the head is often performed before lumbar puncture in the diagnosis of meningitis. This practice

is based on the hypothesis that it is necessary to identify any intracranial abnormalities that may increase intracranial pressure and lead to herniation if a lumbar puncture is performed. This idea was evaluated in a 2001 prospective study of 301 patients with suspected meningitis.²⁰ The study found that of 235 patients who underwent CT of the head, 24% had abnormal results and 5% had evidence of mass effect; lumbar puncture was avoided in some patients with mass effect. Of the patients who underwent lumbar puncture, including seven patients with mild to moderate mass effect on CT, none had herniation within the next week.²⁰

The study sought to identify patients whose clinical findings on exam would prompt the emergency physician to either order or forgo CT before lumbar puncture. In this study, typical age-associated atrophy was considered to be normal. Patients with the following characteristics were statistically significantly more likely to have abnormal CT results: age older than 60 years, immunocompromise, history of a CNS disease, and history of seizures within 1 week of presentation. The following neurologic exam findings were also significantly associated with abnormal CT results: abnormal level of consciousness, inability to answer two consecutive questions correctly, inability to follow two consecutive commands correctly, gaze or facial palsy, abnormal visual fields, arm or leg drift, and language problems such as aphasia or dysarthria. The absence of these features had a negative predictive value of 97%.²⁰ However, these rules have been studied only in adults, and although seizures can occur in up to 30% of children with bacterial meningitis before admission, the rules should not be applied to children.¹¹

TREATMENT OF BACTERIAL MENINGITIS

Antibiotics

Antibiotic therapy for bacterial meningitis should be tailored to the specific bacterium causing the disease. However, in empiric treatment of meningitis in the ED, the pathogen is frequently unknown. As *S pneumoniae* and *N meningitidis* are the most common pathogens in adult disease, antibiotic coverage of these bacteria is most important. In adults in developed countries, the combination of vancomycin plus a third-generation cephalosporin is routinely started empirically.¹¹

In adults older than 50 years, immunocompromised hosts, and patients with head trauma or CSF leak, *L monocytogenes* becomes a more prevalent pathogen in bacterial meningitis. For this reason, ampicillin is added to the empiric treatment regimen.^{11,18}

Historically, penicillin and chloramphenicol were used to treat bacterial meningitis. In the 1970s, treatment changed to cefotaxime or ceftriaxone alone. However, beginning in the late 1980s, a number of patients were found to have persistent symptoms after treatment, due to penicillin-resistant strains of *S pneumoniae*. Most of these patients were successfully treated with the addition of vancomycin; hence the current treatment recommendations.²¹

A recent Cochrane review compared the effectiveness and safety of third-generation cephalosporins with those of the previously favored penicillin or ampicillin-chloramphenicol.²² This review of 19 trials found no significant difference between the two therapies. While this will not likely change practice in developed nations, developing countries with few resources still use penicillin, ampicillin-chloramphenicol, or chloramphenicol alone, as these drugs are much cheaper than the newer cephalosporins.

In the United States, *S pneumoniae* is the leading cause of bacterial meningitis in children 1 to 24 months of age and the second leading cause in children older than 24 months.²¹ In children younger than 1 month, *Streptococcus agalactiae* and *Escherichia coli* are the leading causes, and *L monocytogenes* must also be covered by antibiotics. Current recommendations are similar to those for adults: in children older than 1 month, vancomycin and ceftriaxone or cefotaxime are used, with the addition of ampicillin for *Listeria* coverage in children younger than 1 month.¹¹ Alternatively, in the case of penicillin or β -lactam allergies, vancomycin plus a fluoroquinolone plus trimethoprim/sulfamethoxazole can be used.²³

Timing of antibiotic therapy in patients with bacterial meningitis is a concept that has been analyzed in the medical literature.²⁴ While there are no concrete guidelines on how quickly a patient with suspected meningitis should receive antibiotics, research has demonstrated that delayed CSF sterilization has been associated with increased neurologic complications.²⁵

Yet, in a review of 4,707 patients in 22 studies, a delay of less than 3 to 5 days after symptom onset was not associated with adverse effects or death in patients whose symptoms were nonspecific (nonfocal) at presentation.^{11,26} A recent Cochrane review compared pre-admission antibiotics to placebo or no intervention and found no difference in mortality or neurologic sequelae among patient groups.²⁷ Therefore, while intuitively it seems desirable to treat patients in a timely manner, there have been few studies to suggest a timeline in which treatment must be started.

Additional Therapies

In addition to antibiotics, therapies such as fluids and steroids are important in the treatment of bacterial meningitis. A recent Cochrane review compared outcomes of two treatment groups: a group receiving maintenance fluids and a fluid-restricted group.²⁸ The meta-analysis found no difference between the two groups in number of deaths, mild to moderate adverse outcomes, or severe neurologic outcomes. However, fluid restriction was associated with spasticity, early- and late-onset seizures, and chronic severe neurologic sequelae at 3-month follow-up. This review suggests the importance of maintenance fluids in the treatment of bacterial meningitis.

The use of dexamethasone in the treatment of bacterial meningitis is based on the theory that the inflammatory response within the subarachnoid space contributes greatly to morbidity and mortality in this disease. Steroids are used to attenuate this response and theoretically decrease the consequences of cerebral edema, increased intracerebral pressure, cerebral vasculitis, and neuronal injury.¹¹ Steroids have been associated with decreased mortality and neurologic sequelae, including hearing loss in adults with pneumococcal meningitis.²⁹ A Cochrane review also found dexamethasone to be associated with decreased rates of hearing loss in children with meningitis due to *H influenzae*.³⁰ As dexamethasone does not reverse CNS damage from existing cerebral edema, current recommendations include giving steroids before or with the first dose of antibiotics.¹¹ Currently, a dose of 10 mg every 6 hours for adults or 0.15 mg/kg every 6 hours for children for 2 to 4 days is recommended.¹¹

In patients with worsening clinical condition and decline in consciousness, increased intracranial pressure as a result of meningoencephalitis and brain edema is a concern. Several studies have evaluated the efficacy of reducing intracranial pressure (ICP); however, there are only a few small studies that show lowering the ICP may decrease mortality in bacterial meningitis.^{31,32} The prognosis in cases of elevated ICP is poor and current management is supportive.³² More research is needed to determine if ICP monitoring has a role in meningitis therapy.

In patients who have not responded to treatment within 48 hours, repeated CSF analysis is recommended. In these cases, resistance to penicillin or cephalosporins may be the cause of continued illness, and repeat CSF culture and Gram stain may be helpful. Treatment failures have also been reported in patients who receive dexamethasone therapy in conjunction with vancomycin.³³ When patients appear to have responded to therapy, repeat lumbar puncture is unnecessary, as CSF culture and Gram stain should be negative after 24 hours of appropriate antimicrobial therapy.^{2,11}

COMPLICATIONS

Hearing loss is a common complication after meningitis, affecting up to 40% of survivors of pneumococcal meningitis. It is usually sensorineural, can be unilateral or bilateral, and most likely occurs as a result of suppurative labyrinthitis.³⁴

The complication rates of bacterial meningitis vary by pathogen: fatality rates of pneumococcal meningitis and meningococcal meningitis are 26% and 7%, respectively.³⁵ In a meta-analysis of three studies including a total of 155 adult patients who survived bacterial meningitis, cognitive outcomes were similar in both types of meningitis: cognitive impairment was noted in 28% of meningococcal meningitis patients and 37% of pneumococcal meningitis patients, regardless of time after meningitis. Compared with patients who survived meningococcal meningitis, those who survived pneumococcal meningitis performed worse on memory tasks and more slowly on cognitive testing.³⁵ The use of dexamethasone had no effect on cognitive testing outcomes after recovery.

A 1998 retrospective study of 269 adults with bac-

terial meningitis attempted to correlate symptoms at presentation with poor outcomes.²⁴ It was concluded that adverse outcomes were more likely in patients with meningitis caused by *S pneumoniae* than any other type of meningitis, excluding meningitis caused by *Treponema pallidum*, *Mycobacterium* species, and *Borrelia burgdorferi* (also excluded were patients with intracranial devices). Hypotension, altered mental status, and seizures were independently associated with worse outcomes (defined as mortality and neurologic deficits). Of the survivors, 9% had some form of neurologic deficit at the time of hospital discharge, most commonly hearing loss.²⁴

CONCLUSION

Timely diagnosis and treatment of meningitis is difficult but essential to prevent life-threatening complications of the disease. While research has improved the ability to manage meningitis, many studies are ongoing to discover new elements of testing and diagnosis. Using CT judiciously can help improve the time to treatment and lumbar puncture (when applicable), and new tests such as procalcitonin measurement are also promising in diagnosing this disease. Until new diagnostic tools are more widely available, knowledge of current practice and decision rules is vital to the expedient identification and competent management of meningitis.

EM

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